ORGANIC LETTERS

2011
Vol. 13, No. 5
988–991

Synthesis of the ABC Ring System of Jiadifenin *via* Pd-Catalyzed Cyclizations

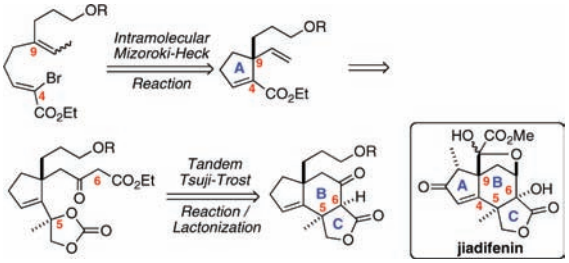
Kenichi Harada,[†] Akiko Imai,[†] Kazuharu Uto,[†] Rich G. Carter,[§] Miwa Kubo,[†] Hideaki Hioki,[‡] and Yoshiyasu Fukuyama*[,†]

Faculty of Parmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan, Department of Chemistry, Faculty of Education, Gunma University, Maebashi, Gunma 371-8510, Japan, and Department of Chemistry, Oregon State University, 153, Gilbert Hall, Corrvallis, Oregon 97331, United States

fukuyama@ph.bunri-u.ac.jp

Received December 14, 2010

ABSTRACT



An efficient route toward the central ABC system of jiadifenin has been developed using two key Pd-catalyzed cyclizations. A protic solvent-activated Mizoroki−Heck reaction was used to construct the C_9 quaternary carbon and the A ring. A cascading Tsuji−Trost cyclization/lactonization sequence was employed to establish the BC ring system and the $C_{5,6}$ stereochemistry.

The genus *Illicium* is distinctive in producing biosynthetically unique *seco*-prezizaane type sesquiterpenes. More than 50 *seco*-prezizaane type sesquiterpenes have been isolated from *Illicium* plants[1] since their initital discovery over 50 years ago.[2,3] In 2002, our laboratory reported the isolation and structure determination of jiadifenin (**1**) from the methanol extract of the pericarps of *Illicium jiadifengpi* indigenous to the southern part of China.[4] This *seco*-prezizaane type sesquiterpene **1** consists of a highly oxygenated, cage-like tetracycle involving a cyclic hemiacetal, a γ-lactone, six stereogenic centers including two separate all-carbon quaternary centers, and an oxo-functionalized carbon at C_{10} (Figure 1). In addition to its unique structure, compound **1** was found to significantly promote neurite outgrowth in primary cultures of fetal rat cortical neurons at concentrations from 0.1 to 10 μM.[4] This bioactivity indicates that jiadifenin is a potential candidate for the treatment of neurodegenerative disorders such as Alzheimer's disease.[5] Danishefsky and co-workers have reported the sole synthesis of (±)-**1** to date.[6] Herein, we report an efficient and flexible synthetic route of the ABC tricyclic core of jiadifenin (**1**).

[†] Tokushima Bunri University.
[‡] Gunma University.
[§] Oregon State University.

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10.1021/ol103024z
Published on Web 01/25/2011

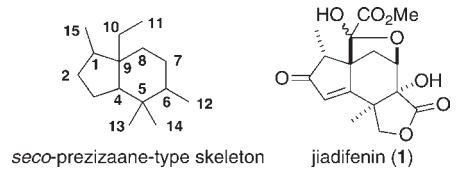
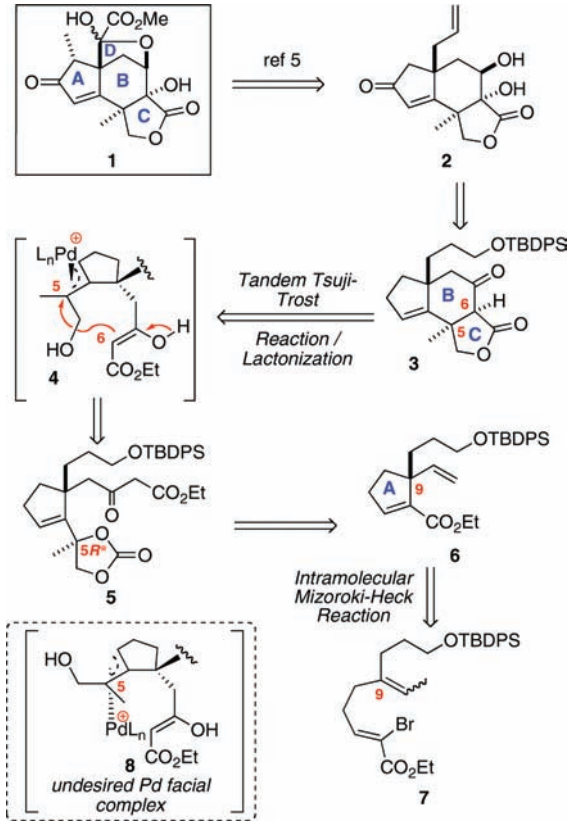


