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SYNTHESIS OF OXIRANYLQUINONES AS NEW POTENTIAL BIOREDUCTIVE ALKYLATING AGENTS

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Abstract—1,4-Benzoquinones and 1,4-naphthoquinones carrying oxiranyl substituents have been synthesized as potential bioreductive alkylating agents. The method presented here involves the syntheses of 1,4-dimethoxybenzalkehydes or 1,4-dimethoxynaphthaldehydes, and conversion of the carbonyl groups into the oxiranyl function using trimethylsulfonium chloride in the presence of powdered sodium hydroxide. 1,4-Dimethoxy-2-oxiranylbenzenes and 1,4-dimethoxy-2-oxiranylnaphthalenes have been oxidized to quinones with silver(II) dipicolinate.

Among various naturally occurring quinones and their simple carbocyclic as well as heterocyclic analogues especially interesting are these being bioreductive alkylating agents, since it was pointed out that quinones of this type might be developed as selective chemotherapeutic agents to attack oxygen-deficient tumor cells.[1,2] It was pointed out that quinones of this type were amenable to quinone methide formation, subsequented to an *in vivo* reduction to the corresponding hydroquinones. The quinone methides thus formed would be reactive alkylating agents and result in the formation of covalent adducts to biological nucleophiles, such as DNA, proteins, and carobhydrates.[3]

Recently many simple benzo-, naphtho- and anthraquinones and their aza-aromatic analogues with one or more $-CH_2-X$ (X = leaving group) substituents were successfully synthesized and their antitumor activity was observed.[4-9]

The mode of action of these bioreductive alkylating quinones is represented, according to hypothesis formulated by Lin and Moore[1,10] (Scheme 1). Similarly, one could expect the action of another, previously unknown, type of quinone having oxiranyl substituents.

The aim of our investigations presented in this paper was to elaborate a convenient synthetic route to 1,4-benzoquinones and 1,4-naphthoquinones bearing oxiranyl group and other substituents, e.g. methyl, methoxyl, alkenyl or bromine. Recently, extending our study on the syntheses of bioquinone analogues and using various oxidants,[11,12] we found that oxidation of 1,4-dimethoxyarenes having oxiranyl group with silver(II) dipicolinate in neutral medium yielded the desired quinones. No cleavage of oxirane ring was observed and three simple oxiranylquinones were obtained this way.[13]

Now we wish to report the full synthetic route for obtaining various oxiranylquinones starting from simple precursors. The method is shown in Scheme 2.

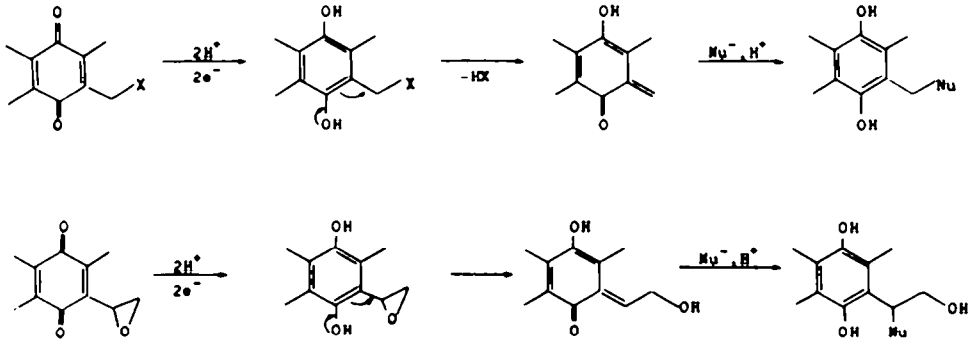
There were three main synthetic problems which had to be resolved: synthesis of 1,4-dimethoxybenzaldehydes or 1,4-dimethoxynaphthaldehydes (**2**), conversion of the carbonyl group into the oxirane ring yielding compounds **3**, and then their selective oxidation to oxiranylquinones (**4**).

Initially we attempted to prepare aldehydes **2** by oxidizing the halomethyl groups with 2-nitropropane potassium salt,[14,15] but with polysubstituted compounds the yields were low or aldehyde was not formed.

