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SYNTHESIS OF 2*H*-NAPHTHO[2,3-*b*]THIOPYRANOQUINONES AND DENSITY FUNCTIONAL STUDY FOR THE DIELS-ALDER REACTION OF A BENZOTHIOPYRANOQUINONE

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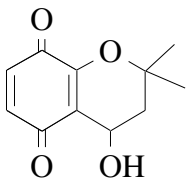
Abstract- The synthesis of benzothiopyranoquinone (**6**) in three step from benzothiopyran (**3**) is described. Diels-Alder reaction of quinone (**6**) with 1,3-pentadiene (**7**), cyclopentadiene, 1-methoxy-1,3-cyclohexadiene (**11**) and 1-dimethylamino-1-aza-1,3-pentadiene (**14**) was studied. The Density Functional Theory was applied to explain the orientation of the cycloaddition reaction of quinone (**6**) with dienes (**7**), (**11**) and (**14**).

We recently reported a new and convergent route to naphtho[2,3-*b*]pyranoquinones through [4+2] cycloaddition reaction of a benzopyranoquinone (**1**) with 1,3-dienes.[1] The usefulness of this method was demonstrated by the synthesis of the cytotoxic heterocyclic quinone (**2**) isolated from *Mansoa alliacea*,[2] and some azaanalogues.[3,4]



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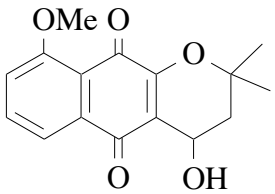

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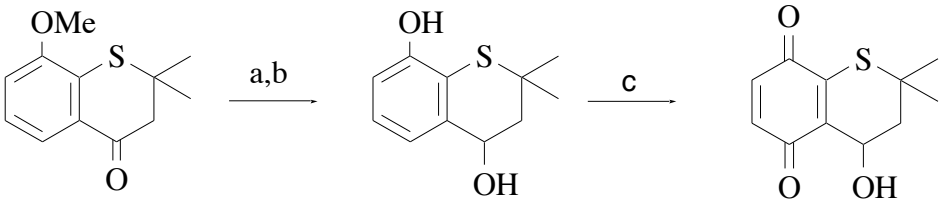
Because this procedure represents an attractive strategy for the synthesis of naphtho[2,3-*b*]pyranoquinones, known for their interesting biological properties,[5] in our continuing effort to obtain compounds with useful biological activity herein we report full details on the synthesis of sulfur bioisosters of naphthopyranoquinones using Diels-Alder methodology.[6]

With the purpose to extend our method to the preparation of sulfur analogues of naphthopyranoquinones with the sulfur atom replacing the heterocyclic oxygen we undertook the synthesis of a benzothiopyranoquinone. Nevertheless the synthesis of benzothiopyrans is well known,[7-10] to our knowledge benzothiopyranoquinones have never been obtained. We chose benzothiopyran (**3**) as the starting material, which was readily prepared by Michael addition of commercially available 2-methoxybenzenethiol to 3-methyl-2-butenoic acid and Friedel-Crafts cyclization of the resultant 3-methyl-3-phenylthiobutanoic acid with polyphosphoric acid.[9]

Hydrolysis of methyl ether (**3**) with hydrobromic acid in acetic acid for 3.5 h under reflux gave phenol (**4**). The reduction of compound (**4**) with lithium aluminum hydride in THF for 3 h at room temperature, and careful elimination of the reducing agent in excess, afforded compound (**5**) in good yield. Oxidation of phenol (**5**) with potassium nitrosodisulfonate (Fremy's salt)[11] in methanol-water (2:1) for 12 h at room temperature gave benzothiopyranoquinone (**6**) in 46% total yield. Then we studied the behavior of quinone (**6**) as dienophile in order to determine its potential as a precursor of 2*H*-naphtho[2,3-*b*]thiopyranoquinones.



3 **5** **6**

Scheme 1. Reagents: a) HBr/AcOH, 84%; b) $AlLiH_4$/THF, 92%; c) $(KSO_3)_2NO$/MeOH-H_2O, 60%.

The reaction of quinone (**6**) with 1,3-pentadiene (**7**) in methylene chloride at room temperature for 4 days afforded a mixture of adducts and aromatic adducts, which was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give a mixture of naphthothiopyranoquinone (**8a**) and (**8b**) in a 2:1 ratio. The ratio of the isomers was estimated by comparison of the integration of the singlets at δ 2.70 and 2.72 ppm for the C-6 and C-9 methyl group of **8b** and **8a** respectively. The mayor isomer (**8a**) could be isolated by column chromatography and its structure was deduced by X-Ray analysis (Figure 1).