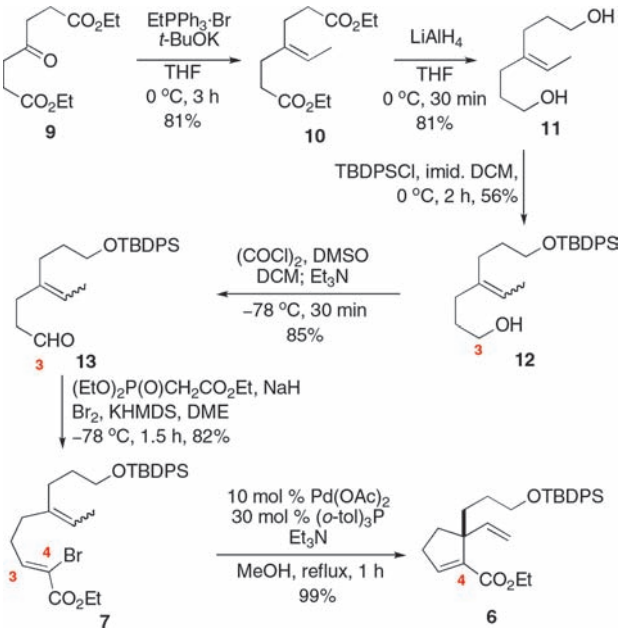
Figure 1. Structures of *seco*-Prezizaane-type skeleton and jiadifenin (**1**).

Scheme 1. Retrosynthetic Analysis of Jiadifenin (**1**)



Our synthetic strategy focused on the construction of the jiadifenin's ABC ring system **3** (Scheme 1). Critical to any synthetic approach is control of the two challenging all-carbon quaternary centers embedded with the scaffold at C_5 and C_9. Our strategy incorporates two key palladium-catalyzed cyclizations to construct the C_5 and C_9 quaternary stereocenters as well as the ABC ring system. A Tsuji–Trost cyclization[7] of cyclic carbonate **5** followed by *in situ* lactonization would generate the BC ring system **3**. Control of the newly formed C_5 quaternary carbon would be derived from the 5*R** stereochemistry in carbonate **5** through a double inversion (net retention) process as shown in intermediate **4**.[5d] While two diastereomeric palladium complexes **4** and **8** can result from the same 5*R** carbonate **5**, only Pd-complex **4** should be a mechanistically viable intermediate for the formation of the desired Tsuji–Trost product **3**. Cyclic carbonate **5** would be accessible from the α,β-unsaturated ester **6**. Palladium-catalyzed intramolecular Mizoroki–Heck reaction[8] of bromide **7** would establish the cyclopentene A ring.

Scheme 2. Construction of A Ring



The construction of the A ring is shown in Scheme 2. Wittig reaction of the commercially available diethyl 4-oxopimelate (**9**) with ethyl triphenyl phosphonium bromide and potassium *tert*-butoxide provided alkene **10** in 81% yield. Subsequent $LiAlH_4$ reduction gave diol **11** in 81% yield. Monoprotection using TBDPSCl and imidazole generated the C_3 alcohol **12** which was oxidized to the aldehyde **13** under the Swern conditions. Next, Horner–Wadsworth–Emmons olefination[9] using *in situ* prepared $(EtO)_2POCHBrCO_2Et$[10] gave rise to α-bromo unsaturated ester **7**. We next explored the key Mizoroki–Heck cyclization of bromide **7**. Initially, we utilized a standard $Pd(OAc)_2$ (10 mol %), (*o*-tol)$_3$P (20 mol %), Et_3N (2 equiv) system[11] in a range of aprotic solvents (e.g., toluene, THF,

