STUDIES ON QUINONES. PART 31.[1] SYNTHESIS AND CYCLIZATION OF SUBSTITUTED 2-ACETYLAMINO-1,4-BENZOQUINONES

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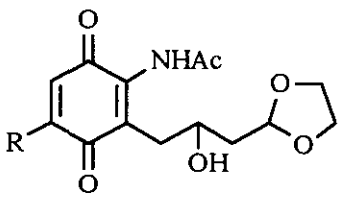
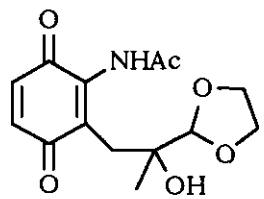
Abstract - The synthesis of 4-acetylamino-5-hydroxybenzo[*b*]furans (**7a**), (**7b**), (**13**), and their oxidative furan ring opening to the corresponding substituted 2-acetylamino-1,4-benzoquinones (**1a**), (**1b**), and (**2**) are reported. The acid-induced cyclization of quinones (**1a**) and (**2**) to afford *N*-heterocyclic quinones (**15**) and (**16**) is also described.

In previous works on the chemistry of activated quinones we have described the preparation of 5-hydroxybenzo[*b*]furans and their application to the synthesis of carbocyclic quinones.[2-8] More recently, we have reported two new routes to highly functionalized 5-hydroxy-2,3-dihydrobenzo[*b*]furans which are based on : a) acid-induced rearrangement of Diels-Alder adducts of activated benzoquinones with (*E*)-1-trimethylsilyloxybuta-1,3-diene[9-11] and b) reaction of benzoquinones with methacrolein N,N-dimethylhydrazone.[12] Our interest to develop new methods for the synthesis of heterocyclic quinones[13-17] led us to investigate the furan ring opening of benzofurans[18] aimed to obtain *N*-heterocyclic quinones.[19,20] In this communication we report the synthesis of substituted 1,4-benzoquinones (**1a**), (**1b**), and (**2**) *via* furan ring opening of substituted 4-acetylamino-5-hydroxybenzo[*b*]furans and the acid-induced cyclization of **1a** and **2** to their corresponding 7- and 6-membered *N*-heterocyclic quinones.



1a. R = H
1b. R = Br



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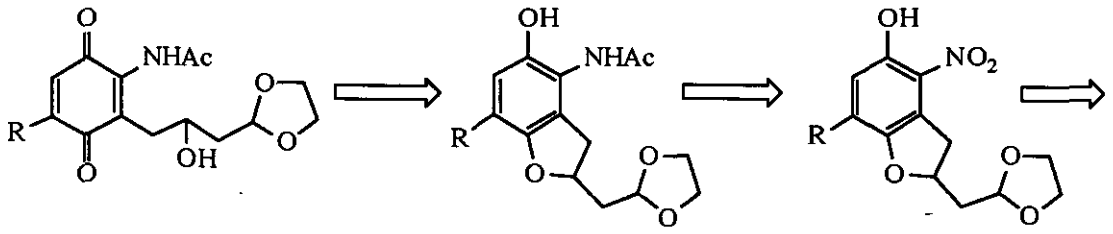
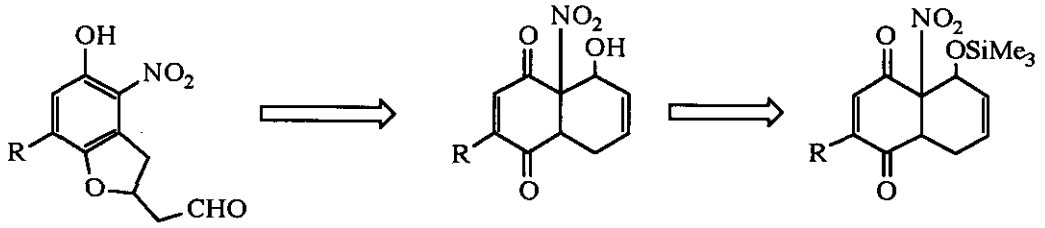
The synthesis of quinones (**1a**) and (**1b**) was explored from the corresponding Diels-Alder adducts (**3a**) and (**3b**). The retrosynthetic sequence outlined in Scheme 1 shows our strategy to prepare these benzoquinones in which the furan ring opening of heterocycles (**7**) is the key step.



