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Second-generation total synthesis of (−)-diversifolin

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ABSTRACT

A second-generation total synthesis of (−)-diversifolin has been achieved by a more straightforward strategy, involving a highly stereochemistry-dependent 10-membered ring-closing metathesis and a stereoselective dihydroxylation/lactone transposition sequence. Compared to our previous synthesis, the present synthesis is improved in the yield of the key intermediate **2** (20% in 12 steps from diol **8**).

(−)-Diversifolin (**1**), a natural product isolated from the leaves of *Tithonia diversifolia*[1a–c] and *Viguiera dentata*,[1d] is a germacrane-type sesquiterpene lactone that is reported to exhibit the anti-inflammatory activity by inhibiting the activation of the transcription factor NF-κB.[1c,2] Structural features of diversifolin are (1) 11-oxabicyclo[6.2.1]undec-2-ene motif including a five-membered cyclic hemiketal, (2) α-methylidene-γ-butyrolactone moiety, and (3) three contiguous stereogenic centers on the 10-membered carbocyclic core. Recently, we reported the first total synthesis of (−)-diversifolin utilizing ring-closing metathesis (RCM) to form the 10-membered carbocycle and lactone transposition (Scheme 1, route A).[3] Previously, our approach to the synthesis of the core skeleton of diversifolin mainly focused on the feasibility of RCM with simplified substrates. The introduction of C4-Me required a multi-step sequence after the construction of a 10-membered ring. C4-Me was first introduced as hydroxymethyl by employing the Mukaiyama-aldol reaction with paraformaldehyde before conversion to α,β-unsaturated aldehyde. Finally, the α,β-unsaturated aldehyde was reduced to a methyl group. In this Letter, we describe our second-generation synthesis of (−)-diversifolin, which involves a more straightforward transformation of the common intermediate **7** into **2** by 10-membered ring-closing metathesis with more advanced substrates and some improvement at the final stage of the total synthesis.

Synthetic strategy of the second-generation synthesis is shown in Scheme 1 (route B). In order to reduce a number of steps, we planned to employ an advanced substrate **A** bearing the requisite C4-Me for RCM, which could be prepared by asymmetric crotylation of aldehyde **7**. After the formation of the 10-membered carbocycle, we intended to adopt a stereoselective dihydroxylation and lactone transposition sequence into key intermediate **2**, as established in the first-generation synthesis.

Because the reactivity of advanced diene **A** toward RCM was considered to be highly dependent on the stereochemistry of the hydroxyl and methyl group,[4] we first attempted to determine the most suitable isomer for RCM (Scheme 2). For this purpose, a set of *syn*-isomers **9** and *anti*-isomers **9** were prepared from the aldehyde **7**, readily obtained from diol **8**,[3a] by the *syn*-selective and *anti*-selective crotylation,[5] respectively. The *syn*-isomers and *anti*-isomers were then separately subjected to a RCM using Grubbs 2nd catalyst.[6] However, the *syn*-isomers did not afford the corresponding cyclization products. In contrast, a cyclization product was obtained as a single isomer in 15% yield (not optimized) when the *anti*-isomers were treated with Grubbs 2nd catalyst in the presence of *p*-benzoquinone.[7] The stereochemistry of the resulting 10-membered carbocycle **10** was determined by NMR analysis as shown in Scheme 2. The formation of RCM product from 3*R*,4*S*-**9**[8] was not detected, and 3*R*,4*S*-**9** might be decomposed during RCM condition. These results indicated that only 3*S*,4*R*-**9** underwent the desired RCM to afford the corresponding 3*S*,4*R*-**10**.

The transition state models which can explain the exclusive cyclization of 3*S*,4*R*-**9** in RCM reaction are proposed in Figure 1. Considering ring strain of 10-membered carbocycles, the RCM reaction of **9** should give *Z*-isomer selectively. Regarding these transition states **TS1-4** which lead *Z*-isomer, transannular strain between C4-Me and C7-H and/or C8-H makes **TS1** and **TS4** unstable. Furthermore, **TS3** is more stable than **TS2** because both C3-OTBS and C4-Me groups occupy pseudoequatorial position in **TS3**. Consequently, only 3*S*,4*R*-**9** might undergo RCM reaction to afford a 10-membered carbocycle through **TS3**.

