Tetrahedron Letters xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Research on Liebeskind-Srogl coupling/intramolecular Diels-Alder reaction cascade

Tomohiro Fujii, Yuta Oki, Masahisa Nakada *

Department of Chemistry and Biochemistry, School of Advanced Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

ARTICLE INFO

Article history:
Received 9 December 2017
Revised 9 January 2018
Accepted 18 January 2018
Available online xxxx

Keywords:
Liebeskind-Srogl
Intramolecular
Diels-Alder
Cascade
Stereoselective

ABSTRACT

The Liebeskind-Srogl coupling/intramolecular Diels-Alder (IMDA) reaction cascade that stereoselectively affords a tricarbocyclic compound with a *trans–trans-cis* fused ring system including an all-carbon quaternary stereogenic center at the ring junction is described. The cascade reactions proceed quickly and stereoselectively afford the products within 2 h at room temperature in the presence of a suitable thioester. The developed protocol as well as the prepared chiral compounds are useful for the enantioselective total synthesis of terpenoids with the *trans–trans-cis* fused ring system.

Diels-Alder reactions are important ring-forming reactions that lead to the simultaneous formation of new bonds and stereogenic centers. Indeed, the efficiency of these reactions has enabled the synthesis of a number of natural products.[1] In general, however, Diels-Alder reactions accompanying the formation of all-carbon quaternary stereogenic centers lead to low product yields because of steric strain even in the presence of a Lewis acid or at elevated temperatures.

Alkenes bearing electron-withdrawing groups are highly reactive toward nucleophiles owing to their low LUMO energy level, which facilitates Friedel-Crafts reactions and Diels-Alder reactions with the concomitant formation of an all-carbon quaternary stereogenic center. For example, α-alkylidene β-keto esters and imides easily undergo cycloadditions, Friedel-Crafts reactions, and Mukaiyama-Michael reactions. In addition, these carbonyl compounds can act as bidentate ligands and coordinate to chiral metal catalysts, thus facilitating carbon–carbon bond-forming reactions via asymmetric catalysis.[2] Reactions of alkenes bearing electron-withdrawing groups along with the formation of an all-carbon quaternary stereogenic center have been employed in natural product synthesis. In our laboratory, the first enantioselective total synthesis of bucidarasins has been accomplished via the highly stereoselective Diels-Alder reaction of an α-alkylidene β-keto ester.[3]

Preparation of alkenes bearing electron-withdrawing groups is sometimes difficult because of their high reactivity. For example, in the case of compound **3**, which is a substrate for the intramolecular Diels-Alder (IMDA) reaction to yield **4** (Scheme 1), the reactive electron-deficient alkene undergoes undesired reactions during the preparation of the substrate.

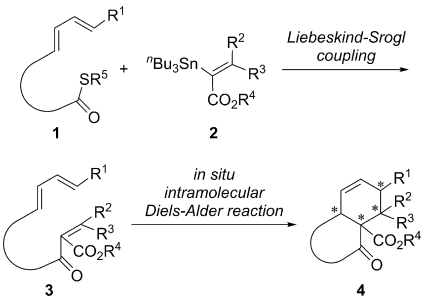
The IMDA reaction proceeds rapidly because of the diene tethered with dienophile moieties; thus, it is beneficial for constructing a polycyclic scaffold. Moreover, it would be a promising method for constructing scaffolds of terpenoids when accompanied by the formation of all-carbon quaternary stereogenic center. Nonetheless, an all-carbon quaternary stereogenic center is generally difficult to be formed by the IMDA reaction because it requires a high activation energy.

To overcome these obstacles, we decided to develop a formation of a substrate/IMDA reaction cascade. We adopted Liebeskind-Srogl coupling because it is a palladium-catalyzed reaction that proceeds under neutral reaction conditions and is suitable for compounds that are sensitive to acidic or basic reaction conditions.[4] In other words, we envisioned Liebeskind-Srogl coupling of a relatively stable thiol ester **1** and alkenylstannane **2** would afford the α-alkylidene β-keto ester **3**, and the subsequent IMDA reaction would furnish **4** (Scheme 1).

