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Total synthesis of (–)-diversifolin

Tomoaki Nakamura, Kazuma Tsuboi, Motoko Oshida, Tomoko Nomura, Atsuo Nakazaki, Susumu Kobayashi *

Faculty of Pharmaceutical Sciences, Tokyo University of Science (RIKADAI), 2641 Yamazaki, Noda-shi, Chiba 278-8510, Japan

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ABSTRACT

First total synthesis of biologically active germacrane-type sesquiterpene (−)-diversifolin has been achieved. The features of the synthesis involve (i) ring-closing metathesis to give a 10-membered carbocycle, (ii) regioselective Mukaiyama aldol reaction of silyl dienol ether with formaldehyde at the α-position, and (iii) lactone transposition of the fully functionalized 11-oxabicyclo[6.2.1]undecane system.

Diversifolin (**1**), isolated from *Tithonia diversifolia*[1a–c] and *Viguiera dentata*,[1d] is a germacrane-type sesquiterpene that inhibits the activation of the transcription factor NF-κB (Fig. 1).[1c,2] Its ability to control NF-κB-dependent gene expression and to regulate cellular functions would hold a potential therapeutic application for inflammatory diseases. The structural features of this compound include (i) a strained 10-membered carbocyclic germacrane skeleton, including a 5-membered cyclic hemiketal, (ii) α-methylidene-γ-butyrolactone moiety implicated in the proposed reaction with Cys-38 in the p65 subunit of NF-κB, and (iii) three contiguous chiral centers (C6-C8) and a quaternary chiral center at C10. Although there have been a number of methodologies for the construction of 10-membered carbocycles,[3] synthesis of the common 11-oxabicyclo[6.2.1]undec-3-ene core has not been reported so far. In this context, we have recently developed the stereoselective synthesis of the functionalized 11-oxabicyclo[6.2.1]undec-3-ene **3** starting from enantioenriched epoxyaldehyde **2**.[4] The tricycle **3** is a potential precursor of the germacrane-type sesquiterpenes including (−)-**1**.

In this Letter, we report the first total synthesis of the proposed structure of diversifolin (**1**). The synthesis involves a ring-closing metathesis[5] to give a 10-membered carbocycle.[6] The synthesis also entails a regioselective Mukaiyama aldol reaction of silyl dienol ether with formaldehyde at the α-position. Finally, lactone transposition in the fully functionalized 11-oxabicyclo[6.2.1]undecane system is achieved.

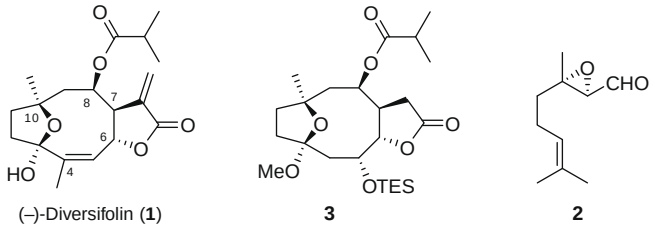

Figure 1. Structures of (−)-diversifolin (**1**) and its potential precursor **3**.

Our synthetic plan for (−)-**1** is shown in Scheme 1. We reasoned that the functionalized oxabicycloundecane **3**, bearing all requisite stereogenic centers, would be a potential intermediate for the synthesis of (−)-**1** (Scheme 1, route A). Unfortunately, despite considerable effort, we were unable to introduce a methyl group equivalent at the C4 position of ketone **5** derived from **3**. It is obvious that the rigid conformation of **5** may prevent the generation of an enolate. Therefore we decided to manipulate the C4 position with a rather flexible compound before constructing the oxabicycloundecane framework (Scheme 1, route B). In this approach, because of the presence of several acidic protons, regioselective manipulation of the β,γ-unsaturated ketone **8** is required.

10-Membered β,γ-unsaturated ketone **7** was synthesized from diene **4** prepared from the enantioenriched epoxyaldehyde **2** via boron-enolate-mediated aldol reaction as a key stereocontrol (Scheme 2).[4] The ring-closing metathesis was performed on a gram scale using the Grubbs second generation catalyst[7] to give a separable mixture of epimers **10a** and **10b** in 39% and 34% yields, respectively. Slow addition of the Grubbs catalyst as well as the

* Corresponding author. Tel./fax: +81 4 7121 3671.
E-mail address: kobayash@rs.noda.tus.ac.jp (S. Kobayashi).

