Five-Membered Aromatic Heterocycles in Diels-Alder Cycloaddition Reactions: Theoretical Studies as a Complement of the Experimental Researches

Romina Brasca[1,2], Claudia Della Rosa[1], María Kneeteman[1,3] and Pedro M.E. Mancini*[,1]

[1]*Área de Química Orgánica, Departamento de Química, Facultad de Ingeniería Química, Universidad Nacional del Litoral, Santiago del Estero 2829, (S3000AOM) Santa Fe, Argentina*

[2]*Doctoral scholarship holder from the National Council of Scientific and Technical Research (CONICET), Argentina*

[3]*National Council of Scientific and Technical Research (CONICET), Argentina*

Abstract: The dienophilic behavior of electron-deficient substituted five-membered aromatic heterocyclices in polar cycloaddition reactions is studied from a theoretical point of view employing the global electrophilicity index to estimate the electrophilic character of the dienophiles and to compare them with the available experimental information. The type of substitution on the heteroatomic ring is also discussed. Complementary some new reactions of these substrates are described.

1. INTRODUCTION

The Diels-Alder (DA) reaction allows the simple construction of a six-member ring from a diene and a dienophile, being one of the most significant and useful tools in synthetic organic chemistry [1].

In view of our interest in the cycloaddition chemistry of properly substituted aromatic carbocycles and heterocycles, we have reported studies on the dienophilic character of aromatic systems such as naphthalenes, furans, pyrroles, thiophenes, selenophenes and indoles all of them substituted with electron-withdrawing groups [2-6].

In the last years, the density functional theory (DFT) has been successful in explaining the feasibility of the cycloaddition process and the chemical reactivity by classifying different dienes and dienophiles within a unique scale of electrophilicity power [7]. The difference in the global electrophilicity power between different diene/dienophile pairs ($\Delta\omega$) was also shown to be a good indication of the polar character of the cycloaddition process.

The main purpose of the present work is to study the dienophilic behavior of electron-deficient substituted five-membered aromatic heterocycles in DA reactions from a theoretical point of view employing the global electrophilicity index to estimate the electrophilic character of the dienophiles and to compare them with the available experimental information. It is necessary to note that non-substituted five-membered aromatic heterocycles as pyrrol and furan can act as electron-rich dienes in reactions with

*Address correspondence to this author at the Área de Química Orgánica, Departamento de Química, Facultad de Ingeniería Química, Universidad Nacional del Litoral, Santiago del Estero 2829, (S3000AOM) Santa Fe, Argentina; Tel: 54-342-4571164; Fax: 54-342-4571162; E-mail: pmancini@fiqus.unl.edu.ar

electron-deficient dienophiles as dimethyl acetylenedicarboxylate (DMAD) in polar DA reactions. Complementary each analyzed reactions have been realized experimentally in new conditions of the already reported ones in order to unify the experimental variables. Moreover we are showing some new reactions.

2. DISCUSSION AND RESULTS

The study of dienophilic character of monosubstituted nitro-aromatic heterocyclopentadienes was carried out employing 2-nitrofuran (**1a**), 3-nitrofuran (**1b**), 1-tosyl-2-nitropyrrole (**2a**), 1-tosyl-3-nitropyrrole (**2b**), 2- and 3-nitrothiophene (**3a**, **3b**), and 2- and 3-nitroselenophene (**4a**, **4b**), methyl-5-nitrofuran-3-carboxylate (**5a**), methyl-1-tosyl-5-nitropyrrole-3-carboxylate (**5b**), methyl-5-nitrothiophene-3-carboxylate (**5c**) and methyl-5-nitroselenophene-3-carboxylate (**5d**). In addition, we selected isoprene (**6**) and 1-methoxy-3-trimethylsiloxy-1,3-butadiene (Danishefsky´s diene) (**7**) as dienes, covering position of low and high nucleophilic character [8].

The 2- and 3-nitrofurans react efficiently with the above mentioned dienes in polar DA reactions, with the nitro group inducing side selectivity. This substituent is easily extruded under thermal conditions giving cycloadducts of high interest. A very strong electron-acceptor group, such as nitro group induces in the furan ring similar reactivity at α- and β-positions.

When **1a** and **1b** react with Danishefsky´s diene afforded the corresponding benzofuran cycloadducts (1:1), which were obtained with moderate to high yield and complete regioselectivity.

