

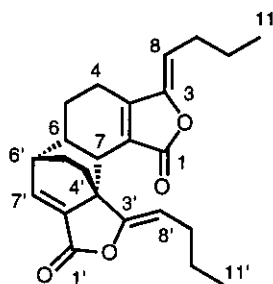
DIELS-ALDER REACTION OF LIGUSTILIDE GIVING LEVISTOLIDE A AND TOKINOLIDE B

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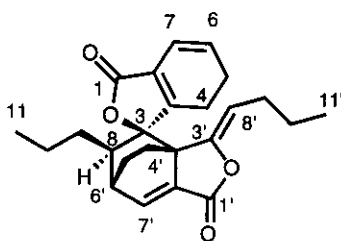
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Abstract - Naturally occurring levistolide A (**1**) and tokinolide B (**2**) were first synthesized by a Diels-Alder reaction of ligustilide (**3**) under the several reaction conditions. The dimer (**2**) was converted into the thermodynamically stable dimer (**1**) at 200 °C. The calculation of HOMO and LUMO of **3** was also carried out by MNDO/PM3 method to explain the regioselectivity.

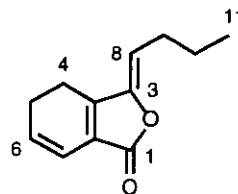
Levistolide A (**1**) and tokinolide B (**2**) occurred in a nature as racemates were recently isolated from the rhizome of *Ligusticum* or *Cnidium* species which were applied frequently to traditional Chinese medicines.¹⁻³ These dimers of ligustilide (**3**) have been shown to be a potent vasodilating activity as calcium channel blockade.³ Synthesis of **1** and **2** has not been reported so far. In this communication we wish to describe herein a first synthesis of these dimers (**1**, **2**) from the monomeric (**3**) by way of a Diels-Alder process and results of calculation of HOMO and LUMO of **3** which could be explained to play a key role in respect of the observed regioselectivity.



Levistolide A (**1**)



Tokinolide B (**2**)

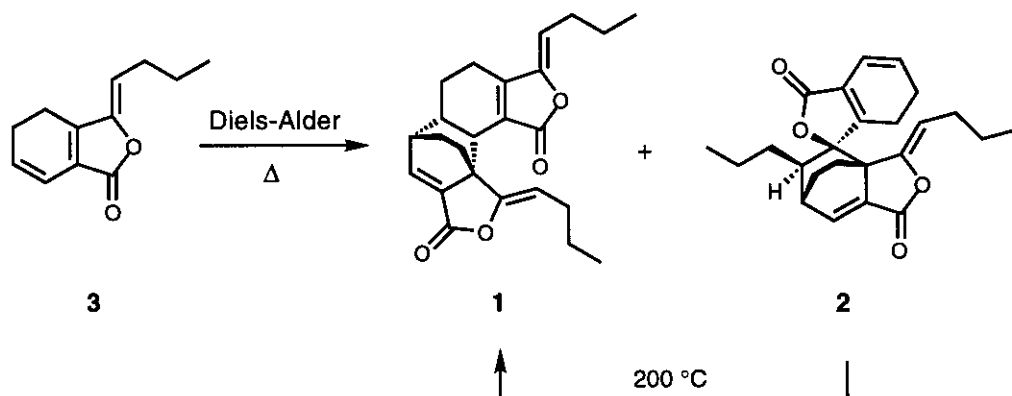


Ligustilide (**3**)

We have already reported the synthesis of **3** using regio- and stereoselective cyclization catalyzed by silver iodide or silver.⁴ Diels-Alder reaction of **3** was carried out for first synthesis of **1** and **2** as shown in Table 1. When **3** was refluxed in benzene for 16 h, dimers (**1**) and (**2**) as *endo* adducts were obtained in 2% and 4% yields, respectively, with recovery of **3** in 56% (Entry 1). The same reaction of **3** without solvent at