We then focused on the stereoselective preparation of 3*S*,4*R*-isomer (Scheme 3). In this case, Roush asymmetric crotylation[9] with aldehyde **7** was not particularly stereoselective, affording a mixture of 3*S*,4*R*-**11** and 3*R*,4*S*-**11** in a ratio of about 6 to 1. In contrast, the desired 3*S*,4*R*-**11** was obtained in 80% yield from diol **8** almost as a single isomer when the aldehyde **7** was treated with the chiral Ti-TADDOL complex derived from D-(−)-diethyl tartrate.[10] After the removal of TMS at the tertiary hydroxyl group,

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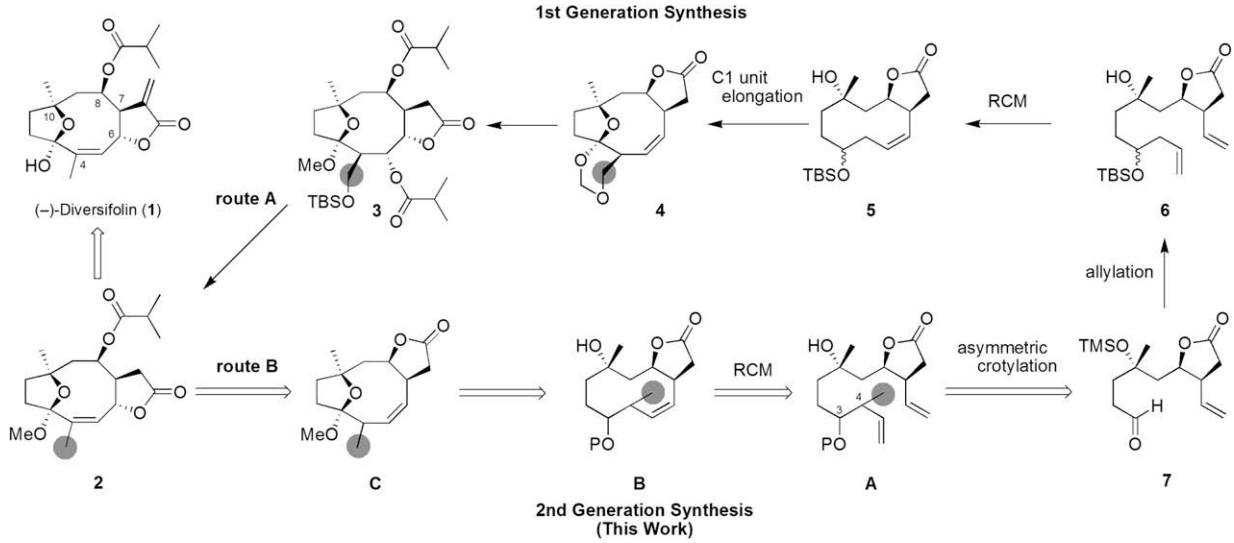
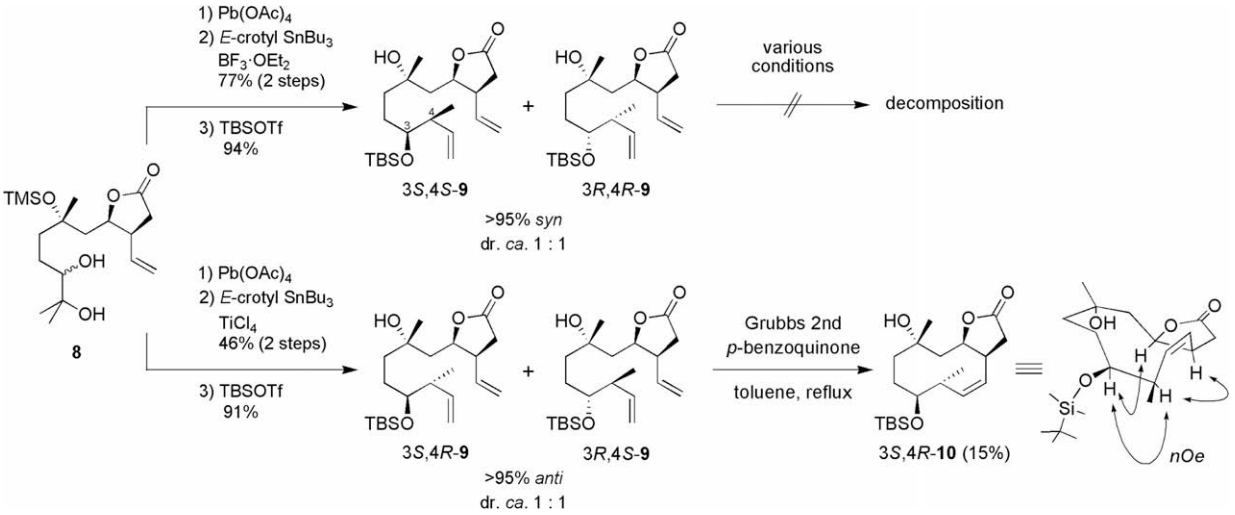


Scheme 1. Synthetic strategy for the second-generation synthesis of (−)-diversifolin.