1a. R = H
b. R = Br

7a. R = H
b. R = Br

6a. R = H
b. R = Br



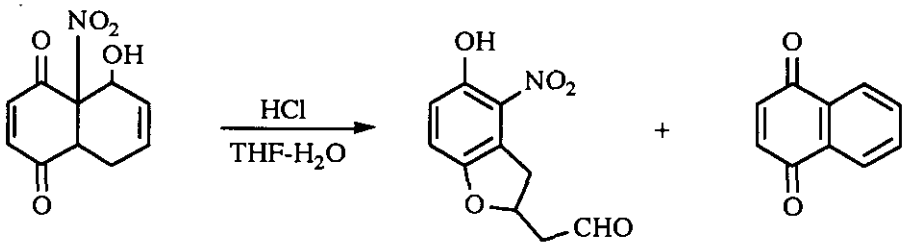
5a. R = H
b. R = Br

4a. R = H
b. R = Br

3a. R = H
b. R = Br

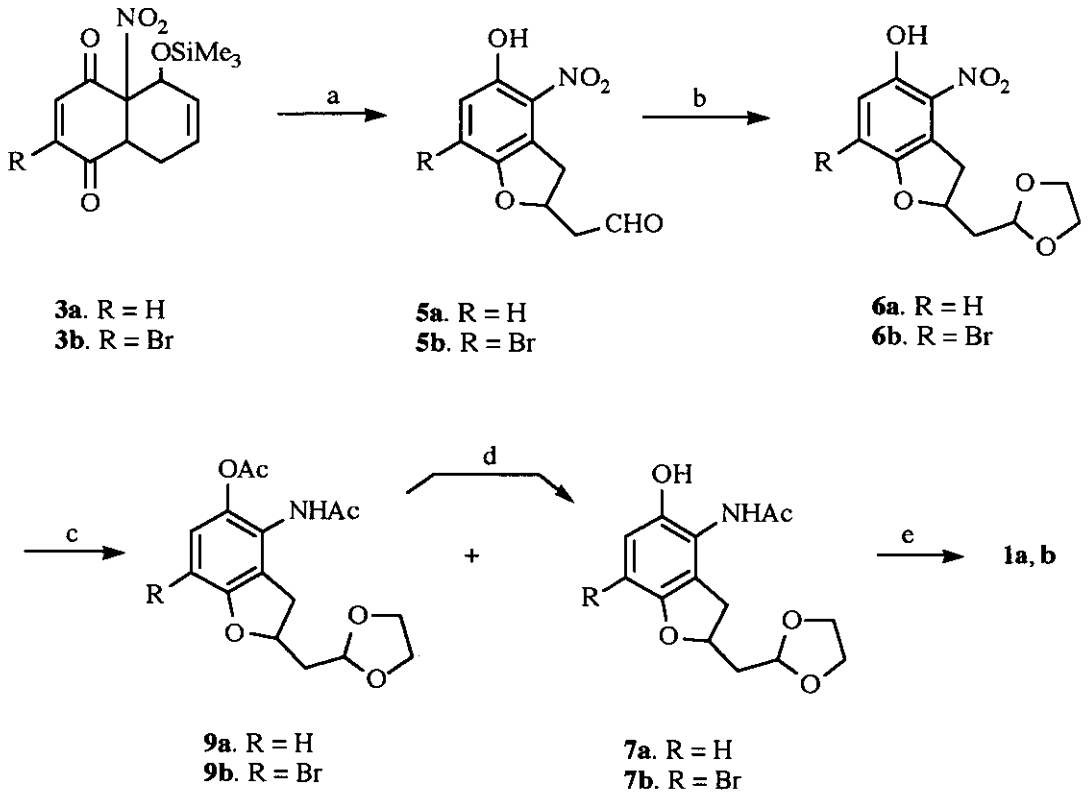
Scheme 1

Alcohol (**4a**) prepared by mild acid hydrolysis from adduct (**3a**)[11] was rearranged to furan (**5a**) by reaction with hydrochloric acid in THF solution. Under these conditions **5a** was formed along with 1,4-naphthoquinone (**8**) as secondary product. Indeed quinone (**8**) was formed from **4** by acid-induced aromatization-elimination reactions. A qualitative experiment demonstrated that the convertion of **4a** to **8** is also induced by thermolysis in refluxing toluene.



4a **5a** **8**

In order to improve the synthesis of furan (**5a**), we studied the rearrangement of adduct (**3a**) with montmorillonite.[21] The reaction of **3a** with montmorillonite KSF was conducted in chloroform at 50°C to afford furan (**5a**) in 95% yield; trace amounts of naphthoquinone (**8**) were detected by TLC and ^{1}H-NMR. Compound (**5a**) was converted to acetal (**6a**) (89%) by reaction with ethylene glycol and *p*-toluenesulfonic acid in benzene.



3a. R = H
3b. R = Br

5a. R = H
5b. R = Br

6a. R = H
6b. R = Br

9a. R = H
9b. R = Br

7a. R = H
7b. R = Br

a) montmorillonite KSF, $CHCl_3$, b) $HOCH_2CH_2OH$, *p*-TsOH, C_6H_6, c) H_2, 10% Pd-C, Ac_2O, CH_2Cl_2, d) K_2CO_3, MeOH, e) CAN, MeCN-H_2O

Scheme 2

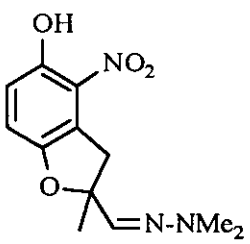
When the rearrangement reaction of adduct (**3a**) to **5a** with acidic clay was scaled up to 1.0 g of substrate (**3a**) a complex mixture of products was generated. The ^{1}H-NMR spectrum of the mixture showed the signals of **5a** and also complex signals attributed to oligomers of aldehyde (**5a**).

We confirmed the presence of these secondary products by treatment of the reaction mixture with ethylene glycol and *p*-toluenesulfonic acid that afforded acetal (**6a**) as the sole product.

Catalytic hydrogenation of acetal (**6a**) on 10% Pd-C in dichloromethane containing acetic anhydride gave a mixture of amides (**7a**) and (**9a**) and then followed by hydrolysis with potassium carbonate in methanol at room temperature to provide amide (**7a**) in 83% yield. When amide (**7a**) was allowed to react with cerium ammonium nitrate (CAN) in acetonitrile-water, quinone (**1a**) was isolated in 97% yield. On the basis of these results the synthesis of benzoquinone (**1b**) was attempted through the same reaction sequence shown in Scheme 2.

The reaction of 2-bromo-1,4-dihydroxy-5-nitrobenzene[12] with (*E*)-1-trimethylsilyloxybuta-1,3-diene and silver(I) oxide afforded the unstable adduct (**3b**), which by rearrangement with montmorillonite in chloroform followed by reaction of the resulting furan (**5b**) with ethylene glycol in the presence of *p*-TsOH, provided **6b**. Heterocycle (**6b**) was then submitted to catalytic hydrogenation on 10% Pd-C in dichloromethane containing acetic anhydride to afford a mixture of amides (**7b**) and (**9b**). Treatment of the mixture with potassium carbonate in methanol at room temperature provided amide (**7b**) in 53% overall yield. Finally, furan ring opening of **7b** with CAN afforded benzoquinone (**1b**) in 61 % yield.

