Study of Diels-Alder Reactions of Purpurogallin Tetra-Acetate with Various Dienophiles †

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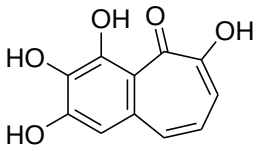
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Abstract: Purpurogallin or (6*E*,8*Z*)-2,3,4,6-tetrahydroxy-5H-benzo[7]annulen-5-one is a benzotropolone possessing a dienic system and ~~is~~ known to inhibit TLR1/TLR2 activation pathway. We have recently described the easy green synthesis of purpurogallin from pyrogallol catalyzed by a copper complex or by vegetable oxidases. The purpurogalline was acetylated and the tetraacetate derivative thus obtained was engaged in a Diels Alder reaction with various dienophiles (benzoquinone, maleic anhydride, ethylmaleimide, phenylmaleimide, etc.). The results obtained will be presented and discussed.

Keywords: purpurogallin; purpurogallin tetra-acetate; [4 + 2] cycloaddition; dienophiles; density functional theory (DFT)

1. Introduction

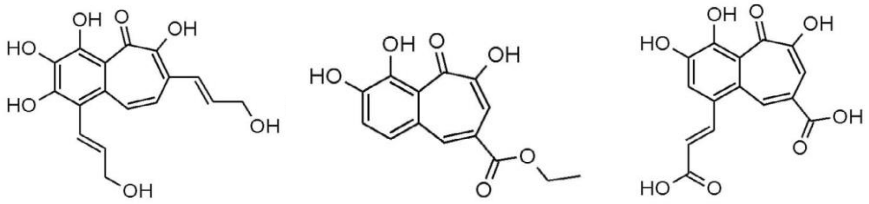
The benzotropolones represent a class of natural products, which consists of a tropolone unit (hydroxycycloheptatrienone) fused to a benzene ring. The most popular is Purpurogallin (**1**) present in Quercus tree and displaying biological properties [1–9].



Purpurogallin (**1**)

Figure 1. Structure of Purpurogallin.

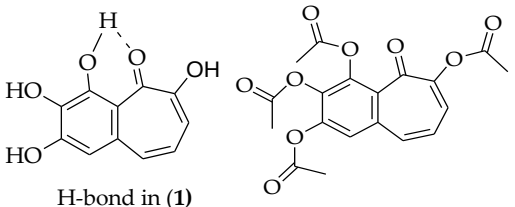
Many benzotropolones are known as secondary metabolites such as Fomentariol from fungus *Fomes fomentarius* [10], Goupiolone A isolated from aerial parts of *Goupia glabra*, a plant from the Amazon region of Peru [11] Crocipodin, a pigment extracted from *fungus Leccinum crocipodium* (Boletales) [12].



(**a**) (**b**) (**c**)

Figure 1. (**a**) Examples of natural benzotropolones Fomentariol; (**b**) Goupiolone A; (**c**) Crocipodin.

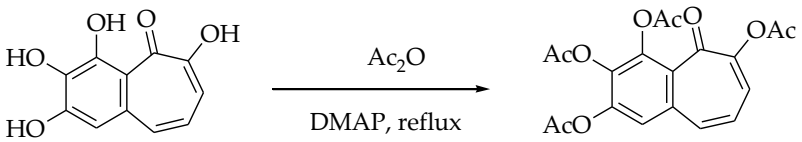
We have shown that Purpurogallin (**1**) can be obtained by catalytic oxidation of pyrogallol according to our previously work [13]. (**1**) presents an intramolecular hydrogen bond which makes it difficult to modify the hydroxyl involved in this bond.



H-bond in (**1**) Purpurogallin tetra-acetate (**2**)

Figure 2. Intramolecular H-bond in pupurogallin (1).

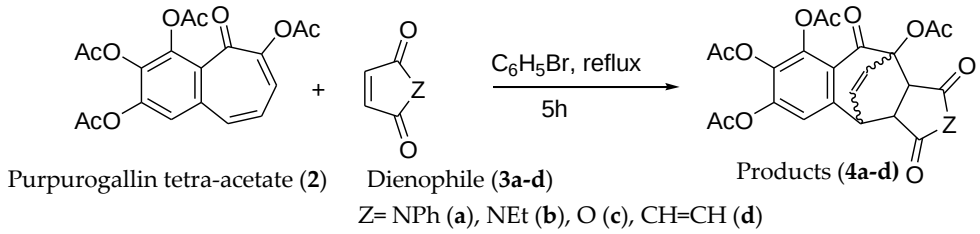
Purpurogallin (**1**) can yet be converted into purpurogallin tetra-acetate by peracetylation with acetic anhydride in the presence of DMAP [14] as catalyst in a yield of 87% (Scheme1).