The further study showed that dimethyl selenoxide may be successfully used as a novel oxidant of the halomethyl group to the aldehyde one. This reagent was more effective than dimethyl sulfoxide sometimes used.[16] We also found that potassium phenylselenite could be used successfully instead of dimethyl selenoxide.

It is noteworthy that the hydroxymethyl group can be oxidized with dimethyl selenoxide to the aldehyde group, e.g. alcohol **1j** was converted into aldehyde **2j** in a good yield.

Some other aldehydes were synthesised using more



Scheme 1.

Table 1.

Product	Yield [%]	m.p. (solvent) or b.p. [°C]	Molecular formula [a]	IR (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-NMR ($CDCl_3$) δ [ppm]
2a	92	220(b) (Ref.[18] 207)	$C_{10}H_{10}O_4$	1655	4.32 (6H,s,-OCH_3); 7.81 (2H,s,ArH); 10.87 (2H,s,-CHO)
2b	83	141(c)	$C_{12}H_{14}O_6$	1670	4.26 (12H,s,-OCH_3); 10.70 (2H,s,-CHO)
2c	80	38(d) (Ref.[12] 37-39)	$C_{11}H_{14}O_5$	1675	4.20, 4.26, 4.30 and 4.32 (12H,s,-OCH_3); 7.40 (1H,s,ArH); 10.60 (1H,s,-CHO)
2d	92	72(d) (Ref.[24] 67.5-68)	$C_{11}H_{14}O_3$	1683	2.50 and 2.56 (6H,s,-CH_3); 4.12 and 4.14 (6H,s,-OCH_3); 7.42 (1H,s,ArH); 10.82 (1H, s,-CHO)
2e	90	84(c)	$C_{11}H_{14}O_5$	1692	4.16 and 4.20 (12H,s,-OCH_3); 7.12 (1H,s,ArH); 10.72 (1H,s,-CHO)
2f	90	149(e)	$C_{12}H_{14}O_4$	1680	2.78 (6H,s,-CH_3); 4.13 (6H,s,-OCH_3); 10.83 (2H,s,-CHO)
2g	87	110(f)	$C_{13}H_{11}O_3Br$	1693	4.34 and 4.40 (6H,s,-OCH_3); 7.90 - 8.04 (2H, m,ArH); 8.40 - 8.62 (2H,m,ArH); 10.86 (1H,s, -CHO)
2h	88	125(e) (Ref.[25] 60-65)	$C_{13}H_{12}O_3$	1675	4.28 and 4.37 (6H,s,-OCH_3); 7.38 (1H,s,ArH); 7.82 - 7.92 (2H,m,ArH); 8.40 - 8.58 (2H,m,ArH); 10.86 (1H,s,-CHO)
2i	70	95(d) (Ref.[19] 88)	$C_{14}H_{14}O_3$	1680	2.95 (3H,s,-CH_3); 4.16 and 4.36 (6H,s,-CHO); 7.72 - 8.02 (2H,m,ArH); 8.32 - 8.52 (2H,m,ArH); 11.03 (1H,s,-CHO)

2j	95	93(c) (Ref.[26] 89-90)	$C_{14}H_{14}O_4$	1670	4.25, 4.30 and 4.35 (9H,s,$-OCH_3$); 7.28 (1H,d, 8Hz,ArH); 7.48 (1H,s,ArH); 7.84 (1H,t,8Hz, ArH); 8.20 (1H,d,8Hz,ArH); 10.88 (1H,s,-CHO)
2k	98	138/0.2mm	$C_{11}H_{13}O_5Br$	1700	4.22, 4.30 and 4.40 (12H,s,$-OCH_3$); 10.64 (1H, s,-CHO)
2l	96	50(g)	$C_{16}H_{16}O_3$	1675	4.03 (2H,m,$-CH_2-$); 4.20 and 4.30 (6H,s,$-OCH_3$); 5.50 (2H,m,$=CH_2$); 6.06 (1H,m,=CH-); 7.70 - 7.90 (2H,m,ArH); 8.20 - 8.42 (2H,m,ArH); 10.75 (1H, s,-CHO)
2m	85	oil[h]	$C_{23}H_{28}O_3$	1670	1.82, 1.87 and 2.09 (9H,s,$-CH_3$); 2.25 (4H,m, $-CH_2CH_2-$); 4.05 (2H,m,$-CH_2-$); 4.12 and 4.32 (6H,s,$-OCH_3$); 5.25 (2H,m,-CH=); 7.65 - 7.82 (2H,m,ArH); 8.17 - 8.40 (2H,m,ArH); 10.80 (1H, s,-CHO)
2n	86	120/0.1mm	$C_{14}H_{18}O_5$	1672	4.05 (2H,m,$-CH_2-$); 4.20, 4.25, 4.30 and 4.32 (12H,s,$-OCH_3$); 5.30 - 5.50 (2H,m,$=CH_2$); 6.30 (1H,m,-CH=); 10.82 (1H,s,-CHO)
2o	79	118(c)	$C_{11}H_{13}O_3Br$	1690	2.54 and 2.66 (6H,s,$-CH_3$); 4.13 (6H,s,$-OCH_3$); 10.66 (1H,s,-CHO)
2p	57	53(d)	$C_{14}H_{14}O_4$	1695	4.29, 4.31 and 4.33 (9H,s,$-OCH_3$); 7.68 - 7.86 (2H,m,ArH); 8.36 - 8.52 (2H,m,ArH); 10.87 (1H, s,-CHO)