On the basis of the facile access to quinones (**1a**) and (**1b**), the synthesis of benzoquinone (**2**) from hydrazone (**10**)[12] by a similar sequence was studied. Heterocycle (**10**) was converted to aldehyde (**11**) in 89% yield by reaction with hydrochloric acid-acetone solution. Compound (**11**) was allowed to react with ethylene glycol and *p*-toluenesulfonic acid to afford acetal (**12**) which was then hydrogenated over 10% Pd-C in dichloromethane followed by treatment of the reaction mixture with acetic anhydride. This provided a mixture of amides (**13a**) and (**13b**) which by reaction with potassium carbonate in methanol afforded furan (**13b**) in good yield. Further reaction of amide (**13b**) with CAN in acetonitrile-water provided benzoquinone (**2**) in 89% yield.



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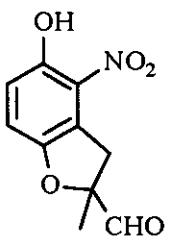

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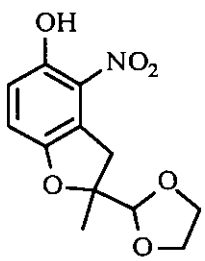

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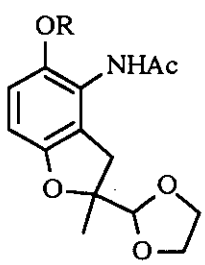
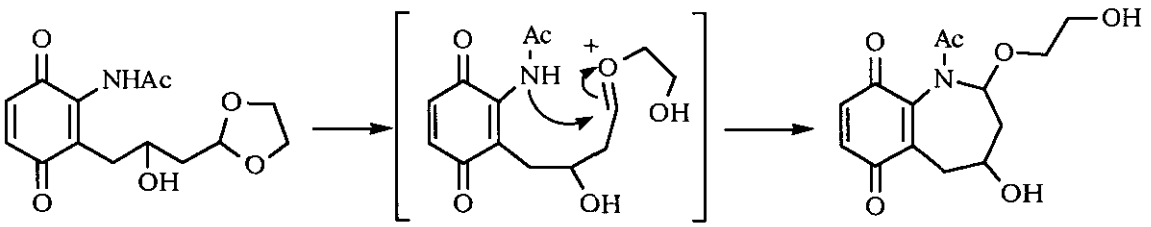


13a. R = Ac
13b. R = H

The reactivity of the functionalized benzoquinones to the cyclization was firstly examined on quinone (**1a**). This compound was dissolved in dichloromethane and a catalytic amount of *p*-toluenesulfonic acid was added to the yellow solution. A fast reaction was observed and a deep red solution was obtained.

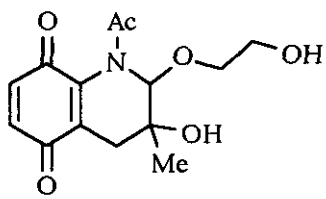
TLC showed the presence of a red substance along with decomposition products. Silica gel chromatography of the mixture afforded benzazepinequinone (**15**). The structure of **15** was assigned by its ^{1}H-NMR spectrum which showed two OH protons (δ 1.68 and 5.89), two coupled vinylic protons (δ 6.56 and 6.61, J = 10 Hz), a CH_3 singlet (δ 2.02), four coupled CH_2 protons (δ3.75-3.96) and six mutually coupled protons (δ 1.77, 2.09, 2.40, 2.96, 4.73, and 4.90).

The formation of heterocyclic quinone (**15**) from benzoquinone (**1a**) probably occurs through intermediate (**14**) in which the C-N bond is formed by nucleophilic attack of the nitrogen atom on the carbocation generated by acid-induced opening of the dioxolane ring.



1a **14** **15**

The reactivity toward the cyclization of quinone (**2**) was examined by employing *p*-toluenesulfonic acid and also trichloroacetic acid however, in both cases extensive decomposition of the substrate was observed by TLC. Relatively better results were obtained by using trifluoroacetic acid in benzene at room temperature. This treatment afforded quinone (**16**) along with heterocycle (**13b**) and decomposition products.



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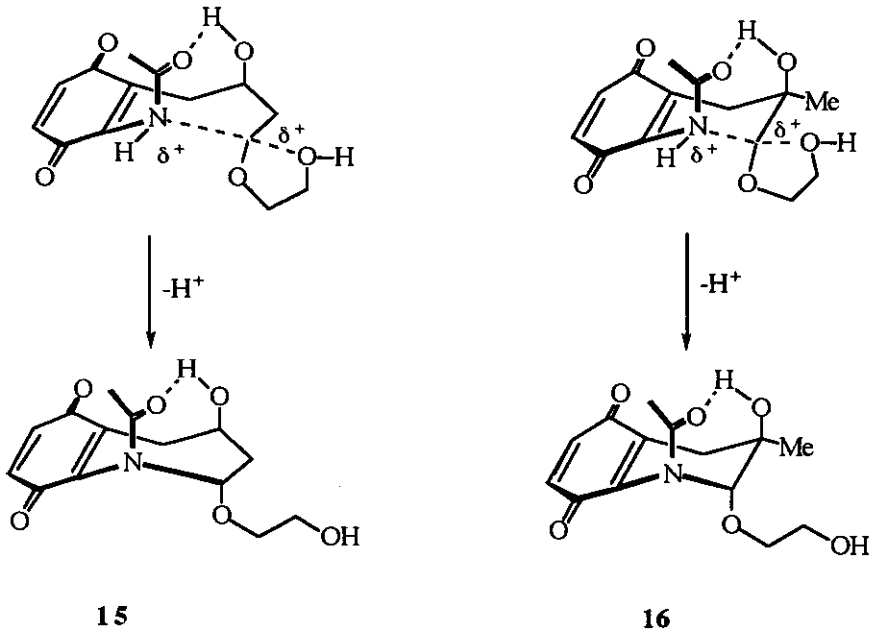
Heterocycles (**13b**) and (**16**) were isolated by silica gel chromatography in 11 and 8% yields, respectively. Benzofurane (**13b**) probably arises through a redox reaction of quinone (**2**) to the respective quinol followed by cyclodehydration. This undesirable competitive reaction was attributed to the steric hindrance between the substituent at 2- and 3-positions in quinone (**2**) which is alleviated by cyclization to the benzofuran (**13b**). It is noteworthy that the structure of heterocyclic quinones (**15**) and (**16**) has two stereogenic centres however, a sole *N*-heterocyclic quinone was detected and isolated in each case.

