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Synthetic Study of Diversifolin: The Construction of 11-Oxabicyclo[6.2.1]undec-3-ene Core Using Ring-Closing Metathesis

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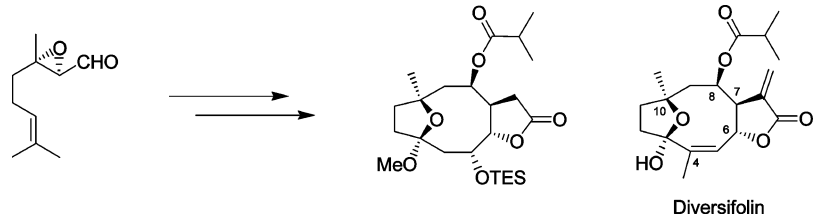
ABSTRACT



Stereoselective synthesis of a potential intermediate bearing 11-oxabicyclo[6.2.1]undec-3-ene core, a common scaffold of biologically active germacrane-type sesquiterpenes, has been achieved. Synthetic features involve formal 1,3-asymmetric induction, unusual ring-closing metathesis constructing a 10-membered carbocycle system, and unique lactone transposition.

A number of densely oxygenated germacrane-type sesquiterpenes have been isolated, including diversifolin[1] (**1**), zexbrevin[2a] (**2**), woodhousin[2f] (**3**), and tagitinins[2a−e] (**4**−**7**) (Figure 1). These compounds have been reported to exhibit significant biological activities. For example, diversifolin (**1**) inhibits the activation of the transcription factor NF-κB.[1c,3] Common structural features of these compounds are (i) a strained 10-membered carbocyclic germacrane skeleton including a 5-membered cyclic hemiketal, (ii) α-methylidene-γ-butyrolactone moiety which is involved in the proposed reaction with Cys-38 in the p65 subunit, and (iii) three contiguous chiral centers (C6−C8) and a quaternary stereogenic center at C10. Although these compounds possess

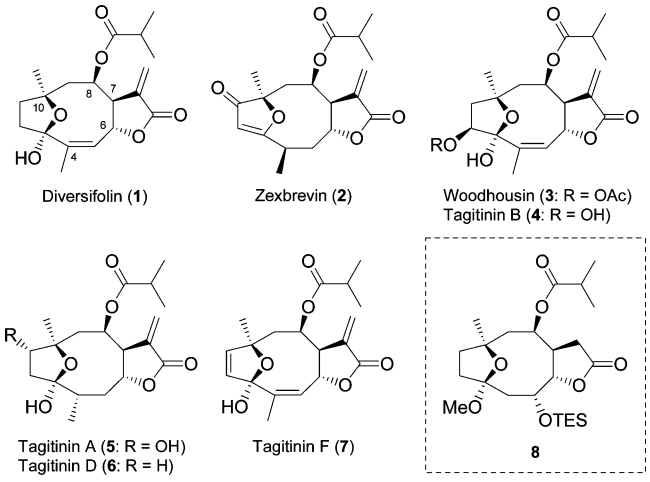


Figure 1. Diversifolin and the related natural compounds.

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(2) (a) Sarma, J. C.; Sharma, R. P.; Jong, R.; Stam, C. H. *Phytochemistry* **1987**, *26*, 2406−2407. (b) Bordoloi, M.; Barua, N. C.; Ghosh, A. C. *Phytochemistry* **1996**, *41*, 557−559. (c) Pereira, P. S.; Dias, D. A.; Vichnewski, W.; Nasi, A. M. T. T.; Herz, W. *Phytochemistry* **1997**, *45*, 1445−1448. (d) Gu, J. Q.; Gills, J. J.; Park, E. J.; Mata-Greenwood, E.; Hawthorne, M. E.; Axelrod, F.; Chavez, P. I.; Fong, H. H. S.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2002**, *65*, 532−536. (e) Herz, W.; Bhat, S. V. *J. Org. Chem.* **1972**, *37*, 906−912.

