



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

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ABSTRACT

The Liebeskind-Srogl coupling/intramolecular Diels-Alder (IMDA) reaction cascade that stereoselectively affords a tricyclic 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.

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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.

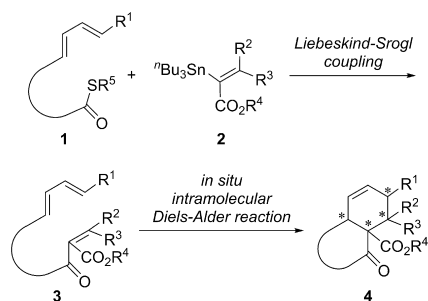
The IMDA reaction proceeds rapidly because of the diene tethered with dienophile moieties; thus, it is beneficial for constructing a polycyclic scaffold. Moreover, it would be a promising method for constructing scaffolds of terpenoids when accompanied by the formation of all-carbon quaternary stereogenic 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).

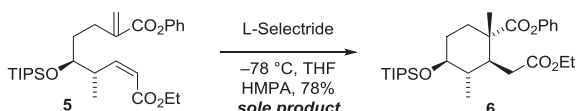
We previously reported a highly stereoselective synthesis of **6** from **5**.⁵ The chiral building block **6** would be useful for the total syntheses of a variety of terpenoids (Scheme 2). Hence, when **6** is converted to the corresponding α -alkylidene β -keto ester via Liebeskind-Srogl coupling,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

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

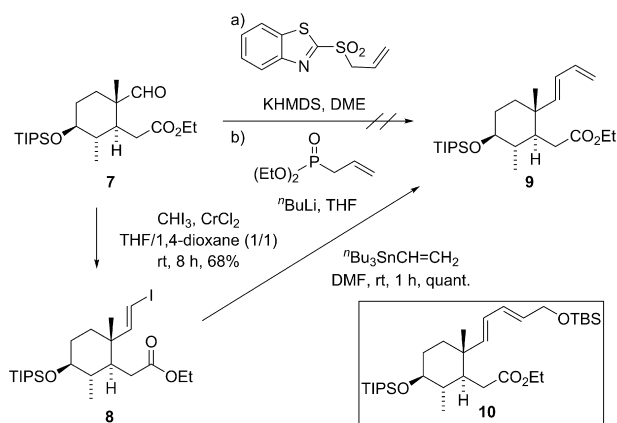
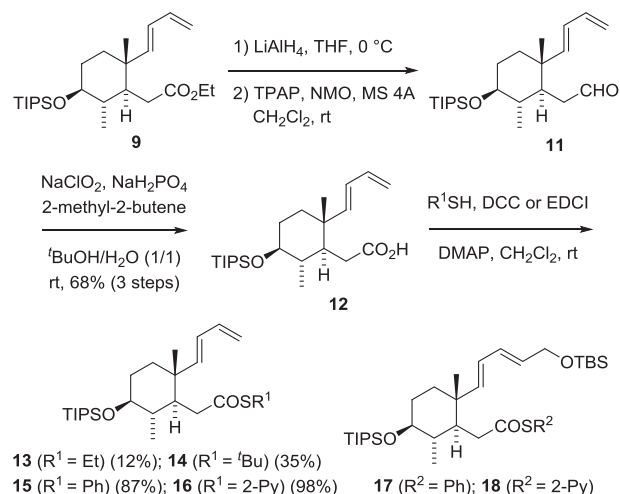


Scheme 2. Highly stereoselective Michael reduction/intramolecular Michael reaction cascade.

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.

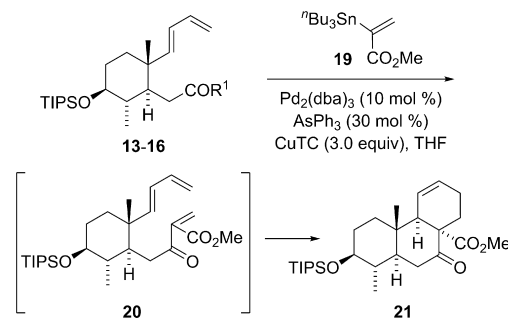
To examine the above cascade, we prepared diene substrates bearing a thiol ester starting from **6**. First, we attempted the Horner-Wittig and Julia-Kocienski reactions of **7** (Scheme 3), which was derived from **6** via the reaction with benzenemethanethiol (76%) and Fukuyama reduction (90%). However, 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 LiAlH₄, 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 carry 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.

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