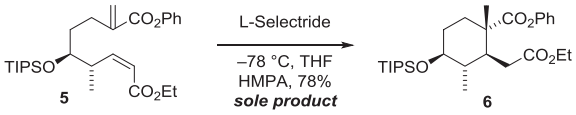
We previously reported a highly stereoselective synthesis of **6** from **5**.[5] The chiral building block **6** would be useful for the total syntheses of a variety of terpenoids (Scheme 2). Hence, when **6** is converted to the corresponding α-alkylidene β-keto ester via Liebeskind-Srogl coupling, the IMDA reaction would afford a

* Corresponding author.
E-mail address: mnakada@waseda.jp (M. Nakada).

https://doi.org/10.1016/j.tetlet.2018.01.046
0040-4039/



Scheme 1. Liebeskind-Srogl coupling/IMDA reaction cascade.

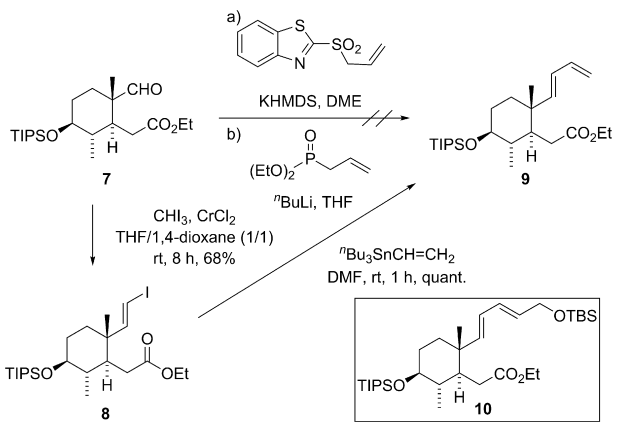


Scheme 2. Highly stereoselective Michael reduction/intramolecular Michael reaction cascade.

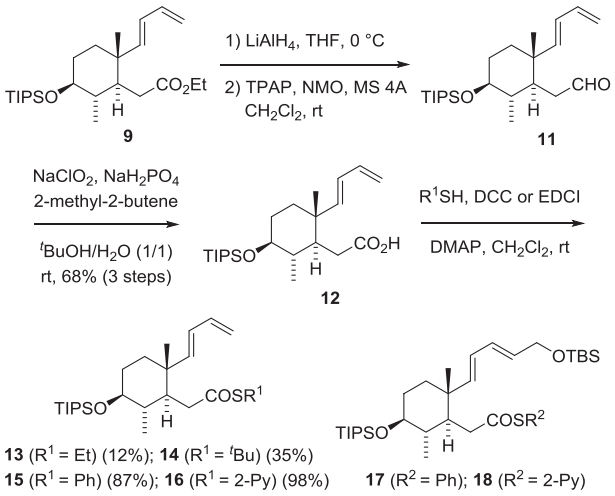
tricyclic product. This product would be used for the stereoselective construction of terpenoids such as atisanes and kauranoids, which contain contiguous stereogenic centers including an all-carbon quaternary stereogenic center. Therefore, **6** was converted to the corresponding thiol esters bearing a diene to examine the Liebeskind-Srogl coupling/IMDA reaction cascade. We report herein the details of the cascades that affords the products in a highly stereoselective manner.

To examine the above cascade, we prepared diene substrates bearing a thiol ester starting from **6**. First, we attempted the Horner-Wittig and Julia-Kocienski reactions of **7** (Scheme 3), which was derived from **6** via the reaction with benzenemethanethiol (76%) and Fukuyama reduction (90%). However, these reactions did not proceed, probably because of steric hindrance. However, **7** was successfully converted to iodoalkene **8** by the Takai reaction, and subsequent Stille coupling afforded diene **9**. Diene **10**[6,7] was prepared according to the same method.