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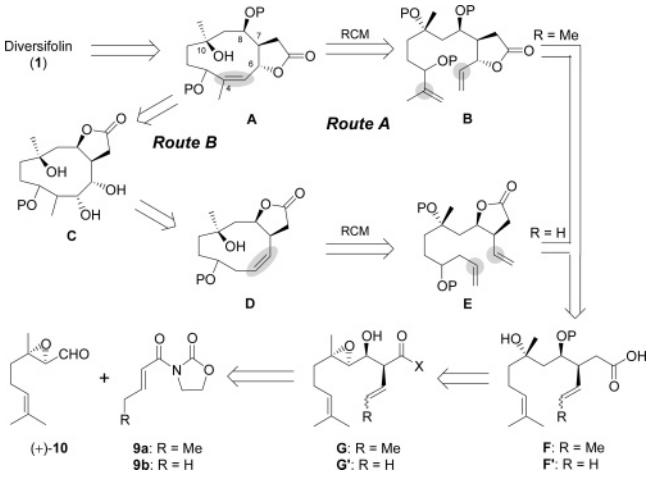
important biological properties, synthetic methodology of the common 11-oxabicyclo[6.2.1]undec-3-ene core has not been reported so far. Therefore, the development of creative solutions for the construction of a germacrane-type framework is strongly demanded. Herein, we describe the stereoselective synthesis of a potential intermediate **8** for the synthesis of this type of compound. The synthetic route involves several significant transformations, such as formal 1,3-asymmetric induction, unusual ring-closing metathesis (RCM) constructing a 10-membered carbocyclic core, and unique lactone transposition.

Retrosynthetic analysis of diversifolin (**1**) is depicted in Scheme 1. We were particularly interested in employing

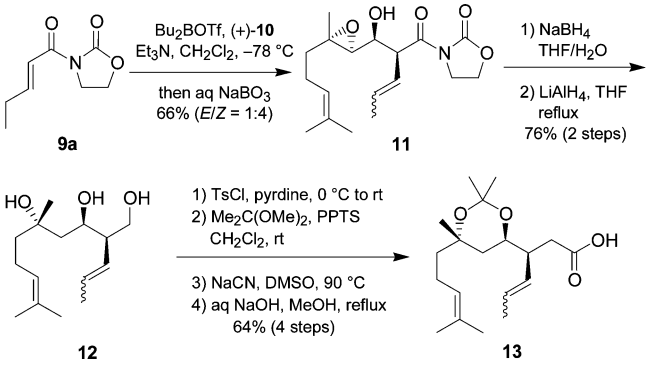
Scheme 1. Synthetic Strategy



RCM for constructing a 10-membered carbocycle. RCM[4] is generally recognized as a pivotal methodology for the construction of medium-sized ring systems. Interestingly, however, there have been very few examples of the successful cyclization of 10-membered carbocycles by RCM.[5] Gennari et al. applied RCM at the later stage of the total synthesis of eleutherobin.[5c−g] Therefore, the construction of a 10-membered carbocycle using RCM might depend on steric and electronic effects of allylic substituents. Thus, we planned two approaches by RCM: (i) direct disconnection to diene **B** at C4−C5 (route A) and (ii) disconnection to more reactive **E** at C5−C6 (route B). The latter approach requires a lactone transposition from **C** to *trans*-lactone **A** after ring closure. In both approaches, key intermediates **F** and **F′** could be readily prepared by the same strategy. For stereocontrol at C7−C9, a formal 1,3-asymmetric induction from the chirality at C10 was envisaged. We anticipated that direct 1,3-asymmetric induction may be difficult due to the tertiary hydroxyl nature of C10. Therefore, we employed an aldol reaction of α,*β*-unsaturated imide **9** with epoxy aldehyde (+)-**10**,[6] followed by selective reduction of the epoxide. Stereoselective oxyfunctionalization at C6 might be possible either by *trans*-selenolactonization of unsaturated carboxylic acid **F** (route A) or stereoselective dihydroxylation of **D** (route B).

At the outset, we attempted the *syn*-selective aldol reaction of imide **9a** (Scheme 2). The aldol reaction of α,*β*-

Scheme 2. Preparation of Carboxylic Acid **13**



unsaturated imide **9a** with (+)-**10** under the standard Evans protocol[7] afforded aldol adduct **11** in 66% yield as a geometric mixture (*E*/*Z* = 1:4) along with 7% of (2*R*,3*S*)-isomer (*E*/*Z* = 2:3).[8] The diastereofacial selectivity was similar to that reported by Nacro et al.[6] After reduction of the imide moiety with $NaBH_4$, the resulting epoxy diol (not shown) was treated with $LiAlH_4$ in refluxing THF to obtain the triol **12** in 76% yield. The triol **12** was transformed into the unsaturated carboxylic acid **13** in good yield by a conventional four-step sequence. Carboxylic acid **13** could be prepared from triol **12** without silica gel column purification on a 10-g scale.