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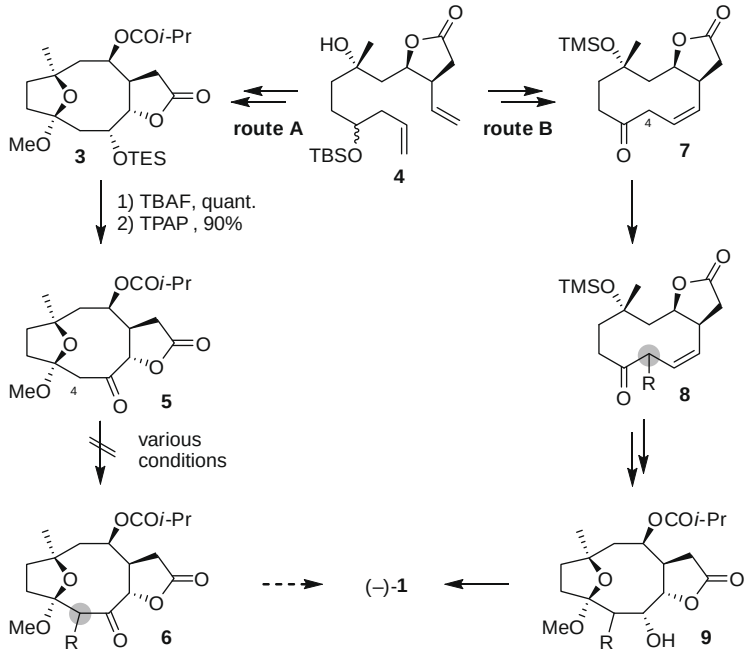
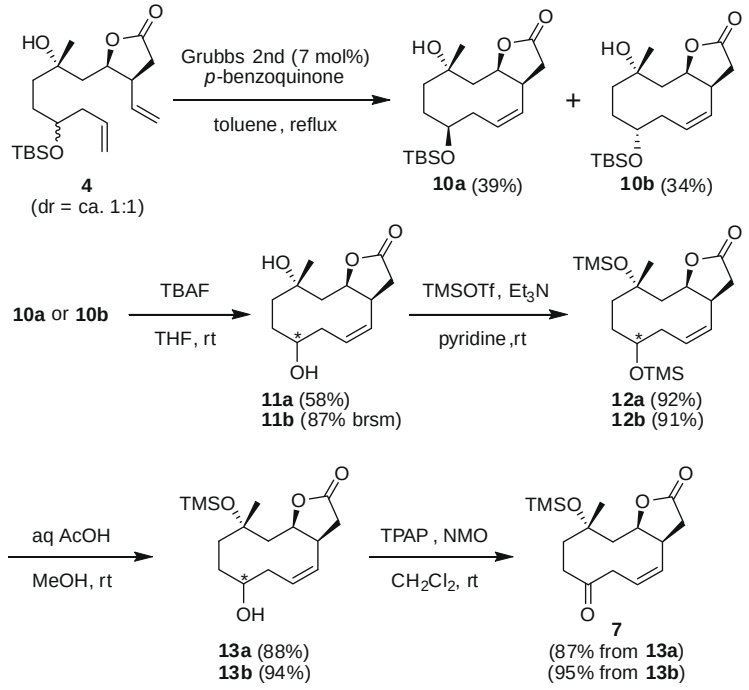


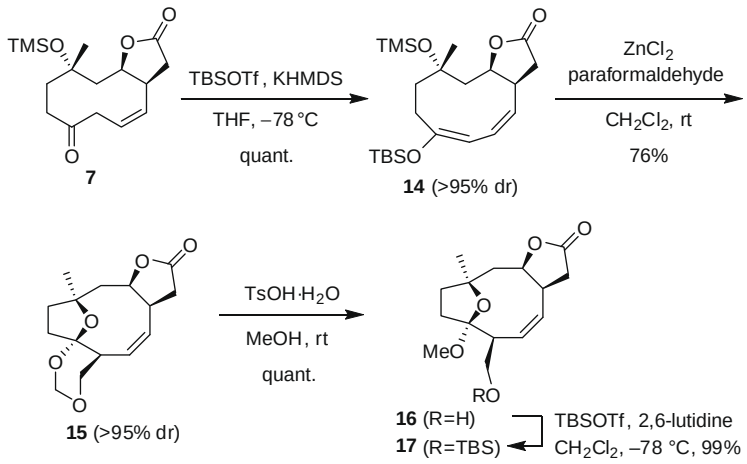
Scheme 1. Two synthetic approaches for (−)-**1**. R = Me or CH_2OH.