a) All products gave satisfactory microanalyses (C ± 0.4% ; H ± 0.3%).
Solvents - b) toluene, c) cyclohexane, d) hexane, e) cyclohexane-benzene, f) heptane, g) light petroleum.
h) Purified by column chromatogryphy on florosil.

Table 2.

Product	Yield [%]	m.p., °C (solvent)	Molecular formula [a]	^{1}H-NMR ($CDCl_3$) δ [ppm]
3a	33	169(b)	$C_{12}H_{14}O_4$	3.02 (2H,dd,6Hz, and 3Hz,-CH_2-); 3.48 (2H,dd,6Hz and 4Hz, -CH_2-); 4.18 (6H,s,-OCH_3); 4.50 (2H,m,-CH=); 7.06 (2H,s,ArH)
3b	24	69-70(c)	$C_{14}H_{18}O_6$	3.42 (2H,dd,6Hz and 4.5Hz,-CH_2-); 3.62 - 3.75 (2H,m,-CH_2-); 4.38 (2H,m,-CH=); 4.22 (12H,s,-OCH_3)
3c	86	66(c)	$C_{12}H_{16}O_5$	3.08 (1H,dd,6Hz and 3Hz,-CH_2-); 3.50 (1H,dd,6Hz and 4Hz, -CH_2-); 4.17, 4.25 and 4.27 (12H,s,-OCH_3); 4.50 (1H,m,-CH=); 6.73 (1H,s,ArH).
3d	75	60(c)	$C_{12}H_{16}O_3$	2.52 and 2.62 (6H,s,-CH_3); 2.82 (1H,dd,6Hz and 3Hz,-CH_2-); 3.01 (1H,dd,6Hz and 4.5Hz,-CH_2-); 4.12 and 4.16 (6H,s,-OCH_3); 4.55 (1H,m,-CH=); 6.82 (1H,s,ArH)
3e	75	44(c)	$C_{12}H_{16}O_5$	3.42 (1H,dd,6Hz and 3Hz,-CH_2-); 3.78 (1H,dd,6Hz and 3Hz, -CH_2-); 4.20 and 4.25 (12H,s,-OCH_3); 4.42 (1H,m,-CH=); 6.88 (1H,s,ArH)
3f	28	164-166(d)	$C_{14}H_{18}O_4$	2.68 (6H,s,-CH_3); 3.30 (2H,dd,6Hz and 3Hz,-CH_2); 2.52 (2H,6Hz and 4Hz,-CH_2-); 4.07 (6H,s,-OCH_3); 4.23 (2H,m,-CH=)
3g	51	152(e)	$C_{14}H_{13}O_3Br$	3.57 (2H,m,-CH_2-); 4.35 and 4.38 (6H,s,-OCH_3); 4.45 (1H,m, -CH=); 7.76 - 7.88 (2H,m,ArH); 8.28 - 8.40 (2H,m,ArH)
3h	80	96(f)	$C_{14}H_{14}O_3$	3.18 (1H,dd,6Hz and 3Hz,-CH_2-); 3.58 (1H,dd,6Hz and 4.5Hz,-CH_2-); 4.30 (6H,s,-OCH_3); 4.76 (1H,dd,4Hz and 3Hz,-CH=); 6.82 (1H,s,ArH); 7.76 - 7.90 (2H,m,ArH); 8.33 - 8.60 (2H,m,ArH)
3i	65	93(c)	$C_{15}H_{16}O_3$	2.43 (3H,s,-CH_3); 3.10 (2H,m,-CH_2-); 3.75 and 3.82 (6H,s,-OCH_3); 3.91 (1H,m,-CH=); 7.30 - 7.47 (2H,m,ArH); 7.92 - 8.10 (2H,m,ArH)
3j	70	81(c)	$C_{15}H_{16}O_4$	3.12 (1H,dd,6Hz and 3Hz,-CH_2-); 3.54 (1H,dd,6Hz and 4.5Hz,-CH_2-); 4.17, 4.25 and 4.30(9H,s,-OCH_3); 4.78 (1H,m,-CH=); 6.86 (1H,s, ArH); 7.22 (1H,d,8Hz,ArH); 7.66 (1H,t,8Hz,ArH); 8.16 (1H,d,8Hz, ArH)

