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Elucidation of the Reactional Mechanisms Using the Indices of Fukui

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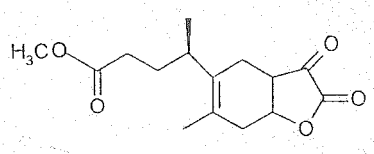
The cycloadditions of Diels-Alder are often used during the synthesis of natural substances. They allow, as private individuals, the formation (by bimolecular or intramolecular reaction) of a cycle with six atoms in a regioselective manner, while authorizing the presence of many functional groups. The recourse to molecular modelling for the elucidation of the reactional mechanisms using the indices of Fukui will contribute to the prediction of the reactional sites.

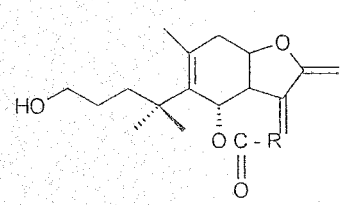
Key Words: Indices of Fukui, DFT, Diels-Alder.

INTRODUCTION

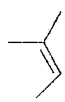
The lactonic cycle corresponds to a structural part very frequently met in the natural products, in particular in sesquiterpenes which have, for some of them, a multiple biological activity[1–6] . One can quote as examples: ivanguline (**1**) and eriolanine (**2**).



Ivanguiline 1



Eriolanine 3 R=



Eriolanine 4 R=

The complexity of these polyfunctional molecules encouraged organic chemists in the search for new ways of synthesis. By examining the reactional sequences which were carried out in the literature to lead to compounds of this type, one sees that, in the majority of the cases, the formation of the lactonic cycle intervenes at the end of the synthesis. It is so, for example, for the two syntheses of eriolanine: one due to Grieco *et al.*[7] and the other due to Robert *et al.*[8]

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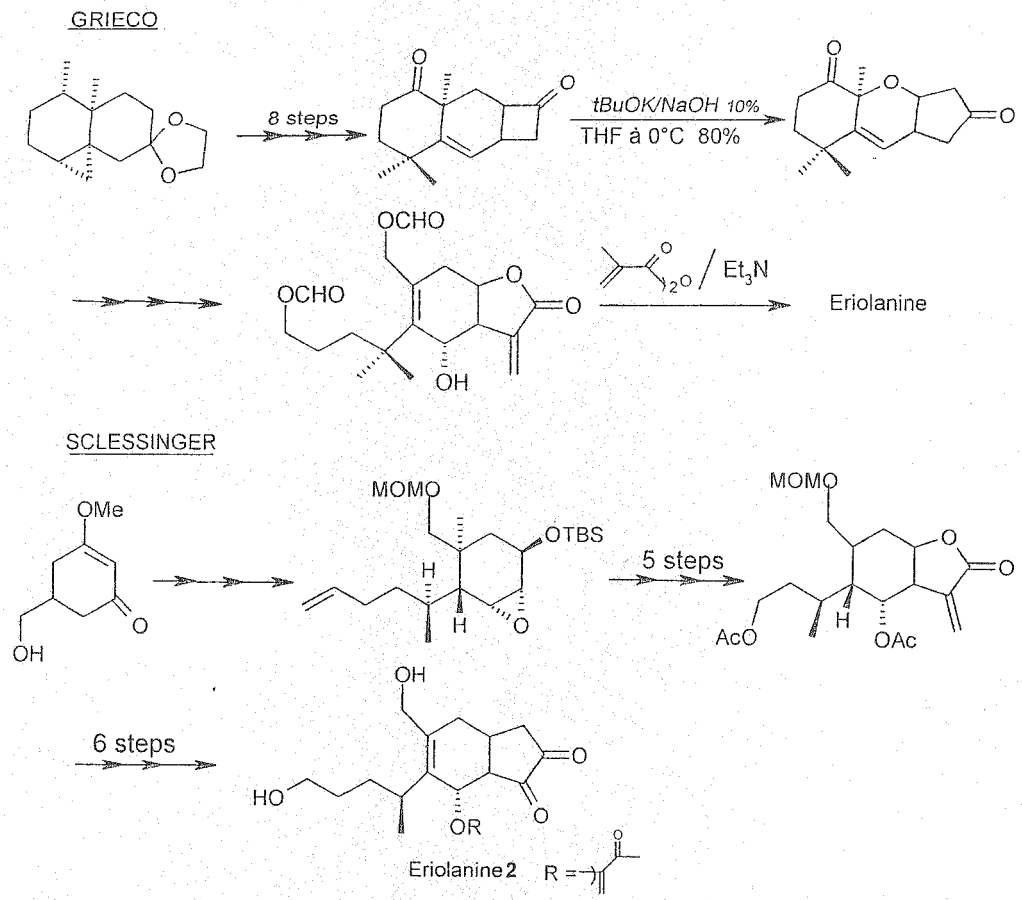
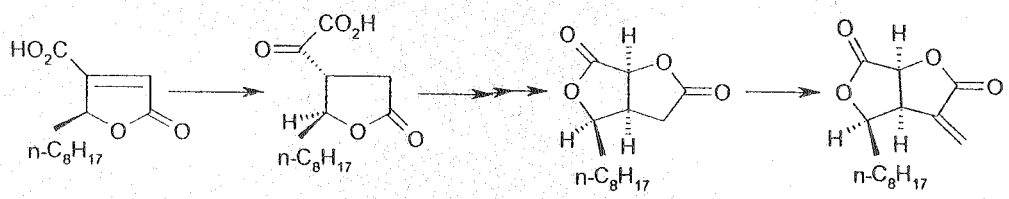
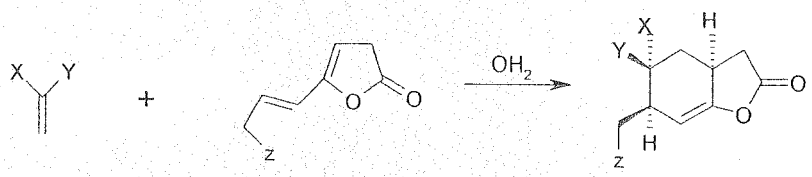


