

Natural Product Synthesis

Total Synthesis of (–)-Jiadifenin**

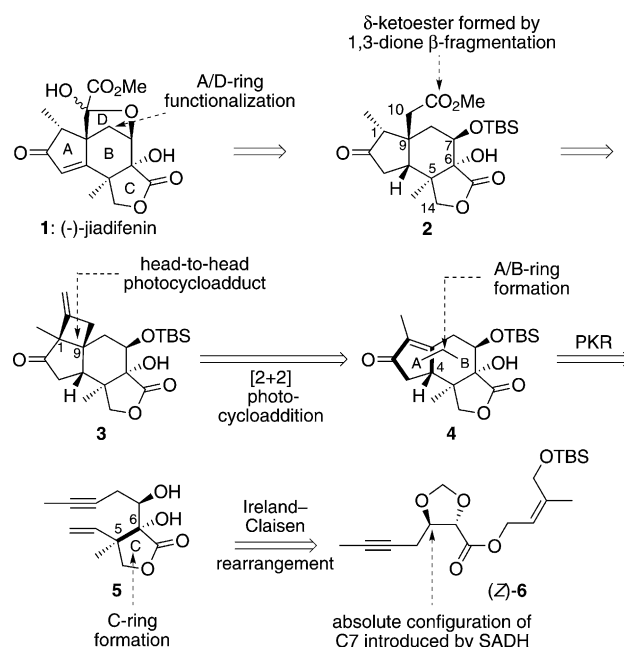
Yang Yang, Xingnian Fu, Jianwei Chen, and Hongbin Zhai*

Dedicated to Professor Matthew S. Platz on the occasion of his birthday

A growing number of the world population suffer from neurodegenerative disorders, such as Alzheimer's, Huntington's, and Parkinson's diseases, as a result of the increased longevity of the population.^[1] Over the past few decades, polypeptidyl neurotrophic factors have played an important role in mediating neuronal survival and outgrowth.^[1b,2] However, as a result of the intrinsic unfavorable pharmacokinetic properties of polypeptidyl neurotrophic agents, non-peptidyl CNS-permeable small-molecule neurotrophins are emerging as attractive alternatives.

In 2002, jiadifenin (**1**, Scheme 1) was isolated from the pericarps of *Illicium jiadifengpi* and characterized as a novel nonpeptidyl neurotrophic modulator, which prominently promoted neurite outgrowth in primary cultures of fetal rat cortical neuronal cells at concentrations of 0.1–10 μM .^[3] This highly oxygenated sesquiterpene features a unique *seco*-prezizaane-type skeleton (A and B rings) decorated with a fused γ -lactone (C ring) and a bridged cyclic hemiacetal (D ring). Densely imbedded in the framework of this compact cage-shaped molecule are six stereocenters, including two separate all-carbon quaternary centers (C5 and C9) and two oxo-functionalized quaternary ones (C6 and C10). The impressive structural complexity together with the potential therapeutic value for neurodegenerative diseases has rendered **1** as an attractive target for synthetic studies. Noteworthy accomplishments include the total syntheses by the groups of Danishefsky^[4] and Theodorakis^[5] with a ring-construction sequence of B $\rightarrow$ AB $\rightarrow$ ABC $\rightarrow$ ABCD and of A $\rightarrow$ AB $\rightarrow$ ABC $\rightarrow$ ABCD, respectively. In addition, a synthetic exploration was reported by Fukuyama and co-workers.^[6] Herein, we wish to describe a novel enantioselective total synthesis of jiadifenin (**1**).

As outlined in Scheme 1, we envisioned that jiadifenin (**1**) may be accessible through a series of transformations



Scheme 1. Retrosynthetic analysis for (–)-jiadifenin. SADH = Sharpless asymmetric dihydroxylation, TBS = *tert*-butyldimethylsilyl.

including regio- and stereoselective [2+2] photo-cycloaddition of **4** with allene^[7] (**4** $\rightarrow$ **3**), ozonolysis and regioselective 1,3-dione β -fragmentation^[7b,c] (**3** $\rightarrow$ **2**), and A-ring dehydrogenation followed by oxidative D-ring formation (**2** $\rightarrow$ **1**), while the 6/5 fused-ring system in **4** may be installed by a strategic intramolecular Pauson–Khand reaction (IMPKR, **5** $\rightarrow$ **4**).^[8] Enyne **5** may be generated from a stereoselective Ireland–Claisen rearrangement^[9] of (*Z*)-**6** followed by desilylation and lactonization, which may establish the two contiguous quaternary centers (C5 and C6, referring to the numbering system for **1**). The (*Z*)-**6** ester may be enantioselectively synthesized from readily accessible starting materials by the Sharpless asymmetric dihydroxylation (SADH).^[10] Overall, the current strategy is characterized by a new ring-construction sequence, that is, C $\rightarrow$ ABC $\rightarrow$ ABCD.