The analysis of the IR spectra of quinones (**15**) and (**16**) showed two sorts of hydroxyl absorptions at 3410/3330 and 3454/3370 cm^{-1} respectively. The ^{1}H-NMR spectra of compounds (**15**) and (**16**) displayed a narrow signal of one interchangeable proton at δ 5.89 and 5.61 ppm respectively which remains almost unaffected with dilution.

These spectral properties indicate that quinones (**15**) and (**16**) have an intramolecular hydrogen bond between the hydroxyl group located on the heterocyclic ring and the carbonyl group at the *N*-1 position.



15 **16**

Figure 1

It is possible that the hydrogen bond interaction makes influence on the stereoselective formation of *N*-heterocyclic quinones (**15**) and (**16**). Taking into account this interaction the formation of the quinones may be tentatively explained by the stabilization of the corresponding transition states.

Figure 1 showed the hypothetical transition states in both cases and their probable relative configurations. The *pseudo-axial* position of the substituent OCH_2CH_2OH in quinones (**15**) and (**16**) is proposed considering the smaller energy of these molecules[22] than those in which this group have a *pseudo-equatorial* orientation.

In conclusion, the results indicate that benzo[*b*]furans (**7a**), (**7b**), and (**13b**) are suitable precursors to provide highly functionalized benzoquinones which are not easily available by other routes. The cyclization reactions of benzoquinones (**1a**) and (**2**) to the corresponding *N*-heterocyclic quinones (**15**) and (**16**) show the potential application of this type of benzoquinones to the synthesis of novel nitrogen containing heterocyclic quinones.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer for KBr disc and the wave numbers are given in cm^{-1}. The ^1H- and ^{13}C-NMR spectra were determined on a Bruker AM-200 in deuteriochloroform. Chemical shifts are reported in δ ppm downfield to TMS, and *J* values are given in Hertz. Microanalysis were performed in the Instituto de Química General (C.S.I.C.) Madrid Spain. Silica gel Merck 60 (70-230 mesh), and DC-Alufolien $60F_{254}$ were used for preparative column and analytical TLC, respectively. Kieselgel S (230-400 mesh) Riedel-de Haën was used for flash chromatography. Montmorillonite KSF was commercialy supply by Aldrich.

5-Hydroxy-4-nitro-2-(2-oxoethyl)-2,3-dihydrobenzo[*b*]furan (5a) A solution of adduct (**3a**) (344 mg, 1.16 mmol) and montmorillonite KSF (2 g) in chloroform (20 mL) was stirred for 30 h at 50°C. The mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was chromatographed on silica gel (eluting with chloroform) to afford pure furan (**5a**) (247 mg, 95%). This compound was identical in all respects (TLC, IR and ^1H-NMR) with an authentical sample prepared in our laboratory.[11]

5-Hydroxy-4-nitro-2-(2-oxoethyl)-2,3-dihydrobenzo[*b*]furan ethylene acetal (6a)

Preparation from **5a**. - A solution of furan (**5a**) (417 mg, 1.87 mmol), dry ethylene glycol (0.12 ml, 2.24 mmol) and *p*-toluenesulfonic acid (100 mg) in benzene (30 mL) was refluxed for 1 h. The mixture was poured into water and the organic layer was washed with saturated aqueous sodium hydrogencarbonate, water and dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude acetal was purified by column chromatography on silica gel (eluting with chloroform) to give pure **6a** (443 mg, 89%) as an orange solid, mp 90-92°C. *Anal.* Calcd for $C_{12}H_{13}NO_6$: C, 53.92; H, 4.91; N, 5.24. Found: C, 54.16; H, 4.90; N, 5.24. ν_{max}: 1540, 1320, and 1220. ^1H-NMR δ: 1.45-2.58 (m, 1H, 1'-H), 2.29 (ddd, 1H, *J* = 14, 8 and 4, 1'-H'), 3.40 (dd, 1H, *J* = 18 and 8, 3-H), 3.70-4.09 (m, 5H, 3-H' and OCH_2CH_2O), 4.98-5.14 (m, 2H, 2- and 2'-H), 6.95 (d, 1H, *J* = 9, 6-H), 7.04 (d, 1H, *J* = 9, 7-H), 10.23 (s, 1H, OH). ^{13}C-NMR δ: 38.54, 40.14, 64.91, 65.03, 80.52, 101.65, 118.98, 119.07, 123.14, 149.54, 153.25.