With the aim of leading to other methods of acquisition of these compounds, our attempt was the lactonic synthesis like starting product. This constitutes a relatively particular approach, although some work using this strategy in the synthesis of similar natural products, such as the work of Yamada[9] on avenaciolide, has been done.



Concerning our work, the application of the reaction of Diels-Alder between a lactonic diene (standard B) and a dienophile (standard A) (sufficiently reactive) gives the product (C).



X = ArSO, Y = CO_2Et ou COR Z = H ou OTHP

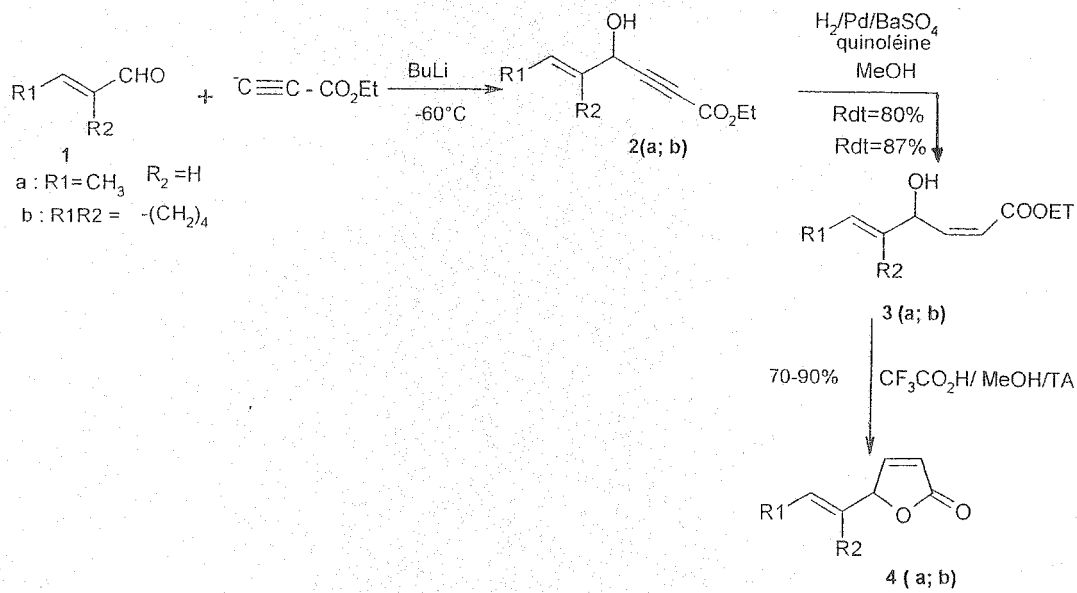
Type A **Type B**

One will note in particular the soft conditions of this reaction, his excellent output, his speed and his stereoselectivity. The formed adduit crystallizes directly in the reactional medium and can thus be insulated easily by a simple reaction.

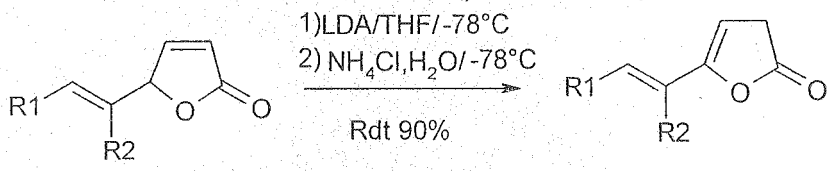
EXPERIMENTAL

IR Spectroscopy, RMN-H and elementary analysis spectra RMN-H were recorded on Varian EM 390 and Bruker 300, with the samples in solution in deuterated chloroform. The absorption spectra in the infrared were recorded by means of a spectrophotometer Nicolet 5DX.

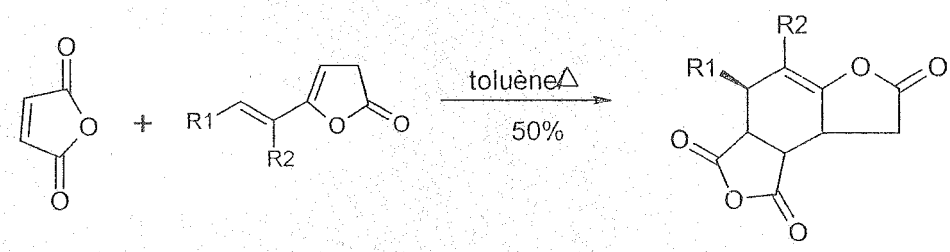
Synthesis of (prop-1-ene) 5-yl(5H) dihydrofuran-2-one **(4a):**



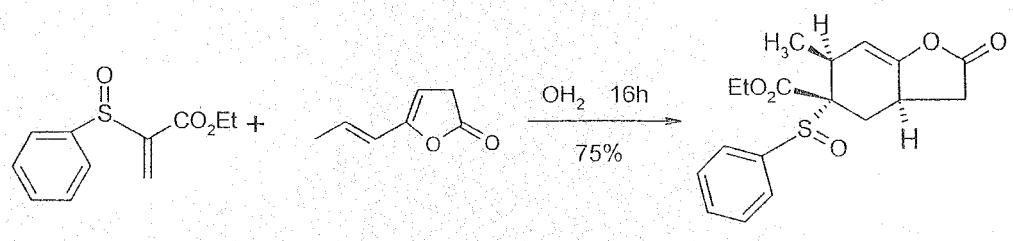
Isomerization of lactone **4a, b** in lactone **5a, b**



4(a; b) **5(a; b)**



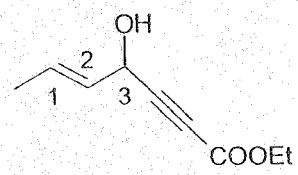
5(a; b) **6(a; b)**



5(a) **7(a)**

4-Hydroxy hept-5-ene-2-yne-oate of ethyl (2a)