We next examined a selenolactonization[9] of **13** (Scheme 3). Initial attempts using standard conditions (PhSeCl, CH_2Cl_2, −78 °C) were unsuccessful due to the high reactivity of the trisubstituted double bond. Surprisingly enough, we

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(4) For reviews on RCM, see: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238. (b) Armstrong, Susan K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450.

(5) (a) Nevalainen, M.; Koskinen, A. M. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 4060−4062. (b) Nevalainen, M.; Koskinen, A. M. P. *J. Org. Chem.* **2002**, *67*, 1554−1560. (c) Caggiano, L.; Castoldi, D.; Beumer, R.; Bayón, P.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44*, 7913−7919. (d) Beumer, R.; Bayón, P.; Bugada, P.; Ducki, S.; Mongelli, N.; Sirtori, F. R.; Telser, J.; Gennari, C. *Tetrahedron* **2003**, *59*, 8803−8820. (e) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 588−591. (f) Castoldi, D.; Caggiano, L.; Bayón, P.; Costa, A. M.; Cappella, P.; Sharon, O.; Gennari, C. *Tetrahedron* **2005**, *61*, 2123−2139. (g) Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Chem. Eur. J.* **2006**, *12*, 51−62.

(6) (a) Nacro, K.; Baltas, M.; Escudier, J.-M.; Gorrichon, L. *Tetrahedron* **1996**, *52*, 9047−9056. (b) Escudier, J.-M.; Baltas, M.; Gorrichon, L. *Tetrahedron Lett.* **1991**, *32*, 5345−5348.

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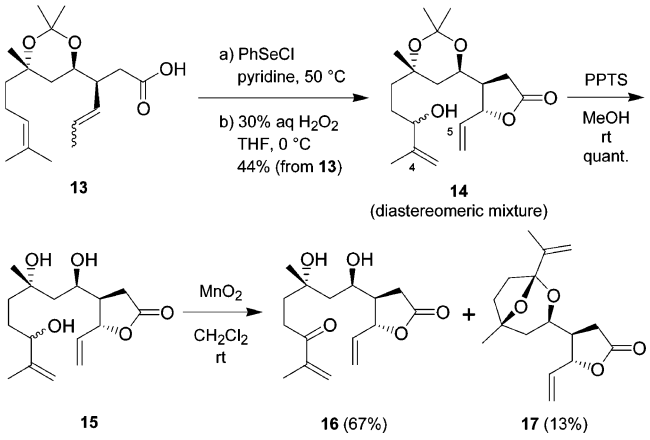
(8) For details, see Supporting Information.

(9) For a recent review on selenolactonization, see: Jones, G. B.; Huber, R. S.; Chau, S. *Tetrahedron* **1993**, *49*, 369−380.

Scheme 3. Selenolactonization and Unexpected Oxidative Rearrangement



found that the treatment of **13** with PhSeCl *in pyridine at 50 °C*, followed by an oxidative workup afforded the unexpected but fortunate dienyl lactone **14**[10] (diastereomeric mixture at C3-hydroxyl), which might serve as a potential intermediate for RCM. Our initial scenario was to transform the terminal trisubstituted olefin into an isopropenyl group by several steps after construction of the lactone moiety. The present methodology can provide the requisite propenyl moiety in a single operation in addition to the programmed selenolactonization−elimination.