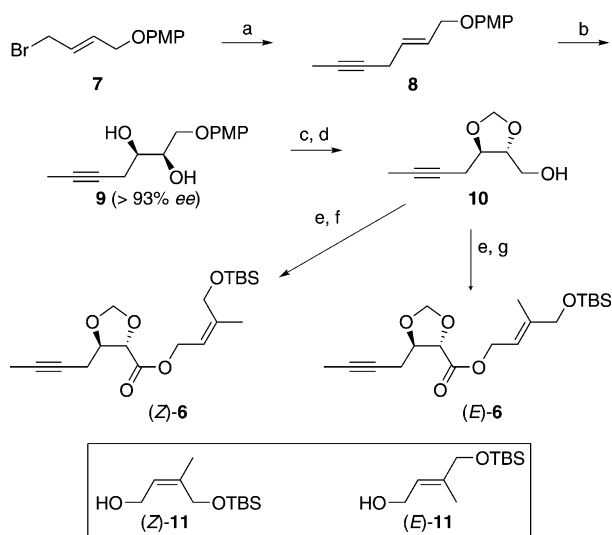
Our synthesis commenced with the coupling of allylic bromide **7**^[10c] with lithiated propyne to give enyne **8** (74%). Asymmetric dihydroxylation^[10a,c] of **8** in the presence of AD-mix- β provided diol **9** (95% yield, >93% *ee*) with the desired configuration at the C7-position (Scheme 2).

At this stage, the choice of an appropriate protecting group of the two vicinal hydroxy groups of **9** proved to be critical for the success of the Ireland–Claisen rearrangement

[*] Dr. Y. Yang, Dr. X. Fu, Dr. J. Chen, Prof. Dr. H. Zhai
Key Laboratory of Synthetic Chemistry of Natural Substances
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (China)
Prof. Dr. H. Zhai
State Key Laboratory of Applied Organic Chemistry
Lanzhou University, Lanzhou 730000 (China)
E-mail: zhaih@lzu.edu.cn

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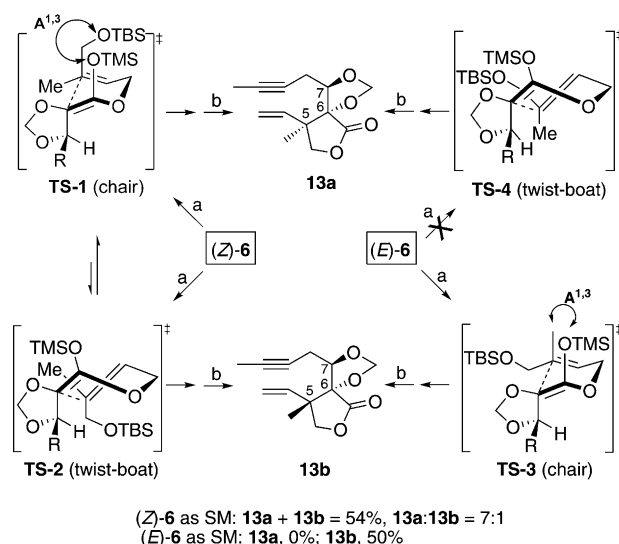
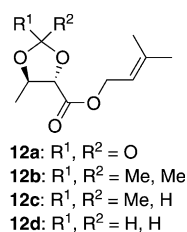
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201203176>.



Scheme 2. Synthesis of esters (Z)-6 and (E)-6: a) 1-bromo-1-propene, *n*BuLi, CuI, THF, -78°C to RT, 74%; b) AD-mix- β , MeSO_2NH_2 , *t*BuOH/ H_2O (1:1), 0°C , 95%, > 93% *ee*; c) KOH, CH_2I_2 , [18]-crown-6, CH_2Cl_2 , reflux, 80%; d) CAN, MeCN/ H_2O (2.5:1), 90%; e) Jones reagent, acetone, -78°C to RT; f) DCC, DMAP, (Z)-11, THF, RT, 70% for 2 steps; g) DCC, DMAP, (E)-11, THF, RT, 56% for 2 steps. DCC = dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, Jones reagent = CrO_3 in diluted H_2SO_4 , PMP = 4-methoxyphenyl, TBS = *tert*-butyldimethylsilyl.

of an ester such as (Z)-6. Preliminary studies showed that when subjected to a base such as LDA, ester **12a** (having a cyclic carbonate unit) underwent a β -elimination, followed by loss of a molecule of CO_2 , rather than a [3,3] sigmatropic rearrangement. Prenyl esters **12b** and **12c** failed to undergo the rearrangement upon exposure to LDA and TMSCl, presumably because of the steric hindrance exerted by the methyl group(s) on the dioxolane ring. We next scrutinized **12d**, a sterically less-demanding ester, which when subjected to the same reaction conditions delivered the Ireland–Claisen rearrangement product. Therefore, the two vicinal hydroxy groups in **9** were protected as a dioxolane. After the dioxolane formation^[11a] of the vicinal diol followed by PMP removal,^[11b] **9** was converted into primary alcohol **10** in 72% yield over two steps (Scheme 2). Jones oxidation^[12] of **10** afforded the corresponding carboxylic acid, which was coupled^[9d,e] with the known alcohols (Z)-11^[13a] and (E)-11^[13b] to deliver the corresponding esters (Z)-6 and (E)-6, respectively.