On the other hand, the reactions of methyl 5-nitrofuran-3-carboxylate (**5a**) with isoprene underwent cycloaddition with

1a R_1= NO_2, R_2=H R_3=H
b R_2= NO_2, R_1=H R_3=H

2a R_1= NO_2, R_2 = H
b R_1= H, R_2= NO_2

3a R_1= NO_2, R_2=H
b R_1 = H, R_2= NO_2

4a R_1= NO_2, R_2 = H
b R_1= H, R_2= NO_2

5 a X= O, R= CO_2CH_3
 b X= N-Ts, R= CO_2CH_3
 c X= S, R= CO_2CH_3
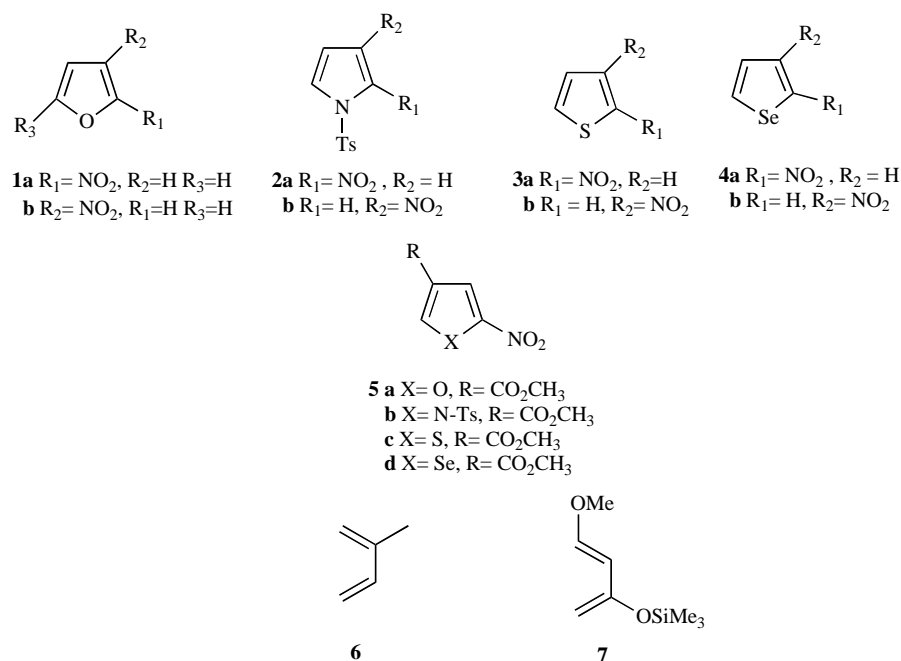 **d** X= Se, R= CO_2CH_3

6

7

Fig. (1).

formation of 1:1 and 2:1 adducts, in both cases of regioisomer mixtures. Moreover, treatment of **5a** with **7** yields 1:1 hydroxy cycloadduct. This last reaction proceeded by addition of the diene selectively to the nitro-substituted double bond of the furan. Exposure of every 2-nitrofurans to electron-rich diene yielded 1:1 adducts with the cycloaddition taking place on the nitrated bond [2, 9].

Also when 2- y 3-tosylnitropyrroles were reacted with the cited dienes under identical reaction conditions, they showed their dienophilic character. When **2a** and **2b** were heated with less reactive isoprene **6**, it gave a mixture of dihydroindoles as the principal products.

The reactions of **5b** with isoprene proceeded to yield the mixture of isomeric cycloadducts 1:1 as the principal products (55%) and a mixture of double addition, in both cases in form of regioisomer mixtures.

Similarly, in the reactions of these substrates with Danishefsky's diene **7** were obtained 1:1 hydroxy cycloadducts with a high yield and complete regioselectivity, which is controlled by the nitro and methoxy groups [3].

In turn when **5c** was heated with the less reactive isoprene, it gave pyrrolyl-thiophene as the principal product formed by a hetero cycloaddition reaction followed by thermal rearrangement. After 72 h at 120ºC, the reaction of **5c** with **7** afforded 45% of benzothiophene, which derives from regioselective cycloaddition to bond nitro substituted, and further aromatization by loss of nitrous acid and methanol. On the other hand, when 2- and 3- nitrothiophene (**3a-b**) were tested with Danishefsky's diene **7** yielding the corresponding benzothiophenol in 25% yield. Meanwhile when isoprene was used as diene (120 ºC, 72 h), traces of the pyrrolyl-thiophene derivative was obtained [4].