2k	93	oil[h]	$C_{12}H_{15}O_5Br$	3.40 (1H,dd,6Hz and 3Hz,-CH_2-); 3.54 (1H,dd,6Hz and 4.5Hz,-CH_2-); 4.24, 4.28, 4.30 and 4.33 (12H,s,-OCH_3); 4.36 (1H,m,-CH=)
2l	93	oil[h]	$C_{17}H_{18}O_3$	3.44 - 3.78 (4H,m,-CH_2-); 4.27 and 4.30 (6H,s,-OCH_3); 4.40 (1H,m, -OCH=); 5.18 - 5.90 (2H,m,=CH_2); 6.18 - 6.22 (1H,m,-CH=); 7.72 - 7.85 (2H,m,ArH); 8.27 - 8.45 (2H,m,ArH)
2m	91	oil[h]	$C_{24}H_{30}O_3$	1.95, 2.01 and 2.20 (9H,s,-CH_3); 2.41 (4H,m,-CH_2CH_2-); 3.52 (2H, m,-OCH_2-); 4.05 (2H,m,-CH_2-); 4.27 and 4.32 (6H,s,-OCH_3); 4.42 (1H,m,-OCH=); 5.30 - 5.65 (2H,m,-CH=); 7.67 - 7.85 (2H,m,ArH); 8.25 - 8.42 (2H,m,ArH)
3n	95	oil[i]	$C_{15}H_{20}O_5$	3.27 - 3.52 (2H,m,-OCH_2-); 3.98 (2H,dd,6Hz and 1Hz,-CH_2-); 4.20, 4.23 and 4.25, 4.28 (12H,s,-OCH_3); 4.70 (1H,m,-OCH=); 5.20 - 5.45 (2H,m,=CH_2); 6.06 - 6.55 (1H,m,-CH=)
3o	56	74(c)	$C_{12}H_{15}O_3Br$	2.50 and 2.60 (6H,s,-CH_3); 3.62 (1H,dd,6Hz and 3Hz,-CH_2-); 3.76 (1H,dd,6Hz and 4.5Hz,-CH_2-); 4.10 and 4.20 (6H,s, -OCH_3); 4.30 (1H,m,-CH=)
3p	56	85(g)	$C_{15}H_{16}O_4$	3.50 (1H,dd,6Hz and 4.5Hz,-CH_2-); 3.76 (1H,dd,6Hz and 3Hz, -CH_2-); 4.30 and 4.34 (9H,s,-OCH_3); 4.54 (1H,m,-CH=); 7.70 - 7.82 (2H,m,ArH); 8.32 - 8.46 (2H,m,ArH)

a) All products gave satisfactory microanalyses (C, ±0.5% ; H, ±0.3%).
Solvents - b) acetone, c) hexane, d) carbon tetrachloride, e) benzene-cyclohexane, f) hexane-carbon tetrachloride, g) cyclohexane.
h) Purified by column chromatography on basic Al_2O_3.
i) Purified by column chromatography on MgO.

Table 3.