The assembly comprising a tricol of 250 mL provided with a thermometer at low temperature, of a nitrogen entry, a guard of $CaCl_2$ and a septum is dried by nitrogen sweeping. One places, using a syringe, 6.9 mL of diisopropylamine (50 mmol) in coldly distilled THF (100 mL). The unit is cooled at –50°C; then are added 31 mL (52 mmol) of a solution of 1.6 M of *n*-BuLi in hexane. After 10 min, one cools at 78°C and adds 4.9 g (50 mmol) ethyl propiolate followed, 30 min after, by 3.5 g (50 mmol) of crotonaldehyde. After 3 h of agitation, the solution hydrolyzes with 60 mL of a solution saturated with NH_4Cl. After decantation, the aqueous phase is washed with ether (3 × 60 mL). The organic phases are filtered, washed with a solution saturated with NaCl (3 × 50 mL), dried on $MgSO_4$ and evaporated. Yield: 6.7 g (80%) the acetylenic one **(3a)**.

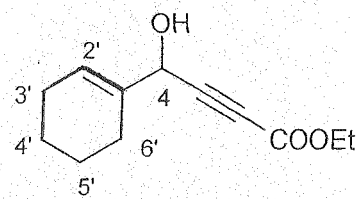


2a

RMN ($CDCl_3$) (δ ppm): 1.30 (3H, t, J = 7.5 Hz) CH_3 ester, 1.76 (3H, d, J = 5 Hz) CH_3—C═CH_2, 2.80 (1H, s, large) OH, 4.30 (2H, q, J = 7.5 Hz) CH_2 ester, 5.01 (1H, d, J = 6 Hz) H_3, 5.60–6.20 (2H, m) H_1 and H_2. IR (KBr, cm^{-1}): 3420 ν(OH), 2250 ν(C═C) and 1718 ν(C═O).

1-Cyclohexene-4-yl-4-hydroxybut-2-yne-oate of ethyl (2b)

According to the procedure below, starting from 8.83 g (80.3 mmol) of cyclohexene carboxaladehyde, 14.5 g (69.7 mmol) of the acetylenic one **(2b)** is obtained (Rdt: 87%)



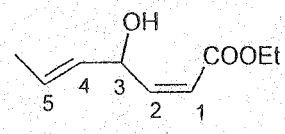
2b

RMN ($CDCl_3$) (δ ppm): 1.30 (3H, t, J = 7.5 Hz) CH_3 ester, 1.5 to 1.90 (4H, massif) CH_2 (4′,5′), 2.00 to 2.40 (4H, massif) CH_2 (3′,6′), 3.50 (1H, s large) OH, 4.30 (2H, q, J = 7.5 Hz) CH_2 ester, 4.93 (1H, s large) H(4), 6.02 (1H, s large) H(2). IR (KBr, cm^{-1}): 3400 ν(OH), 2232 ν(C═C) and 1713 ν(C═O).

4-Hydroxy-hepta-2,5-dienoate of ethyl (3a)

In an erlen of 500 mL ground, Pd 750 mg/$BaSO_4$ with 20% in 150 mL of MeOH is placed, then agitated during 10 min under normal hydrogen pressure. Then added 2 mL quinoline followed by 5 g (30 mmol) of acetylenique (à) and one agitates until absorption of 635 mL hydrogen (28.5 mmol). The catalyst is filtered, washed several times with ether and the filtrate is washed with (3 × 60

mL) of a solution of HCl (1 N), then with water (3 × 60 mL). The aqueous phase is dried on $MgSO_4$, then evaporated. 4.3 g diene (87%) **(3a)** is obtained.

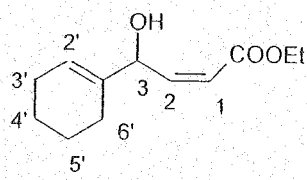


3a

RMN ($CDCl_3$) (δ ppm): 1.30 (3H, t, J = 7.5 Hz) CH_3 ester, 1.76 (3H, d, J = 5 Hz) CH_3—C═CH_2, 2.80 (1H, s large) OH, 4.30 (2H, q, J = 7.5 Hz) CH_2 ester, 5.01 (1H, d, J = 6 Hz) H_3, 5.60 to 6.20 (2H, m) H_1 and H_2. IR (KBr, cm^{-1}): 3420 ν(OH), 2250 ν(C═C) and 1718 ν(C═O).

