

Photocyclodimers from *Z*-ligustilide. Experimental results and FMO analysis

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Abstract—The irradiation of the natural phthalide *Z*-ligustilide (**1**) gave the natural dimeric phthalide riligustilide (**5**), and three novel dimeric phthalides **7**, **8** and **9**. The chemo- and regio-selectivity involved in the formation of the photocyclodimers were analyzed by use of frontier molecular orbital methods and the preference in the formation of **7** was supported by the theoretical analysis. © 2005 Elsevier Ltd. All rights reserved.

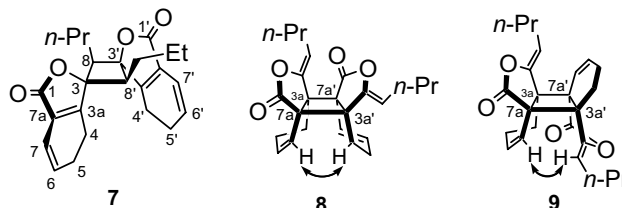
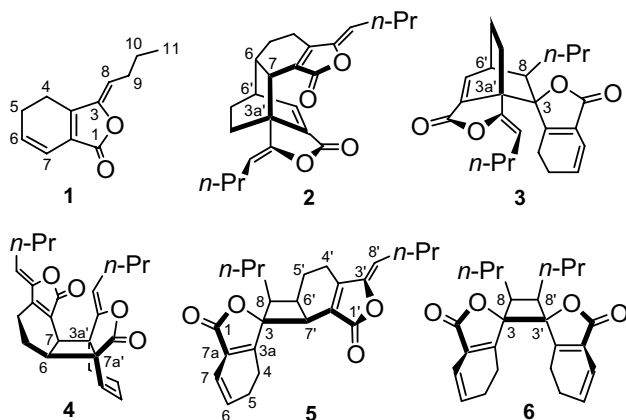
Z-Ligustilide (**1**) is a bioactive secondary metabolite isolated from umbelliferous plants¹ which are widely used in traditional medicine of different parts of the world.² Over last years, several researches on the reactivity of the monomeric phthalide **1**³ as well as of the natural dimers diligustilide (**2**)^{4,5} and tokinolide B (**3**)⁶ have been performed. Besides diligustilide (**2**) and tokinolide B (**3**), other dimeric phthalides isolated from Umbelliferae species are tokinolide A (**4**),⁷ riligustilide (**5**)¹ and *endo*-*Z,Z'*-(3.3',8.8')-diligustilide (**6**).⁸

Z-Ligustilide (**1**) may be considered as the biogenetic precursor of these dimeric phthalides derived from $[\pi 4s + \pi 2s]$ (compounds **2** and **3**) and $[\pi 2s + \pi 2s]$ (compounds **4–6**) cycloadditions. Some cyclodimers as diligustilide (**2**) and tokinolide B (**3**) have been obtained by relay synthesis from **1**.^{4,9}

Here we report the results of the photodimerization of *Z*-ligustilide (**1**) and the analysis of experimental results by use of frontier molecular orbital (FMO) methods.

Z-Ligustilide (**1**) possesses three different C–C double bonds and under photochemical conditions could afford several $[\pi 2s + \pi 2s]$ photocyclodimers, considering the chemo-, regio- and stereo-chemical possibilities.

Treatment of *Z*-ligustilide (**1**)¹⁰ under photochemical conditions using a mercury lamp afforded four main products: the natural product riligustilide (**5**) and three novel dimeric phthalides *endo*-*Z,Z'*-(3.8',8.3')-diligustilide (**7**), *endo*-*Z,Z'*-(3a.7a',7a.3a')-diligustilide (**8**) and *exo*-*Z,Z'*-(3a.7a',7a.3a')-diligustilide (**9**).¹¹



Keywords: *Z*-Ligustilide; Riligustilide; Photodimerization; Theoretical analysis.

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The presence of the natural product riligustilide (**5**) as one of the products was confirmed by direct comparison with an authentic sample and this constitutes a relay synthesis of **5**.^{1,12}

The structures of the dimeric phthalides **7–9** were elucidated by comparison of ¹H and ¹³C NMR data relative to *Z*-ligustilide (**1**).

