Natural Product Synthesis

DOI: 10.1002/anie.201203176

Total Synthesis of (−)-Jiadifenin**

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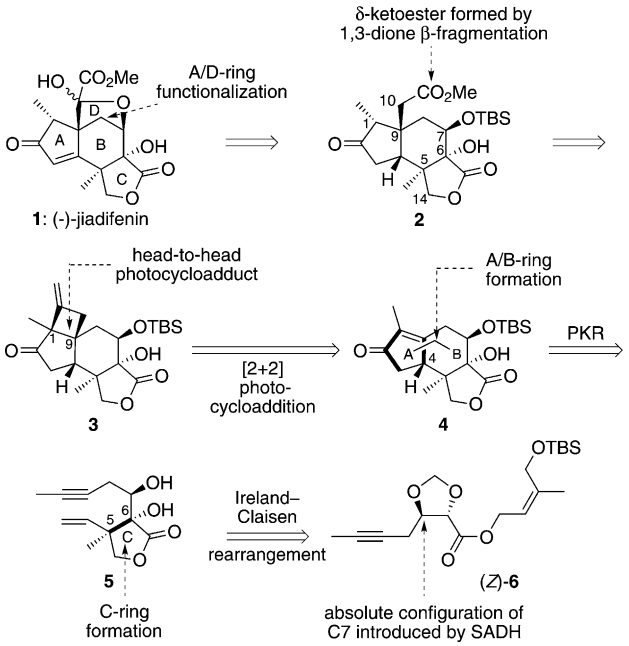
Dedicated to Professor Matthew S. Platz on the occasion of his birthday

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, nonpeptidyl 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→AB→ABC→ABCD and of A→AB→ABC→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**→**3**), ozonolysis and regioselective 1,3-dione β-fragmentation[7b,c] (**3**→**2**), and A-ring dehydrogenation followed by oxidative D-ring formation (**2**→**1**), while the 6/5 fused-ring system in **4** may be installed by a strategic intramolecular Pauson–Khand reaction (IMPKR, **5**→**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→ABC→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

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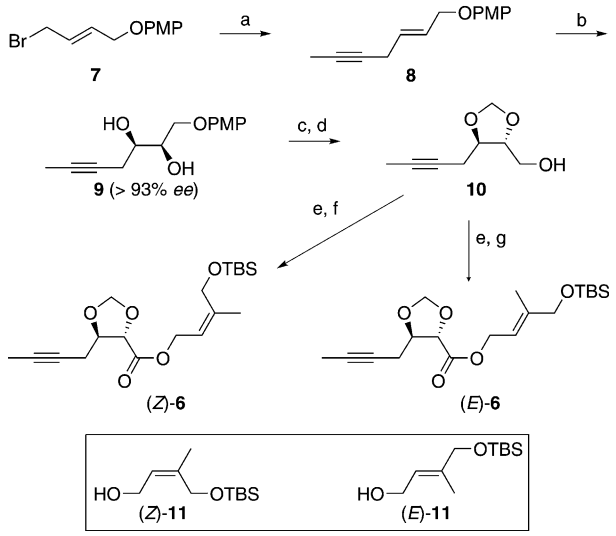
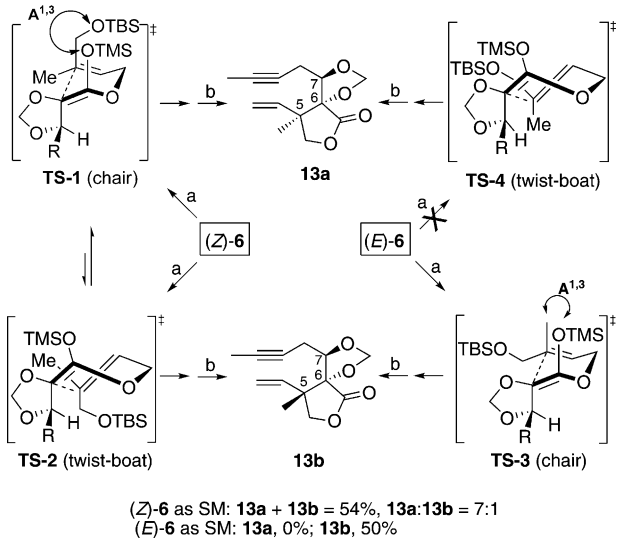
[**] We thank the National Basic Research Program of China (973 Program: 2010CB833200),the NSFC (21172100), the Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT: IRT1138), and "111" Program of MOE for financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.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.

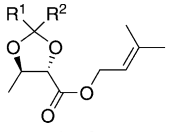


(*Z*)-**6** as SM: **13a** + **13b** = 54%, **13a**:**13b** = 7:1
(*E*)-**6** as SM: **13a**, 0%; **13b**, 50%

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.