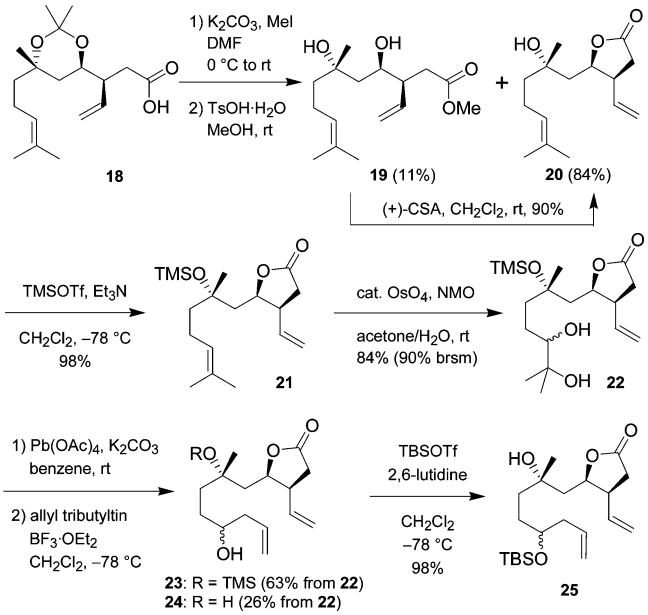
The resulting dienyl lactone **14** was treated with PPTS to give the triol **15**, which was then oxidized to enone **16** with MnO_2. These diene derivatives, **14**, **15**, and **16**, were subjected to RCM. However, all efforts using a variety of different conditions failed.[11] These results might be due to steric congestion around each olefin and/or entropically unfavorable conformation by the *trans*-γ-butyrolactone moiety.

We then attempted the alternative approach using **E** as a RCM precursor (see Route B in Scheme 1). Although this approach requires a lactone transposition into the desired *trans*-γ-butyrolactone after ring closure, we expected that **E** might undergo RCM much more readily than previous substrates **14**−**16** due to the reduced steric hindrance around each olefin and the conformational advantage of a *cis*-lactone. Scheme 4 shows the preparation of the RCM precursor **25** from **18**, prepared in a manner similar to that used for **13**. After esterification of **18** with K_2CO_3−MeI, acidic treatment with *p*-TsOH gave diol **19** and hydroxyl *cis*-lactone **20** in 11% and 84% yields, respectively. Dihydroxy ester **19** was converted into **20** in good yield by treating with (+)-CSA. After protection of tertiary alcohol as the TMS ether, trisubstituted olefin in **21** was transformed into aldehyde (not shown) by regioselective dihydroxylation with OsO_4−NMO, followed by oxidative cleavage with $Pb(OAc)_4$. When the aldehyde was treated with allyl tributyltin in the presence

(10) Scope and limitation as well as a mechanistic study of PhSeCl-mediated oxidative rearrangement of olefin will be reported elsewhere.

(11) First- or second-generation Grubbs catalysts under direct heating, microwave irradiation, or in the presence of $Ti(OiPr)_4$.

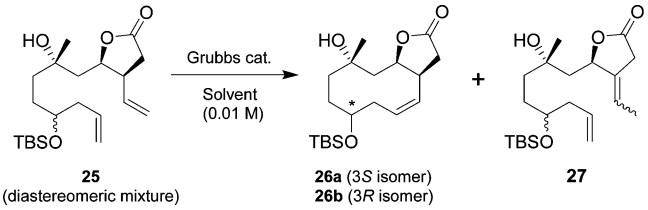
Scheme 4. Synthesis of *cis*-Lactone **25** as a RCM Precursor



of BF_3·OEt_2, allylated product **23** was obtained in 63% yield as a diastereomeric mixture at C3 from diol **22**, along with the desilylated **24** in 26% yield. The former was desilylated to give **24** quantitatively, and the secondary hydroxyl group in **24** was selectively protected with TBS group to obtain the RCM precursor **25** in 98% yield.

With diene **25** in hand, we then examined RCM of **25** using Grubbs first- and second-generation catalysts. As shown in Table 1, Grubbs first-generation catalyst was

Table 1. Ring-Closing Metathesis



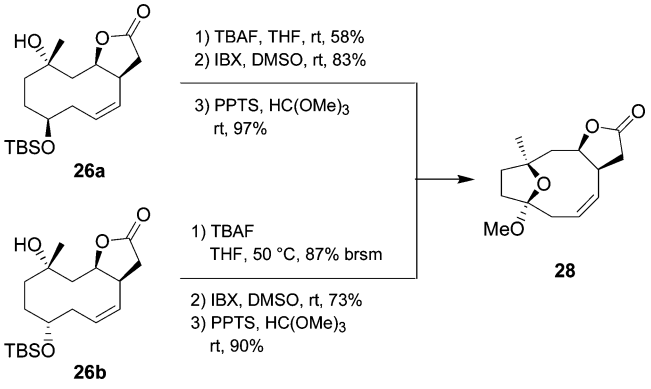
				yield (%)			
entry	Grubbs cat. (mol %)	solvent	T (°C)	**25**	**26a**	**26b**	**27**
1	first (10)	DCE	reflux	86	0	0	0
2	first (10)	toluene	100	82	0	0	0
3	second (10)	DCE	80	0	0	0	15
4	second (10)	toluene	reflux	17	trace	27	35
5[a]	second (20)	toluene	reflux	0	40	31	0