Scheme 2. Synthesis of 10-membered β,γ-unsaturated ketone **7**.

presence of *p*-benzoquinone[8] was necessary for this transformation. The obtained cyclodecenes **10a** and **10b** were independently converted into the common intermediate **7**. Thus, removal of the TBS group in homoallyl silyl ether **10** and silylation of both hydroxy groups by using TMSOTf provided the corresponding silyl ether **12**. Regioselective deprotection of the TMS group on the secondary alcohol of **12** using a weak acid followed by Ley oxidation[9] provided enone **7** in good overall yield.

Having the indispensable β,γ-unsaturated ketone **7**, we next surveyed the regioselective manipulation at the C4 position (Scheme 3). Direct introduction of a methyl group into enone **7** using MeI and KHMDS afforded only 10% of the desired methylated ketone along with undesired methylated products and a significant quantity of recovered **7**. The undesired products included unreacted cyclodecene bearing the monomethylated lactone moiety and 4,4-dimethyl derivative. We also examined a number of other bases (LDA, LHMDS, NHMDS, KO*t*-Bu, and KDA) but none were found to be effective. When a combination of KHMDS and MeOTf was used, the reaction slightly enhanced the yield of desired compound (16%) along with the *O*-methyl enol ether (49%). In order to



Scheme 3. Key one-carbon homologation of **7** through the regioselective Mukaiyama aldol reaction of silyl dienol ether **14**.

improve chemoselectivity and chemical yield of the one-carbon homologation, we next focused on the Mukaiyama aldol reaction of the silyl enol ether **14**. Although **14** possesses two potential reaction sites in the dienol ether unit, the most reactive site would be at the α-position because, according to computational calculations, each C–C double bond is twisted. Based on this consideration, we expected the C4-selective aldol reaction to be successful. To obtain the silyl dienol ether **14**, treatment of enone **7** with 3 equiv of KHMDS at −78 °C in THF and then with 3 equiv of TBSOTf afforded **14** in quantitative yield as a single diastereomer. The geometry of the generated alkene was determined by NOESY analysis as an *E* configuration.

Next, we examined the key Mukaiyama aldol reaction of **14**. Exposure of **14** with 10 equiv of paraformaldehyde in the presence of $ZnCl_2$ in CH_2Cl_2 at rt led to the tetracycle **15** in 76% yield as a single diastereomer. The structure of **15** was determined by X-ray crystallographic analysis (Fig. 2).[10] Our results indicate that the Mukaiyama aldol reaction proceeded with perfect facial and regioselectivity. A 1,3-dioxane moiety was then cleaved by means of an acidic methanolysis to obtain methyl ketal **16**. Finally, the resulting primary hydroxy group in **16** was protected as the TBS ether to give **17** including the C1 unit at the C4-position in good overall yield from **15**.

We next explored the stereocontrolled synthesis of the 11-oxabicyclo[6.2.1]undec-3-ene core with trans-fused lactone (Scheme 4). Diastereoselective dihydroxylation of alkene **17** was achieved by using OsO_4/TMANO in the presence of pyridine to give the corresponding diol **18** in moderate yield as a single diastereomer. The relative stereochemistry of the newly generated stereogenic centers was tentatively assigned on the basis of the conformation of tetracycle **15**.[11] The lactone transposition of **18** with concomitant acylation of the C5 and C8 hydroxy groups was carried out under the previously developed conditions (3 equiv of NaH, pyridine; 3 equiv of isobutyryl chloride)[3] affording the desired *trans*-lactone **19** in excellent yield. After removal of the TBS group of **19**, treatment of the resulting alcohol **20** with IBX in DMSO at rt gave enal **21** in 84% yield as a single geometry. Sequential oxidation and elimination was thus achieved in a single operation. Luche reduction[12] of enal **21**, mesylation of the resulting allyl alcohol, followed by reduction of allyl mesylate provided the requisite intermediate **23** in good overall yield. The geometry of the trisubstituted alkene in **23** was determined by NOE experiments.