1-Cyclohexene-4-yl-4-hydroxybut-2-yn-oate of ethyl (3b)

According to the procedure below, using 14.5 (69.7 mmol) of acetylene **(2b)**, 12.5 g diene (86%) **(3b)** is obtained.

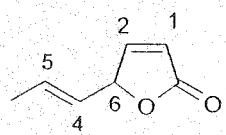


3b

RMN ($CDCl_3$) (δ ppm): 1.33 (3H, t, J = 7.5 Hz) CH_3 ester, 1.52 to 1.86 (4H, massif) CH_2 (4′,5′), 2.04 to 2.40 (4H, massif) CH_2 (3′,6′), 3.50 (1H, s large) OH, 4.35 (2H, q, J = 7.5 Hz) CH_2 ester, 5.20 to 6.00 (4H, m), H(1), H(1), 6.38 (1H, m) H(2). IR (KBr, cm^{-1}): 3420 ν(OH) and 1718 ν(C═O).

Prop-1-ene-5-yl(5H) dihydrofuran-2-one (4a)

6 g (35 mmol) of hydroxy ester **(3d)** and 500 mg of *p*-TsOH in 120 mL of toluene is carried to backward flow during 2 h. The mixture is diluted in 100 mL ether, then washed with a solution of $NaHCO_3$ (3 × 30 mL) and a solution saturated with NaCl (3 × 30 mL). The organic phase is dried on $MgSO_4$, then the ether is evaporated. 2.85 g (65%) lactone **(4a)** is obtained.

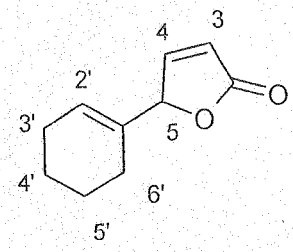


4a

RMN ($CDCl_3$) (δ ppm): 1.75 (3H, d, J = 7 Hz) CH_3, 5.40 (1H, m) H_4, 5.50 (1H, S) H_6, 5.95 (1H, q, J = 7 Hz) H_5, 6.20 (1H, d, J_{12} = 6 Hz) H_1, 7.60 (1H, d, J_{21} = 6 Hz) H_2. IR (KBr, cm^{-1}): 1758 ν(C═O) and 1604 ν(C═C).

Cyclohex-1-ene-5-yl(5H) furan-2-one (4b)

Starting from 10.40 g (50 mrnol) from **(3b)** 6.97 g (42.5 mmol) (85%) lactone **(4b)** is obtained.

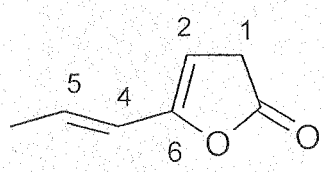


4b

RMN ($CDCl_3$) (δ ppm): 1.63 (4H, m) CH_2 (3′,6′), 1.73 to 2.23 (4H, massif) CH_2 (4′,5′), 5.43 (1H, s) H tertaire, 5.97 (1H, m) H (2′), 6.22 (1H, dd, J_{34} = 6 Hz, J_{35} = 1.5 Hz) H(3), 7.52 (1H, dd, J_{34} = 6 Hz, J_{45} = 1.5 Hz) H(4). IR (KBr, cm^{-1}): 1757 ν(C═O) and 1600 ν(C═C)

Prop-1-ene-5-yl (3H) clihydrofuran-2-one (5a)

The assembly comprising a tricol, a thermometer at low temperature, a nitrogen entry and an agitator, is dried with the flame, then 2.7 mL (20 mmol) of diisopropylamine are added in 50 mL of THF coldly distilled, followed by 12.4 mL of a solution (1.6 M) of *n*-BuLi in hexane to –50°C. After 15 min, 2.5 g (20 mmol) lactone **(4a)** is added to –78°C. After 2 h of agitation at this temperature, reaction is completed by protonation with 2 mL of acetic acid and 60 mL of a solution saturated with NH_4Cl. The mixture is elutriated and the aqueous phase extracted with ether (3 × 50 mL). The organic phase is washed with a solution saturated with NaCl (3 × 40 mL), then dried on $MgSO_4$. The solvents are eliminated under PR and the residue is chromatographed on 60 g of silica (eluant: cyclohexane/AcOEt 95/5). 1.55 g (62%) of lactone **(5a)** is obtained.

