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SYNTHETIC STUDIES ON KERAMAPHIDIN B: FORMATION OF A MACROCYCLIC RING BY INTRAMOLECULAR DIELS-ALDER REACTION

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Abstract – The possibility of constructing the macrocyclic ring of keramaphidin B via an intramolecular Diels-Alder (IMDA) reaction has been investigated. The IMDA reaction of a substrate possessing dihydropyridone and diene moieties, which were tethered by an alkyl chain including a linear triple bond, was found to proceed in the presence of $SnCl_4$ at 80 °C.

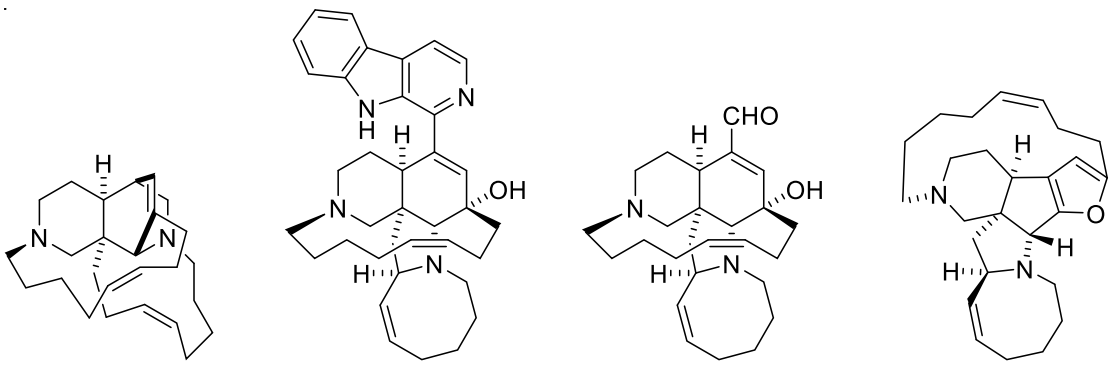
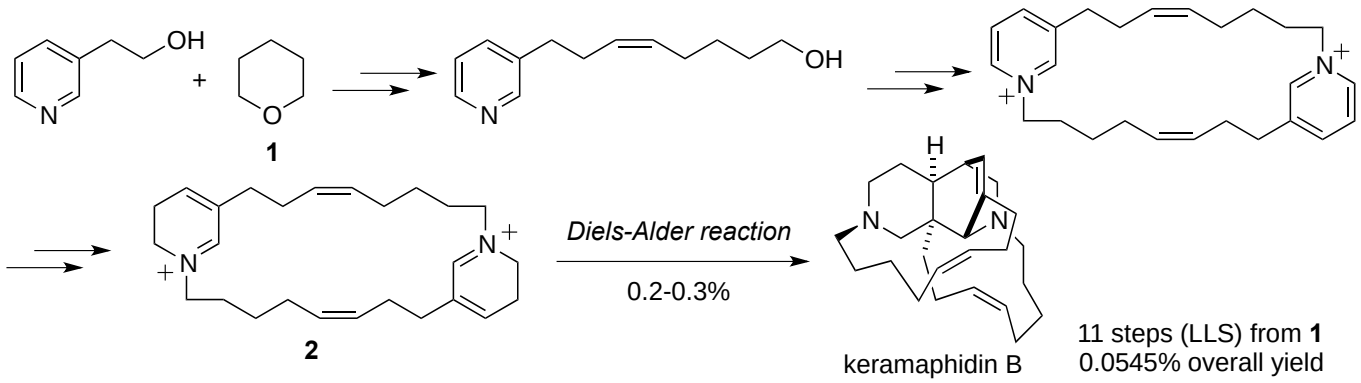


Figure 1. The structures of keramaphidin B and members of the manzamine family

Keramaphidin B (Figure 1) was isolated from the marine sponge *Amphimedon* sp. collected off the Kerama Islands, Okinawa, by Kobayashi and co-workers in 1994.[1] Extensive NMR studies and X-ray crystallographic analysis of keramaphidin B have revealed its unique pentacyclic structure, which features a 1,4-etheno-2,7-decahydronaphthylidene core with two macrocyclic rings and four successive stereogenic centers including one all-carbon quaternary stereogenic center. Keramaphidin B has been