Preparation from **3a**.- A mixture of **3a** (1.157 g, 3.92 mmol) and montmorillonite KSF (7 g) in chloroform (40 mL) was vigorously stirred at 50°C for 5 h. The mixture was filtered and the solid was thoroughly washed with chloroform. The filtrate was evaporated and ethylene glycol (292 mg, 4.71 mmol), *p*-toluensulfonic acid (600 mg) and benzene (20 mL) were added to the residue and the mixture was refluxed for 2 h. After the usual work-up the crude was purified by column chromatography (eluting with chloroform) to afford pure acetal (**6a**) (677 mg, 65%).

4-Acetylamino-5-hydroxy-2-(2-oxoethyl)-2,3-dihydrobenzo[*b*]furan ethylene acetal (7a)

To a suspension of 10% palladium on charcoal (133 mg) in dichloromethane (23mL), were added furan (**6a**) (166 mg, 0.621 mmol) and then acetic anhydride (139 mg, 1.36 mmol). The mixture was stirred at rt in a Parr hydrogenation apparatus at 35 psi for 2.5 h. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was stirred with ice-water at ambient temperature and the mixture was neutralized with potassium hydrogencarbonate. The resulting mixture was extracted with ethyl acetate (4x25 mL) and the dried organic layer was evaporated under reduced pressure. The residue was dissolved in metanol (20 mL) and potassium carbonate (300 mg) were added. After stirring for 5 min at rt, water was added. The resulting mixture was extracted with ethyl acetate and the organic extract was washed with water and dried over magnesium sulfate. Evaporation of the solvent followed by PLC (85:15 chloroform:methanol) afforded benzofuran (**7a**) (144 mg, 83%) as white solid mp 88-90°C (chloroform). *Anal.* Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 59.98; H, 6.14; N, 5.02. ν_{max}: 3300, 3160, and 1660. ^{1}H-NMR δ: 1.93-2.06 (m, 1H, 1'-H), 2.13-2.36 (m, 1H, 1'-H'), 2.26 (s, 3H, COMe), 2.89 (dd, 1H, *J* = 15 and 8, 3-H), 3.23 (dd, 1H, *J* = 15 and 9, 3-H'), 3.85-4.05 (m, 4H, OCH_2CH_2O), 4.96 (m, 1H, 2-H), 5.06 (dd, 1H, *J* = 5 and 4, 2'-H), 6.59 (d, 1H, *J* = 9, 6-H), 6.79 (d, 1H, *J* = 9, 7-H), 7.18 (br s, 1H, NH), 7.81 (s, 1H, OH). ^{13}C-NMR δ: 23.64, 34.60, 40.05, 64.87, 64.96, 79.77, 101.8, 108.19, 118.83, 122.52, 119.37, 143.32, 153.20, 170.36 .

2-Acetylamino-3-(2-hydroxy-4-oxobutyl)-1,4-benzoquinone ethylene acetal (1a) A solution of CAN (470 mg, 0.85 mmol) in water (8.5 mL) was added dropwise with stirring to a solution of **7a** (120 mg, 0.428 mmol) in acetonitrile (21 mL) and the stirring was continued by 30 min at rt. The orange solution was diluted with water, extracted with chloroform and the organic layer dried over magnesium sulfate. Evaporation of the solvent afforded crude quinone (**1a**) which was purified by column chromatography (eluting with chloroform) to provide pure **1a** (122 mg, 97%), as yellow solid mp 135-136°C. *Anal.* Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.98; N. 4,70. Found: C, 57.12; H, 5.74; N, 4.87. ν_{max}: 3420, 3220, 1680, 1660, 1600, and 1520. ^{1}H-NMR δ: 1.70 (ddd, 1H, *J* = 15, 10, and 5, 3'-H), 1.94 (ddd, 1H, *J* = 15, 3 and 2, 3'-H'), 2.08 (br s, 1H, OH), 2.12 (s, 3H, COMe), 2.58 (dd, 1H, *J* = 13.5 and 8, 1'-H), 2.72 (dd, 1H, *J* = 13. 5 and 3, 1'-H'), 3.73-4.01 (m, 4H, OCH_2CH_2O), 4.16 (m, 1H, 2'-H), 4.96 (dd, 1H, *J* = 5 and 3, 4'-H), 6.70 (d, 1H, *J* = 10, 6-H), 6.75 (d, 1H, *J* = 10, 5-H), 8,76 (br s, 1H, NH). ^{13}C-NMR δ: 23.52, 32.40, 39.69, 64.74, 64.98, 68.63, 103.15, 134.41, 135.84, 136.26, 140.97, 169.41, 181.45, 187.00.

7-Bromo-5-hydroxy-4-nitro-2-(2-oxoethyl)-2,3-dihydroxybenzo[*b*]furan (5b) A mixture of 2-bromo-1,4-dihydroxy-5-nitrobenzene (100 mg, 0.427 mmol), silver(I) oxide (157 mg, 0.678 mg) and magnesium sulfate (100 mg, 0.83 mmol) in benzene (20 mL) was vigorously stirred for 30 min at rt. Then a solution of (*E*)-1-trimethylsilyloxybuta-1,3-diene (70 mg, 0.492 mg) in benzene (2 mL) was added dropwise and the mixture was stirred at room temperature for 16 h. The solution was filtered and the solvent was removed under reduced pressure to afford 2-bromo-4a-nitro-5-trimethylsilyloxy-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (**3b**), as an unstable yellow oil (140 mg, 88%). ν_{max}: 1710, 1680, 1060, and 850. ^{1}H-NMR δ: -0.03 (s, 9H, Me_3SiO), 2.19 (dd, 1H, *J* = 20 and 7, 8-H), 3.20 (dd, 1H, *J* = 20 and 3, 8-H), 4.18 (d, 1H, *J* = 7, 8a-H), 4.91 (d, 1H, *J* = 7, 5-H), 5.6-6.0 (m, 2H, 6- and 7-H), 7.31 (s, 1H,