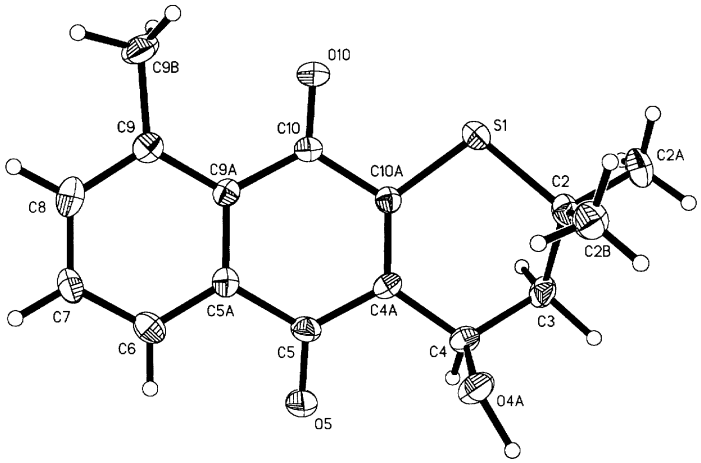
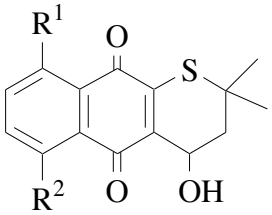
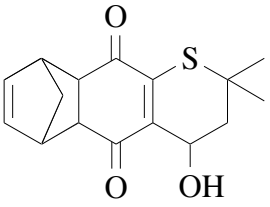
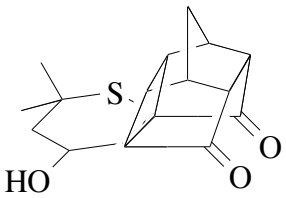


Figure 1: X-Ray structure for compound (**8a**)

When a mixture of quinone (**6**) and cyclopentadiene in methylene chloride was allowed to react at room temperature for 24 h, a 2:1 mixture of diastereomers (**9**) was obtained. The ratio of the adducts was determined by ^{1}H-NMR spectroscopy, where the OH proton and CH proton resonated at δ 3.3 and 4.90 ppm, and δ 4.03 and 4.84 ppm respectively. The *endo* configuration of the adducts was confirmed by irradiation of the mixture to yield the cage structure (**10**). It is interesting to note that the reaction of 1-hydroxybenzyl-1,4-benzoquinone with cyclopentadiene gave a 1:1 mixture of diastereoisomeric *endo* adducts.[12]



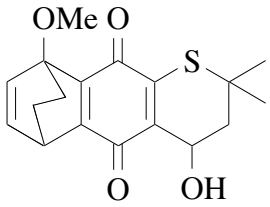




8a R^1 = Me , R^2 = H **9** **10**

8b R^1 = H , R^2 = Me

Then, the reaction of the quinone (**6**) with 1-methoxy-1,3-cyclohexadiene (**11**)[13] in methanol at room temperature for 24 h, followed by treatment with sodium hydride, and silver(I) oxide afforded compound (**12**). Aromatization of compound (**12**) by heating in xylenes gave naphtho[2,3-*b*]thiopyranoquinone (**13**) in 40% overall yield from **6**. The product showed proton and carbon spectral properties similar to those reported for the oxygen analog 4-hydroxy-9-methoxy-2*H*-naphtho[2,3-*b*]pyranoquinone (**2**),[3] but the definitive proof of the structure of quinone (**13**) was obtained by X-Ray crystal analysis (Figure 2).



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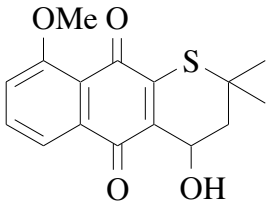

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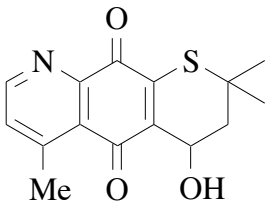

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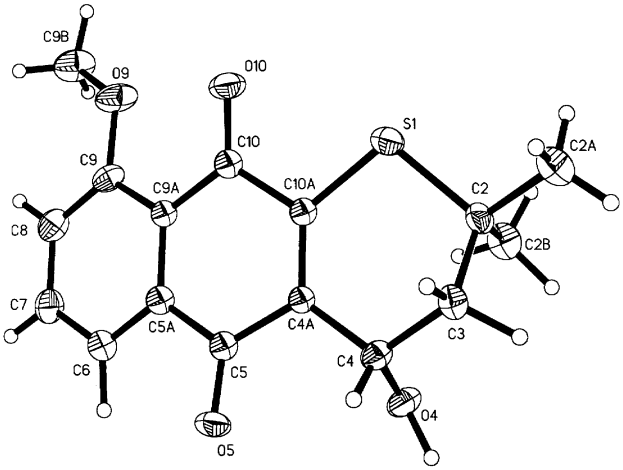


Figure 2: X-Ray structure for compound (**13**)

Finally, the reaction of the quinone (**6**) with 1-dimethylamino-1-aza-1,3-pentadiene(**14**)[14] in dichloromethane at room temperature gave an unstable adduct, which was oxidized *in situ* with silver(I) oxide to afford quinolin[3,2-*g*]thiopyranoquinone (**15**) in 29 % yield. In this cycloaddition the structural assignment is based on the observed previous regiochemistry of quinone (**6**) and, also on the prediction of theoretical calculations as explained below.