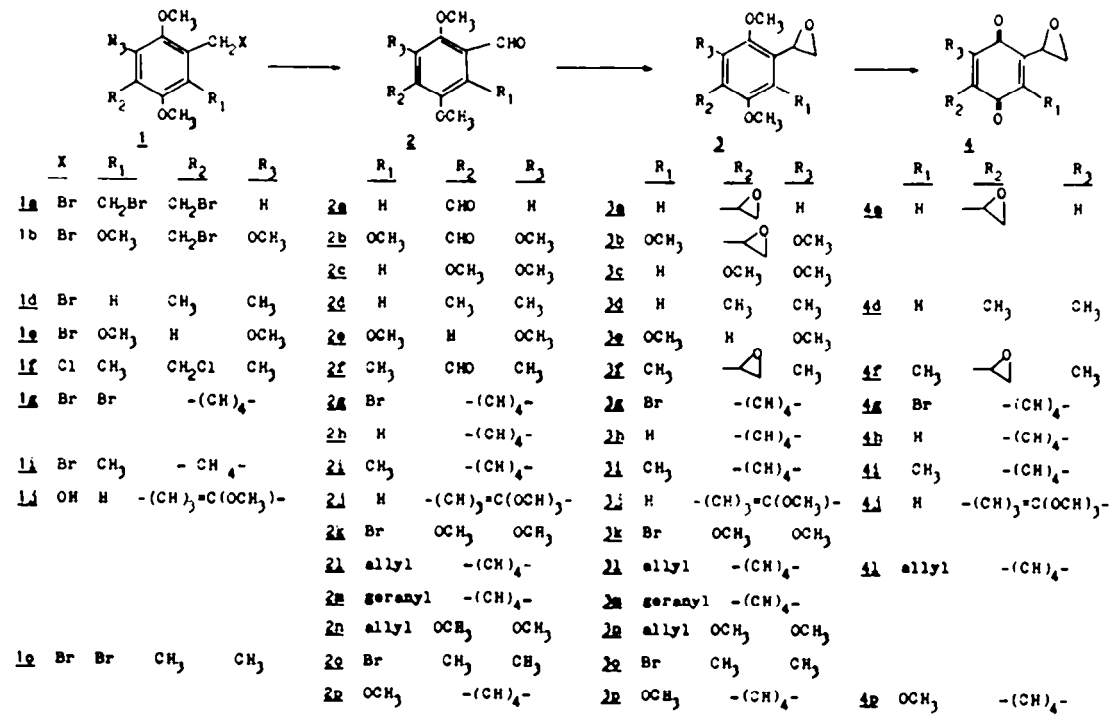
Product	Yield [%]	m.p., °C (solvent)	Molecular formula [a]	IR (KBr) $\nu_{C=O}$, cm^{-1}	^{1}H-NMR ($CDCl_3$) δ [ppm]
4a	76	155(b) dec.	$C_{10}H_8O_4$	1648	3.16 (2H,dd,6Hz and 3Hz,-CH_2-); 3.52 (2H,dd, 6Hz and 4.5Hz,-CH_2-); 4.30 - 4.45 (2H,m,-CH=); 7.37 (2H,s,ArH)
4d	54	42-44(c) dec.	$C_{10}H_{10}O_3$	1640	2.42 (6H,s,-CH_3); 2.95 (1H,dd,6Hz and 3Hz, -CH_2-); 3.47 (1H,dd,6Hz and 4.5Hz,-CH_2-); 4.29 (1H,m,-CH=); 6.80 (1H,s,ArH)
4f	73	113(a) dec.	$C_{12}H_{12}O_4$	1655	2.50 (6H,s,-CH_3); 3.10 (2H,dd,6Hz and 3Hz, -CH_2-); 3.47 (2H,dd,6Hz and 4.5Hz,-CH_2-); 4.05 - 4.22 (2H,m,-CH=)
4g	79	73-74(e) dec.	$C_{12}H_7O_3Br$	1678	3.60 (2H,d,3Hz,-CH_2-); 4.35 (1H,m,-CH=); 8.00 - 8.12 (2H,m,ArH); 8.32 - 8.46 (2H,m,ArH)
4h	67	103(d) dec.	$C_{12}H_8O_3$	1662	3.30 (1H,dd,6Hz and 3Hz,-CH_2-); 3.77 (1H,dd, 6Hz and 4.5Hz,-CH_2-); 4.66 (1H,m,-CH=); 7.33 (1H,s,ArH); 8.20 - 8.37 (2H,m,ArH); 8.52 - 8.67 (2H,m,ArH)
4i	77	63-64(d) dec.	$C_{13}H_{10}O_3$	1657	2.20 (3H,s,-CH_3); 2.70 (1H,dd,6Hz and 3Hz, -CH_2-); 3.08 (1H,dd,6Hz and 4.5Hz,-CH_2-); 3.78 (1H,m,-CH=); 7.50 - 7.67 (2H,m,ArH); 7.85 - 8.00 (2H,m,ArH)