Scheme 2. Investigation of the stereochemistry-dependent RCM.

the resulting diol **12** was selectively silylated with TBS triflate at the secondary hydroxyl group to obtain the RCM precursor **9**. The RCM was best carried out by the slow addition of Grubbs 2nd catalyst and **9** into a refluxing toluene solution containing *p*-benzoquinone to afford **10** in 59% yield. Notably, slow addition of both **9** and catalyst was crucial for attaining good yield. Indeed, simple heating of the mixture of **9**, Grubbs 2nd catalyst, and *p*-benzoquinone decreased the yield of **10** to only 24%. We assumed that the competitive thermal decomposition of Grubbs 2nd catalyst is diminished by slow addition. Removal of the TBS group was performed with TBAF to give the diol **14** in moderate yield. Thus, we selected the TES ether as a more easily removable protecting group. Fortunately, RCM of the TES ether **13** was achieved in the same manner as **9** to afford the desilylated diol **14**[11] in 63% yield.

With the 10-membered carbocycle **14** in hand, we proceeded to explore the transformation of **14** into the core oxabicyclo[6.2.1]undec-2-ene core skeleton **2** (Scheme 4). Oxidation of the secondary hydroxy group in **14** by IBX resulted in a simultaneous cyclization of the initially formed hydroxyketone to give **15**. Treatment of **15** with *p*-TsOH in trimethyl orthoformate then afforded the methyl ketal **16** in high yield. Dihydroxylation of **16** with OsO_4 and NMO gave **17** in moderate yield as a single isomer. The stereochemistry of **17** was tentatively assigned as shown by

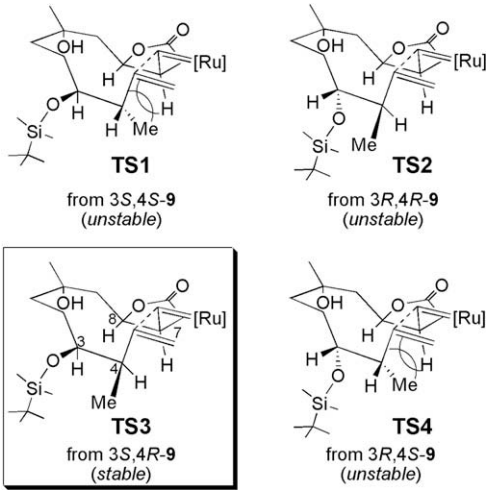
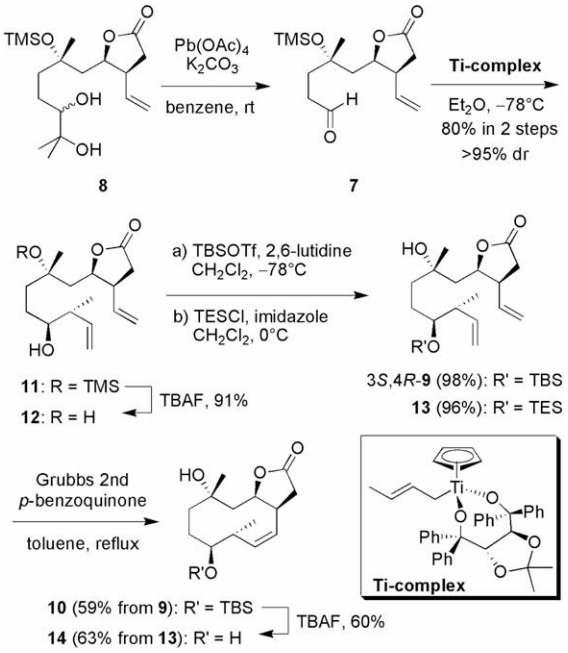
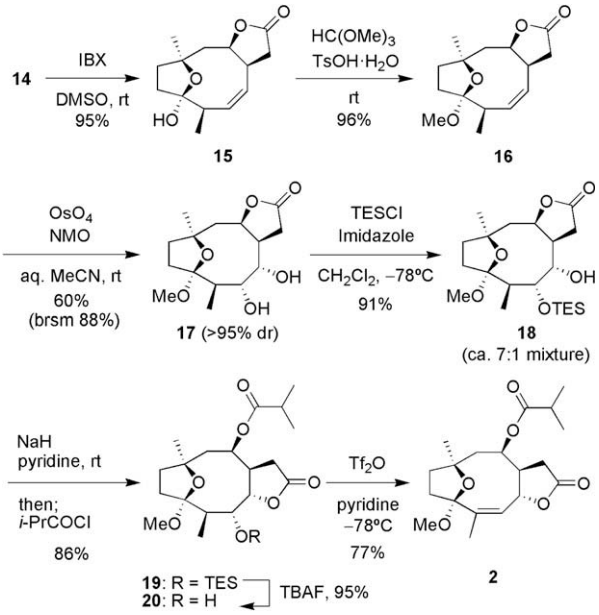


Figure 1. Possible transition states for RCM reaction.