3-H). A solution of adduct (**3b**) (118 mg, 0.315 mmol), montmorillonite KSF (700 mg) in chloroform (10 mL) was stirred for 30 h at 50°C. The mixture was filtered, washed thoroughly with chloroform and the filtrate was evaporated under reduced pressure to afford crude furan (**5b**) which was purified by column chromatography (eluting with chloroform); red solid (44 mg, 46%), mp 133-134°C. *Anal.* Calcd. for: $C_{10}H_8NO_5Br$: C, 39.87, H, 2.68, N, 4.65; Br, 26.22. Found: C, 40.20; H, 2.82; N, 4.90; Br, 26.17. ν_{max}: 3160, 1710. ^{1}H-NMR δ: 3.02 (dd with fine coupling, 1H, *J* = 18 and 6.5, 1'-H), 3.19 (ddd, 1H, *J* = 18, 6.5 and 1; 1'-H'), 3.46 (dd with fine coupling, 1H, *J* = 18 and 8, 3-H), 4,12 (dd with fine coupling, 1H, *J* = 18 and 8, 3-H'); 5.31-5.46 (m, 1H, 2-H), 7.26 (s, 1H, 6-H), 9.87 (t, 1H, *J* = 1, CHO), 10.25 (s, 1H, OH). ^{13}C-NMR δ: 39.32, 49,30, 78.88, 113.56, 122.15, 123.19, 149.69, 150.65, 198.4.

7-Bromo-5-hydroxy-4-nitro-2-(2-oxoethyl)-2,3-dihydrobenzo[*b*]furan ethylene acetal (6b) A solution of furan (**5b**) (145 mg, 0.48 mmol), dry ethylene glycol (0.05 mL, 0,96 mmol) and *p*-toluenesulfonic acid (100 mg) in benzene (25 mL) was refluxed for 2 h. The mixture was washed consecutively with water, aqueous 5% hydrogencarbonate and water , and dried over magnesium sulfate. The solvent was removed and the residue was purified by PLC on silica gel (eluting with chloroform) to provide acetal (**6b**) (137 mg, 82%) as orange solid mp 123-124°C. *Anal.* Calcd for $C_{12}H_{12}NO_6Br$: C, 41.64; H, 3.49; N, 4.05. Found: C, 41.90; H, 3.70; N, 4.12. ν_{max}: 3230, 1520, and 1280. ^{1}H-NMR δ: 1.98-2.11 (m, 1H, 1'-H), 2.31 (ddd, 1H, *J* = 14, 14, and 7.0, 1'-H'); 3.46 (dd, 1H, *J* = 18.5, and 8, 3-H), 3.85-4.08 (m, 5H, 3-H and OCH_2CH_2O), 7.19 (s,1H, 7-H), 10.23 (s, 1H, OH). ^{13}C-NMR δ: 39.51, 39.94, 64.93, 65.02, 80.97, 101.36, 113.42, 121.75, 123.87, 149.38, 150.96.

4-Acetylamino-7-bromo-5-hydroxy-(2-oxoethyl)-2,3-dihydrobenzo[*b*]furan ethylene acetal (7b) To a suspension of 10% palladium on charcoal (50 mg) in ethyl acetate (20 mL), were added compound (**6b**) (100 mg, 0.289 mmol) and then acetic anhydride (139 mg, 1.36 mmol). The mixture was stirred at rt in a Parr hydrogenation apparatus at 35 psi for 2 h. The mixture was filtered and sodium hydrogencarbonate (100 mg) and water (1 mL) were added to the filtrate. The resulting mixture was stirred for 30 min and then evaporated under reduced pressure. The residue was treated with ice-water and the resulting solid was collected by filtration and washed with water. The solid was poured into methanol (20 mL) and the solution was stirred in the presence of potassium carbonate (300 mg) for 5 min at rt and then diluted with water. The resulting mixture was extracted with ethyl acetate and the organic extract was washed with water and dried over magnesium sulfate. Evaporation of the solvent followed by PLC (eluting with 70:30 ethyl acetate-ligh petroleum) afforded benzofuran (**7b**) (173 mg, 53%) as a white solid mp 210-212°C. High-resolution Ms Calcd for $C_{14}H_{16}NO_5Br$: 359.01914. Found: 359.01782. ν_{max}: 3080, 3300, 1650. ^{1}H-NMR δ (acetone-d_6): 2.21-2.30 (m, 2H, 1'-H), 2.23 (s, 3H, COMe), 3.15 (dd, 1H, *J* =18 and 7, 3-H), 3,53 (dd, 1H, *J* = 18 and 7, 3-H'), 3.88-4.04 (m, 4H, OCH_2CH_2O), 5.06 (m, 2H, 2-H and 2'-H), 6.91 (s, 1H, 6-H), 9.23 (br s, 2H, OH and NH). ^{13}C-NMR δ (acetone-d_6): 23.45, 37.01, 41.17, 65.77, 65.82, 81.67, 102.58, 99.40, 123.62, 124.56, 120.96, 146.25, 151.27, 171.92 .