Purpurogallin (**1**) Purpurogallin tetra-acetate (**2**)

Scheme 1. Acetylation of purpurogallin.

Purpurogallin which possesses an antiaromatic tropolone nucleus is able to behave like a diene [15]. So, we described herein the Diels–Alder reaction of Purpurogallin tetraacetate with different dienophiles in refluxing bromobenzene (154 °C) according to the Scheme 2.



Purpurogallin tetra-acetate (**2**) Dienophile (**3a-d**) Products (**4a-d**)

Z= NPh (**a**), NEt (**b**), O (**c**), CH=CH (**d**)

Scheme 2. Diels-Alder reactions between Purpurogallin tetraacetate and various dienophiles (**3a–d**).

The products formed were isolated by chromatography on a silica column and were identified by NMR and mass spectroscopy. The results are summarized in the Table, the yields corresponding to the pure isolated products.

2. Materials and Methods

Melting points were measured on a Kofler apparatus and are reported uncorrected. IR spectra were obtained with solids with a Fourier transform Perkin-Elmer Spectrum One with ATR accessory. The frequencies of absorption are given in cm^{-1}. Only significant absorptions are listed. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded while using $CDCl_3$ or DMSO-d6 with TMS as an internal standard on a Bruker DPX 400 NMR spectrometer. Chemical shifts are reported in ppm. Mass spectra were recorded on a Xevo G2- XS QTof WATERS, mass range (50–1000 *m*/*z*), source temperature 120 °C, desolvatation temperature 500 °C, with electrospray ionization (ESI, positive mode), lock spray PEG.

We already reported the synthesis of purporogallin from pyrogallol under green conditions [13].

The geometries of the neutral molecules were optimized using B3LYP. The single point calculations were performed using the B3LYP/6-31G* method of the Spartan program [16]. Calculations in bromobenzene (ε = 5.4) were performed using SM8 [17,18].

2.1. Synthesis of Purpurogallin Tetraacetate (2)

In a 100 mL flask fitted with a condenser and a magnetic bar and a $CaCl_2$ guard, 0.1 mole of purpurogallin is dissolved in a mixture of 40 mL of acetic anhydride and N,N-dimethyl-4-aminopyridine (DMAP) (4 mmol). The reaction mixture is heated to 130 °C for 20 h. After cooling, the solvent is evaporated off, a solid is recovered which is purified by column chromatography with as eluent: hexane/ ethyl acetate: (1:1). A yellow solid is obtained with 87% yield.

m.p = 190–192°C

FT-IR (cm^{-1}): 2940; 1769; 1631.

^{1}H NMR δ (400 MHz, DMSO-d6, ppm): δ 7.26 (1H, s,); 6.91 (1H, d); 6.58 (1H, d); 6.34 (1H, dd,); 2.13 (3H, s,); 2.11 (3H, s); 2.09 (3H, s); 2.06 (3H, s).

^{13}C NMR (100 MHz, DMSO d6, ppm): δ 180.9, 168.2, 167.8, 167.2, 166.6, 149.9, 145.2, 143.8, 136.9, 134.7, 134.0, 128.0, 123.5, 123.1, 122.3, 20.5.

HRMS: for $C_{19}H_{16}O_9$, (M + 1Na): found 411.

2.2. General Experimental Procedure for [4 + 2] Cycloaddition

Products 4a–d

The purpurogallin tetraacetate **(2)** (10 mmol) and the (3a–d) compound (20 mmol) were dissolved in 10 mL of bromobenzene. The mixture is heated under reflux at 150 °C for 5 h. The reactional mixture was chromatographied on a silica column with cyclohexane/ethyl acetate (1/1) as solvent.

The product (**4a**) was obtained from N-phenylmaleimide:

White solid, Yield: 39%, m.p > 276 °C

FT-IR (cm^{-1}): 2989; 1781; 1713; 1598.