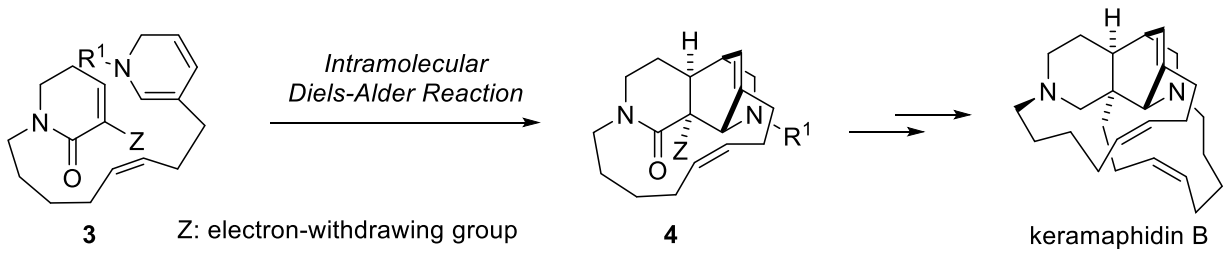
reported to exhibit cytotoxicity against P388 murine leukemia and KB human epidermoid carcinoma cells (IC_{50} = 0.28 and 0.3 μg/mL, respectively).[1]



Scheme 1. Baldwin's biomimetic total synthesis of keramaphidin B[4]

Keramaphidin B is regarded as a biogenetic intermediate of the manzamine alkaloids (Figure 1),[1,2] and its unique structural features and cytotoxic activity have drawn substantial interest from synthetic organic chemists. Although a number of synthetic studies[3] have been reported, only one total synthesis of keramaphidin B has been accomplished to date.

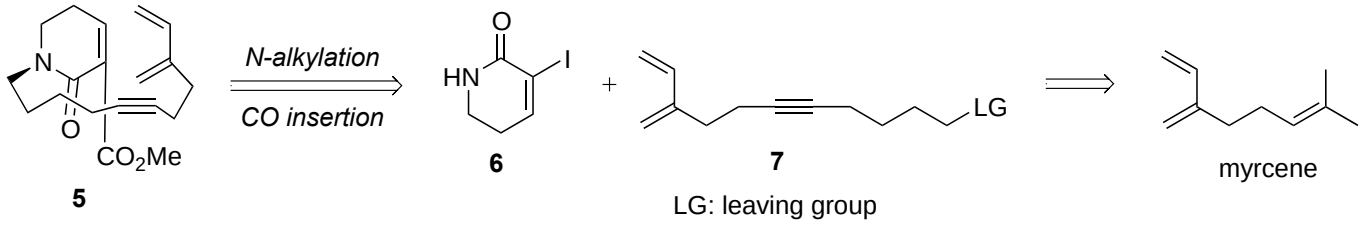
Baldwin *et al.* achieved the total synthesis of keramaphidin B based on their proposed biogenesis pathway (Scheme 1).[4] They prepared compound **2** from compound **1** and subjected it to an intramolecular Diels-Alder reaction, which gave a detectable amount (0.2–0.3%) of keramaphidin B. The overall yield of their synthesis was very low, therefore the development of a new synthetic method, which can be used to supply an appropriate amount of keramaphidin B, is required for further studies on keramaphidin B. Hence, we started to develop a new synthetic approach toward keramaphidin B and as a preliminary study, we investigated the possibility of constructing the macrocyclic ring of keramaphidin B via an intramolecular Diels-Alder (IMDA) reaction. Herein we report the results of this feasibility study.



Scheme 2. Our planned synthetic approach toward keramaphidin B

Scheme 2 shows our synthetic approach toward keramaphidin B. This approach features the efficient construction of the keramaphidin B core scaffold that contains the macrocyclic ring with four stereogenic

centers. Compound **3** possesses tethered 1,2-dihydropyridine and 3,4-dihydropyridin-2(1*H*)-one moieties. Hence, the IMDA reaction of **3** is challenging because the heterocyclic diene and dienophile will cause severe steric repulsion in the transition state and moreover, the formation of a 13-membered ring will suffers from the negative entropy change. However, we envisaged that the IMDA of **3** could afford compound **4** because 1,2-dihydropyridine and 3,4-dihydropyridin-2(1*H*)-one can act as the electron-rich diene and electron-deficient dienophile in the proposed IMDA reaction, respectively, which is a requirement for the efficient Diels-Alder reaction.