Sequential treatment of (Z)-6 with LDA and TMSCl effected the expected Ireland–Claisen rearrangement^[9d,e] to form a pair of inseparable diastereomers **13a/13b** (7:1) in 54% combined yield after acid-promoted lactonization (Scheme 3). Good diastereoselectivity was observed for the rearrangement. The α -hydroxy group of the ester is an effective chelator^[9d] of lithium ions that can ensure chelation control in the deprotonation step leading to the (Z)-ketene acetal. The latter underwent thermal rearrangement to deliver the desired carboxylic acid, the precursor of

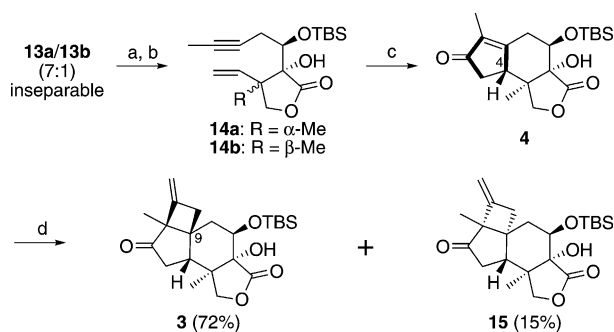


Scheme 3. Ireland–Claisen rearrangement of (Z)-6 and (E)-6 and the subsequent lactonization: a) LDA, TMSCl, THF, -78°C to RT to reflux; b) TsOH· H_2O , MeOH, reflux. LDA = lithium diisopropylamide, R = 2-butynyl, TMS = trimethylsilyl.

13a, as a major product via a preferred chair-like transition state (TS-1), while the minor product (**13b**) arose from the less-favored twist-boat-like transition state (TS-2) in the rearrangement step. Note that intermediate **13a** contains two contiguous quaternary centers at C5 and C6 with correct configurations, which were controlled by the stereochemistry at C7 of (Z)-6. In comparison with the case of (Z)-6, enyne **13b**^[14] was produced as the sole product from (E)-6 upon the Ireland–Claisen rearrangement (via chair-like transition state TS-3) and the subsequent lactonization, thus indicating that the twist-boat-like TS-4 essentially had no contribution to the reaction outcome. Furthermore, the presence of a more severe $\text{A}^{1,3}$ interaction in TS-1 than in TS-3 might account for the fact that **13a** was not the exclusive product for the same reaction sequence starting from (Z)-6.

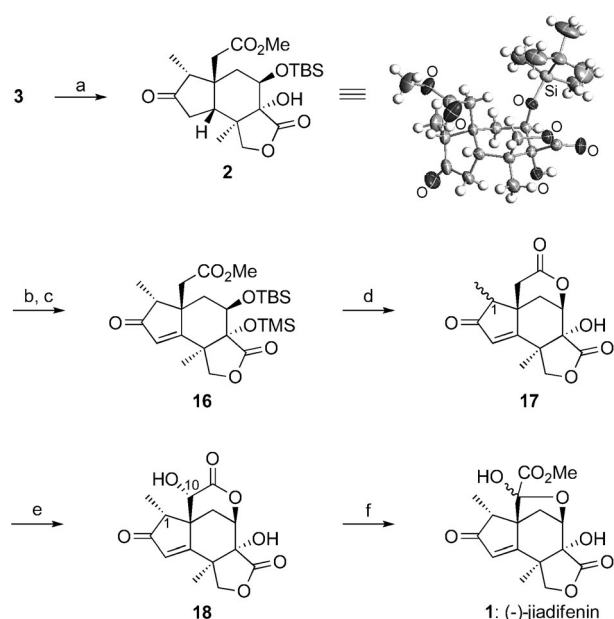
Upon dihydroxy deprotection^[15] and selective silylation of the secondary hydroxy group at C7, the **13a/13b** mixture (derived from (Z)-6, as mentioned above) was converted into enynes **14a/14b** in 51% combined overall yield (Scheme 4). Treatment of the **14a/14b** mixture with $[\text{Co}_2(\text{CO})_8]$ effected an IMPKR^[8d] to produce tricyclic enone **4** (67%) and *epi*-**4** (6%) along with a trace amount of enyne/ $\text{Co}_2(\text{CO})_6$ complexes. Whereas **14a** furnished **4** and *epi*-**4**, lactone **14b** only resulted in the formation of the enyne/ $\text{Co}_2(\text{CO})_6$ complex without further cyclization. The structure of **4** was confirmed by NOESY experiments. With significant quantities of **4** in hand, irradiation^[7b,c] of **4** in the presence of a large excess of allene in THF at -78°C was carried out to furnish a mixture of head-to-head photocycloadducts **3** (72%) and **15** (15%). The structure of **3** was assigned by assuming that the allene approached the enone from the β -face of **4** in the photocycloaddition step.