^{1}H NMR δ (400 MHz, $CDCl_3$, ppm): **δ** 7.46 (1H, t, J = 7.3 Hz) ; 7.41 (2H, dd, J = 7.3 Hz, J = 4.0 Hz); 7.22 (2H, d, J = 4 Hz); 6.79 (1H, s); 6.68 (1H, d, J = 8.0 Hz); 6.06 (1H, dd, J = 8.0 Hz; J = 9.9 Hz) ; 4.72 (1H, dd, J = 9.9, J = 1.8 Hz); 4.39 (1H, d, J = 5.8 Hz); 3.64 (1H, dd, J = 5.8 Hz, J = 1.8 Hz) ; 2.32 (3H, s); 2.30 (6H, s) ; 2.24 (3H, s);

^{13}C NMR (400 MHz, $CDCl_3$ ppm): δ 175.1; 169.5; 168.1; 167.6; 167.1; 166.9; 146.6; 146.5; 140.6; 136.1; 135.0; 131.5; 129.3; 129.0; 126.4; 126.2; 120.2; 83.8; 47.3; 43.3; 41.1; 23.1; 21.5; 20.8: 20.7; 20.5.

HRMS: for, ($C_{29}H_{23}NO_{11}Na$): calculated: 584.1169; found 584.1

The product (**4b**) was obtained from N-ethylmaleimide:

White solid, Yield: 36%, m.p > 276 °C

FT-IR (cm^{-1}): 2983; 1780; 1711; 1601.

^1H NMR δ (400 MHz, $CDCl_3$, ppm): δ 6.71 (1H, s); 6.62 (1H, d, J = 7.8 Hz); 6.02 (1H, dd, J = 8.7 Hz, J = 7.8 Hz), 4.32 (1H, d, J = 6.2 Hz); 3.60 (2H, q, J = 7.2 Hz); 3.55 (1H, dd, J = 6.2, J = 1.8 Hz); 3.48 (1H, dd J = 8.7, J = 1.8 Hz); 2.33 (3H, s); 2.32 (3H, s); 2.29 (3H, s); 2.27 (3H, s); 1.16 (3H, t, J = 7.2 Hz)

^{13}C NMR (400 MHz, $CDCl_3$, ppm): δ 175.1; 169.5; 168.1; 168.0; 167.1; 166.4; 147.6; 146.6; 146.4; 136.0; 134.1; 131.3; 129.2; 120.1; 112.2; 84.2; 47.2; 43.7; 40.1; 34.5; 21.2; 20.8, 20.5; 20.1; 13.0.

HRMS: for ($C_{25}H_{23}NO_{11}Na$): calculated: 536.1169 found 536.1.

The product (**4c**) was obtained from maleic anhydride:

White solid, Yield: 58%, m.p > 276

FT-IR (cm^{-1}): 2979; 1777; 1715; 1599.

^1H NMR δ (400 MHz, $CDCl_3$, ppm): δ 6.63 (1H, dd, J = 9.2 Hz, J = 7.1 Hz); 6.48 (1H, s); 6.15 (1H, d, J = 7.1 Hz); 4.17 (1H, dd, J = 7.4 Hz, J = 2.1 Hz); 3.77 (1H, d, J = 7.4 Hz); 3.65 (1H, dd, J = 9.2 Hz, J = 2.1 Hz); 2.31 (3H, s); 2.29 (3H, s); 2.26 (3H, s); 2.23 (3H, s).

^{13}C NMR (400 MHz, $CDCl_3$, ppm): δ 176.1; 172.6; 168.0; 167.4; 167.1; 166.4; 152.0; 137.1; 136.1; 134.7; 133.9; 131.3; 127.4; 121.7; 106.2; 88.3; 48.7; 47.5; 43.5; 21.2; 20.7; 20.4; 20.2.

HRMS: for, ($C_{23}H_{18}O_{12}Na$): calcule: 509.0938 found 509.1.

The product (**4d**) was obtained from 1,4-benzoquinone:

Green solid, Yield: 41%, m.p > 276 °C

FT-IR (cm^{-1}): 2979; 1777; 1715; 1599.