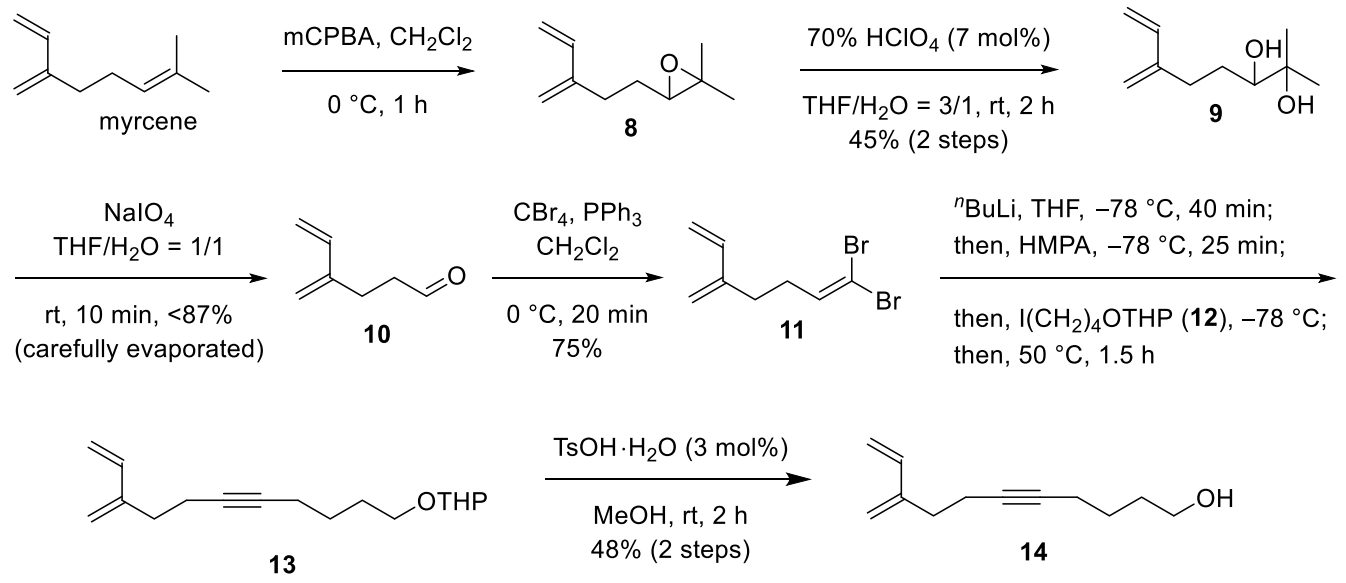


Scheme 3. Retrosynthetic analysis of compound **5**, the substrate of our proposed IMDA