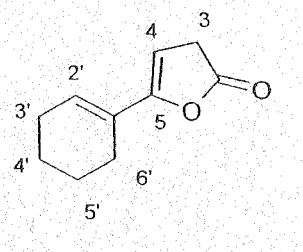


5a

RMN ($CDC1_3$) (δ ppm): 1.85 (3H, d, J = 7 Hz) CH_3, 3.31 (2H, m) H_1, 5.33 (1H, m) H_2, 5.80 to 6.50 (2H, m) H_3, H_4. IR (KBr, cm^{-1}): 1802 ν(C═O) and 1611 ν(C═C).

Cyclohex-1-ene-yl (3H) furan-2-one (5b)

Starting from 5.45 g (3.2 mmol) of lactone **(4b)**, 5.75 g lactone **(5b)** is obtained which is chromatographed on 100 g of SiO_2 (eluant: cyclohexane/AcOEt 9/1) to give 3.17 g (58%) (19.3 mmol) of white crystals, m.p. = 76–78°C.

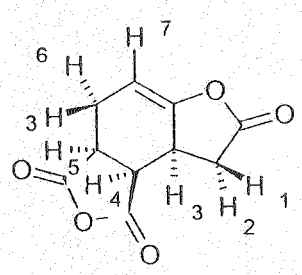


5b

RMN ($CDCl_3$) (δ ppm): 1.46 to 1.87 (4H) CH_2 (4′,5′), 1.93 to 2.32 (4H) CH_2 (3′,6′), 3.30 (2H, s) CH_2 (3), 5.27 (1H, t, J = 1.5 Hz) H(4), 6.33 (1H, s) H(2). IR (KBr, cm^{-1}): 1800 ν(C=O), 1657 ν(C=C) and 1613 ν(C=C). m.f. $C_{10}H_{12}O_2$ Calcd.: 164.0837, Tr.: 164.0843, M^+ = 164 (100).

Anhydride of the acid 6-methyl 2-oxo-a,4,5,6-tetrahydro(3H)benzofuran-2-one-4,5-dicarboxylic (6b)

In a balloon of 50 mL are placed dienic lactone 5 mmol and 5 mmol of maleic anhydride in 5 mL of water. The mixture is agitated for one night. The solid product which forms is filtered, washed several times at ether then dried with a desiccator.



6a

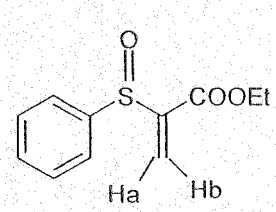
RMN ($CDCl_3$) (δ ppm):

δ (ppm)	H_1	H_2	H_3	H_4	H_5	H_6
6a	3.04	3.21	3.28	3.85	3.46	2.69
J (Hz)	1–2	1–3	2–3	3–4	4–5	5–6
6a	18.9	6.1	11.6	6.7	8.5	7.3

IR (KBr, cm^{-1}): 1825 ν(CO anhydride), 1775 ν(CO lactone) and 1690 ν(C=C). Analysis (%) Calcd. (Found) for $C_{11}H_{10}O_5$: C, 59.57 (59.46); H, 4.53 (4.26); O, 36.00 (36.01).

Phenylsulfunyl acrylate of ethyl (8)

2-Phenylthio acrylate of ethyl (25.6 g, 125 mmol) is cooled with –78°C in 250 mL of CH_2Cl_2, then added to 25.6 g (125 mmol) of 85% *m*-chloroperbenzoic acid, in 250 mL of CH_2Cl_2. The solution is agitated for 2 h at this temperature, then washed after return to room temperature with 4 × 100 mL of a solution saturated with $NaHCO_3$ and 3 × 50 mL with a solution saturated with NaCl and dried on $MgSO_4$. After elimination of vacuum solvent, 26.2 g (95%) of gross product is obtained that one chromatographs on silica 300 g (eluant: cyclohexane/AcOEt 9/1); one thus obtains 21.1 g (77%) of compound **(8).**