Computational Details

Optimized geometry for all the chemical species considered here was calculated at the PM3 level[15] since it has been proven to be accurate in predicting the reactivity and regioselectivity of Diels-Alder reactions.[16] *Ab initio* 6-31G* RHF molecular orbital calculations were also done in some cases to compare energies and frontier properties with those of PM3 results. Moreover, vibrational analysis was done at the PM3 level for each transition state (TS) structure search thus obtaining only one imaginary vibrational frequency corresponding to the formation of new bonds along the Diels-Alder adduct

formation. Activation energies were obtained from *Ab initio* methods (at the 6-31G* level) on the previous PM3 optimized geometries. All the calculations and surface maps were performed using the Spartan package.[17]

We will make use of the hardness concept of Density Functional Theory (DFT) to account for the regioselectivity of the Diels-Alder reaction of quinone (**6**) with the different electron-rich dienes reported here. This hardness concept is useful to assess compound reactivity in the spirit of the hard-soft acid-base theory (HSAB) proposed time ago by Pearson[18] and recently established on solid and almost quantitative grounds by means of DFT.[19] Moreover, the local use of the general behavior " soft likes soft" and " hard likes hard" has become a very attractive approach to explain the chemical reactivity of a wide variety of systems.[20,21] Here we plan to make use of the molecular hardness change of an electron acceptor molecule (A) like thioquinone (**6**), due to the potential chemical attack at a specific site carried out by an electron donor molecule (D). We will see that this strategy is very useful when the various electronic and steric effects of substituents and heteroatoms might make predictions of reaction sites difficult.

For a molecular system made out from electrons and nuclei reaching an equilibrium state, global electronic properties like electronegativity χ and the absolute hardness η are written as derivatives of the electronic energy with respect of the number of electrons,

$$\chi = -\left(\frac{\delta E}{\delta N}\right)_v = \frac{I + A}{2} \qquad , \qquad \eta = -\frac{1}{2}\left(\frac{\delta \chi}{\delta N}\right)_v = \frac{I - A}{2} \tag{1}$$

where I and A are the ionization potential and electron affinity, respectively. Besides, in DFT the Koopmans' theorem is obeyed for the frontier orbitals so that I and A are replaced by the HOMO and LUMO energies.

The molecular electronegativity surface map to which the molecular hardness map was encoded was drawn following a similar approach already stated elsewhere.[22] Briefly, the electrostatic potential $\phi(\mathbf{r})$ that the electrons and nuclei of a molecule create at each point $\mathbf{r}$ in the surrounding space is given rigorously by equation 2.

$$\phi(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \tag{2}$$

where Z_A is the charge on nucleus A located at $\mathbf{R}_A$, and $\rho(\mathbf{r})$ is the electronic density function of the molecule, $\rho(\mathbf{r}) = \sum_{i=1}^{occ} n_i |\psi_i(\mathbf{r})|^2$ for each occupied molecular orbital $\psi_i(\mathbf{r})$. Interestingly, $\phi(\mathbf{r})$ is a real

physical property derived from diffraction experiments so that any molecular reactivity index deduced from it will correspond also to useful experimental parameters.

In DFT the molecular electrostatic potential $\phi(\mathbf{r})$ is directly related[22] to the molecular electronegativity and since the latter is constant within the molecular space there exists a set of $\mathbf{r}_\chi$ position values at which the equality

$$\chi = \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \quad ; \quad \mathbf{r} = \text{set}\{\mathbf{r}_\chi\} \qquad (3)$$

is obeyed. This defines the electronegativity surface map for the molecule. In addition, its derivative against the number of electrons N at $\{\mathbf{r}_\chi\}$ yields the molecular hardness as a surface map at the set $\{\mathbf{r}_\chi\}$,

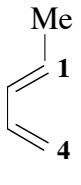
$$\left(\frac{\delta\chi}{\delta N}\right)_v = -\int \frac{\rho_{frontier}(r')dr'}{|r' - r_\chi|} = -2\eta_{frontier}(\mathbf{r}_\chi) \qquad (4)$$

Two possible phenomena were analyzed : (a) an electrophilic attack over the donor molecule D (thereby HOMO is involved for the δN electron transfer process) yielding $2\eta_-(\mathbf{r}_\chi)$ and (b) a nucleophilic attack over the acceptor molecule A (LUMO involved) yielding $2\eta_+(\mathbf{r}_\chi)$.