We then examined the conversion of **9** to its thioesters (Scheme 4). Direct conversion of **9** to the corresponding thioester was unsuccessful. Interestingly, hydrolysis of **9** under a variety of conditions did not afford the desired product **12**, presumably due to the low reactivity of **9** resulting from steric hindrance. Hence, **9** was reduced to the corresponding alcohol with $LiAlH_4$, followed by TPAP oxidation to afford **10**; then Pinnick oxidation of **11** gave



Scheme 3. Preparation of diene **9** and structure of **10**.

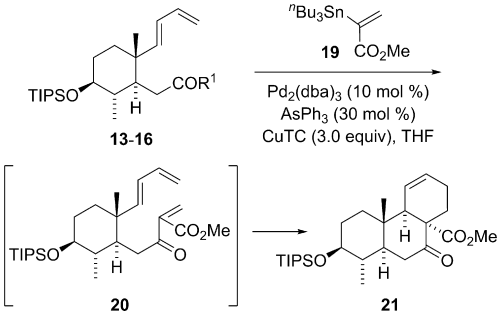


Scheme 4. Preparation of **13**–**16** and structures of **17** and **18**.

12. Finally, condensation of **12** with thiols afforded thioesters **13**–**16**. Thioesters **17** and **18** were prepared by the same method.[6]

Having prepared **13**–**18**, we first examined the Liebeskind-Srogl coupling/IMDA reaction cascade of **13**–**16** with alkenylstannane **19**.[8] We employed the standard reaction conditions for Liebeskind-Srogl coupling, as described in Table 1. The reactions of ethyl and *tert*-butyl thioesters (**13** and **14**, entries 1 and 2, respectively) with **19** did not give the desired products even at 50 °C, and the starting materials were recovered. However, the reactions of phenyl thioester **15** and 2-pyridyl thioester **16**, which are known as reactive thioesters, gave different results. The reaction of phenyl thioester **15** under the same reaction conditions proceeded at room temperature to afford the product as the single isomer in 58% yield (entry 3). 2-Pyridyl thioester **16** reacted faster than phenyl thioester **15** to afford the product in 81% yield exclusively (entry 4). In the above mentioned cascade reactions, β-keto ester **20** was not detected on the TLC, indicating that the subsequent IMDA reactions affording **21** proceeded quickly. Although we did not carried out the reaction of **20** in the absence of the palladium or copper catalyst, it cannot be denied that the used metal catalyst accelerated the IMDA reaction of **20**.

Table 1
Liebeskind-Srogl coupling/IMDA reaction cascades of **13**–**16** with **19**.



Entry	R^1	Temp (°C)	Time (h)	Yield (%)[a]
1	Et (**13**)	rt to 50	2–12	Trace
2	^{t}Bu (**14**)	rt to 50	1–12	NR
3	Ph (**15**)	rt	3	58[b]
4	2-Py (**16**)	rt	0.5	81[b]

[a] Isolated yield.
[b] Single isomer.

The relative configuration of the product **21**, which possesses a *trans–trans-cis* fused ring system, was elucidated as shown in Table 1 which was supported by the NOE studies (Fig. 1).

The stereoselectivity of the IMDA reaction of **20** could be explained using the proposed transition states depicted in Fig. 2. Two energetically favored transition states, ***TS1*** and ***TS2***, should be considered in the IMDA reaction of **20**. The conformation of the two fused six-membered rings in ***TS1*** is boat-boat, with a methyl ester group at the pseudo axial position. Meanwhile, ***TS2*** adopts a chair-boat conformation, with a methyl ester group at the axial position, which suffers from 1,3-diaxial interaction. Hence, ***TS1*** was favored in this reaction, which explains the exclusive stereoselectivity.