[a] 20 mol % of 1,4-benzoquinone was added.

ineffective for this substrate **25** (entries 1 and 2). By contrast, treatment of **25** with Grubbs second-generation catalyst in toluene under heating resulted in the formation of the desired **26b** as a single diastereomer together with isomerized

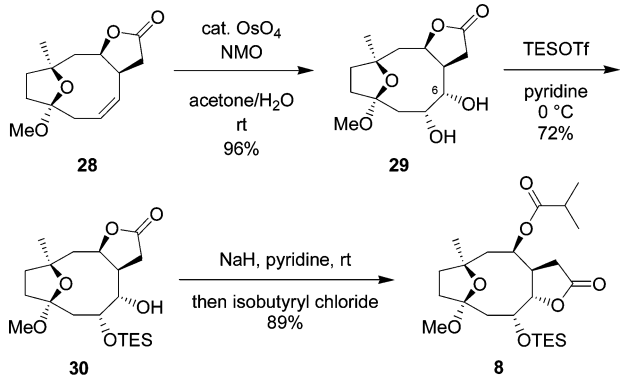
product **27**[12] as a major component (entry 4). This result indicates that **25b** readily underwent RCM, whereas **25a** was mainly subject to isomerization. Grubbs et al. reported that the addition of 1,4-benzoquinone prevents the isomerization of a less reactive olefin.[13] Indeed, it was gratifying to find that RCM using 20 mol % of catalyst and 1,4-benzoquinone gave **26a** and **26b** in 40% and 31% yields, respectively (entry 5). Stereochemistry of resulting **26a** and **26b** were determined by NOE experiments as shown in Supporting Information. Each isomer, **26a** and **26b**, was successfully transformed into the same 11-oxabicyclo[6.2.1]undec-3-ene **28** by three-step sequence of reactions (Scheme 5).

Scheme 5. Construction of 11-Oxabicyclo[6.2.1]undec-3-ene Core



With 11-oxabicyclo[6.2.1]undec-3-ene **28** in hand, we attempted the introduction of C6 hydroxyl group by diastereoselective dihydroxylation (Scheme 6). As expected, dihydroxylation of **28** with OsO_4−NMO occurred from the outside of the 10-membered ring, affording **29** as a single stereoisomer. The stereochemistry of **29** was assigned as shown by NOE experiments. To our delight, regioselective monosilylation of diol **29** was possible by the treatment with TESOTf and pyridine to afford **30** in 72% yield. The relatively low reactivity of the C6 hydroxyl group might be rationalized by considering the transannular hydrogen-

Scheme 6. Transposition to the *cis*-Lactone **8**



bonding interaction with the bridging oxygen based on MMFF calculation. We also observed a crucial lactone transposition of *cis*-fused lactone **30** into *trans*-fused lactone by the treatment with sodium hydride in pyridine. Further, the addition of isobutyryl chloride in the above reaction mixture afforded the isobutyrylated **8** in 89% yield. Structure of **8** was confirmed by NMR analyses (HMBC and HMQC). Although the mechanism of lactone transposition is unclear at present, but we assume the following three possible pathways: (i) trace amount of NaOH-mediated hydrolysis and subsequent relactonization, (ii) direct attack of C6-alkoxide to lactone carbonyl, and (iii) C6-alkoxide-promoted ketene formation and relactonization.

In summary, we were able to accomplish the construction of the common tricyclic core skeleton **8**, which could be transformed to diversifolin (**1**) and related germacrane-type sesquiterpenes. The characteristic features of the present approach are (i) formal 1,3-asymmetric induction using epoxy aldehyde, (ii) unusual RCM affording a 10-membered carbocycle, and (iii) unique lactone transposition from a *cis*-fused lactone into a *trans*-fused lactone.

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Supporting Information Available: Experimental procedures, characterization data, and copies of spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For example, see: Hanessian, S.; Giroux, S.; Larsson, A. *Org. Lett.* **2006**, *8*, 5481−5484 and references therein.

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