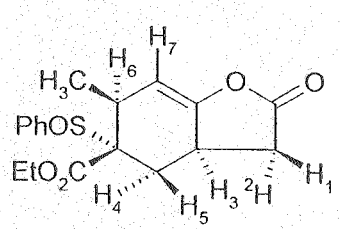


8

RMN ($CDCl_3$) (δ ppm): 1.13 (3H, t, J = 7.5 Hz) CH_3 ester, 0.46 (2H, q, J = 7.5 Hz) CH_2 ester, 6.83, 6.90 (1H, s) and (1H, s) Ha and Hb, 7.5 (3H) and 7.8 (2H) H aromatic. IR (KBr, cm^{-1}): 1713 ν(C=O), 1620 ν(C=C), 1584 ν(C=C arom.) and 1051 ν(S=O).

5-Ethoxycarbonyl-6-methyl-5-phenylsulfunyl-3a,4,5,6-tetrahydro (3H) benzofuran-2-one (7a)

In a round bottom flask of 50 mL, dienic lactone 5 mmol (**5a**) and sulfoxide 5 mmol are placed (**8**) in water 5 mL. The mixture is agitated for one night. The solid product which forms is filtered, then washed several times with ether, then dried in a desiccator (yield = 75%; m.p. = 110–111°C).



7a

H	δ (ppm)	m	J (Hz)
H_1	1.87	dd	$J_{13} = 9.9$
H_2	2.93	dd	$J_{12} = 14.6$
H_3	3.57	m	$J_{23} = 7.3$
H_4	2.44	dd	$J_{53} = 12$
H_5	2.86	dd	$J_{45} = 16.8$
H_6	2.70	m	$J_{43} = 8.6$
H_7	5.23	m	
CH_3	1.13	d	$JCH_{3-6} = 6.4$

IR (KBr, cm^{-1}): 1809 ν(CO lactone) and 1725 ν(CO ester).

Analysis (%) Calcd. (Found) for $C_{18}H_{20}O_5S$: C, 62.04 (61.74); H, 5.97 (5.97); O, 22.96 (22.95); S, 9.21 (9.55).

Theoretical method

The relatively recent works[10–12] showed that indications of Fukui can provide information can help to illuminate certain reactional mechanisms, by the behaviour of atoms in a molecule. In this work we will use these values while defining them before interpreting them.

Function of Fukui (f^+, f^-, f^0):

$f_k^+ = (k(M^-) - k(M)) = (k(N + 1) - k(N))$ for the nucleophilic attack.

$f_k^- = (kM) - k(M^+)) = (k(N) - k(N - 1))$ for the electrophilic attack.

$f_k^0 = [(kM^-) + (kM^+)]/2 = [k(N + 1) - k(N - 1)]/2$ for the radicalar attack.

with: k(M): the electronic load of the k atom in the neutral molecule Mr.

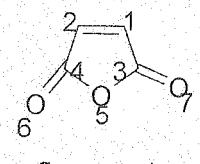
$k(M^+)$: the electronic load of the k atom in the molecule neutral M^+.

$k(M^-)$: the electronic load of the k atom in the molecule neutral M^-.

For an electrophilic attack the site must be negative load, for which f^- is maximum.

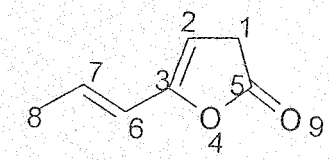
For a nucleophilic attack the site must be positive load, for which f^+ is maximum.