2-Acetylamino-5-bromo-3-(2-hydroxy-4-oxobutyl)-1,4-benzoquinone ethylene acetal (1b) According to the above procedure, quinone (**1b**) was prepared from **7b** (29 mg, 0.08 mmol) and CAN (88

mg, 0.16 mmol) in acetonitrile (4 mL). Purification of crude quinone by column chromatography (eluting with 95:5 dichloromethane-methanol) afforded pure **7b** (18 mg, 61%) as yellow solid mp 130-132°C. High-resolution Ms Calcd for $C_{14}H_{16}NO_6Br$: 377.029703. Found 377.028900. ν_{max}: 3460, 3260, 1720, 1660, 1640, and 1600. ^{1}H-NMR δ: 1.65 (s, 1H, OH), 1.73 (ddd, 1H, *J* = 15, 10, and 5, 3'-H), 2.03 (ddd, 1H, *J* = 15 and 3, 3'-H'), 2.17 (s, 3H, COMe), 2.68 (dd, 1H, *J* = 13.5 and 8, 1'-H), 2.82 (dd, 1H, *J* = 13.5 and 3, 1'-H'), 3.81-4.05 (m, 4H, OCH_2CH_2O), 4.23 (m, 1H, 2'-H), 5.01 (dd, 1H, *J* = 5 and 3, 4'-H), 7.30 (s, 1H, 5-H), 8.86 (br s, 1H, NH). ^{13}C-NMR δ: 23.57, 33.20, 39.27, 64.82 65.06, 68.84, 103.26, 133.64, 136.86, 141.73, 137.42, 169.35 , 178.69, 179.59 .

2-Formyl-5-hydroxy-2-methyl-4-nitro-2,3-dihydrobenzo[*b*]furan (11) A solution of hydrazone (**10**)[12] (283 mg, 1.06 mmol), hydrochloric acid (7 mL, 15%) and acetone (2 mL) was stirred at rt for 30 min. The mixture was diluted with water and extracted with dichloromethane (10 mL). The extract was washed with water, dried over magnesium sulfate and evaporated to afford a solid residue. Column chromatography provided pure aldehyde (**11**) (211 mg, 89%) as red solid mp 121-123°C. High-resolution Ms Calcd for $C_{10}H_9NO_5$: 223.04807. Found: 223.04803; ν_{max}: 3480-3200, 1760, 1530, and 1270. ^{1}H-NMR δ: 1.60 (s, 3H, Me), 3.46 (d, 1H, *J* = 19, 3-H), 4.00 (d, 1H, *J* = 19, 3-H'), 7.02 (d, 1H, *J* = 10, 6-H), 7.13 (d, 1H, *J* = 10, 7-H), 9.71 (s, 1H, CHO), 10.26 (s, 1H, OH). ^{13}C-NMR δ: 17.37, 35.88, 87.32, 115.45, 115.86, 117.73, 146.34, 148.17, 195.53.

2-Formyl-2-methyl-5-hydroxy-4-nitro-2,3-dihydrobenzo[*b*]furan ethylene acetal (12) A solution of **11** (968 mg, 4.34 mmol), ethylene glycol (323 mg, 5.21 mmol), and *p*-toluensulfonic acid (100 mg) in benzene (100 mL) was refluxed for 2 h. Work-up afforded crude acetal (**12**) which was purified by column chromatography (eluting with dichloromethane) yielded pure **12** (1.079 g, 93%) as red-orange solid mp 129-130°C; *Anal.* Calcd for $C_{12}H_{13}NO_6$: C, 53.93; H, 4.90; N, 5.24. Found: C, 53.80; H, 4.96; N, 5.35. ν_{max}: 3240, 1600, 1520, and 1280. ^{1}H-NMR δ: 1.49 (s, 3H, Me), 3.33 (d, 1H, *J* = 18, 3-H), 3.78 (d, 1H, *J* = 18, 3-H'), 3.88-4.12 (m, 4H, OCH_2CH_2O), 4.94 (s, 1H, 1'-H), 6.89 (d, 1H, *J* = 9, 6-H), 6.98 (d, 1H, *J* = 9, 7-H), 10.23 (s, 1H, OH). ^{13}C-NMR δ: 22.11, 39.81, 65.84, 65.91, 89, 38, 105.57, 118.88, 118.94, 123.03, 131.25, 149.60, 152.86.

4-Acetylamino-2-formyl-5-hydroxy-2-methyl-2,3-dihydrobenzo[*b*]furan ethylene acetal (13b) To a suspension of 10% palladium on charcoal (100 mg) in ethyl acetate (30ml), was added heterocycle (**12**) (200 mg, 0.749 mmol). The mixture was stirred at rt in a Parr hydrogenation apparatus at 35 psi for 2.5 h. The reaction mixture was filtered, acetic anhydride (0.2 ml) was added and the resulting solution was left at rt for 9 h. The mixture was concentrated under reduced pressure and the residue was treated with ice-water with stirring for 2 h and then extracted with ethyl acetate (4x25 mL). The extract was washed with water, aqueous 5% hydrogencarbonate, water and dried over sodium sulfate. The residue obtained by evaporation of the solvent was dissolved in methanol (20 mL), potassium carbonate (300 mg) was added and the solution was stirred for 5 min at rt. Work-up followed by PLC (eluting with 85:15 chloroform-methanol) afforded pure compound (**13**) (160 mg, 77%) as white solid mp 177-178°C (chloroform-ligh petroleum); High-resolution Ms Calcd for $C_{14}H_{17}NO_5$: 279.110673. Found: 279.110720.

ν_{max}: 3120, 3360, 1660, and 1600. ^{1}H-NMR δ: 1.45 (s, 3H, Me), 2.25 (s, 3H, COMe), 2,81(d, 1H, *J* = 16, 3-H), 3.26 (d, 1H, *J* = 16, 3-H'), 3.87-4.12 (m, 4H, OCH_2CH_2O), 4.93 (s, 1H, 1'-H), 6.59 (d, 1H, J = 9, 6-H), 6.80 (d, 1H, *J* = 9, 7-H), 7.09 (br s , 1H, NH), 7.81 (s, 1H, OH). ^{13}C-NMR δ: 21.67, 23.61 , 35.99, 65.85, 65.79, 88.77, 105.48, 108.20, 119.48, 118.39, 122.43, 143.33, 152.79, 170.29.