4j	79	131-132(f) dec.	$C_{13}H_{10}O_4$	1650	2.98 (1H,dd,6Hz and 3Hz,-CH_2-); 3.55 (1H,dd,6Hz and 4.5Hz,-CH_2-); 4.39 (3H,s,-OCH_3); 4.46 (1H,m,-CH=); 7.06 (1H,s,ArH); 7.66 (1H,t,6Hz,ArH); 8.04 (2H,m,ArH)
4l	62	53(c) dec.	$C_{15}H_{12}O_3$	1660	3.15 (1H,dd,6Hz and 3Hz,-OCH_2-); 3.52 (1H,dd,6Hz and 4Hz,-OCH_2-); 3.93 (2H,dd,6Hz and 1Hz,-CH_2-); 4.25 (1H,m,-OCH=); 5.25 - 5.58 (2H,m,=CH_2); 5.92 - 6.37 (1H,m,-CH=); 7.88 - 8.00 (2H,m,ArH); 8.22 - 8.38 (2H,m,ArH)
4p	47	93-95(i) dec.	$C_{13}H_{10}O_4$	1647, 1680	3.40 (1H,dd,6Hz and 4.5Hz); 3.60 (1H,dd,6Hz and 3Hz,-CH_2-); 4.23 (1H,m,-CH=); 4.51 (3H,s,-OCH_3); 7.94 - 8.02 (2H,m,ArH); 8.24 - 8.36 (2H,m,ArH)

a) All products gave satisfactory microanalyses (C, ±0.5% ; H, ±0.3%).

Solvents - b) acetone, c) ethyl ether - light petroleum, d) hexane, e) hexane - chloroform, f) ethyl acetate, g) recrystallized on dry-ice bath from hexane, h) recrystallized on dry-ice bath from acetone.

i) Purified by column chromatography on silica gel, eluted with ethyl acetate



Scheme 2.

conventional procedures. Thus, aldehyde **2c** was brominated with NBS in trifluoroacetic acid to give bromoaldehyde **2k**. The substitution of the bromine atom in benzene or naphthalene derivatives needed protection of the carbonyl group by acetalization.[12] The conversion of bromo derivatives **5** and **6** into allyl or geranyl derivatives could be done in one-pot process carried out under argon at low temperature (−78°C). We observed that the yield of product significantly increased when a ligand binding cuprous ions was added together with CuI. The best results were achieved with triethyl phosphite but isolation of product was difficult so dimethyl sulfide or dimethyl selenide were the most convenient compounds.

2,3,4,5-Tetramethoxybenzaldehyde **2c** was obtained, as we reported previously,[12] by formylation of 1,2,3,4-tetramethoxybenzene with the N - methyl - N - phenylformamide phosphorus oxychloride complex. Similarly, aldehyde **2h** was synthesized from 1,4-dimethoxynaphthalene. This aldehyde was oxidized with hydrogen peroxide in the presence of small amounts of 2-nitrophenylselenic acid to 2 - hydroxy - 1,4 - dimethoxynaphthalene **7**. Phenol **7** was methylated to 1,2,4-trimethoxynaphthalene **8** and a new aldehyde group was introduced into molecule by lithiation and reaction with DMF. All aldehydes obtained are listed in Table 1.