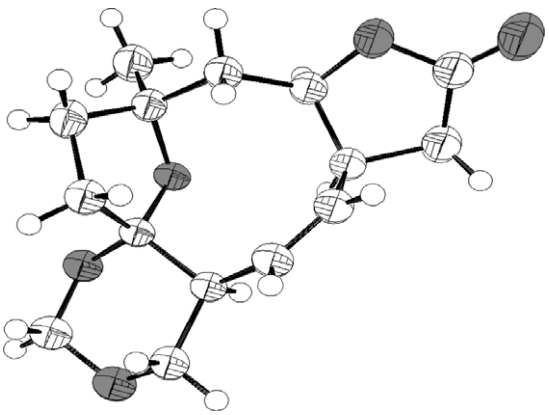
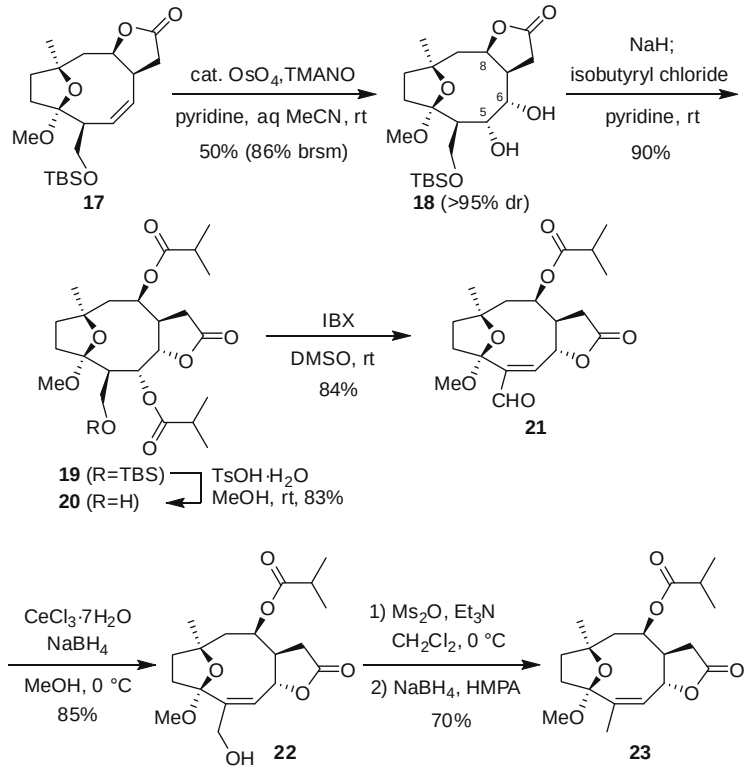


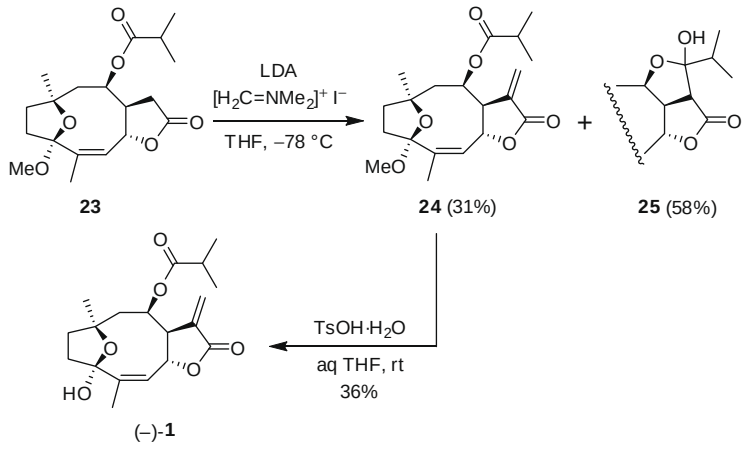
Figure 2. X-ray crystal structure of **15**.