Equation (4) establishes that the frontier orbital electrostatic potential at different values of $\mathbf{r}_\chi$ is a measure of the hardness achieved by the molecule in response to a perturbation represented by the chemical attack of either an electrophile or a nucleophile. By this procedure a contour surface for η encoded to χ around the molecule was built to learn about which site yields the hardest molecular value for a given chemical attack. These statements conform with the Principle of Maximum Hardness (PMH)[23,24] that has been invoked to deduce regiospecificity in Diels-Alder reactions. [4,25] The local use of the general behavior "soft likes soft" and "hard likes hard" when confronting nucleophilic sites of (D) with electrophilic sites of (A) allow us to apply a similar approach for Diels-Alder reactions and here we plan to show that theory and experiments agree on this matter.

Figure 3 shows the molecular hardness map for the nucleophlilic attack over thioquinone (**6**), encoded at the molecular electronegativity χ isosurface value obtained as $\chi = -(\varepsilon_{homo} + \varepsilon_{lumo})/2$ using the data shown in Table 1. In principle, one finds that C7 site is harder than C6 site by 3 kcal/mole thus indicating that preferential orientation occurs against a nucleophile like (**7**), (**11**) or (**14**). Moreover, the HSAB principle together with the data in Table 1 allow us to decide that , for example, C1 of diene (**7**) will react against

C7 of thioquinone (**6**) whereas C4 of diene (**7**) will react against C6 of thioquinone (**6**) yielding naphthothiopyranoquinone (**8a**) as the main product for the Diels-Alder reaction.



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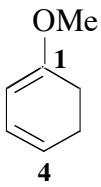

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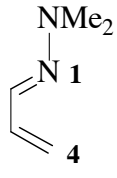

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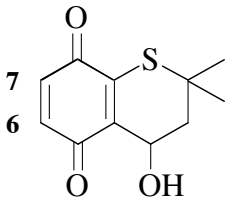

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A similar analysis can be done for the Diels Alder reaction between diene (**11**) and thioquinone (**6**): the main product for the reaction is found to be naphtho[2,3-*b*]thiopyranoquinone (**13**). It turns out also that reaction of azadiene (**14**) with the same substrate yields quinone (**15**) as the main product. These results represent a trend about the most probable isomer formation and it is very gratifying that these theoretical findings are in perfect agreement with the experimental results described here.

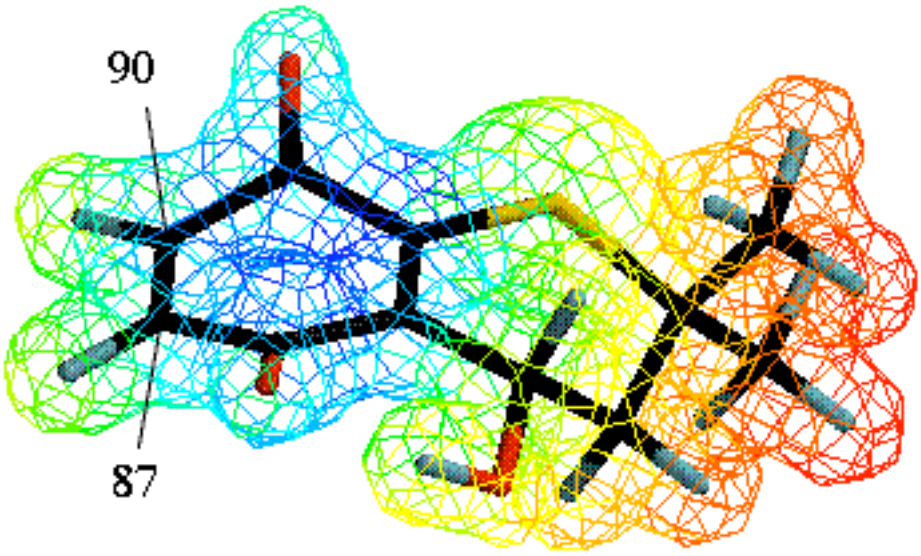
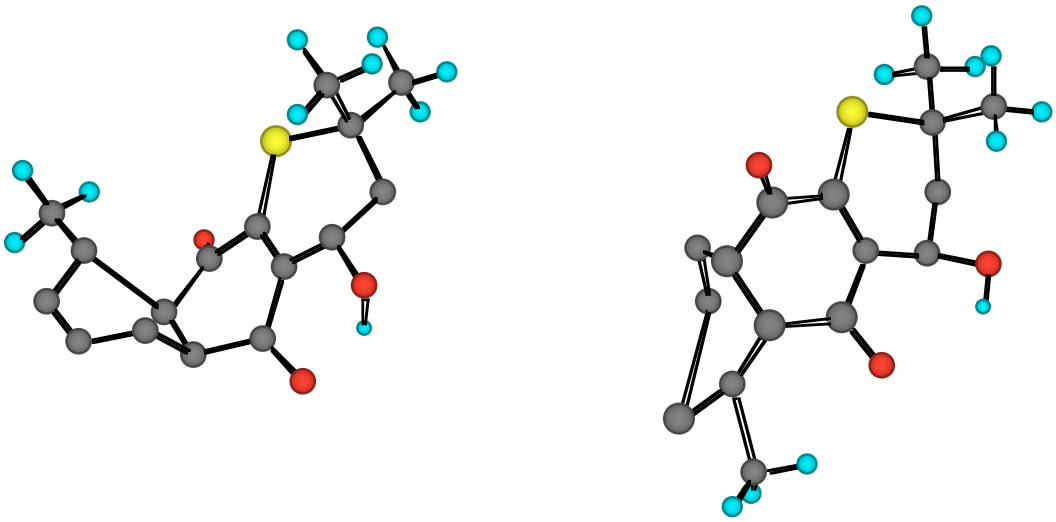