2-Acetylamino-3-(2-methyl-2-hydroxy-3-oxopropyl)-1,4-benzoquinone ethylene acetal (**2**) A solution of CAN (1,13 g, 2.063 mmol) was added dropwise to a stirring mixture of heterocycle (**13b**) (288 mg, 1.03 mmol) in acetonitrile (60 mL) at rt and the stirring was mantained for 45 min. Work-up of the reaction mixture followed by column chromatography (95:5 chloroform-methanol) provided quinone (**2**) (272 mg, 89%) as yellow solid mp 123-124°C. High-resolution Ms Calcd for $C_{14}H_{17}NO_6$: 295.10425. Found: 295.10492. ν_{max}: 3400, 3280, 1710, 1650, and 1600. ^{1}H-NMR δ: 1.08 (s, 3H, Me), 2.12 (s, 3H, COMe), 2.71 (d, 1H, *J* = 14, 1'-H), 2.77 (d, 1H, *J* = 14, 1'-H'), 2.87(br s, 1H, OH), 3.83-4,09 (m, 4H, OCH_2CH_2O), 4.66 (s, 1H, 3'-H), 6.71 (d, 1H, *J* = 10, 6-H), 6.76 (d, 1H, *J* = 10, 5-H), 8.82 (br s, 1H, NH). ^{13}C-NMR δ: 22.58, 23.49, 31.71, 65.66, 65.69, 76.42, 106.35, 133.83, 135.99, 136.13, 141.56, 169.29, 181.27, 187.05.

Reaction of benzoquinone (1a) with *p*-toluensulfonic acid To a stirred solution of quinone (**1a**) (129 mg, 0.438 mmol) in benzene (5mL) were added two crystals of *p*-toluensulfonic acid and the mixture was maintained with stirring for 1 h at rt. The reaction mixture was partitioned between water-chloroform and the organic layer was washed with water, aqueous sodium hydrogencarbonate and water. The dried extract was evaporated under reduced pressure and chromatographed on column (eluting with 97:3 chloroform-methanol) to afford *N*-acetyl-4-hydroxy-2-(2-hydroxyethoxy)-1,2,3,4-tetrahydro-5*H*-1-benzazepine-6,9-quinone (**15**) (23.55 mg, 18%) as red solid mp: 142-143°C. *Anal.* Calcd for: $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 57.10; 5.92; N, 4.72. ν_{max}: 3410, 3330, 1690, 1670, 1630, and 1600. ^{1}H-NMR δ: 1.68 (s, 1H, OH), 1.77 (ddd, 1H, *J* = 15, 6.5 and 3.5, 3-H), 2.02 (s, 3H, COMe), 2.09 (ddd, 1-H, *J* = 15, 9, and 3.5, 3-H'), 2.40 (dd, 1H, *J* = 13.5 and 3.5, 5-H), 2.96 (dd, 1H, *J* = 13.5 and 9.5, 5-H'), 3.75-3.96 (m, 4H, OCH_2CH_2O), 4.73 (m, 1H, 4-H), 4.90 (dd, 1H, *J* = 6.5 and 3.5, 2-H), 5.89 (s, 1H, OH), 6.56 (d, 1H, *J* = 10, 8-H), 6.61 (d, 1H, *J* = 10, 7-H). ^{13}C-NMR δ: 21.33, 28.61, 37.80, 64.74, 64.90, 69.92, 101.71, 107.93, 131.95, 139.32, 145.26, 172.22, 183.49, 184.60.

Reaction of benzoquinone 2 with trifluoroacetic acid A solution of trifluoroacetic acid in dichloromethane (1.5 mL, 23%) was added dropwise during a period of 7 h to a mixture of **2** (51 mg, 0.172 mmol) in dichloromethane (6 mL) at rt. The reaction mixture was successively washed with water, aqueous 5% sodium hydrogencarbonate, water, and the dried organic extract was evaporated. The residue obtained was purified by flash chromatography (eluting with 70:30 ethyl acetate-ligh petroleum) to afford heterocycle (**13b**) (5.05 mg, 11%) and *N*-acetyl-3-hydroxy-2-(2-hydroxyethoxy)-3-methyl-1,2,3,4-tetrahydroquinoline-5,8-quinone (**16**) (4.2 mg, 8%) as red solid mp>330 °C; High-resolution Ms Calcd for $C_{14}H_{17}NO_6$: 295.10559. Found: 295.10580. ν_{max}: 3454, 3370, 1735, 1680 , and 1630. ^{1}H-NMR δ: 1.49 (s, 1H, Me), 2.02 (s, 1H, COMe), 2.75 (d, 1H, *J* = 15, 4-H), 2.40 (d, 1H, *J* = 15, 4-H'), 3.96-4.05 (m, 4H, OCH_2CH_2O), 5.19 (s, 1H, 2-H), 5.61 (s, 1H, OH), 6.60 (d, 1H, *J* = 10, 7-H), 6.64 (d, 1H, *J* =

10, 6-H). ^{13}C-NMR δ: 18.79, 22.64, 28.15, 65.78, 65.82, 85.49, 104.30, 109.27, 131.90, 139.60, 145.97, 170.52, 183.66, 185.32.

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22. Calculation of the energy of molecular models having the OCH_2CH_2OH group at *pseudo-axial* and *pseudo-equatorial* orientations indicate that the former possess the lower energy: Quinone (**15**), *pseudo-axial:*: 53 kcal/mol, *pseudo-equatorial:*: 77 kcal/mol; Quinone (**16**), *pseudo-axial:*: 6.7 kcal/mol; *pseudo-equatorial* : 36 kcal/mol. Calculation were performed by using the Spartan Version 4.1 (Wavefunction, Inc. Irvine, California 9275, USA).

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