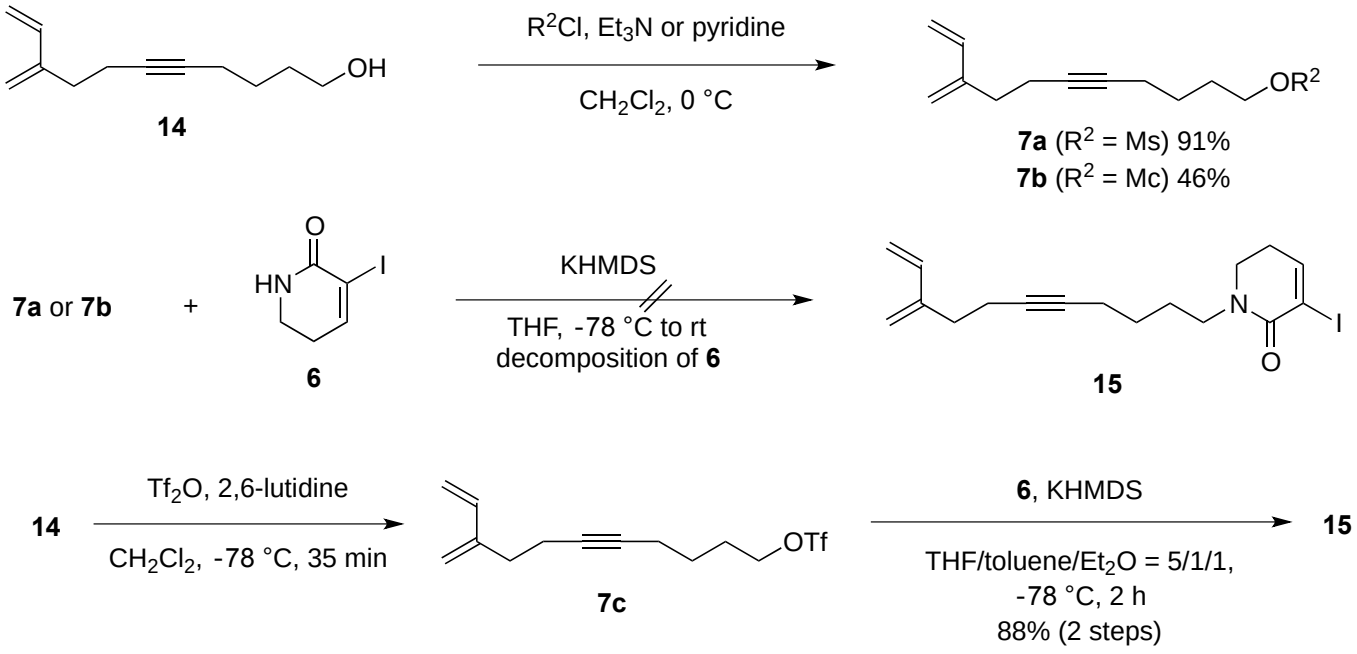
To investigate the possibility of our proposed IMDA reaction, which is accompanied by the formation of a macrocyclic ring, we decided to carry out the IMDA reaction of compound **5** (Scheme 3) as a model study because **5** can be easily prepared via *N*-alkylation of readily available **6**[5] with compound **7**, which itself can be prepared from commercially available myrcene. The diene and dienophile in **5** are tethered by an alkyl chain including a triple bond due to the simplicity of its preparation.

Scheme 4 shows the preparation of alcohol **14**, which is the precursor of **7**. The synthesis of aldehyde **10** from myrcene has been previously reported.[6] Thus, epoxidation of myrcene afforded **8**, which was treated with perchloric acid to give diol **9**, followed by reaction of **9** with sodium metaperiodate to give aldehyde **10**. Aldehyde **10** was converted into dibromoalkene **11** followed by treatment with *n*-butyllithium and iodide **12**[7] to afford compound **13**. Finally, removal of the THP group in **12** under acidic conditions gave compound **14**.

Subsequently, we examined the *N*-alkylation of compound **6** (Scheme 5). Mesylate **7a** was prepared using conventional reagents and subjected to the *N*-alkylation reaction with **6**. However, the *N*-alkylation reaction resulted in no reaction and the decomposition of **6** was observed. The decomposition of **6** gradually proceeded when **6** was treated with KHMDS at 0 °C prior to the addition of compound **7a**. Hence, to enhance the reaction rate, we examined the *N*-alkylation of **6** with monochlate **7b** (R^2 = Mc (chloromethanesulfonyl)),[8] which has been reported to be more reactive than the corresponding mesylate, but no reaction occurred and the decomposition of **6** was observed again.



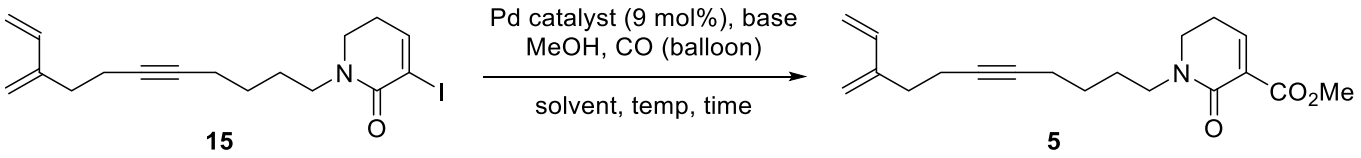
Scheme 4. Preparation of **14**, a precursor of **7**



Scheme 5. *N*-Alkylation of compound **6**

Therefore, the reaction with more reactive triflate **7c** was examined, but **7c** readily decomposed during silica gel column chromatography, and when dissolved in THF, the polymerization of THF was observed. Accordingly, triflate **7c** was used in the *N*-alkylation of **6** without any purification. Thus, crude triflate **7c** was dissolved in diethyl ether and the resulting solution was added to the anion derived from **6** in THF. This operation successfully afforded compound **15** in 88% yield from alcohol **14**.