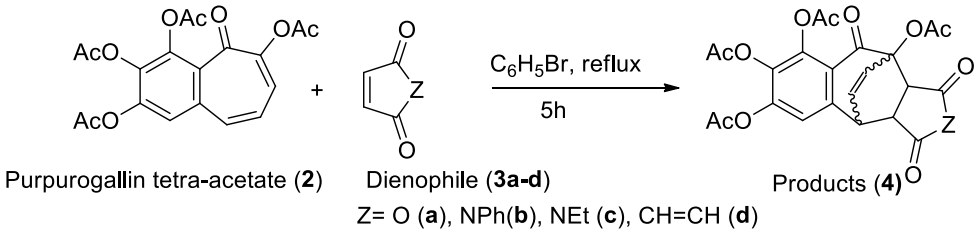
^1H NMR δ (400 MHz, $CDCl_3$, ppm): 6.76 (1H, s); 6.66 (1H, dd, J = 17.2 Hz, J = 8.4 Hz); 6.12 (1H, d, J = 17.2 Hz); 4.54 (1H, dd, J = 7.3 Hz, J = 3.1 Hz); 4.09 (1H, d, J = 7.3 Hz); 3.37 (1H, dd, J = 8.4 Hz, J = 3.1 Hz); 2.31 (9H, s); 2.13 (3H, s).

^{13}C NMR (400 MHz, $CDCl_3$, ppm): δ 171.5; 168.5; 167.7; 167.4; 164.5; 161.0; 146.9; 143.5; 142.4; 140.7; 137.2; 134.8; 130.0; 121.3; 89.3; 48.6; 46.6; 46.0; 31.3; 30.9; 21.4; 21.0; 20.7; 19.7.

HRMS: for, ($C_{25}H_{20}O_{11}Na$): calculated: 519.0903; found 519.1.

3. Result and Discussion

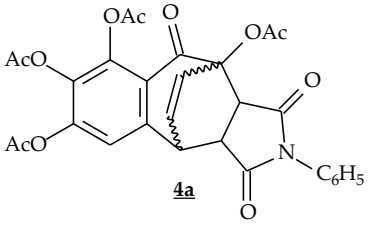
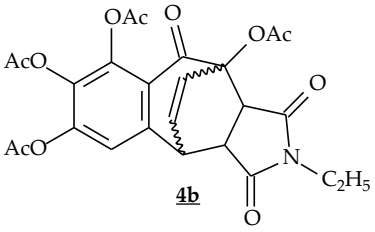
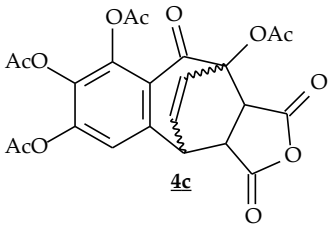
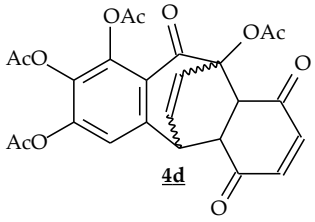
The study of the reactivity of purpurogalline led us to consider the diene system present in this molecule to carry out [4 + 2] cycloaddition reactions with different dienophiles. However, the purpurogalline was previously acetylated to avoid any interaction of phenolic OHs in the cycloaddition reaction (Scheme 3).



Scheme 3. Diels-Alder reaction of purpurogallin tetraacetate with dienophiles.

The dienophiles for which the cycloaddition reaction has given acceptable results are cyclic dienophiles which have withdrawing groups (maleimides, maleic anhydride and benzoquinone). The reaction was carried out without catalysts in refluxing bromobenzene. The results obtained are shown in Table 1 below:

Table 1. Products of Diels-Alder reaction isolated.

Entry	Dienophile	Product (3a-d)	Yield
a	N-phenylmaleimide	 **4a**	39%
b	N-Ethylmaleimide	 **4b**	36%
c	Maleic Anhydrid	 **4c**	58%
d	Benzoquinone	 **4d**	41%

3.1. Theoretical Studies

The frontier orbitals of purpurogallin tetra-acetate (2) and dienophiles (**3a–d**) were calculated using the DFT-B3LYP with the 6-31G(d) basis set in vacuum and then in bromobenzene (dielectric constant ε = 5.4) using Continuum Solvation Models, SM8 and are reported in the Table 2.

Table 2. Frontier orbitales calculated.

