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Diels–Alder adducts derived from the natural phthalide *Z*-ligustilide

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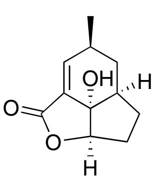
Abstract—*Z*-Ligustilide, a naturally occurring phthalide isolated from *Ligusticum porteri*, underwent Diels–Alder reactions with different dienophiles yielding novel tricyclic products with potentially interesting biological properties. Where selectivity was possible, the reactions performed showed regio- and stereoselectivity. The experimental results with ethyl acrylate were compared with the selectivity predicted by ab initio calculations.

The tricyclic fungal metabolite (−)-galiellalactone (**1**), produced by the ascomycete *Galiella rufa* via an enzyme-catalysed intramolecular Diels–Alder reaction, has been shown to be a selective and potent inhibitor of interleukin-6 (IL-6) signaling in HepG2 cells. Galiellalactone acts by inhibiting the dimer of STAT3 (Signal Transducer and Activator of Transcription), a protein which acts as a molecular switch that activates the gene expression initiated by IL-6 signaling.[1] STAT3 has recently been identified as an ideal target for cancer therapy,[2] and there is consequently an interest in the biological evaluation of its inhibitors. In search of new analogues that are structurally similar to galiellalactone we were inspired by the plant metabolites diligustilide (**2**), and tokinolide B (**3**). Both **2** and **3** are dimers of phthalide *Z*-ligustilide (**4**), a hexaketide present in large amounts in the roots of *Ligusticum porteri*.[3] They can be considered to be derived from cycloadditions of the monomer acting as both diene and dienophile. The dimers are also natural products that have been isolated from the same source, but can be prepared synthetically from the monomer.[4]



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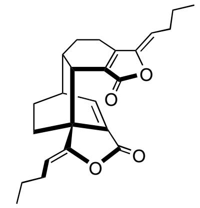

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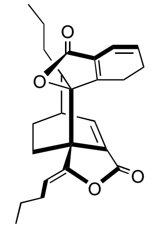

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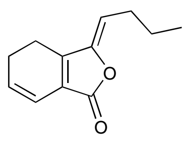

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Diels–Alder reactions with *Z*-ligustilide (**4**) as the diene and different dienophiles could result in products structurally similar to galiellalactone (**1**). If the dienophile has a nucleophilic center in the allylic position, a subsequent or preceding addition to the exocyclic double bond by the dienophile could give products with a similar ring system.

Z-Ligustilide has been reported to react with maleic anhydride to give the corresponding Diels–Alder adduct,[5] and in our hands the reaction yielded the expected 3:1 *endo*/*exo* isomeric mixture in 78% yield with *endo* isomer **5a** as the major and *exo* isomer **5b** as the minor products (see Scheme 1, entry 1). Reactions with the unsymmetric dienophile ethyl acrylate (entry 2) showed both regio- and stereoselectivity, and all four isomers were obtained in a 100:19:4.9:1.9, **6a**:**6b**:**6c**:**6c**,

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Keywords: *Z*-Ligustilide; Galiellalactone; STAT3; Diels–Alder; Ab initio.