Figure 3. Molecular hardness surface map encoded on the molecular electronegativity isosurface value at 126.9 Kcal/mol for thioquinone (**6**). All values are in Kcal/mol.

Finally, to corroborate the theoretical findings discussed above we have investigated the nature of the transition state geometry for the Diels-Alder adduct formation between **6** and **7**. The resulting geometries and energy barriers shown in Figure 4 confirm that **8a** formation goes through a lower energy barrier than **8b** in agrement with experimental results and with the theoretical analysis done in this paper.



E_{activ} = 41.6 Kcal/mol E_{activ} = 168.3 Kcal/mol

Figure 4. Transition State Geometry [PM3] and Activation Energy [6-31G* *Ab-initio* calculation on the semiempirical geometry] for the **6** and **7** adduct formation isomers.

TABLE 1. Frontier orbital energy and Hardness values (eV) **for Diels-Alder Reactions**

Compound	HOMO	LUMO	Site	η	DA adduct sites
6	-9.263	-1.746	6	3.751	
η^A = 3.759 eV			7	3.881	
7	-9.205	0.277	1	4.923	1-7 and 4-6
η^D = 4.741 eV			4	4.495	4-7 and 1-6
11	-8.497	0.343	1	4.614	1-7 and 4-6
η^D = 4.420 eV			4	4.294	4-7 and 1-6
14	-8.787	0.110	1	4.718	1-7 and 4-6
η^D = 4.339 eV			4	2.873	4-7 and 1-6

(A): acceptor molecule (D): donor molecule

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are not corrected. IR spectra were recorded on a Bruker Model Vector 22 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-200 and AM-250 spectrometer, using tetramethylsilane as internal reference. Column chromatography

was perfomed on silica gel Merck 60 (70-230 mesh). Elemental analysis was carried out on a FISONS EA 1108 CHNS-O analyser. Accurate MS measurements were determined at the SERC Mass Spectrometry Centre, Leicester University.

2,3-Dihydro-8-hydroxy-2,2-dimethyl-4*H*-1-benzothiopyran-4-one (**4**)

A solution of benzothiopyran (**3**) (1.0 g, 4,5 mmol) in acetic acid (20 mL) and 47% aqueous hydrobromic acid (50 mL) was heated to reflux for 3.5 h. After cooling, the reaction mixture was extracted with dichloromethane (3x75 mL) and the combined extracts were washed with 5% $NaHCO_3$ and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using dichloromethane as eluent to give benzothiopyran (**4**) (0.79 g, 84%) as a light yellow solid which sublimes at 109 °C (benzene-ethyl acetate). IR (KBr): 3160 (OH), 1645 (C=O), 1590 (C=C) and 1160 (OH) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 1.48 (6 H, s, 2xCH_3), 2.90 (2 H, s, CH_2), 5.50 (1 H, s, OH), 7.06 (1 H, dd, *J* = 2.0 and 7.9 Hz, 7-H), 7.10 (1 H, t, *J* = 7.9 Hz, 6-H), 7.78 (1 H, dd, *J* = 2.0 and 7.9 Hz, 5-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 28.7, 45.0, 53.8, 119.8, 121.3, 125.1, 127.0, 130.9, 151.9, 195.0. HRMS calcd for $C_{11}H_{12}O_2S$: 208.0558. Found: 208.0559.