The mass spectrum of compound **7**¹¹ showed the molecular ion peak at *m/z* 380 while only twelve signals were observed in its ¹³C NMR spectrum indicating that it was a symmetrical dimer. The disappearance of the ¹H NMR signal for H-8 (δ 5.22) and ¹³C NMR signals assigned to the C(3)–C(8) (δ 148.6 and 112.8) double bond in the starting material (**1**) clearly indicated that this bond was involved in the formation of the photocyclodimer **7**; besides that, a methine (δ 45.5) and a quaternary carbon (δ 93.5) not present in the ¹³C NMR spectrum of **1** were observed. The regio- and stereochemistry of **7** were established by the isochrony in the resonance of H-4a and H-4b (δ 2.60), reflecting their enantiotopic relationship and a highly symmetrical structure. This phenomenon is not feasible for the *exo* stereoisomers or for the regioisomer **6**, since in these compounds H-4a and H-4b display a diastereotopic relationship.

Compounds **8** and **9** were also symmetrical dimers, proof of that was the mass spectra of both compounds that showed the molecular ion peak at *m/z* 380, together with their ¹³C NMR spectra which showed twelve signals. The main differences observed in the spectroscopic data of these compounds, in comparison with those of the starting material (**1**);¹⁰ were the presence of two quaternary carbons at δ 51.6 and 50.4 for compound **8** and at δ 49.7 and 49.4 for compound **9**,¹¹ while ¹³C NMR signals assigned to the C(3a)–C(7a) (δ 147.0 and 124.0) double bond in the starting material (**1**) were not observed. In addition, the ¹H NMR signal assigned to H-8 in **1** (δ 5.22) was shifted to high field, at δ 4.85 for compound **8** and at δ 4.79 for compound **9**, due to a shielding effect. Therefore, the C(3a)–C(7a) double bond was involved in the formation of photocyclodimers **8** and **9**.

The regio- and stereo-selectivities were established by the observed correlations in the NOESY spectra of **8** and **9**, respectively. The structures of both photocyclodimers were determined without ambiguity by the observed crosspeak between H-7 and H-4'a in the NOESY spectrum of **8**, while compound **9** showed a crosspeak between H-7 and H-8' in its NOESY spectrum. Moreover, the structure and stereochemistry of compound **8** was confirmed by X-ray analysis (Fig. 1).¹³

In order to have a better understanding on the formation of compounds **5**, **7**, **8** and **9** we carried out molecular structure calculations at semiempirical AM1 level. For this purpose the molecular structure of **1** was modeled and optimized for the ground and the first excited (triplet) states. For the ground state the restricted

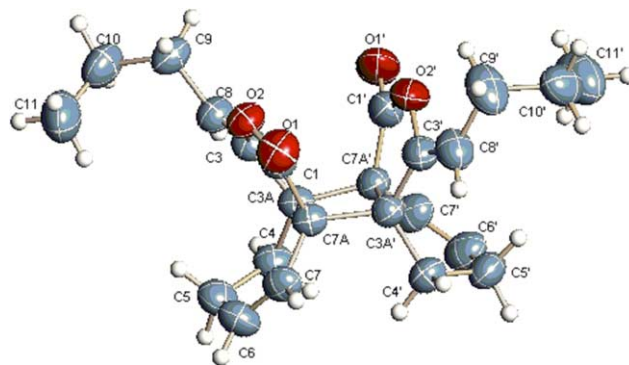


Figure 1. ORTEP-like view of compound **8**.

method was used, whereas for the triplet the unrestricted was performed. All our calculations were done with the suite of programs in Gaussian 98.¹⁴

We realized that the value of the dihedral angle {C(3), C(8), C(9), C(10)} of **1** was critical in the photocyclodimers formation. A relaxed potential energy scan showed that the most stable conformations have an angle of 170.5° and 148.6° for the triplet and the ground states, respectively. This means that for the triplet state all the atoms in the chain are coplanar to the lactone (Fig. 2), whereas for the ground state this is not observed (Fig. 3). This difference between both molecular conformations brings down the steric hindrance for the formation of photocyclodimers.

Table 1 shows the total energies obtained for the optimized structure of **1** in ground and excited states, and also includes the Müliken's charges¹⁶ for atoms of the double bonds of **1** involved in the formation of photocyclodimers **5**, **7**, **8** and **9**.