The next step of the synthesis involved conversion of the aldehydes **3** into oxiranes **4**. This reaction is usually carried out using dimethyl methylenesulfoxide.[17] Unfortunately, reactivity of this reagent toward the carbonyl group of some aldehydes under investigation was too low and the oxirane ring was not formed. When trimethylsulfonium iodide was used, reaction ran smoothly. The use of dry tetrahydrofuran as the a solvent and powdered sodium hydroxide activated by TEBA and trimethylsulfonium chloride as reagents provides the oxiranylbenzenes and oxiranylnaphthalenes (characterized in Table 2) in good yields. This procedure permitted isolation of the product without partitioning between water and organic solvent, thus the deleterious effect of water was eliminated.

The oxidative demethylation of 1,4-dimethoxybenzenes or 1,4-dimethoxynaphthalenes bearing oxiranyl groups was carried out using silver(II) dipicolinate as oxidant.[13] In this work the two-phase system benzene-water or cyclohexane-water was used as reaction medium instead of acetonitrile-water, giving an improvement of yields of desired 1,4-benzo- and 1,4-naphthoquinones. However, some quinones bearing oxiranyl group, particularly these with methoxy and alkenyl substituents, could not be isolated. It seems possible that quinones formed are extremely unstable and side reactions involving the ring destruction occur during the reaction. Nevertheless, nine oxiranylquinones (listed in Table 3) were obtained in good yields and now are screened against tumor cells.

The appropriate substrates **1** used as precursors of aldehydes **2** were obtained in various ways. Thus, 1,2,4,5-tetramethoxybenzene with bromomethyl methyl ether in the presence of trifluoroacetic acid gave a mixture of compounds **1b** and **1e**. The molar ratio of both products depended strongly on the ratio of reagent used. Excess of ether led to **1b** as the main product. 1,4 - Dimethoxy - 2,5 - dimethylbenzene in excess of chloromethyl methyl ether in the presence of anhydrous $ZnCl_2$ gave product **1f** in excellent yield.

In the cases of compounds **1a**, **1d**, **1h** and **1i** the best results were achieved when bromomethylation was carried out with paraformalkehyde and hydrogen bromide in acetic acid.

2 - Bromomethyl - 1,4 - dimethoxynaphthalene **1h** and

2-Bromomethyl-1,4-dimethoxynaphtalene **1h** and **1d** were brominated with bromine giving 3-bromo-2-bromomethyl-1,4-dimethoxynaphtalene **1g** and **1o** respectively.

As was mentioned earlier, the substrate for aldehyde **2j** was alcohol **1j**. This compound was obtained starting from 1,8-dimethoxynaphthalene in four steps. Thus, the substrate formylated according to literature[21] gave 4,8 - dimethoxy - 1 - naphthaldehyde **9**. The Baeyer–Villiger oxidation of **9** was accomplished in the same way as oxidation of aldehyde **2h**. Our methodology consists in oxidation of aldehyde with 30% hydrogen peroxide in dichloromethane in the presence of o-nitrophenylselenic acid as the catalyst. This procedure is much more convenient and cheaper than the procedure depending on application of m-chloroperbenzoic acid. The catalyst is insoluble in the reaction mixture and may be removed through filtration. Resulting from the oxidation formyl ester of 1 - hydroxy - 4,8 - dimethoxynaphthalene (**10**) was hydrolysed with hydrochloric acid in acetone. Phenol **10** reacted with paraformaldehyde in the presence of phenylboric acid giving 2 - phenyl - 4H - 1,3,2 - naphthodioxaborin **11** which, after chromatography on silica gel impregnated with 2,2 - dimethyl - 1,3 - propanediol, gave 1 - hydroxy - 2 - hydroxymethyl - 4,8 - dimethoxynaphthalene **12**. Methylation of **12** with dimethyl sulphate under phase-transfer conditions gave desirable product **1j**.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Tesla 100 MHz apparatus in $CDCl_3$ using HMDS as external standard. IR spectra were obtained with a Perkin–Elmer 621 spectrophotometer. 2,3,4,5-Tetramethoxybenzaldehyde (**2c**) was obtained from 1,2,3,4-tetramethoxybenzene as reported in Ref. 12.