We then examined the cascade reaction with (*E*)-alkenyl stannane **22** (*E*/*Z* = 20/1).[2a] Because phenyl thioester **15** and 2-pyridyl thioester **16** underwent the Liebeskind-Srogl coupling, as described above, their cascade reactions with **22** were examined (Table 2). Both cascade reactions (Table 2, entries 1 and 2) exclusively afforded **24** as the single isomer, but better reaction yields were achieved when using **15** (Table 2, entry 1). These results differ from those depicted in Table 1. 2-Pyridyl thioester **16** also reacted faster than **15** and disappeared after 0.5 h from the start of the reaction, though an increase in the reaction time did not improve the yield. These results could be attributed to the fact that **16** is sensitive to the reaction conditions. The relative configuration of **24** (Table 2) was determined based on NOESY studies of **24a** (Fig. 3), a derivative of **24**. The high stereoselectivity could be well explained via the same transition states as those depicted in Fig. 2. Note that **23** was not detected on the TLC during the reaction, indicating that it was highly reactive and its IMDA reaction proceeded quickly.

We also carried out the cascade reaction of **15** and **16** with **25** (*E*/*Z* = 1/4)[9] (Table 3). The reaction of **15** with **25** stereoselectively afforded **27**, but the yield was low (31%, **27**/isomer = 6:1[10] Table 3, entry 1). To our surprise, the reaction of **16** did not afford the product (Table 3, entry 2) and **16** could not be recovered. Intermediate **26** was not detected during the reaction in both cases. The structure of **27** (Table 3) was elucidated by NOESY studies of its derivative **27a** (single isomer) (Fig. 4). The high stereoselectivity of the reaction could be explained by the same transition states as those in Fig. 2.

The cascade reactions of thioesters with alkenyl stannanes **22** and **25** afford α-alkylidene β-keto esters bearing a substituent at the terminal position of the dienophile moiety. Hence, we also examined the cascade reactions of **17** and **18**, which possess a diene with a substituent at the terminal position (Table 4).

The reaction of phenyl thioester **17** with **19** afforded **29** as the single isomer, but the yield was low (33% yield, Table 4, entry 1). The yield was improved to 62% when **18** was used (entry 2). In the above reactions, the coupling product **28** was not observed.

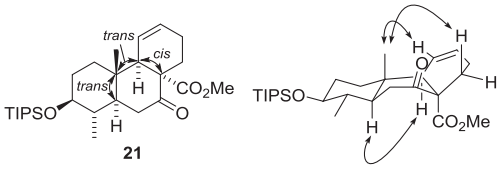


Fig. 1. NOE correlations found in the NOESY studies of **21**.

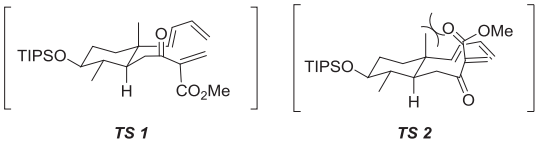
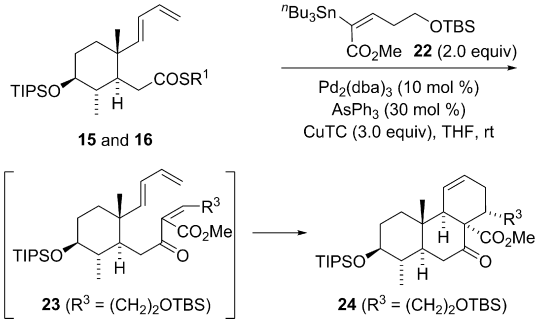


Fig. 2. Proposed transition states ***TS1*** and ***TS2*** for the IMDA reaction of **20**.

Table 2
Liebeskind-Srogl coupling/IMDA reaction cascade of **15** and **16** with **22**.



Entry	R^1	Time (h)	Yield (%)[a]
1	Ph (**15**)	2	66[b]
2	2-Py (**16**)	0.5	44[b]

[a] Isolated yield.
[b] dr = >20/1 (by ^{1}H NMR analysis).