Scheme 3. Synthesis of 10-membered carbocycles from 3*S*,4*R*-isomer.



Scheme 4. Synthesis of the key intermediate **2**.

analogy to the intermediate of the first-generation synthesis.[12] The diol **17** was then subjected to a selective silylation of the hydroxyl group at C5[13] with TESCl and imidazole in CH_2Cl_2 at −78 °C to afford **18** in 91% yield (ca. 7:1 selectivity). Predominant silylation at C5 hydroxyl group could be explained by the low reactivity of C6 hydroxyl group due to the hydrogen bonding between the bridgehead oxygen as well as steric environment. Lactone transposition of **18** proceeded smoothly by the treatment with NaH, and the addition of isobutyryl chloride into the reaction mixture gave the isobutyrylated *trans*-lactone **19** in 86% yield. TBAF-mediated desilylation of **19** was cleanly achieved to furnish **20** in 95% yield. Because the C5 hydroxyl group and the C4 hydrogen are in *syn*-relationship, we initially attempted a *syn*-dehydration using Burgess' reagent,[14] Martin's sulfurane[15], or Chugaev elimination.[16] All attempts were unsuccessful, and we reasoned that the rigid bicyclic core structure did not allow the *syn*-periplanar conformation required for *syn*-elimination. This consideration led us to examine an alternative E1 elimination. The desired dehydration product **2** was obtained in 77% yield by the treatment of the alcohol **20** with triflic anhydride in pyridine at −78 °C. The spectral data of **2** were identical in all respects with those of our previous intermediate in the first-generation synthesis.

The formal total synthesis was thus achieved; however, the final conversion of **2** to diversifolin (*exo*-methylenation[17] and hydrolysis) was not well optimized in the previous synthesis. Improvements to this final step are outlined in Scheme 5. The yield of *exo*-methylenation product **21** was slightly improved to 41% yield when the reaction was carried out at −90 °C. This procedure gave a Dieckmann-type product **22** (51% yield), which was readily formed even at low temperature. The undesired **22** was found to be converted to the starting **2** in 79% yield by the treatment with potassium hydride in THF at 0 °C. Thus, the conversion yield of **21** was calculated to be 68%. Final deprotection of methyl ketal was accomplished in 71% yield by the treatment with *p*-TsOH in aqueous THF at room temperature.

In conclusion, we were able to establish an improved synthesis of diversifolin. The most striking feature of the present synthesis is the RCM with a diene bearing the C4-Me group. Moreover, we found that only one of four stereoisomers underwent RCM to construct the 10-membered carbocycles. Using this synthetic route, the key intermediate **2** was obtained in 12 steps and 20% overall yield from the diol **8** (cf., 19 steps and 10% overall yield for the previous synthesis).

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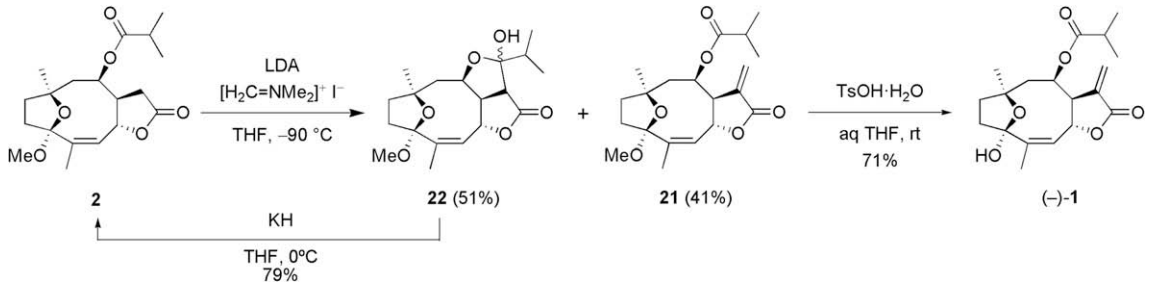
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.012.



Scheme 5. Optimization of the final stage of total synthesis.

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