In the case of substituted selenophene **4a** and **4b** when isoprene was used as diene no pyrrolyl-derivatives from hetero DA were detected. The reactions yield the mixture of isomeric cycloadducts. The reactive behaviour of nitroselenophenes appears as opposed to that reported for nitrothiophenes when isoprene was used as diene [5]. When **4a** and **4b** reacted with Danishefsky's diene **7** it afforded aromatic cycloadduct **8a** and **8b** with loss of the nitro group (Scheme **1**, Table **4**). The results of cycloaddition studies between nitroselenophenes with the above mentioned dienes under different reaction conditions show their behaviour as normal dienophiles [10].


4a R_1= NO_2, R_2 = H
b R_1= H, R_2= NO_2

8a G_1= OH, G_2 = H
b G_1= H, G_2= OH
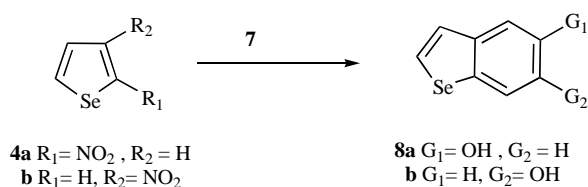
Scheme 1.

Similar exposure of disubstituted selenophene **5d** to isoprene **6** yielded the mixture of isomeric benzoselenophenes **9a** and **9b** (Scheme **2**, Table **4**). These reactions proceeded by selective addition of the diene to the nitro-substituted double bond of the selenophenes. No *bis*-adduct from the double cycloaddition of the diene was detected [11].

5d

9a G_1= Me, G_2=H
b G_1=H, G_2=Me
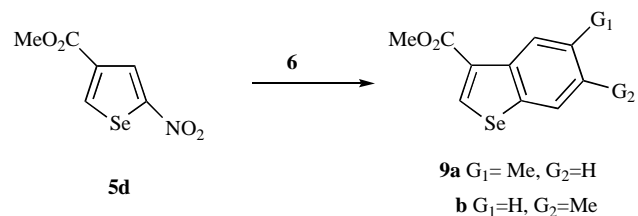
Scheme 2.

In the reaction of **5d** with **7**, cycloadduct **10** was obtained with moderate yield and complete regioselectivity (Scheme **3**, Table **4**) [12].

5d → **7** → **10**
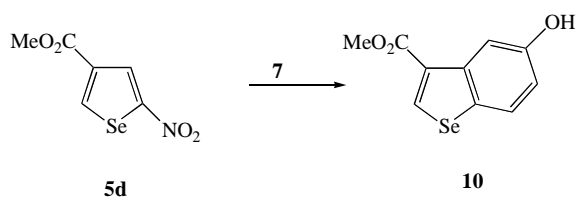
Scheme 3.

All cycloaddition products show extrusion of the nitro group as nitrous acid. The irreversible character of the extrusion of nitrous acid makes to domino reaction thermodynamically feasible.

3. COMPUTATIONAL STUDIES

The gas-phase equilibrium geometries of all species were obtained by full optimization at the B3LYP/6-31G(d) level using the GAUSSIAN03 program [13]. All stationary points found were characterized as true minima by frequency calculations.

The chemical hardness (η) describes the resistance of the chemical potential to a change in the number of electrons. The electronic chemical potential (μ) is usually associated with the charge-transfer ability of the system in its ground state geometry [14]. The global electrophilicity index (ω), introduced by Parr *et al.*, is useful descriptor of reactivity that allows a quantitative classification of the global electrophilic character of a molecule within a unique relative scale [15, 16]. Recently, the empirical nucleophilicity index was introduced by Domingo *et al.* [17]. This index is based on the HOMO energies obtained by the Kohn-Sham scheme

and this nucleophilicity scale takes tetracyanoethylene as a reference [18].

These indices were calculated using expressions 1-4.

$$\eta = (\varepsilon_{LUMO} - \varepsilon_{HOMO}) \quad (1) \qquad \mu = \frac{(\varepsilon_{LUMO} - \varepsilon_{HOMO})}{2} \quad (2)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (3) \qquad N = E_{HOMO\,(Nu)} - E_{HOMO(TCE)} \quad (4)$$

Optimized Geometries

The most stable conformation of the Danishefsky's diene is the antiperiplanar. This conformation is shown to be more stable than the synclinal arrangement (2.60 kcal mol^{-1}) where the two double bonds are twisted by 33° [19]. However, in the calculations the *cisoid* geometry was used because this is the required conformation of the diene in order to react with the dienophile.