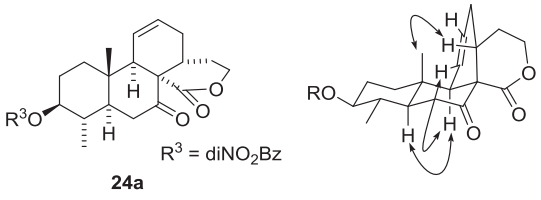
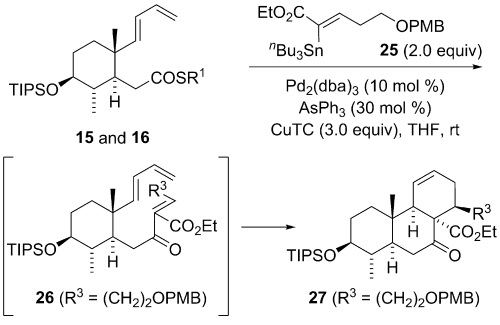


Fig. 3. NOE correlations found in the NOESY studies of **24a**.

Table 3
Liebeskind-Srogl coupling/IMDA reaction cascade of **15** and **16** with **25**.



Entry	R^1	Time (h)	Yield (%)[a]
1	Ph (**15**)	2	31[b]
2	2-Py (**16**)	0.5	Trace

[a] Isolated yield.
[b] Yield of an inseparable mixture of **27** and an unidentified isomer with a ratio of 6:1.

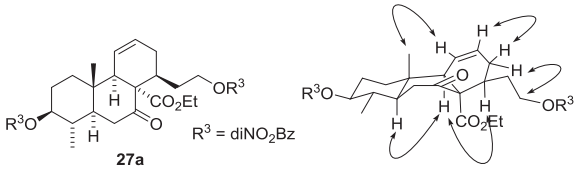
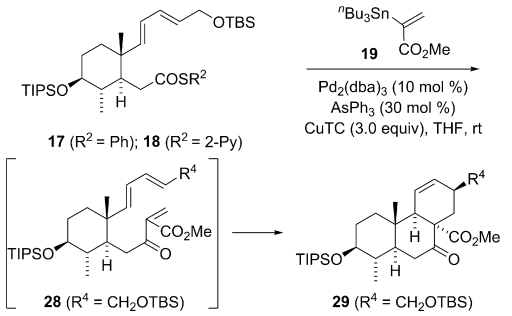


Fig. 4. NOE correlations found in the NOESY studies of **27a**.

Table 4
Liebeskind-Srogl coupling/IMDA reaction cascade of **17** and **18** with **19**.



Entry	R^2	Time (h)	Yield (%)[a]
1	Ph (**17**)	10	33[b]
2	2-Py (**18**)	2	62[b]

[a] Isolated yield.
[b] Single isomer.

The structure of **29** was elucidated based on the NOESY studies of **29a**, a derivative of **29** (Fig. 5). Hence, the stereoselectivity of the above reactions could be explained by transition state models in Fig. 2.

Next, we carried out the cascade reactions of **17** and **18** with **22** (Table 5). Since all the substrates and stannane bear a substituent, large steric repulsion was expected in the transition states. Thus, the reactions of **17** and **18** with **22** were expected to proceed with

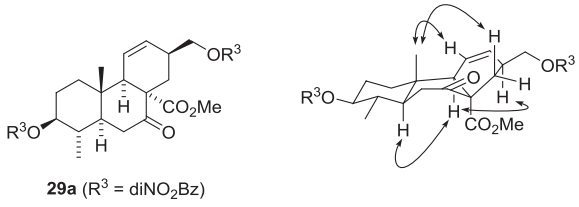
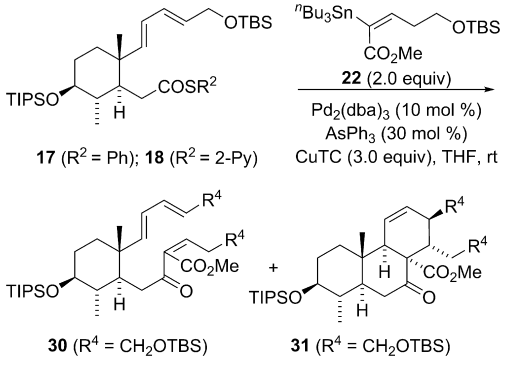


Fig. 5. NOE correlations found in the NOESY studies of **29a**.