SEMI-EMPIRICAL CALCULATION, METHOD AM1, DFT (established in Gaussian 94)



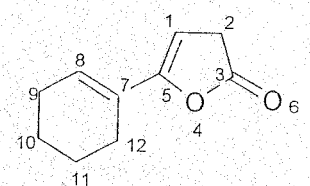
Structure A

	Calculation of the loads			Calculation of the indices of Fukui		
Atoms (k)	$\rho(k^0)$	$\rho(k^+)$	$\rho(k^-)$	f^+	f^-	f^0
C1	–0.161	–0.107	–0.238	–0.077	–0.054	–0.172
C2	–0.167	–0.107	–0.238	–0.077	–0.054	–0.172
C3	0.612	0.682	0.530	–0.081	–0.070	0.606
C4	0.612	0.680	0.530	–0.081	–0.069	0.606
O5	–0.459	–0.371	–0.522	–0.063	–0.088	–0.447
O6	–0.414	–0.185	–0.593	–0.178	–0.229	–0.389
O7	–0.414	–0.185	–0.593	–0.178	–0.229	–0.389



Structure 5A

	Calculation of the loads			Calculation of the indices of Fukui		
Atoms (k)	$\rho(k^0)$	$\rho(k^+)$	$\rho(k^-)$	f^+	f^-	f^0
C1	–0.222	–0.106	–0.300	–0.078	–0.116	–0.203
C2	–0.412	–0.440	–0.368	0.044	0.028	–0.404
C3	0.392	0.456	0.358	0.034	–0.064	0.407
O4	–0.493	–0.442	–0.502	–0.009	–0.051	–0.472
C5	0.614	0.635	0.579	–0.035	–0.021	0.607
C6	–0.168	–0.152	–0.237	–0.069	–0.016	–0.195
C7	–0.103	–0.395	–0.176	0.073	0.292	–0.286
C8	–0.491	–0.522	–0.450	0.041	0.031	–0.486
O9	–0.444	–0.319	–0.547	–0.103	–0.125	–0.433

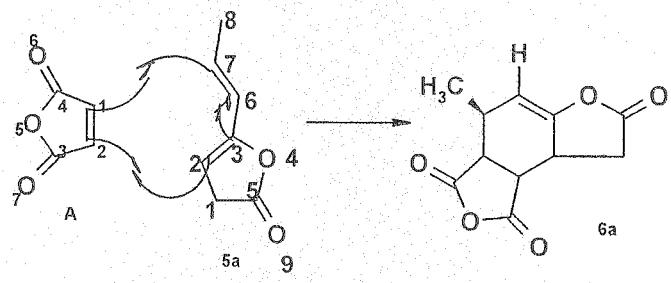


Structure 5B

	Calculation of the loads			Calculation of the indices of Fukui		
Atoms (k)	$\rho(k^0)$	$\rho(k^+)$	$\rho(k^-)$	f^+	f^-	f^0
C1	–0.118	–0.113	–0.240	–0.122	–0.005	–0.176
C2	–0.176	–0.152	–0.249	–0.073	–0.024	–0.200
C3	0.598	0.618	0.516	–0.082	–0.020	0.567
O4	–0.470	–0.445	0.554	0.024	–0.025	0.054
C5	0.003	–0.019	0.084	0.081	0.022	0.033
O6	–0.466	–0.354	–0.354	–0.154	–0.320	0.223
C7	0.205	0.237	0.209	0.004	–0.032	0.223
C8	–0.186	–0.040	–0.211	–0.025	–0.146	–0.125
C9	0.297	–0.358	–0.275	0.022	0.061	–0.316
C10	–0.266	–0.290	–0.251	0.015	0.024	–0.275
C11	–0.266	–0.290	–0.251	0.015	0.024	–0.270
C12	–0.340	–0.374	–0.322	0.018	0.034	–0.348

RESULTS AND DISCUSSION

Reactional mechanism



Indices of Fukui bring us the information relating to the reactivity of system atoms TO (maleic anhydride) and **5a** compound lactonic.

Conclusion

The originality of this work resides in the utilization of water as solvent in reactions of Diels-Alder, what shows the big interest of the process that avoids the prolonged heating of reagents since the reaction makes himself to ambient temperature. These features should permit, in the future, to fully use all possibilities of this reaction. The choice of the diene and the dienophile, to achieve the reaction of Diels-Alder, should make himself according to the structure natural target. The theoretical calculation by the utilization of indices of Fukui shows an acceptable agreement for the distinction of the atom behavior in a molecule for possible reactions.

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