In all the ground state structures of the dienophiles the nitro group is coplanar with the carbocyclic and heterocyclic plane, as well as the ester plane. Theoretical calculations revealed a small energy difference between C=O *cis* and *trans* in furan-3-carboxaldehyde, pyrrole-3-carboxaldehyde and thiophene-3-carboxaldehyde [19]. Therefore, all the geometries were optimized from the *transoid* geometry.

Global DFT Properties of the Reagents Involved in these DA Reactions

The electrophilicity power ω of the reagents involved in these DA reactions is shown in Tables **1-5**. The classifications were made in decreasing order of electrophilicity. We can assume that high electrophilicity corresponds to one extreme of this scale. In these tables we also included some

Table 1.   Global Properties for Furan and Furan Derivatives and Yield of the Diels-Alder Reactions.

Dienophile	μ[a]	η[a]	ω[a]	Yield (%) reaction whit 6 [b]	Yield (%) reaction whit 7 [b]
Methyl-5-nitrofuran-3-carboxylate (**5a**)	-5.16	4.94	2.70	53	62
2-Nitrofuran (**1a**)	-4.93	4.83	2.51	53	60
3-Nitrofuran (**1a**)	-4.81	4.92	2.35	40[c]	55
Furan	-2.79	6.64	0.58		

[a]All quantities are shown in eV.
[b]Yield in percentage based on consumed dienophile, and isolated yield.

Table 2.   Global Properties for 1-Tosylpyrrole and 1-Tosylpyrrole Derivatives and Yield of the Diels-Alder Reactions

Dienophile	μ[a]	η[a]	ω[a]	Yield (%) reaction whit 6 [b]	Yield (%) reaction whit 7 [b]
Methyl-1-tosyl-5-nitropyrrole-3-carboxylate (**5b**)	-4.72	4.83	2.30	55	58
1-Tosyl-2-nitropyrrole (**2a**)	-4.50	4.73	2.14	45	49
1-Tosyl-3-nitropyrrole (**2b**)	-4.54	4.80	2.14	45	50
1-Tosylpyrrole	-3.68	4.77	1.41		

[a]All quantities are shown in eV.
[b]Yield in percentage based on consumed dienophile, and isolated yield.

Table 3.   Global Properties for Thiophene and Thiophene Derivatives and Yield of the Diels-Alder Reactions

Dienophile	μ^a	η^a	ω^a	Yield (%) reaction whit 6 [b]	Yield (%) reaction whit 7 [b]
Methyl-5-nitrothiophene-3-carboxylate (**5c**)	-5.23	4.81	2.84	23[d]	52
2-Nitrothiophene (**3a**)	-5.02	4.73	2.66	traces[c]	22
3-Nitrothiophene (**3b**)	-4.88	4.95	2.40	traces[c]	-
Thiophene	-3.27	6.13	0.87	-	-

[a]All quantities are shown in eV.
[b]Yield in percentage based on consumed dienophile, and isolated yield.
[c]products by heterocycloaddition, detected by GC-MS and TLC. Spraying the TL with a solution of *p*-methoxybenzaldehyde, acetic acid, ethanol and sulfuric acid (3:1:1:4), pyrrolyl-thiophenes were developed as red spots by heating.
[d]mixture of products by normal addition and heterocycloaddition.

Table 4.   Global Properties for Selenophene and Selenophene Derivatives and Yield of the Diels-Alder Reactions

Dienophile	μ^a	η^a	ω^a	Yield (%) reaction whit 6 [b]	Yield (%) reaction whit 7 [b]
Methyl-5-nitroselenophene-3-carboxylate (**5d**)	-5.17	4.67	2.85	59	55
2-Nitroselenophene (**4a**)	-4.98	4.61	2.68	45	52
3-Nitroselenophene (**4b**)	-4.83	4.91	2.38	54	62
Selenophene	-3.32	5.97	0.92		

[a]All quantities are shown in eV.
[b]Yield in percentage based on consumed dienophile, and isolated yield.

Table 5.   Global Properties for the Dienes

Diene	μ^a	η^a	ω^a	N^a
Isoprene (**6**)	-3.29	5.34	1.01	3.45
Danishefsky's diene (**7**)	-2.69	5.33	0.68	4.05

[a]All quantities are shown in eV.

global properties such as the chemical potential µ and the chemical hardness η. A good electrophile is characterized by a high value of µ and a low value of η [20].