150 or 200 °C in a sealed tube exclusively afforded **1** in 26 and 23% yields, respectively, with both a slight increase of the yield and a high regioselectivity at the elevated temperature (Entries 4-5). To overcome the problem of this low yield, we have also pursued a high-pressure Diels-Alder reaction⁵ for **3** at 11 kbar at room temperature, but unfortunately the reaction proceeded in an unexpected manner in low yield (Entry 6). It was also confirmed that **2** was converted into thermodynamically stable **1** at 200 °C with formation of **3**. It should be considered that high recovery of **3** in these reactions was attributed to retro-Diels-Alder reaction. Although Diels-Alder reaction of **3** in the presence of several Lewis acids such as boron trifluoride diethyl etherate, titanium(IV) isopropoxide or diethylaluminum chloride was also performed, none of the desired dimers was observed under these Lewis acids-promoted conditions, consequently, the starting monomer (**3**) remained in high recovery. The spectral data (IR, ¹H NMR, MS) of **1** and **2** were identical with those of the natural products.^{3, 6}

Table 1: Diels-Alder reaction^a of **3**



Entry	Solvent	Temp. (°C)	Time (h)	1 Yield (%)	2 Yield (%)	3 Recovery (%)
1	benzene	reflux	16	2	3	56
2	-	50 ^b	15	0	0	89
3	-	100 ^b	7	4	2	64
4	-	150 ^b	5	26	0	34
5	-	200 ^b	1	23	0	60
6	-	rt ^c	24	6	4	82

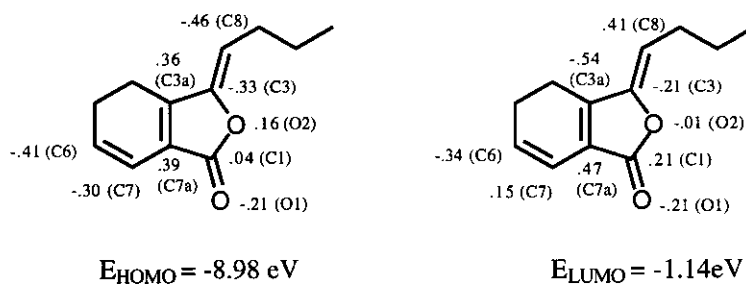
a) All reactions were carried out under argon atmosphere. b) The reaction was carried out in a sealed tube without solvent. c) The reaction was carried out at high pressure (11 kbar) without solvent.

DISCUSSION

It is envisioned to be possible that six *endo* adducts⁷ including **1** and **2** and the corresponding six *exo*

adducts would be theoretically generated during the course of a Diels-Alder reaction of **3**. In order to compare the transition states for **1** and **2** with those for the other dimers, the coefficients of HOMO and LUMO of **3** were calculated using semiempirical MNDO/PM3 method⁸ (Figure 1). Although the results of calculation suggest that the transition states for **4** and **5** are more favorable for primary orbital interactions (HOMO-LUMO ; **4** : C3a - C7a, C6 - C3a, **5** : C3a - C3a, C6 - C7a) than those for **1**, **2**, **6** and **7** (HOMO-LUMO ; **1** : C3a - C7, C6 - C6, **2** : C3a - C3, C6 - C8, **6** : C3a - C6, C6 - C7, **7** : C3a - C8, C6 - C3), the transition states for **1** and **2** are more favorable for secondary orbital interactions (HOMO-LUMO ; **1** : C7a - C7a, O2 - C1, C8 - O1, O1 - C3, **2** : C7a - C3a, C3 - C7a, C8 - C1) as reported in the literatures⁹ than those for **4**, **5**, **6** and **7** (**4** : C7a - C1, C7 - C3, **5** : C7a - C3, C7 - C1, **6** : C7 - C7a, **7** : C7 - C3a). The transition states for **4** and **5** have also unfavorable antibonding interactions (HOMO-LUMO ; **4** : O2 - O1, **5** : O2 - C8) in the secondary orbital interactions. On the other hand, the six *exo* transition states do not play an effective role in the secondary orbital interactions based on the values of P_z coefficients of the HOMO and LUMO of **3**. It was a noteworthy observation that the regioselectivity of a Diels-Alder reaction of **3** leading to **1** and **2** was controlled by the secondary orbital interactions.