2,3-Dihydro-4,8-dihydroxy-2,2-dimethyl-2*H*-1-benzothiopyran (**5**)

A solution of benzothiopyran (**4**) (500 mg, 2.4 mmol) in tetrahydrofuran (20 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (115 mg, 3 mmol) in tetrahydrofuran (15 mL) at 0 °C, and the mixture was stirred for 3 h at rt. After cooling at 0 °C the reaction mixture was quenched by careful addition of 0.1 N hydrochloric acid (1.0 mL) and then filtered. The filtrate was washed with brine, dried and concentrated to give benzothiopyran (**5**) (460 mg, 92%) as a white solid; mp 136-137 °C (benzene-ethyl acetate). IR (KBr): 3550 (OH), 1590 (C=C) and 1090 (OH) cm^{-1}; ^{1}H-NMR (200 MHz, C_2D_6CO) δ: 1.46 (3 H, s, CH_3), 1.47 (3 H, s, CH_3), 2.08 (2 H, eight lines, CH_2), 3.41 (1 H, br s, OH), 4.86 (1 H, dd, *J* = 5.2 and 10.4 Hz, CH), 6.77 (1 H, d, *J* = 7.8 Hz, 7-H), 6.97 (1 H, t, *J* = 7.8 Hz, 6-H), 7.25 (1 H, d, *J* = 7.8, 5-H), 9.01 (1 H, br s, OH); ^{13}C-NMR (75 MHz, C_2D_6CO) δ: 32.8, 42.1, 48.3, 67.6, 113.9, 119.9, 12.0 (d), 125.0, 139.9, 153.4. Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71; S, 15.22. Found: C, 62.84; H, 6.60; S, 15.21.

2,3-Dihydro-4-hydroxy-2,2-dimethyl-2*H*-1-benzothiopyran-5,8-dione (**6**)

To a stirred solution of benzothiopyran (**5**) (100 mg, 0,48 mmol) in methanol (10 mL) containing potassium hydrogenphosphate (20 mg, 0.12 mmol), was added a solution of potasium nitrososulphonate

(410 mg, 1.53 mmol) in methanol-water (2:1, 10 mL). After stirring overnigth at rt, the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (2x100 mL). The combined extracts were dried ($MgSO_4$), concentrated and the residue was purified by column chromatography using dichloromethane-ethyl acetate (9:1) as eluent. Evaporation of the solvent gave benzothiopyran-5,8-dione (**6**) (64 mg, 60%) as a red solid, mp 64-66 °C (benzene-ethyl acetate). IR (KBr): 3400 (OH), 1645 and 1620 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.41 (3 H, s, CH_3), 1.50 (3 H, s, CH_3), 2.07 (2 H, eight lines, CH_2), 3.64 (1 H, br s, OH), 4.96 (1 H, t, *J* = 6.5 Hz, CH), 6.72 (1 H, d, J = 10.1 Hz, 6-H or 7-H), 6.80 (1 H, d, *J* = 10.1 Hz, 7-H or 6-H). ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ: 29.5, 29.8, 42.8, 43.1, 63.5, 133.9, 136.3, 137.8, 147.5, 183.9, 185.0. Anal. Calcd for $C_{11}H_{12}O_3S$: C, 58.91; H, 5.39; S, 14.99. Found: C, 59.17, H 5.21, S, 14.32.

3,4-Dihydro-4-hydroxy-2,2,9-trimethyl-2*H*-naphtho[2,3-*b*]thiopyran-5,10-dione (**8a**)

To a solution of benzothiopyran-5,8-dione (**6**) (100 mg, 0.45 mmol) in dichloromethane (10 mL), 1,3-pentadiene (**7**) (31 mg, 0.45 mmol) was added and the mixture was left for at rt. After 48 h, DDQ (165 mg, 0.72 mmol) was added and the mixture was stirred for 8 h at rt. The reaction mixture was filtered and the organic layer was washed with 5% $NaHCO_3$ and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel using dichloromethane-ethyl acetate (20:1) as eluant. Evaporation of the solvent gave 85 mg (66%) of a mixture of **8a** and **8b** (**8a**:**8b**=2:1 by ^{1}H-NMR). After flash chromatography (eluent dichloromethane-ethyl acetate 20:1) of the mixture, 40 mg (31%) of the mayor isomer (**8a**) was obtained; mp 168-169 °C (benzene-ethyl acetate). IR(KBr): 3435 (OH), 1650 (C=O) and 1620 (C=C) cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.44 (3 H, s, CH_3), 1.52 (3 H, s, CH_3), 2.05-2.20 (2 H, m, CH_2), 2.72 (3 H, s, $ArCH_3$) 4.02 (1 H, br s, OH), 5.12 (1 H, t, *J* = 6.6 Hz, CH), 7.48 (1 H, dd, *J* = 7.6 and 1.0 Hz, 8-H), 7.59 (1 H, t, J = 7.6 Hz, 7-H), 8.03 (1 H, dd, J = 7.6 and 1.0 Hz, 6-H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 20.5, 29.5, 29.9, 42.8, 42.9, 64.1, 125.6, 129.4, 133.5, 133.6, 135.0, 137.4, 141.9, 151.5, 183.0, 183.1. Crystal structure details: triclinic, *P*1, *a* = 8.276 (3), *b* = 9.424 (2), *c* = 9.992 (3) Å; a = 112.16°, b = 90.61°, g = 102.81°, V = 686.5 (4) $Å^3$, Z = 2, *D* = 1.395 g/cm^3, *F* (000) = 304, *T* = 293 K. HRMS calcd for $C_{16}H_{16}O_3S$: 288.0821. Found: 288.0820.