As it was expected, we can appreciate that the structural and electronic effects induced by the chemical substitution produce different responses in the electrophilicity power of heterocyclic dienophiles and dienes. Thus, substitution of one hydrogen atom in all the heterocyclic dienophiles by one of the most powerful electron-withdrawing groups, the nitro group, produces an increase in the electrophilicity character. Moreover, the 2-nitrosubstituted heterocycles **1-4a** show higher electrophilicity power than the 3-nitrosubstituted heterocycles **1-4b** probably due to the proximity of the nitro group with the heteroatom (see Tables **1-4**).

The heterocyclic dienophiles **5a-d** substituted by two different electron-withdrawing groups (methyl carboxylate and nitro groups) show the highest values in electrophilicity power within each series, from 2.30 eV (**5b**) to 2.85 eV (**5d**), indicating that these disubstitutions are suitable in order to increase the reactivity of these heterocyclic dienophiles in polar DA reactions. This suggests that they will in general act as electron acceptors during their interaction with dienes.

On the other hand, the electrophilicity of isoprene **6** is 1.10 eV, a value that falls in the range of moderate electrophiles within of the electrophilicity scale proposed by

Domingo *et al.* [7a]. When electron-donating substituents, -OCH_3 and -$OSi(CH_3)_3$, are incorporated into the structure of butadiene, a decrease in the electrophilicity power is observed; 0.68 eV (**7**). Therefore, the electrophilicity of Danishefsky´s diene **7** falls in the range of marginal electrophiles, good nucleophiles, within of the electrophilicity scale. This behavior indicates that the nucleophilic activation in Danishefsky's diene **7** is greater than in isoprene **6**, in clear agreement with the high nucleophilicity index of the diene **7**, N =4.05 eV, than isoprene **6**, N = 3.45 eV (see Table **5**). These nucleophilicity indices indicate that these dienes will more likely behave as electron donor species (i.e. as nucleophiles).

As consequence of the high electrophilic character of these substituted dienophiles and the high nucleophilic character of the dienes, it is expected that these DA reactions proceed with polar character. The polarity of the process is assessed comparing the electrophilicity index of the diene/dienophile interacting pairs, that is Δω. The noticeable differences in electrophilicity power between the disubstituted derivatives and dienes (1.20-2.07 eV) indicate the polar character of these DA reactions. Evidently, the differences in the global electrophilicity power (Δω) are higher for the Danishefsky's diene **7** than for isoprene **6**. Therefore, a high reactivity and a high regioselectivity are expected for the pair dienophile/Danishefsky's diene.

Finally, the flux of the electron-density in these polar cycloaddition reactions is also supported by means of a DFT analysis based on the electronic chemical potentials μ of the reagents [19]. The electronic chemical potentials μ of the substituted heterocyclic dienophiles, in the ranges from −4.54 eV (**2b**) to −5.23 eV (**5c**), are higher than those of the dienes: −2.69 eV (**6**) and −3.28 eV (**7**), thereby suggesting that the net charge transfer will take place from these electron-rich dienes towards the aromatic dienophiles.

CONCLUSIONS

As it has been demonstrated, when aromatic heterocyclic systems have nitro group substitution they are potential electrophiles that can react with dienes of variable nucleophilicity in polar cycloaddition reactions. Moreover, the disubstitution (in these cases nitro and methyl carboxilate groups) increase the dienophilic reactivity in front of the same dienes.

On the other hand we can see that the tendency of the major index coincides with an increase of the yields with both, isoprene **6** and the Danishefsky´s diene **7**. In view of these results, when **7** was used as diene an increase of the yield of cycloadduct is observed related isoprene **6**. This fact is in agreement with the nucleophilic character of these dienes.

However, when the values of the thiophene derivatives are compared this tendency is not viable. In this cases in spite of it showed ωvalues of similar magnitude that the selenophene derivatives, the yield is lower in the reactions of disubstituted thiophene with isoprene **6**. On the other hand, the monosubstituted thiophene afforded only trace of heterocycloaddition product. At the same time, when the mononitrated thiophene reacted with Danishefsky´s diene **7** the yield drops dramatically, in particular 3-nitrothiophene did not undergo cycloaddition, probably this behavior is a consequence of the especial reactivity of this substrate connected with its aromaticity [21].