Ozonolysis^[7b,c] of **3** followed by ring opening with methanolic NaOMe led to **2** (89%) as a fragmentation product,^[7b] the structure of which was confirmed by X-ray



Scheme 4. Synthesis of tetracycle **3**: a) $\text{Ph}_3\text{C}\cdot\text{BF}_4$, CH_2Cl_2 , reflux, 60%; b) TBSOTf, Et_3N , CH_2Cl_2 , RT, 85%; c) $[\text{Co}_2(\text{CO})_8]$, Bu_3PS , toluene, RT to 75°C , 67%; d) $h\nu$, allene, THF, -78°C , **3** (72%), **15** (15%). TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate.

crystallographic analysis (Scheme 5).^[16] By applying the Ito–Saegusa oxidation protocol,^[17] **2** was regioselectively converted into α,β -unsaturated ketone **16** in 92% yield over the two steps. Upon exposure to TBAF,^[18] tandem desilylation and lactonization of enone **16** furnished dilactones **17** in 96% yield, although partial epimerization was observed at C1. Encouraged by the relevant findings by Theodorakis and co-workers,^[5b] treatment of the diastereomeric mixture of **17** sequentially with NaHMDS (3 equiv) and Davis oxaziridine^[19] (1 equiv) produced α -hydroxy lactone **18** as a single diastereomer in 55% (or 74%, based on recovered starting material) yield.^[20] Finally, **18** was transformed into (–)-jiadifenin (**1**) by Jones oxidation and a subsequent methanol-



Scheme 5. Synthesis of (–)-jiadifenin: a) (i) O_3 , MeOH, CH_2Cl_2 , then Me_2S , -78°C to RT; (ii) NaOMe, MeOH, 89%; b) LDA, TMSCl, Et_3N , THF, -78°C to -20°C ; c) $\text{Pd}(\text{OAc})_2$, O_2 , DMSO, 75°C , 92% (2 steps); d) TBAF, THF, RT, 96%; e) NaHMDS, (–)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine, THF, -78°C , 55% (74%, brsm); f) Jones reagent, acetone, 0°C , then MeOH, RT, 46%. The X-ray crystal structure of **2** is shown with thermal ellipsoids at 30% probability. DMSO = dimethyl sulfoxide, HMDS = hexamethyldisilazane, TBAF = tetrabutylammonium fluoride.

ysis, according to a known procedure.^[4a,5b] The spectroscopic data (^1H and ^{13}C NMR spectroscopy; HRMS) of both **17** and our synthetic **1** were identical to those reported in the literature; the optical rotation value ($[\alpha]_{\text{D}}^{25} = -126.6^\circ \text{cm}^3 \text{g}^{-1}$ ($c = 0.08 \text{ g cm}^{-3}$, EtOH)) of **1** was similar to the literature data (Ref. [5b]: $[\alpha]_{\text{D}}^{24} = -123.8^\circ \text{cm}^3 \text{g}^{-1}$ ($c = 0.17 \text{ g cm}^{-3}$, EtOH); Ref. [3]: $[\alpha]_{\text{D}}^{22} = -152.9^\circ \text{cm}^3 \text{g}^{-1}$ ($c = 0.24 \text{ g cm}^{-3}$, EtOH)).

In summary, we have accomplished a novel asymmetric total synthesis of (–)-jiadifenin in eighteen reaction steps from the known compound **7**.^[10c] Key features of the current synthesis include: 1) the Ireland–Claisen rearrangement to produce the two contiguous quaternary centers at C5 and C6 simultaneously, 2) the intramolecular Pauson–Khand reaction (IMPKR) to concurrently construct the A and B rings, and 3) the [2+2] photo-cycloaddition to generate the all-carbon quaternary center at C9.

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- [20] Compound **18** was obtained from (1*R*)-**17** (with α -methyl at C1) in three steps consisting of Luche reduction of ketone carbonyl, α -hydroxylation of lactone, and Jones oxidation in the literature, see Ref. [4a,b]. In contrast, both diastereomers of **17** were converted into **18** in only one step in our case.