3,4,5a,6,9,9a-Hexahydro-4-hydroxy-6,9-methano-2,2-dimethyl-2*H*-naphtho[2,3-*b*]thiopyran-5,10-dione (**9**)

To a solution of benzothiopyran-5,8-dione (**6**) (100 mg, 0.45 mmol) in dichloromethane (10 mL), was added freshly distilled cyclopentadiene (120 mg, 1.82 mmol) and the mixture was stirred for 24 h at rt.

After evaporation of the solvent the product was separated by flash column chromatography using dichloromethane-ethyl acetate (19:1) as eluent, to give 115 mg (88 %) of compound (**9**) as a mixture of diastereoisomeric adducts in a 2:1 ratio; mp 140 °C (decomp) (benzene-ethyl acetate). IR (KBr): 3470 (OH) and 1650 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.33 and 136 (3 H, s, CH_3), 1.39 and 142 (3 H, s, CH_3), 1.40-1.60 (2 H, m, bridgehead CH_2), 1.95-2.05 (2 H, m, CH_2), 3.22-3.34 (2 H, m, 5a-H and 9a-H), 3.54 (2 H, m, 6-H and 9-H), 3.83 (0.66 H, d, J 2.4, OH), 4.03 (0.33 H, d, J = 2.4 Hz, OH), 4.84 (0.33 H, dt, J = 2.4 and 6.4 Hz, CH), 4.90 (0.66 H, dt, *J* = 2.4 and 6.4 Hz, CH), 6.0-6.2 (2 H, m, 7-H and 8-H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 29.0 (29.4), 29.5 (29.8), 42.3, 42.5 (42.7), 48.0, 48.1, 48.8, 49.2 (49.4), 49.7(50.0) 64.3 (63.9), 134.7, 135.1 (135.3), 153.6, 196.0, 197.0. HRMS calcd for $C_{15}H_{18}O_3S$: 290.0977. Found: 290.0977.

Photocyclization of **9**.

A solution of compound (**9**) (100 mg, 0.34 mmol) in benzene (20 mL) was irradiated under nitrogen at 20 °C in a pyrex vessel with a 125 W mercury lamp for 1 h. The solvent was removed to give a white residue (100 mg). Recrystallization (benzene-ethyl acetate) gave pure **10** as white solid (90 mg, 90%); mp 148-150 °C. IR (KBr): 3470 (OH) and 1740 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.36 (3 H, s, CH_3), 1.47 (3 H, s, CH_3), 1.67-2.06 (4 H, m, bridgehead CH_2 and 3-H), 2.80-3.00 (3 H, m), 3.01-3.20 (1 H, m), 3.30-3.45 (1 H, m), 4.20-4.40 (1 H, m, OH). HRMS calcd for $C_{15}H_{18}O_3S$: 290.0977. Found: 290.0977.

6,9-Ethano-3,4,6,9-tetrahydro-4-hydroxy-9-methoxy-2,2-dimethyl-2*H*-naphtho[2,3-*b*]thiopyran-5,10-dione(**12**)

To a solution of benzothiopyran-5,8-dione (**6**) (100 mg, 0.45 mmol) in methanol (10 mL), 1-methoxy-1,3-cyclohexadiene (**11**) (275 mg, 1.7 mmol) was added and the mixture was stirred for 24 h at rt. After evaporation of the solvent the residue was passed through a silica gel plug using dichloromethane-ethyl acetate (99:1) as eluent. The mixture of adducts was disolved in tetrahydrofuran (10 mL) and, it was added dropwise to a suspension of 60% sodium hydride (100 mg, 4.17 mmol) in tetrahydrofuran (10 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C, and then quenched by the addition of a saturated aqueous ammonium chloride solution. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water, and dried ($MgSO_4$). After evaporation of the solvent, the residue was dissolved in tetrahydrofuran and then silver(I) oxide (180 mg, 1.45 mmol) and magnesium sulfate (200 mg, 1.66 mmol) were added. The suspension was stirred for 2 h and filtered through Celite, and after removal of the solvent the residue was purified by column chromatography using dichloromethane-ethyl acetate (9:1) as eluent to afford quinone (**12**) (75 mg, 50%)