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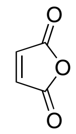
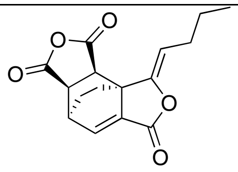
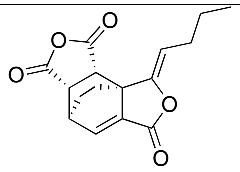
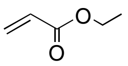
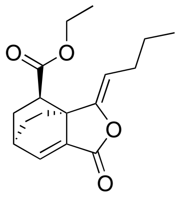
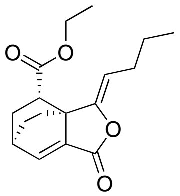
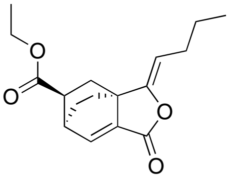
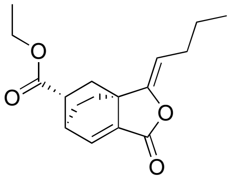
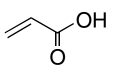
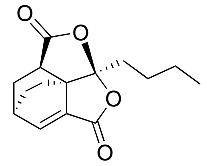
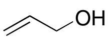
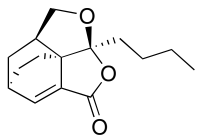
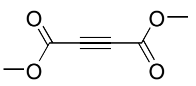
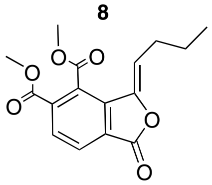
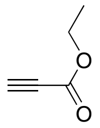
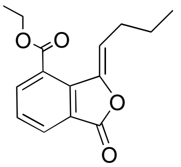
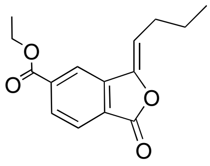
relationship (see Scheme 1, entry 2). In order to understand the stereochemical outcome of the reaction, ab initio transition state calculations (Table 1) were performed.[6]

The theoretical results suggest the ratios between the different *endo*/*exo* products **6a**/**6b** and **6c**/**6d** to be 4.4 and 1.7, respectively, which are satisfyingly close to the ratios of isolated products (5.3 and 2.6). Regarding

Entry	Dienophile	Conditions[a]/ Isolated yield	Main product	Side products
1		Sealed tube, 4 days/ 59% (**5a**) and 19% (**5b**)	 **5a**	 **5b**
2		Sealed tube, 3 days/ 57% (**6a**) and 15% (mixture of **6b**, **6c** and **6d** in a 10:2.5:1 relationship)	 **6a**	 **6b**  **6c**  **6d**
3		Sealed tube, 3 days/ 39% (**7**)	 **7**	
4		*p*-TsOH, sealed tube, 2 days/ 51% (**8**)	 **8**	
5		Reflux, 2 days/ 57% (**9**)	 **9**	
6		Sealed tube, 3 days/ 65% (**10a**) and 3%(**10b**)	 **10a**	 **10 b**

Scheme 1. Diels–Alder reactions performed using *Z*-ligustilide (**4**) as the diene. (a) All reactions, except entry 4 which was performed in allyl alcohol with *p*-TsOH, were performed in toluene. Reactions in a sealed tube were heated at 145 °C.

Table 1. Total and relative energies of transition states for the Diels–Alder reaction between ethyl acrylate and *Z*-ligustilide

Transition state	HF/6-31G* (Hartrees) in gasphase	HF/6-31G* (Hartrees) in benzene	$\Delta\Delta E$ (kcal/mol) in benzene
6a	−955.933572	−955.957543	0
6b	−955.933494	−955.955599	1.22
6c	−955.931733	−955.954313	2.03
6d	−955.931610	−955.953599	2.47

the regioselectivity, the theoretical ratios between regio products **6a**/**6c** and **6b**/**6d** is 11.5 and 4.5, respectively, compared to the observed ratios 20 and 10. As the desired isomer for our purposes, **6a**, was found to be the major product, we now turned our focus toward dienophiles that could also attack the exocyclic double bond of **4**. The reaction with acrylic acid gave the product derived from a Diels–Alder reaction and an addition, following Markovnikov's rule, of the carboxylic acid to the exocyclic double bond, although it was not possible to establish the order of events, yielding **7** as the only isolable product (Scheme 1, entry 3). Lactone **7** contains a similar three-ring system to that present in galiellalactone (**1**). The reaction with allyl alcohol, which required acid (*p*-TsOH) to proceed, gave the corresponding product **8**. Optimization of the reaction conditions by varying the amount of *p*-TsOH showed that the best yield was obtained by using one equivalent of acid. The reaction also showed that an inverse electron-demand Diels–Alder reaction with *Z*-ligustilide was possible. However, attempts to carry out the corresponding reaction with 3-buten-1-ol were unsuccessful, at 145 °C as well as at 190 °C. The structure of **8** was confirmed by X-ray analysis[7] (Fig. 1), and **8** displays an overall 'dragonfly' conformation. The cyclohexane and cyclohexene rings adopt a boat conformation while the tetrahydrofuran ring assumes a twisted conformation with a pseudo two-fold axis passing between the C6 and C9 carbon bonds. The gamma lactone ring is essentially planar within experimental error. The butyl side chain adopts a fully extended conformation. The enantiomer illustrated in Figure 1 was not determined by the X-ray experiment but selected arbitrarily, the relative configuration of the chiral centers are 4*R*,9*R*,10*S*,11*R*.