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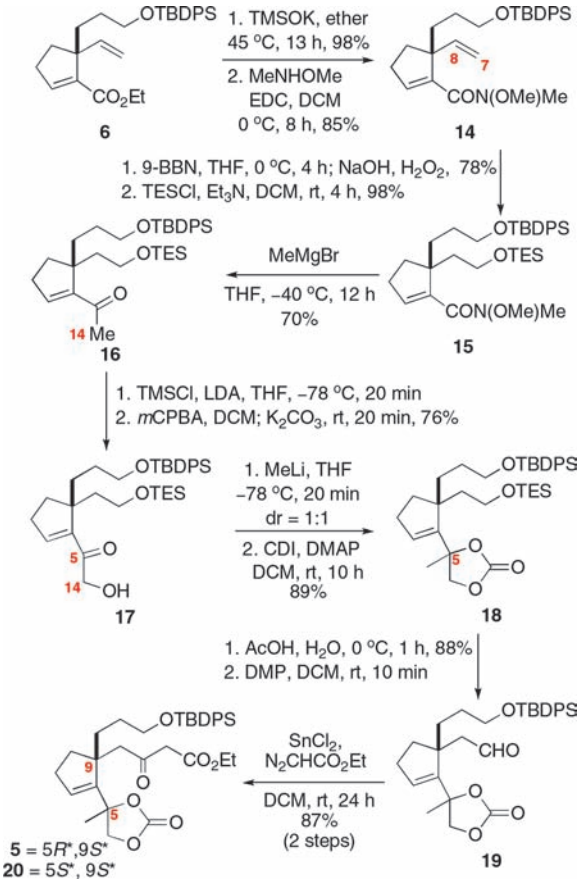
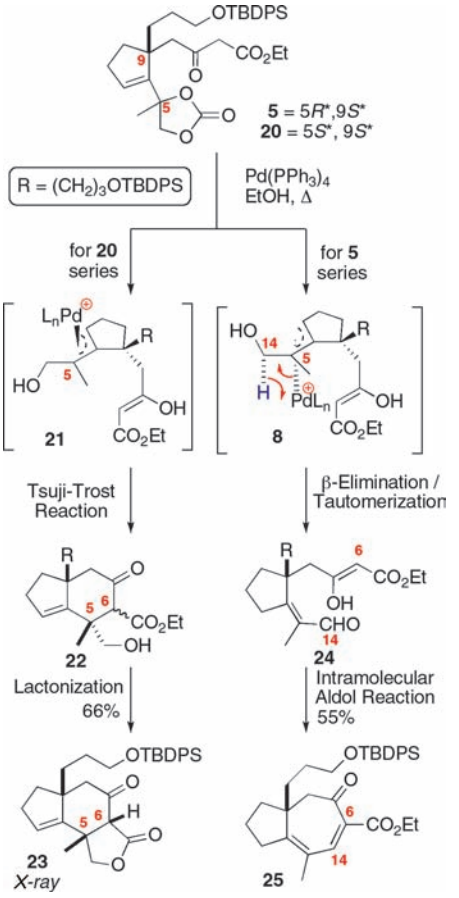
Scheme 3. Preparation of Cyclic Carbonate



Scheme 4. Attempted Tsuji–Trost Cyclization of Carbonate Diastereomers **5** and **20**



CH_3CN, DMF, and DMSO); however, these conditions were not effective, generating low (0–39%) chemical yields. Interestingly, the use of MeOH as solvent[12] led to a dramatic increase in the chemical yield (99%) of the desired product **6**. Other protic solvents such as EtOH and *t*-BuOH were also effective, and the catalyst loading could be reduced to 5 mol % without affecting the chemical yield. Very recently, Felpin, Sotiropoulos and co-workers reported a similar effect of alcoholic solvents during an aryldiazonium salt Heck coupling, which they attributed to a MeOH-stabilized oxidative addition intermediate.[13]

With a viable route to the cyclopentane **6**, we turned our attention to the synthesis of the Tsuji–Trost precursor **5** (Scheme 3). Hydrolysis of ethyl ester **6** with TMSOK, followed by conversion of carboxylic acid to Weinreb amide with EDC and DMAP, proceeded in 84% yield over two steps. Subsequent hydroboration at $C_{7,8}$ followed by oxidative workup and silylation produced the TES ether **15**. Next, treatment of Weinreb amide **15** with methylmagnesium bromide generated the methyl ketone **16**. Rubottom oxidation[14] at C_{14} provided the α-hydroxy ketone **17**. Introduction of the C_{13} methyl group was accomplished using excess MeLi to afford a 1,2-diol as a 1:1 diastereomeric mixture at C_5. Attempts to improve the stereoselectivity of this transformation have been unsuccessful to date. The diol could be readily converted to cyclic carbonate using CDI, Et_3N, and DMAP. The C_7 TES ether was selectively removed using mildly acidic conditions (AcOH–H_2O, rt). Finally, Dess–Martin oxidation at C_7 followed by treatment of the resultant aldehyde **19** with ethyl diazoacetate/$SnCl_2$ yielded *β*-keto ester **5/20** in 87% yield.[15]

We next investigated the Pd-catalyzed cyclization to form the BC ring system using the individual diastereomers[16] **5** and **20** separately (Scheme 4).[17] Mechanistically, we had expected that only diastereomer **5** would be a viable substrate for the production of tricycle **5**. As we

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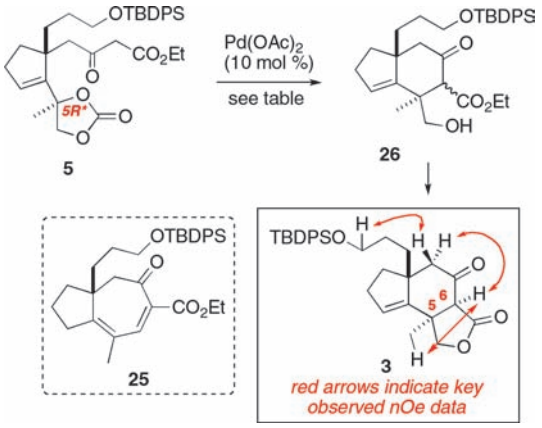
(16) The identity of which diastereomer corresponds to the 5*R** and 5*S** stereochemistries is based on the correlation to the observed Tsuji–Trost products.