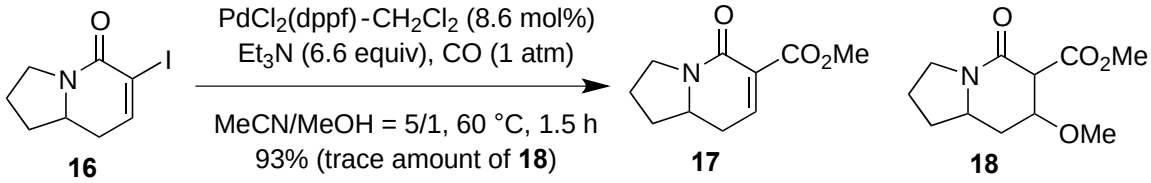
Table 1. Palladium-catalyzed carbonylation of compound **15**



15 **5**

Entry	Catalyst	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	$PdCl_2(dppf)_2$-CH_2Cl_2	Et_3N (6.6)	MeCN	rt	1.5	59
2	$PdCl_2(dppf)_2$-CH_2Cl_2	Et_3N (6.6)	MeCN	rt, 50	0.5, 4.0	-[b]
3	$PdCl_2(PhCN)_2$	Et_3N (6.6)	MeCN	rt, 50	0.5, 4.0	-[b]
4	$PdCl_2(dppf)_2$-CH_2Cl_2	Et_3N (6.6)	THF	rt, 40	2.5, 1.5	<63[c]
5	$Pd(PPh_3)_4$	Et_3N (6.6)	THF	rt, 40	2.5, 1.5	<65[c]
6	$Pd(PPh_3)_4$	K_2CO_3 (2.0)	THF	rt	14	-[c]

[a]Isolated yield. [b]A complex mixture was formed. [c]The product was formed with an inseparable mixture of by-products.



16 **17** **18**

Scheme 6. Palladium-catalyzed carbonylation of **16** reported by Levinson *et al.*[9]

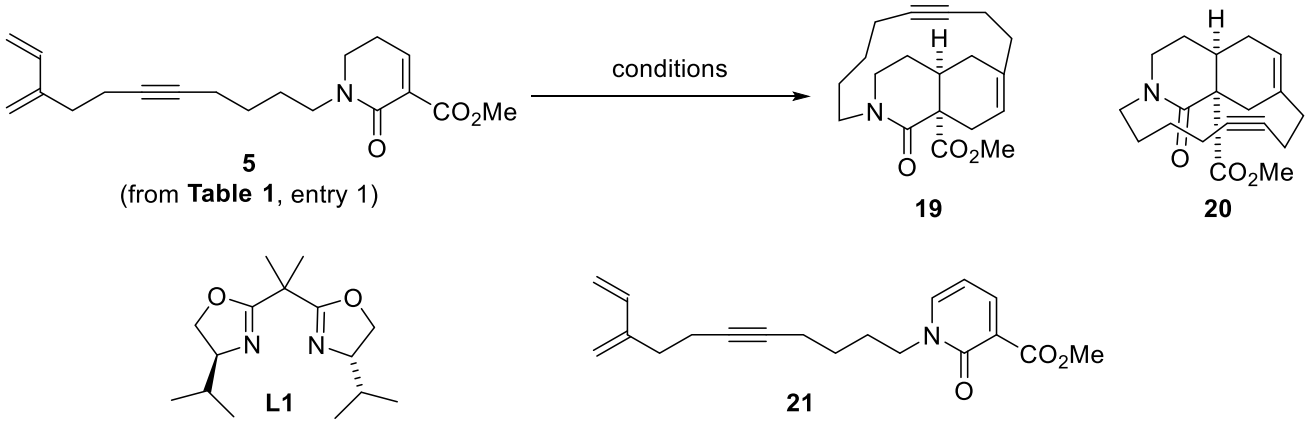
Having prepared compound **15**, its palladium-catalyzed carbonylation reaction was examined (Table 1).[9-11] Product **5** was formed with a side-product; however, this side product disappeared during purification by silica gel column chromatography (Table 1, entry 1).