ACKNOWLEDGMENTS

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[8]   Reactions were performed under thermal conditions. An ampoule containing a solution of the corresponding dienophile and the required amount of diene in dry benzene was cooled in liquid nitrogen, sealed, and then heated to 120 ºC in an oil bath. After the reaction time was completed (72ºC), it was cooled once more in liquid nitrogen and opened. The solution was evaporated and the residue purified by column chromatography alumina using hexane/ethyl acetate mixtures as eluent.

[9]   In the same direction and due to the impossibility of obtaining 3-nitrofuran, we exposed 2,5-dimethyl-3-nitrofuran to **6** and **7** the DA reaction at 200 ºC proceeded to furnish the mixture of regioisomers.

[10]   **8a** ^{1}H NMR δ 5.25 (br s, 1H, O_H_), 6.84 (dd, J = 8.8,2.4 Hz, 1H, H-6), 6.95 (d, 1H, J = 4.5 Hz, H-3), 7.28 (d, J = 2.4 Hz, 1H, H-3), 7.41 (d, J = 4.4 Hz, 1H, H-2), 7.73 (d, J = 8.8 Hz, 1H, H-7). ^{13}C NMR δ 111.2 (C-4), 114.4 (C-6), 124.5 (C-7), 125.6 (C-3), 127.2 (C-2), 131.0 (C-7a), 143.1 (C-3a), 156.4 (C-5). IR: 3357.51 (OH) cm^{-1}. **8b** ^{1}H NMR δ 5.35 (br s, 1H, O_H_), 7.00 (d, J = 4.3 Hz, 1H, H-3), 7.33 (m, 2H), 7.41 (d, J = 4.4 Hz, 1H, H-2), 7.67 (d, J = 8.7 Hz, 1H, H-4). ^{13}C NMR δ 107.8 (C-7), 116.8 (C-5), 127.5 (C-3), 128.2 (C-4), 130.1 (C-2), 135.6 (C-3a), 148.6 (C- 7a), 156.3 (C-6). IR: 3357.50 (OH) cm^{-1} . HMRS *m/z* 197.0971 (Calcd C$_8$H$_6$OSe 197.0950).

[11]   **9a** ^{1}H NMR δ 2.51 (s, 3H), 3.94 (s, 3H, CO$_2$C_H$_3$_), 7.63 (dd, J = 8.3, 1.4 Hz, 1H, H-6), 7.74 (d, J = 1.4 Hz, 1H, H-4), 8,05 (d, J = 8.3 Hz, 1H, H-7), 8.25 (s, 1H, H-2). ^{13}C NMR δ 25.2 (CH$_3$), 51.9 (CO$_2$_C_H$_3$), 127.4 (C-6), 127.9 (C-7), 128.4 (C-4), 129.1 (C-3), 135.3 (C-7a), 135.8 (C-3a), 138.3 (C-3a), 143.5 (C-5), 164.4 (_C_O$_2$CH$_3$). HMRS *m/z* 253.1614 (Calcd C$_{11}$H$_{10}$O$_2$Se 253.1592).
9b ^{1}H NMR δ 2.50 (s, 3H), 3.94 (s, 3H, CO$_2$C_H$_3$_), 7.32 (m, 2H), 7.70 (d, J= 8.4 Hz, H-4), 8.28 (s, 1H, H-2). ^{13}C NMR δ 25.2 (CH$_3$), 51.9 (CO$_2$CH$_3$), 126.6 (C-4), 129.9 (C-5), 130.2 (C-3), 130.6 (C-7), 134.0 (C-3 a), 136.1 (C-6), 138.2 (C-2), 141.2 (C-7 a), 164.4 (_C_O$_2$CH$_3$).

[12]   **10** ^{1}H NMR δ 3.94 (s, 3H, CO$_2$C_H$_3$_), 5.90(br s, 1H, O_H_), 7.65 (dd, J = 8.4, 2.4 Hz, 1H, H-6), 7.72 (d, J = 2.4 Hz, 1H, H-4), 8.10 (d, J = 2.4 Hz, 1H, H-4), 8.26(s, 1H, H-2). ^{13}C NMR δ 51.92 (CO$_2$_C_H$_3$), 110.6 (C-4), 115.5 (C-6), 125.4 (C-7), 127.1 (C-3), 132.3 (C-7a), 138.1 (C-2), 138.5 (C-3a), 155.5 (C-5), 164.6 (_C_O$_2$CH$_3$). IR: 1693.93 (CO$_2$Me), 3343.64 (OH) cm^{-1}. HMRS *m/z* 255.1338 (Calcd C$_{10}$H$_8$O$_3$Se 255.1317).

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