Table 5
Liebeskind-Srogl coupling/IMDA reaction cascade of **17** and **18** with **22**.



Entry	R^2	Time (h)	Yield[a]	
			30 (%)	**31** (%)
1	Ph (**17**)	3	58[b]	0
2	2-Py (**18**)	0.5	53[b]	0

[a] Isolated yield.
[b] The product was a mixture of geometrical isomers of the trisubstituted alkene moiety of **30**.

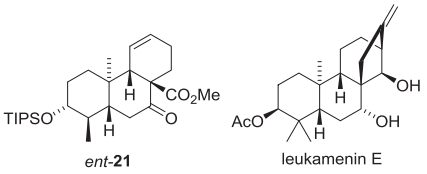


Fig. 6. Structures of *ent*-**21** and leukamenin E.

difficulty. Indeed, all the attempted cascade reactions stopped at the first stage, and only the coupling product **30** was formed. The desired product **31** was not obtained in the reactions (Table 5, entries 1 and 2). The reaction of **17** gave **30** with higher yield (entry1). Unfortunately, **30** did not undergo the IMDA reaction in the presence of a Lewis acid or upon heating.

In the reactions depicted in Tables 1–5, the Liebeskind-Srogle coupling of 2-pyridyl thioesters **16** and **18** with alkenylstannane **19** bearing no substituent as well as the IMDA reactions of the corresponding products **20** and **28** were fast, and the final products were formed in higher yields when compared to those of the reactions of phenyl thioesters **15** and **17**. On the other hand, **15** and **17** gave better results in the reactions with alkenylstannanes **22** and **25**, which bear a substituent. The reason for this trend is not clear at present, but the low yields in the reactions of 2-pyridyl thioesters with sterically hindered alkenylstannanes **22** and **25** could be due to the slow Liebeskind-Srogle couplings because reactive thioesters were consumed during the coupling reactions via unidentified processes and loss of more reactive 2-pyridyl thioester could be faster.

In summary, we have developed the Liebeskind-Srogl coupling/IMDA reaction cascade that stereoselectively affords a tricarbocyclic compound with a *trans–trans-cis* fused ring system including an all-carbon quaternary stereogenic center at the ring junction. The cascade reactions proceed quickly and afford the products within 2 h at room temperature in the presence of a suitable thioester. Thus, the 2-pyridyl thioester was suitable for reactions with alkenylstannanes bearing no substituent at the β-position, and the phenyl thioester was suitable for reactions with alkenylstannane bearing a substituent at the β-position. The observed trends can form the basis for further optimization of the reaction conditions. Reactions of substrates bearing a substituent at the terminal position of the diene with tri-substituted alkenylstannanes did not undergo the cascade reaction and stopped at the first coupling stage. These results indicate the limitations of the developed protocol in this study. However, the developed protocol as well as the prepared chiral compounds are useful for the enantioselective total synthesis of terpenoids with the *trans–trans-cis* fused ring system such as leukamenin E,[11] which includes the same tricyclic scaffold as that of *ent*-**21** (Fig. 6), so further investigations of the cascade reaction is underway.

Acknowledgments

We acknowledge supports of the Materials Characterization Central Laboratory, Waseda University – Japan, for characterization of new compounds. This work was financially supported in part by the Grant-in-Aid for Scientific Research on Innovative Areas 2707 Middle molecular strategy from MEXT – Japan and a Waseda University Grant for Special Research Projects.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.01.046.