Levinson *et al.* reported that the palladium-catalyzed carbonylation of dihydropyridine derivative **16** afforded compound **17** along with a trace amount of compound **18**. They proposed that **18** would be formed via an oxa-Michael reaction of **17** with methanol (Scheme 6).[9] Hence, the palladium-catalyzed carbonylation of compound **15** should afford the same by-product as **18**, which would be converted to **5** during the purification.

Product **5** was unstable because the dihydropyridine moiety is activated by the introduced ester group. Indeed, the reaction of **15** at the elevated temperature resulted in the formation of a complex mixture (Table 1, entries 2 and 3). The reaction in THF (Table 1, entry 4) and the use of $Pd(PPh_3)_4$ in THF (Table

1, entry 5) afforded **5** with the almost same yield as that of entry 1, but at least two inseparable by-products were formed. The use of other bases did not improve the reaction yield. For example, using K_2CO_3 resulted in the formation of a complex mixture (Table 1, entry 6). Hence, product **5**, which was obtained in entry 1, was used for the key IMDA reaction.

Table 2. The key IMDA of compound **5**



Entry	Lewis acid (equiv)	Solvent (M)	Temp (°C)	Time (h)	Yield (%)[a]
1	-	mesitylene (0.005)	100, 135	2.0, 16	-[b]
2	$Cu(OTf)_2$-**L1** (1.05)	toluene (0.005)	60, 80	1.0, 2.5	-[c]
3	$MgBr_2$ (1.0)	$(CH_2Cl)_2$ (0.005)	0, rt, 80	2.0, 1.5, 1.5	-[b]
4	$Zn(OTf)_2$ (1.0)	$(CH_2Cl)_2$ (0.005)	0, rt, 80	2.0, 1.5, 15	NR[d]
5	$ZnBr_2$ (1.0)	$(CH_2Cl)_2$ (0.005)	0, rt, 55, reflux	1.0, 19, 6.0, 13	<9[e]
6	$InCl_3$ (1.0)	$(CH_2Cl)_2$ (0.005)	0, rt, 80	2.0, 1.5, 15	10
7	$SnCl_4$ (1.0)	$(CH_2Cl)_2$ (0.005)	–20, rt, 80	2.0, 1.5, 1.5	13
8	$SnCl_4$ (1.0)	$(CH_2Cl)_2$ (0.001)	80	17	32

[a]Isolated yield. [b]Unidentified products were formed. [c]The formation of **21** was indicated by ^{1}H-NMR spectroscopy, but it was not fully characterized. [d]NR: no reaction. [e]Inseparable unidentified by-products were formed.

The results of the IMDA reaction using compound **5** are summarized in Table 2. The IMDA reaction did not proceed at room temperature and the reaction conducted with heating resulted in the formation of unidentified products (Table 2, entry 1). Hence, we examined the IMDA reaction in the presence of a Lewis acid. The reaction using $Cu(OTf)_2$ and bis-oxazoline ligand **L1** (Table 2, entry 2)[11] did not afford

the desired product, but afforded **21**, the formation of which was indicated by ^{1}H-NMR spectroscopy. This reaction was carried out using degassed solvent, therefore this result can be explained by the oxidation of **5** mediated by $Cu(OTf)_2$ and bis-oxazoline ligand **L1**. The IMDA reaction using $MgBr_2$ (Table 2, entry 3) afforded a product that showed a similar ^{1}H-NMR spectrum to that of **5**, indicating that the product may be a chelated $MgBr_2$ complex of **5**. Hence, its structure was not fully characterized. The use of $Zn(OTf)_2$ resulted in no reaction (Table 2, entry 4), but the IMDA reactions carried out using $ZnBr_2$, $InCl_3$, and $SnCl_4$ afforded the expected product **19**, but in low yield (Table 2, entries 5–7). However, to our delight, the IMDA reaction carried out in the presence of 1.0 equivalent of $SnCl_4$ at 80 °C under dilute conditions (0.001 M) afforded the desired product **19** in 32% yield (Table 2, entry 8).