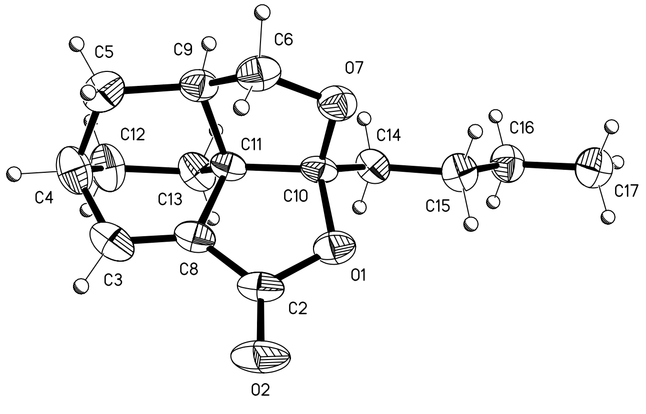


Figure 1. ORTEP-like view of compound **8**. Thermal ellipsoids at 30% probability level.

Diels–Alder reactions were also performed with the alkynes dimethyl acetylenedicarboxylate, entry 5, and ethyl propiolate, entry 6, and the latter showed the same regioselectivity as the reactions discussed above. The reaction with propargyl alcohol did not yield any isolable product. The aromatic products **9**, **10a**, and **10b** are derived from a Diels–Alder reaction followed by a retro-Diels–Alder reaction with ethene as the leaving group. Attempts were made to isolate the intermediate in the reaction leading to **9**, by decreasing the reaction temperature.[8] An NMR spectrum of the crude reaction mixture after 24 h at 70 °C showed a characteristic doublet from the unsaturated β-proton (7.37 ppm), but the intermediate could not be isolated. The reaction did not proceed well even at lower temperatures.

In conclusion, *Z*-ligustilide (**4**) was shown to react in Diels–Alder cycloadditions with electron-poor dienophiles in moderate to good yields. Transition state calculations predicted the regio- and stereoselectivity in the reaction between **4** and ethyl acrylate to an acceptable extent. Inverse electron–demand Diels–Alder reactions failed with 3-buten-1-ol and propargyl alcohol as dienophiles, but yielded the single isomer **8** with allyl alcohol. The tetracyclic products **7** and **8** will be assayed for inhibitory effects on STAT3.

Acknowledgments

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Supplementary data

Electronic supplementary data: experimental procedures, characterization of compounds and computational method included in the present study. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.059.

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7. X-Ray analysis data of compound **8**. All data were collected on a Siemens P4/PC diffractometer with graphite monochromated MoKα radiation ($\lambda = 0.71073$ Å) using the θ–2θ scan technique at 293(2) K. The structure was solved and refined using SHELXTL.[9] Molecular formula $C_{15}H_{20}O_3$; orthorhombic space group $P2_12_12_1$, $a = 7.4756(9)$ Å, $b = 12.248(2)$ Å, $c = 14.354(2)$ Å, $V = 1314.3(3)$ Å^3, $Z = 4$, dc = 1.255 Mg/m^3, θ range for data collection 2.19–24.99°. The structure solution is based on 2304 reflections, which converged to $R = 0.0472$. Refinement method: full-matrix least squares on F^2, goodness of fit = 1.062. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 277093. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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