References

1. Researches on natural product syntheses via the IMDA reaction by us, see: (a) Suzuki T, Nakada M. *Tetrahedron Lett*. 2002;43:3263;
(b) Suzuki T, Tanaka N, Matsumura T, Hosoya Y, Nakada M. *Tetrahedron Lett*. 2006;47:1593;
(c) Suzuki T, Tanaka N, Matsumura T, Hosoya Y, Nakada M. *Tetrahedron Lett*. 2007;48:6483;
(d) Tanaka N, Suzuki T, Hosoya Y, Nakada M. *Tetrahedron Lett*. 2007;48:6488;
(e) Tanaka N, Suzuki T, Matsumura T, Hosoya Y, Nakada M. *Angew Chem Int Ed*. 2009;48:2580;
(f) Yamakoshi S, Hayashi N, Suzuki T, Nakada M. *Tetrahedron Lett*. 2009;50:5372;
(g) Kobayakawa Y, Mori Y, Okajima H, Terada Y, Nakada M. *Org Lett*. 2012;14:208;
(h) Kobayakawa Y, Nakada M. *Angew Chem Int Ed*. 2013;52:7569;
(i) Kobayakawa Y, Nakada M. *Heterocycles*. 2014;88:669;
(j) Kobayakawa Y, Nakada M. *J Antibiot*. 2014;67:483;
(k) Nakada M. *Chem Rec*. 2014;14:641;
(l) Usui K, Suzuki T, Nakada M. *Tetrahedron Lett*. 2015;56:1247.
2. (a) Orimoto K, Oyama H, Namera Y, Niwa T, Nakada M. *Org Lett*. 2013;15:768;
(b) Oyama H, Nakada M. *Tetrahedron Asymmetry*. 2015;26:195;
(c) Oyama H, Orimoto K, Niwa T, Nakada M. *Tetrahedron Asymmetry*. 2015;26:262;
(d) Enomoto K, Oyama H, Nakada M. *Chem Eur J*. 2015;21:2798;
(e) Nagatani K, Hoshino Y, Tezuka H, Nakada M. *Tetrahedron Lett*. 2017;58:959;
(f) Nagatani K, Minami A, Tezuka H, Hoshino Y, Nakada M. *Org Lett*. 2017;19:810.
3. (a) Usui K, Kanbe M, Nakada M. *Org Lett*. 2014;16:4734;
(b) Usui K, Nakada M. *Heterocycles*. 2015;91:332.
4. (a) Liebeskind LS, Srogl J. *J Am Chem Soc*. 2000;122:11260;
(b) Yu Y, Liebeskind LS. *J Org Chem*. 2004;69:3554;
(c) Villaobos JM, Srogl J, Liebeskind LS. *J Am Chem Soc*. 2007;129:15734;
(d) Wittenberg R, Srogl J, Egi M, Liebeskind LS. *Org Lett*. 2003;5:3033;
(e) Tomizawa T, Orimoto K, Namera Y, Niwa T, Nakada M. *Org Lett*. 2012;14:6294;
(f) Orimoto K, Tomizawa T, Namera Y, Oyama H, Niwa T, Nakada M. *Heterocycles*. 2013;87:827.
5. Fujii T, Orimoto K, Nakada M. *Tetrahedron Lett*. 2014;55:1100.
6. Compound **10** was prepared as an inseparable mixture of geometrical isomers (*E*/*Z* = 10/1) using *tert*-butyldimethyl(3-tributylstannylallyloxy)silane (*E*/*Z* = 10/1).[7] Compounds **17** and **18** were formed as an inseparable mixture of isomers (*E*/*Z* = 10/1), accordingly.
7. Oderinde MS, Froese RDJ, Organ MG. *Angew Chem Int Ed*. 2013;52:11334.
8. Nielson TE, Quement SL, Juhl M, Tanner D. *Tetrahedron*. 2005;61:8013.
9. Shibahara S, Fujino M, Tashiro Y, Takahashi K, Ishihara J, Hatakeyama S. *Org Lett*. 2008;10:2139.
10. The unidentified isomer could be derived from (*E*)-**25**. It cannot be denied that isomerization of the trisubstituted alkene of **26** occurred prior to the Diels-Alder reaction.
11. Zhao Y, Pu J-X, Huang S-X, et al. *J Nat Prod*. 2009;72:988.

Please cite this article in press as: Fujii T., et al. Tetrahedron Lett. (2018), https://doi.org/10.1016/j.tetlet.2018.01.046