	Product	HOMO (eV)	LUMO (eV)	m debye	HOMO (eV)	LUMO (eV)	m debye
		In Vacuum			With Solvent: Bromobenzene		
Dienes (Donnor)	Purpurogallin (**1**)	−5.54	−1.89	2.71	−5.59	−1.86	3.36
	Tetraacetylpurpurogallin	−6.43	−1.97	11.07	−6.10	−1.69	12.84
	Tetramethylpurpurogallin	−5.66	−1.44	2.52	−5.65	−1.48	2.88
Dienophiles (Acceptor)	Maleic anhydride **3c**	−8.18	−3.75	3.64	−7.99	−2.88	4.15
	N-Phenyl maleimide **3a**	−6.50	−2.74	0.91	−6.46	−2.50	1.31
	N-Ethyl maleimide **3b**	−7.37	−2.58	0.63	−7.27	−2.33	0.85
	Benzoquinone **3d**	−7.36	−3.54	0	−7.11	−3.22	0

From the position of the frontier orbitals, i.e difference between $HOMO^d$ and $LUMO^a$ and difference between $HOMO^a$ and $LUMO^d$, the most probable Diels-Alder reaction appears as normal demand with a transfer of electrons from the purpurogallin tetraacetate or tetramethyl purpurogallin as donor to acceptor dienophile in the 4 cases studied. In the

case of non-benzenoid aromatic compounds like purpurogallin or tetraacetate purpurogallin, the antiaromaticity leads to normal-electron-demand Diels-Alder reactions.

The bromobenzene solvent somewhat facilitates the reaction by lowering the HOMO (−6.43 eV in vacuum to −6.10 eV) of the purpurogallin tetraacetate which appears to be quite polar (12.84 D) compared to the non-acetylated purpurogallin (3.36 D).

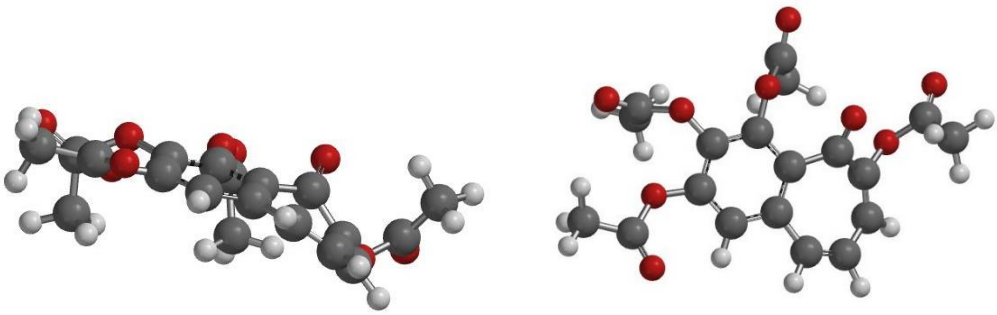
The reaction appears however more difficult than with tetramethylpurpurogallin (HOMO −5.65 eV) which has been used in the literature. In bromobenzene, according to the energy values of the LUMOs of dienophiles, benzoquinone (−3.22 eV) is more reactive than maleic anhydride (−2.88 eV), than N-phenylmaleimide (−2.50 eV), than N-ethylmaleimide (−2.33 eV).

The positions of frontier orbitals in vacuum and in bromobenzene show that increasing polarity has a beneficial effect on DA reaction (use of DMF). Unfortunately, we did not have the means to verify this experimentally due to the circumstances.

3.2. Stereochemistry

The Diels-Alder reaction is a supra-supra cycloaddition; depending on the arrival of the dienophile relative to the diene (purpurogallin), an exo or endo compound is obtained.

The tetraacetylpurpurogallin (2) molecule is almost flat and there is very little difference between the upper faces (exo attack) and the lower face (endo attack) on the other hand in the cycloaddition products the diedral angles of CH-CH (CO); CH(CO)-CH (CO) are very similar in the two diastereoisomers according to the molecular modelisation after optimization of the exo and endo products, it is not possible to know if a single isomer or two is formed.



Tetraacetylpurpurogallin (2)

4. Conclusions

Tetraacetylpurpurogallin leads to reaction of Diels-Alder with cyclic dienophiles in moderate yield under thermal activation. The use of a solvent more polar than bromobenzene and catalyst should be able to increase the yields. The reactions of purpurogallin tetraacetate **2** with the different dienophiles **3a–d** correspond at a Normal Electron Demand (NED) Diels-alder reactions and the stereochemistry shows that it is an endo cycloaddition.

Conflicts of Interest: The authors declare no conflict of interest.

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