as an orange solid; mp 158-159 °C (benzene-ethyl acetate). IR (KBr): 3440 (OH), 1645 (C=O) and 1150 (C-O) cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.38 (3 H, s, CH_3), 1.47 (3 H, s, CH_3), 2.05-2.20 (2 H, m, CH_2) 3.54 (1 H, br s, OH), 3.57 (3 H, s, OCH_3), 4.28 (1 H, m, bridgehead H), 4.94 (1 H, t, *J* = 6.3 Hz, CH), 6.30-6.40 (1 H, m, 7-H), 6.52 (1 H, d, *J* = 7.9, 8-H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ: 25.1, 30.0, 30.2, 31.7, 34.0, 40.3, 40.4, 56.1, 63.8, 85.3, 131.6, 132.1, 135.5, 145.6, 148.5, 150.0, 179.9, 181.5. Anal. Calcd for $C_{18}H_{20}O_4S$: C, 65.04; H, 6.06; S, 9.64. Found: C, 64.81; H, 6.29; S,9.34.

3,4-Dihydro-4-hydroxy-9-methoxy-2,2-dimethyl-2*H*-naphtho[2,3-*b*]thiopyran-5,10-dione (**13**)

A solution of quinone (**12**) (70 mg, 0.21 mmol) in xylene (15 mL) was heated under reflux for 3 h. Removal of the solvent under reduced pressure and recrystallization from benzene-hexanes gave compound (**13**) (51 mg, 80%) as orange crystals ; mp 176-178 °C. IR (KBr): 3400 (OH), 1645 and 1620 (C=O) cm^{-1}; ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 1.41 (3 H, s, CH_3), 1.51 (3 H, s, CH_3), 2.05-2.20 (2 H, m, CH_2), 4.00 (3 H, s, OCH_3), 4.01 (1 H, br s, OH), 5.10 (1 H, t, *J* = 6.6 Hz, CH), 7.25 (1 H, dd, *J* = 1.0 and 8.2 Hz, 8-H),7.67 (1 H, t, *J* = 8.2 Hz, 7-H)), 7.75 (1 H, dd, J = 1.0 and 8.2 Hz, 6-H); ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ: 29.4, 29.9, 42.7, 42.9, 56.5, 64.1, 117.4, 119.4, 134.2, 134.3, 135.5, 152.6, 159.9, 180.7 and 182.6. Crystal structure details: triclinic, *P*1, *a* = 8.217 (2), *b* = 9.695 (2), *c* = 10.034 (3) Å; a = 111.43°, b = 95.51°, g = 104.07°, V = 706.5 (3) $Å^3$, Z = 2, *D* = 1.431 g/cm^3, *F* (000) = 320, *T* = 293 K. Anal. Calcd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30; S, 10.53. Found: C, 63.12; H, 5.36; S, 10.44.

3,4-Dihydro-4-hydroxy-2,2,7-trimethyl-2*H*-quinolin[3,2-*g*]thiopyran-5,10-dione (**15**)

A stirred solution of benzothiopyran-5,8-dione (**6**) (100 mg, 0.45 mmol) in dichloromethane (10 mL) was treated with 1-dimethylamino-1-aza-1,3-pentadiene (**14**) (112 mg, 0.9 mmol) and the mixture was stirred for 4 h at rt. Silica gel (500 mg) and silver(I) oxide (250 mg, 1.08 mmol) were added and the mixture was stirred for 24 h at rt. The mixture was filtered and the solid filter was rinsed thoroughly with dichloromethane. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel using hexane-ethyl acetate (2:1) as eluant. Evaporation of the solvent gave compound (**15**) (38 mg, 29 %); mp 190 °C (benzene-ethyl acetate) (decomp). IR (KBr): 3420 (OH) and 1665 (C=O) cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.47 (3 H, s, CH_3), 1.55 (3 H, s, CH_3), 2.05-2.20 (2 H, m, CH_2), 2.82 (3 H, s, CH_3), 3,80 (1 H, br s, OH), 5.13 (1 H, t, *J* = 6.6 Hz, CH), 7.44 (1 H, d, *J* = 4.9 Hz, 7-H), 8.78 (1 H, d, *J* = 4.9 Hz, 8-H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.5, 29.6, 29.7, 42.9, 43.0, 63.9, 127.7, 131.5, 136.8, 148.7, 148.9, 150.8, 152.8, 180.7 (s) and 184.6 (s). HRMS calcd for $C_{15}H_{15}NO_3S$: 289.0773. Found: 289.0777.

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