Figure 1: P_z coefficients of the HOMO and LUMO of **3** calculated by MNDO/PM3 method



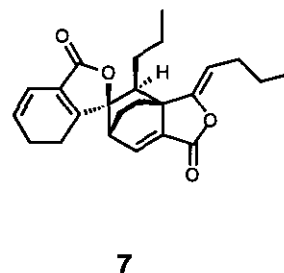
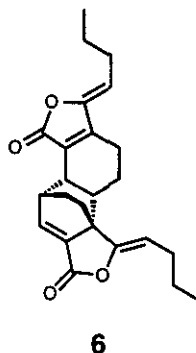
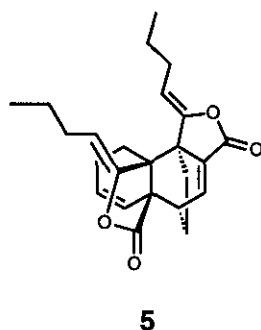
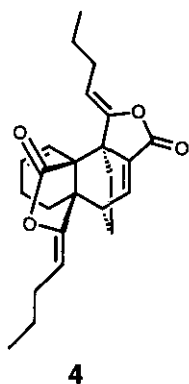
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6. **1** : mp 126-128 °C (lit.,³ mp 127.5-129 °C) ; IR (KBr) ν_{\max} 1778 (C=O), 1758 (C=O) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.92 (3H, t, $J=7.4$ Hz), 0.93 (3H, t, $J=7.4$ Hz), 1.30 (1H, ddt, $J=5.0$, 2.8, 12.7 Hz), 1.38-1.57 (6H, m), 1.88 (dddd, $J=12.7$, 9.8, 3.3, 2.8 Hz), 1.91-1.95 (1H, m), 2.04 (1H, ddd, $J=12.7$, 9.8, 5.0 Hz), 2.04-2.11 (1H, m), 2.18-2.23 (1H, m), 2.14-2.22 (2H, m), 2.29 (2H, dt, $J=7.9$, 7.5 Hz), 2.53-2.56 (1H, m), 2.98 (1H, ddt, $J=6.6$, 2.0, 2.8 Hz), 3.25 (1H, d, $J=8.9$ Hz), 4.99 (1H, t, $J=7.5$ Hz), 5.06 (1H, t, $J=7.9$ Hz), 7.34 (1H, d, $J=6.6$ Hz) ; HRMS m/z 380.19920 (380.19876 calcd for $\text{C}_{24}\text{H}_{28}\text{O}_4$, M^+), **2** : mp 118-120 °C (lit.,³ mp 120.5-122 °C) ; IR (KBr) ν_{\max} 1786 (C=O), 1756 (C=O) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.82 (3H, t, $J=7.4$ Hz), 0.88 (3H, t, $J=7.1$ Hz), 1.09-1.17 (1H, m), 1.24-1.38 (6H, m), 1.43-1.51 (1H, m), 1.67 (1H, dddd, $J=9.2$, 5.3, 1.8, 1.7 Hz), 1.98 (1H, ddt, $J=14.2$, 6.8, 7.6 Hz), 2.03-2.21 (4H, m), 2.26-2.32 (2H, m), 2.47-2.54 (1H, m), 3.10 (1H, dddd, $J=6.7$, 2.9, 2.2, 1.9 Hz), 4.62 (1H, dd, $J=8.7$, 6.8 Hz), 5.92 (1H, dt, $J=9.6$, 4.2 Hz), 6.17 (1H, dt, $J=9.6$, 2.1 Hz), 7.51 (1H, d, $J=6.7$ Hz) ; HRMS m/z 380.19864 (380.19876 calcd for $\text{C}_{24}\text{H}_{28}\text{O}_4$, M^+).
7. Four other possible dimers (endo adducts) are illustrated as follows.



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