Completion of the total synthesis of (−)-**1** is depicted in Scheme 5. Oxabicycloundecene **23** was treated with 4 equiv of LDA at −78 °C, and then with 5 equiv of Eschenmoser's salt[13] at the same temperature affording the desired enoate **24** along with hemiketal **25**, which was derived via an intramolecular Claisen condensation of lactone enolate to isobutyryl ester. In this case, enoate **24** was formed without adding a promoter of the elimination reaction such as MeI. Although the chemical yield of **24** was low, the desired **24** was best obtained using the conditions described above. For example, when the reaction was carried out at temperatures greater than −78 °C, only a trace amount of the desired **24** was formed. In addition, exposure of a mixture of **23** and Eschenmoser's salt to LDA resulted in undesired side reactions. Methyl ketal **24** was then hydrolyzed under conventional conditions to obtain the proposed structure of (−)-diversifolin (**1**). The ^1H and ^{13}C NMR spectra of synthetic (−)-**1** were consistent with those of the corresponding naturally occurring compound.[1d]

In conclusion, we have accomplished the first total synthesis of (−)-**1** from the 10-membered carbocycle **10**, which is readily obtainable through ring-closing metathesis. Our synthetic strategy involves some interesting chemistry. The regio- and stereoselective Mukaiyama aldol reaction of silyl dienol ether with formaldehyde and lactone transposition of the fully functionalized 11-oxabicyclo[6.2.1]undecane system were key steps in the synthetic route to (−)-**1**. Our synthetic methodology would provide a new entry for the construction of related germacrane-type sesquiterpenes.



Scheme 4. Transformation to 11-oxabicyclo[6.2.1]undecene **23**.



Scheme 5. Completion of the total synthesis of (−)-**1**.

Acknowledgments

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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.2009.03.192.

References and notes

1. (a) Cicció, J. F.; Castro, V. H.; Calzada, J. G. *Rev. Latinoamer. Quim.* **1979**, *10*, 134–135; (b) Schuster, A.; Stokes, S.; Papastergiou, F.; Castro, V.; Poveda, L.; Jakupovic, J. *Phytochemistry* **1992**, *31*, 3139–3141; (c) Rüngeler, P.; Lyß, G.; Castro, V.; Mora, G.; Pahl, H. L.; Merfort, I. *Planta Medica* **1998**, *64*, 588–593; (d) Gao, F.; Miski, M.; Gage, D. A. G.; Mabry, T. J. *J. Nat. Prod.* **1985**, *48*, 316–318.
2. (a) Hehner, S. P.; Heinrich, M.; Bork, P. M.; Vogt, M.; Ratter, F.; Lehmann, V.; Schulze-Osthoff, K.; Dröge, W.; Schmitz, M. L. *J. Biol. Chem.* **1998**, *273*, 1288–1297; (b) Lyß, G.; Knorre, A.; Schmidt, T. J.; Pahl, H. L.; Merfort, I. *J. Biol. Chem.* **1998**, *273*, 33508–33516; (c) Rüngeler, P.; Castro, V.; Mora, G.; Gören, N.; Vichnewski, W.; Pahl, H. L.; Merfort, I.; Schmidt, T. J. *Bioorg. Med. Chem.* **1999**, *7*, 2343–2352; (d) García-Piñeres, A. J.; Castro, V.; Mora, G.; Schmidt, T. J.; Strunck, E.; Pahl, H. L.; Merfort, I. *J. Biol. Chem.* **2001**, *276*, 39713–39720.
3. For a review on the synthesis of germacrane-type sesquiterpenes, see: Minnaard, A. J.; Wijnberg, J. B. P. A.; de Groot, A. *Tetrahedron* **1999**, *55*, 2115–2146.
4. Nakamura, T.; Oshida, M.; Nomura, T.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 5533–5536.

5. For recent reviews on ring-closing metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388; (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.
6. Several examples of the successful cyclization of 10-membered carbocycles by RCM have been reported: (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.
7. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
8. (a) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161; (b) Larrosa, I.; Da Silva, M. I.; Gomez, P. M.; Hannen, P.; Ko, E.; Lenger, S. R.; Linke, S. R.; White, A. J. P.; Wilton, D.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2006**, *128*, 14042–14043.
9. Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627.
10. CCDC 719975 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
11. Although the stereochemistry of **15** was not determined at this point, the stereochemistry was eventually assigned by leading to (−)-**1**.
12. Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.
13. Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 330–331.