(17) The reaction did not proceed in relatively nonpolar solvents such as toluene and THF. Using more polar solvents such as DMF and DMSO, preferential *O*-alkylation (over *C*-alkylation) of *β*-ketoester was observed.

Table 1. Tandem Cyclization of Carbonate **5**



entry	ligand	base	solvent	% yield 3	25	26
1	PPh_3[a]	-	EtOH	-	55	-
2	DPPB	-	EtOH	22	28	-
3	(*R*)-BINAP	-	EtOH	27	-	23
4	(*R*)-BINAP	-	*t*BuOH	38	-	14
5	(*R*)-BINAP	LiOAc[b]	*t*BuOH	57	-	-

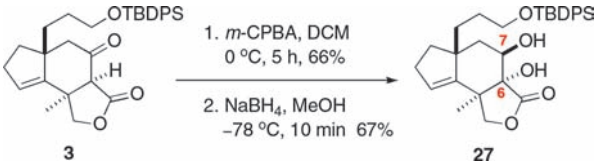
[a] $Pd(PPh_3)_4$ was used as catalyst. [b] 2.4 equiv were used.

had predicted, diastereomer **20** produced the undesired ABC tricycle **23**[18] with incorrect stereochemistries at C_5 and C_6 in 66% yield. This result was in agreement with the "double inversion" model[7d] for the Trost−Tsuji reaction and demonstrated the potential of our strategy to access the 5,6,5-tricyclic scaffold necessary for constructing jiadifenin (**1**). Disappointingly, the alternate diastereomer **5** did not produce the desired product **3**, but instead yielded cycloheptenone **25** in 55% yield. This compound **25** may arise from unwanted *diastereomeric* π-allyl Pd complex **8**, which undergoes preferential β-hydride elimination at C_{14}, tautomerization, and intramolecular aldol condensation.

While neither carbonate diastereomer **5** nor **20** had yielded the desired product, we suspected that alteration of the catalyst might change the reaction outcome (Table 1). Using $Pd(OAc)_2$ as the palladium source, we first screened a range of monodentate ligands (e.g., *n*-Bu_3P, *t*-Bu_3P, and Cy_3P); however, none of these conditions significantly altered the reaction outcome. In contrast, use of bidentate ligands such as DPPB and (*R*)-BINAP *did* produce the desired product **3** in modest (22−27%) chemical yield along with the uncyclized ethyl ester **26** as a byproduct

(18) This structure was confirmed by X-ray crystallographic analysis. See Supporting Information for full details.

Scheme 5. B Ring Functionalization



(entry 3). The stereochemistry of the tricycle **3** was established via extensive 2D NMR including the key nOe data shown in Table 1. Replacement of the reaction solvent from EtOH to *t*-BuOH suppressed formation of ethyl ester **26** (entry 4). Finally, the addition of LiOAc as a base further increased the chemical efficiency to 57% yield (entry 5).[19] The interplay between mono- and bidentate ligands in the product distribution has yet to be clarified, and we are actively exploring this divergent reactivity.

Exploration of functional group manipulation of the ABC tricyclic core was also investigated (Scheme 5). Compound **3** was readily functionalized by *m*CPBA oxidation.[6] Subsequent reduction using $NaBH_4$ gave the diol **27** in a highly stereoselective manner. Advanced intermediate **27** contains the central ABC ring system and all the configurationally stable stereochemistry present in jiadifenin (**1**).

In conclusion, we have established an efficient route for the ABC ring system of jiadifenin. The protic solvent-promoted Mizoroki−Heck reaction was used to construct the A ring moiety in high yield. A tandem Tsuji−Trost cyclization/lactonization sequence was employed to construct the BC system. Key knowledge in the relation between carbonate stereochemistry and successful Tsuji−Trost cyclization has been disclosed. This work should lay a strong foundation for the total synthesis of jiadifenin, and further synthetic studies will be reported in due course.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (Priority Area, 19790027, 22790030). R.G.C. is a Japan Society for the Promotion of Science Fellow (L-10568). Ms. Yasuko Okamoto (Tokushima Bunri University) is acknowledged for mass spectra data.

Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) Although these conditions used (*R*)-BINAP, the same results were observed using (±)-BINAP.