Müliken's charge analysis suggests that for a charge driven reactivity the preferred double bond to form photocyclodimers is C(3)–C(8), since it exhibits opposite charges signs and the largest charge difference between the atoms. In the second place would be C(6)–C(7)

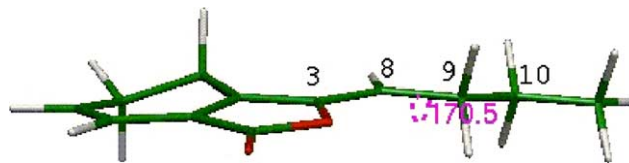


Figure 2. The most stable conformation of *Z*-ligustilide (**1**) in the triplet state.¹⁵



Figure 3. The most stable conformation of *Z*-ligustilide (**1**) in the ground state.¹⁵

Table 1. Total energies and atom charge for **1**

Atom	Charge	
	Ground state	Excited state
3	0.03	0.05
8	−0.19	−0.20
3a	−0.10	−0.15
7a	−0.13	−0.15
6	−0.26	−0.22
7	−0.15	−0.10

Energy for ground state = −0.0672 a.u. Energy for excited state = −0.0470 a.u.

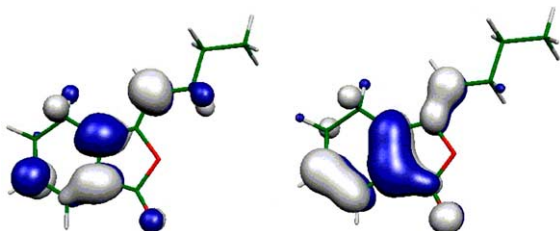
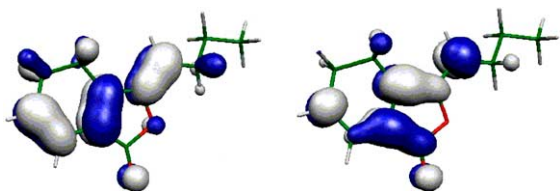
double bond, and C(3a)–C(7a) double bond would be the less reactive to form photocyclodimers.

The regiochemistry involved in the formation of the photocyclodimers **5**, **7**, **8** and **9** may be explained through the analysis of coefficients and energies of the FMOs of the interacting monomers of *Z*-ligustilide (**1**). The considered MOs are higher (HSOMO) and lower (LSOMO) singly occupied MO for the triplet (Fig. 4), and the HOMO and LUMO for the ground state (Fig. 5). The MO energies and coefficients are given in Table 2.

The expected preference in bond formation for the photocyclodimers may be estimated from these MO properties, and it resides in the magnitude of the two-centre MO interaction factor *Sr* in Eq. 1 in $\gamma^2/\text{a.u.}$ units (γ is a resonance integral).^{17,18}

$$\begin{aligned} Sr &= (C_i^* C_j)^2 / \Delta E (\text{HSOMO} - \text{LUMO}) \\ &\quad + (C_i^* C_j)^2 / \Delta E (\text{LSOMO} - \text{HOMO}) \\ &= Sr1 + Sr2 \end{aligned} \quad (1)$$

where C_i^* is the reaction point coefficient for HSOMO or LSOMO of photoexcited **1**, and C_j is the reaction point coefficient for HOMO or LUMO of **1** in the ground-state.

**Figure 4.** HSOMO and LSOMO of *Z*-ligustilide (**1**).¹⁵**Figure 5.** HOMO and LUMO of *Z*-ligustilide (**1**).¹⁵**Table 2.** FMOs' coefficients for excited and ground states of **1**

Atom	Coefficients			
	HSOMO	LSOMO	LUMO	HOMO
3	0.14	0.62	0.22	0.30
8	0.50	0.23	−0.47	0.39
3a	−0.19	0.24	0.59	−0.37
7a	−0.38	−0.07	−0.48	−0.41
6	0.58	−0.08	0.36	0.41
7	−0.12	−0.26	−0.14	0.31

Energy for HSOMO = −0.3092 a.u. Energy for LSOMO = −0.3604 a.u. Energy for LUMO = −0.0408 a.u. Energy for HOMO = −0.3272 a.u.

Table 3. Frontier molecular orbitals interaction factors

Compound	Formed bond	Sr1	Sr2	Sr
7	C(3)–C(8')	0.016	1.761	1.777
7	C(8)–C(3')	0.045	0.143	0.188
5	C(3)–C(7')	0.001	1.113	1.114
5	C(8)–C(6')	0.121	0.268	0.389
8, 9	C(7a)–C(3'a)	0.187	0.020	0.207
8, 9	C(3a)–C(7'a)	0.031	0.292	0.323

The calculated *Sr*1 and *Sr*2 values using data in Table 2 are given in Table 3.