Figure 2. A summary of the COSY, NOESY, and HMBC results obtained for compound **19**

The structure of **19** was fully characterized using NMR and mass spectrometry. The COSY and NOESY spectra of **19** revealed that the allylic proton H*a* was adjacent to the alkenyl proton, and the HMBC spectrum of **19** showed correlations between the allylic proton H*a* and amide carbonyl carbon (Figure 2). Another possible structure for the product was **20**, but this was ruled out by the correlations described above.

The four possible transition states for the IMDA reaction of **5** are shown in Figure 3. **TS-1** and **TS-3** are energetically unfavorable due to the severe strain generated by the *exo*-mode approach of the diene moiety. On the other hand, less-strained **TS-2** and **TS-4** are energetically more favorable. The regioselectivity of the IMDA of **5** can be explained by frontier molecular orbital theory. That is, a strong interaction will take place between the centers on the frontier molecular orbitals of the diene having an electron-donating alkyl group and the dienophile having two electron-withdrawing groups with the largest orbital coefficients, resulting in the favorable formation of **19** via **TS-2**.

In summary, the IMDA reaction of **5** was found to proceed in the presence of $SnCl_4$ at 80 °C. Considering that the IMDA reaction of **5** including a linear triple bond in the tether alkyl chain hardly proceeds because it is accompanied by the negative entropy change, the 32% yield obtained for the reaction is reasonable. This successful result indicates that the dihydropyridone moiety, which is activated by an electron-withdrawing ester group, can be used for the IMDA reaction accompanied by the formation of a

macrocyclic ring. However, the IMDA reaction of **3** suffers from severe steric strain in the transition state because **3** possesses bulky 1,2-dihydropyridine and 3,4-dihydropyridin-2(1*H*)-one moieties acting as the diene and dienophile, respectively. Hence, the design of the substrate suitable for the IMDA reaction that is applicable for the total synthesis of keramaphidin B is an important issue to address and further studies toward the total synthesis of keramaphidin B are currently underway in our laboratory.

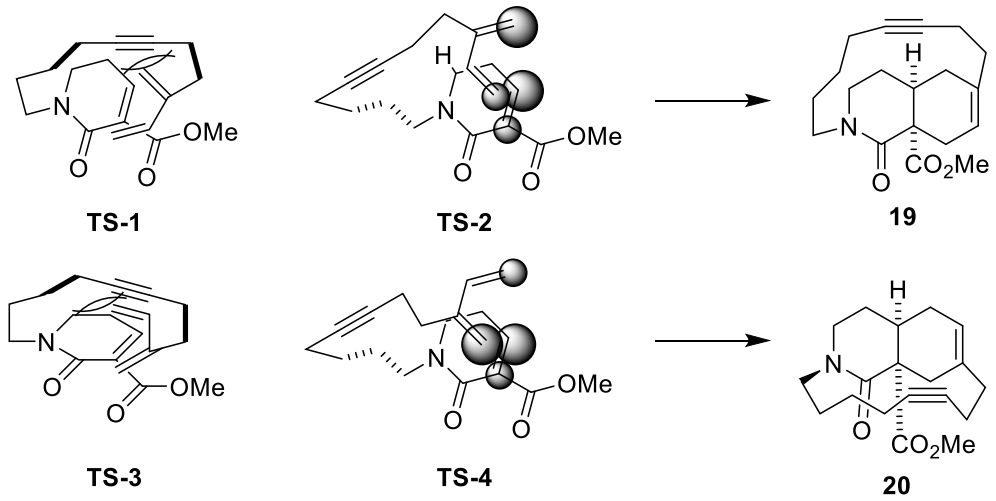


Figure 3. The proposed transition states of the IMDA of compound **5**

ACKNOWLEDGEMENTS

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SUPPORTING INFORMATION

The supporting information includes experimental information and ^{1}H and ^{13}C NMR, IR, and HRMS data for compounds **11**, **13-15**, **5**, and **19**. The data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26391/100/1.

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