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 alchol **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

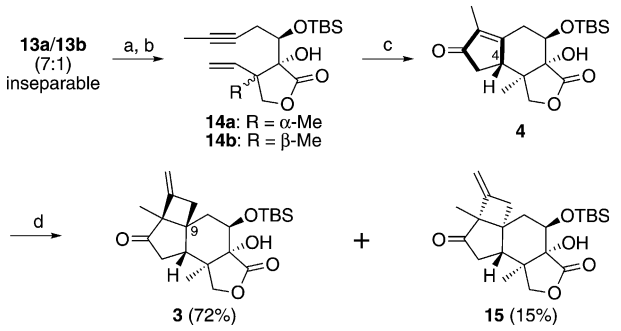


12a: R^1, R^2 = O
12b: R^1, R^2 = Me, Me
12c: R^1, R^2 = Me, H
12d: R^1, R^2 = H, H

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 $A^{1,3}$ 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**.

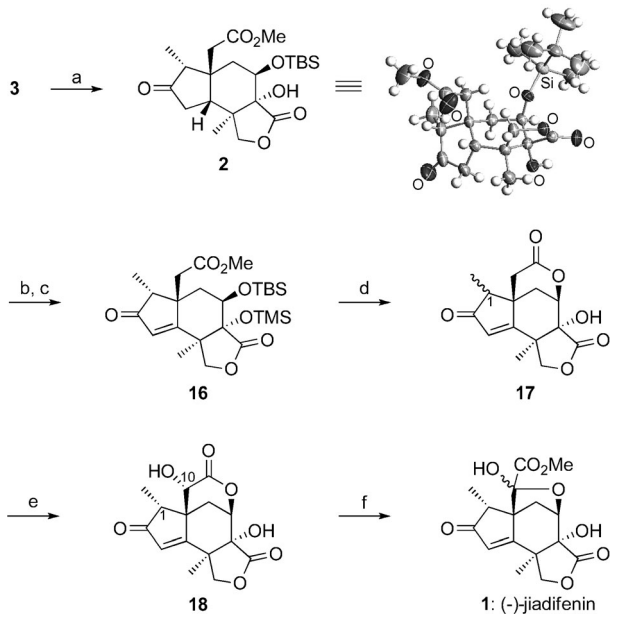
Upon dihydroxy deprotection[15] and selective silylation of the secondary hydroxy group at C7, the **13a**/**13b** mixture (derived from (*Z*)-**6**, as mentioned above) was converted into enynes **14a**/**14b** in 51% combined overall yield (Scheme 4). Treatment of the **14a**/**14b** mixture with $[Co_2(CO)_8]$ effected an IMPKR[8d] to produce tricyclic enone **4** (67%) and *epi*-**4** (6%) along with a trace amount of enyne/$Co_2(CO)_6$ complexes. Whereas **14a** furnished **4** and *epi*-**4**, lactone **14b** only resulted in the formation of the enyne/$Co_2(CO)_6$ 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) $Ph_3C{\cdot}BF_4$, CH_2Cl_2, reflux, 60%; b) TBSOTf, Et_3N, CH_2Cl_2,RT, 85%; c) $[Co_2(CO)_8]$, Bu_3PS, toluene, RT to 75°C, 67%; d) *hν*, 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 coworkers,[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) $Pd(OAc)_2$, 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 ($[\alpha]^{25}_D = -126.6\ cm^3\,g^{-1}\,cm^{-1}$ ($c = 0.08\ g\,cm^{-3}$, EtOH)) of **1** was similar to the literature data (Ref. [5b]: $[\alpha]^{24}_D = -123.8\ cm^3\,g^{-1}\,cm^{-1}$ ($c = 0.17\ g\,cm^{-3}$, EtOH); Ref. [3]: $[\alpha]^{22}_D = -152.9\ cm^3\,g^{-1}\,cm^{-1}$ ($c = 0.24\ g\,cm^{-3}$, 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.

Received: April 25, 2012
Published online: August 24, 2012

Keywords: cycloaddition · Pauson–Khand reaction · photochemistry · sesquiterpene · total synthesis

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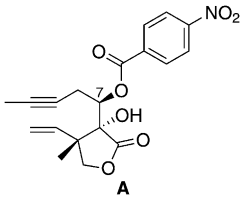
[14] Dihydroxy deprotection[15] of **13b** followed by selective formation of *p*-nitrobenzoate at the secondary hydroxy group led to ester **A**, the structure of which was confirmed by X-ray crystallographic analysis. CCDC 881252 (**A**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



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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.