From the values reported in Table 3, it may be noticed that the largest value for *Sr* is for photocyclodimer **7**, suggesting a preference in the formation of this compound; in the second place the natural product riligustilide (**5**), and finally, by the isomers **8** and **9**. These observations are in agreement with the Mülliken's charge analysis (Table 1).

This theoretical analysis supports the experimental result that the major yield is obtained for photocyclodimer **7**.¹¹

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10. Z-Ligustilide (**1**) was isolated from the acetonic extract of the roots of *Ligusticum porteri* by successive column chromatographies eluted with *n*-hexane. **1**: Yellow oil. UV (MeOH) λ_{\max} nm (ϵ): 205.5 (11150.5), 272 (7887.9), 321.0 (6582.8). IR (CHCl₃) ν_{\max} cm⁻¹: 2963, 2935, 2874, 1756, 1668, 1462, 1274, 1056, 1015, 968. ¹H NMR (500 MHz, CDCl₃; assignments by COSY and HETCOR) δ : 6.29 (1H, dt, J = 4.5, 9.5 Hz, H-7), 6.01 (1H, dt, J = 4.5, 10.0 Hz, H-6), 5.22 (1H, t, J = 8.0 Hz, H-8), 2.60 (1H, td, J = 1.0, 10.0 Hz, H-4), 2.60 (2H, m, H-4), 2.47 (2H, m, H-5), 2.39 (2H, m, H-9), 1.51 (2H, m, H-10), 0.96 (3H, t, J = 7.5 Hz, H-11). ¹³C NMR (125 MHz, CDCl₃; assignments by DEPT and HETCOR) δ : 167.6 (C-1), 148.6 (C-3), 147.0 (C-3a), 129.8 (C-6), 124.0 (C-7a), 117.1 (C-7), 112.8 (C-8), 28.1 (C-9), 22.4 (C-5), 22.4 (C-10), 18.5 (C-4), 13.7 (C-11). EIMS m/z (rel. int.): 190 [M⁺], 162 (17), 161 (100), 148 (96), 134 (17), 133 (16), 120 (12), 106 (32), 105 (31), 78 (16), 77 (16), 55 (37).
11. Photochemical irradiation of Z-ligustilide (**1**). A solution of **1** (155 mg) in acetone (15 mL) was deoxygenated by bubbling nitrogen for 1 h. The mixture was irradiated with a low-pressure mercury lamp surrounded by a quartz water jacket under a nitrogen stream for 3 h. After irradiation, the solvent was removed under reduced pressure. The last procedure was performed sixteen times to obtain the crude product (2.52 g) which was purified by successive column chromatographies (*n*-hexane/ethyl acetate gradient) to afford photocyclodimers: riligustilide (**5**, 141.0 mg, 7.0%), *endo*-Z,Z'-(3.8',8.3')-diligustilide (**7**, 716.5 mg, 18.5%), *endo*-Z,Z'-(3a.7a',7a.3a')-diligustilide (**8**, 214.5 mg, 11.0%) and *exo*-Z,Z'-(3a.7a',7a.3a')-diligustilide (**9**, 149.0 mg, 7.5%), besides recovering starting material and a minor complex mixture of unidentifiable compounds. Compound **7**: white solid, mp: 124–125 °C, R_f : 0.30 (*n*-hexane/EtOAc 96:4, 4 times). UV (MeOH) λ_{\max} nm (ϵ): 205.5 (23714), 288.5 (8551). IR (CHCl₃) ν_{\max} cm⁻¹: 2962, 2934, 1776, 1645, 1277, 1063, 1014, 959. ¹H NMR (300 MHz, CDCl₃; assignments by COSY and HETCOR) δ : 6.14 (1H, ddd, J = 9.9, 1.9, 1.9 Hz, H-7), 5.96 (1H, ddd, J = 9.9, 4.3, 4.3 Hz, H-6), 2.78 (1H, m, H-8), 2.60 (2H, m, H-4), 2.38 (2H, m, H-5), 1.57 (2H, m, H-9), 1.13 (2H, m, H-10), 0.87 (3H, t, J = 7.5 Hz, H-11). ¹³C NMR (75 MHz, CDCl₃; assignments by DEPT and HETCOR) δ : 169.3 (C-1), 158.3 (C-3a), 130.4 (C-6), 126.1 (C-7a), 116.6 (C-7), 93.5 (C-3), 45.5 (C-8), 30.7 (C-9), 22.5 (C-5), 21.7 (C-4), 20.6 (C-10), 14.1 (C-11). EIMS m/z (rel. int.): 380 [M⁺] (4), 379 (1), 378 (2), 294 (1), 264 (3), 245 (1), 210 (1), 192 (13), 191 (95), 190 (35), 189 (26), 188 (43), 162 (14), 161 (46), 159 (40), 149 (11), 148 (100), 146 (18), 135 (8), 120 (6), 106 (10), 105 (14), 103 (6), 78 (7), 77 (8), 55 (10). Compound **8**: white solid, mp: 89–91 °C, R_f : 0.36 (*n*-hexane/EtOAc 96:4, 3 times). UV (MeOH) λ_{\max} nm (ϵ): 206 (3388). IR (CHCl₃) ν_{\max} cm⁻¹: 2961, 2935, 2871, 1786, 1702, 1164, 1100, 1040, 1016. ¹H NMR (500 MHz, CDCl₃; assignments by COSY, HMQC and NOESY) δ : 6.20 (1H, ddd, J = 10.0, 6.5, 2.2 Hz, H-6), 5.80 (1H, ddd, J = 10.1, 1.5, 0.8 Hz, H-7), 4.85 (1H, t, J = 7.5 Hz, H-8), 2.21 (1H, ddd, J = 7.5 Hz, H-9a), 2.13 (1H, m, H-5a), 2.13 (1H, ddd, J = 7.5 Hz, H-9b), 1.91 (2H, m, H-4a, H-5b), 1.85 (1H, m, H-4b), 1.42 (2H, sextuple, J = 7.5 Hz, H-10), 0.96 (3H, t, J = 7.5 Hz, H-11). ¹³C NMR (125 MHz, CDCl₃; assignments by DEPT and HMQC) δ : 172.7 (C-1), 148.8 (C-3), 134.1 (C-6), 120.8 (C-7), 107.8 (C-8), 51.6 (C-3a), 50.4 (C-7a), 27.4 (C-9), 24.5 (C-5), 22.5 (C-10), 20.7 (C-4), 13.7 (C-11). EIMS m/z (rel. int.): 380 [M⁺] (1), 351 (1), 256 (2), 192 (10), 191 (70), 190 (100), 161 (39), 149 (10), 148 (79), 134 (9), 133 (7), 120 (6), 116 (5), 105 (13), 104 (10), 91 (6), 81 (7), 77 (7), 55 (20), 41 (6), 39 (2). Anal. Calcd for C₂₄H₂₈O₄: C, 75.78; H, 7.36; O, 16.84. Found: C, 75.53; H, 7.59; O, 16.88. Compound **9**: white solid, mp: 89–91 °C, R_f : 0.72 (*n*-hexane/EtOAc 96:4, 3 times). UV (MeOH) λ_{\max} nm (ϵ): 205 (30210). IR (CHCl₃) ν_{\max} cm⁻¹: 2961, 2934, 2874, 1780, 1699, 1450, 1348, 1333, 1102, 1043, 1028, 1005, 883. ¹H NMR (300 MHz, CDCl₃; assignments by COSY, HETCOR and NOESY) δ : 6.12 (1H, m, H-6), 5.82 (1H, dt, J = 9.9, 1.8, 1.8 Hz, H-7), 4.79 (1H, t, J = 7.5 Hz, H-8), 2.21 (1H, quintuple, J = 7.5 Hz, H-9a), 2.13 (2H, m, H-5), 2.09 (1H, quintuple, J = 7.5 Hz, H-9b), 1.88 (2H, m, H-4), 1.40 (2H, sextuple, J = 7.5 Hz, H-10), 0.90 (3H, t, J = 7.5 Hz, H-11). ¹³C NMR (75 MHz, CDCl₃; assignments by DEPT and HETCOR) δ : 173.7 (C-1), 150.2 (C-3), 132.2 (C-6), 121.7 (C-7), 108.4 (C-8), 49.7 (C-3a), 49.4 (C-7a), 27.4 (C-9), 27.1 (C-4), 22.7 (C-10), 20.9 (C-5), 13.6 (C-11). EIMS m/z (rel. int.): 380 [M⁺] (1), 322 (1), 279 (2), 190 (100), 162 (8), 161 (38), 148 (78), 147 (11), 134 (7), 105 (8), 91 (4), 78 (4), 77 (4), 55 (13), 28 (7).
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