2,5-Dimethoxyterephthaldicarboxaldehyde **2a**. Bromide **1a** (9.7 g, 30 mmol), potassium phenylselenite (PPS) (12.5 g; 55 mmole), and dipotassium hydrogen phosphate (6.0 g; 34 mmole) in acetonitrile were refluxed with vigorous stirring for 16 h. After cooling the reaction mixture was diluted with water (200 ml), solid filtered off and recrystallized from toluene to give **2a** (Table 1). From the filtrate, toluene was evaporated *in vacuo* and the solid residue was recrystallized from methanol to yield pure diphenyl diselenide (6.4 g, 91%), m.p. 63°.

2,3,5,6-Tetramethoxyterephthaldicarboxaldehyde (**2b**). Bromide **1b** (4.0 g, 10 mmole), PPS (4.7 g, 20 mmole), and dipotassium hydrogen phosphate (2.0 g, 11 mmole) in acetonitrole 30 ml were refluxed for 7 h yielding **2b** (Table 1) and diphenyl diselenide (2.0 g, 62%).

2,5 - Dimethoxy - 3,4 - dimethylbenzaldehyde **2d**. To solution of dimethyl selenoxide, DMSeO (6.0 g; 48 mmole) in 1,2-dichloroethane (70 ml) dipotassium hydrogen phosphate (12 g, 69 mmole) and bromide **1d** (5.2 g, 20 mmole) were added and the reaction mixture was refluxed with vigorous stirring for 8 h. After cooling water (100 ml) was added and the layers separated. The organic layer was dried over $MgSO_4$, the solvent was removed *in vacuo* to yield **2d** (Table 1).

2,3,5,6-Tetramethoxybenzaldehyde **2e**. To solution of DMSeO (1.0 g, 8 mmole), 1,2-dichloroethane (70 ml) dipotassium hydrogen phosphate (5.0 g, 29 mmole) and bromide **1e** (1.8 g, 5 mmole) were added and the reaction mixture was refluxed with vigorous stirring for 6 h. Then DMSeO (1.0 g) was added and the mixture was refluxed for additional 6 h. After this period the third portion of DMSeO (1.0 g) was added and reaction was completed within 6 h. The reaction mixture was worked up as described for **2d** to yield **2e** (Table 1).

3,6 - Dimethoxy - 2,5 - dimethylterephthaldicarboxaldehyde **2f**. Chloride **1f** (2.6 g, 8 mmole), PPS (3.3 g, 15 mmole), dipotassium hydrogen phosphate (2.0 g, 11 mmole), and 18 - crown - 6 (0.3 g) were refluxed with vigorous stirring for 24 h yielding **2f** (Table 1) and diphenyl diselenide (1.8 g, 77%).

3 - Bromo - 1,4 - dimethoxy - 2 - naphthaldehyde **2g**. Bromide **1g** (10.8 g, 33 mmole), PPS (6.9 g, 30 mmole), dipotassium hydrogen phosphate (5 g, 29 mmole), and 18 - crown - 6 (0.5 g) in acetonitrile (90 ml) were refluxed with vigorous stirring for 22 h yielding **2g** (Table 1) and diphenyl diselenide (3.2 g, 68%).

1,4-Dimethoxynaphthaldehyde (**2h**). To N - methyl - N - phenylformamide (5.4 g, 35 mmole), freshly distilled $POCl_3$ (3.8 ml, 41 mmole) was added and the mixture ws left at room temp for 30 min. 1,4-dimethoxynaphthalene was added and mixture left for 15 h at room temp. and then was maintained at 50–60° for 9 h. After cooling water was added and crystalline aldehyde **2h** (Table 1) was filtered off, dried and recrystallized.

1,4 - Dimethoxy - 3 - methyl - 2 - naphthaldehyde **2i**. Bromide **1i** (3.1 g, 11 mmole), PPS (2.3 g, 10 mmole), dipotassium hydrogen phosphate (1.5 g, 8.6 mmole), and 18 - crown - 6 (0.2 g) in acetonitrile (30 ml) were refluxed with vigorous stirring for 20 h. After cooling the reaction mixture was diluted with water (200 ml), solid filtered off and dried. Aldehyde **2i** (2.2 g, 95%) was separated from diphenyl diselenide (1.45 g, 93%) on silica gel using $CHCl_3$ followed by $CHCl_3$–AcOEt (10:1) as eluents.

1,4,8-Trimethoxy-2-naphthaldehyde **2j**. The solution of DMSeO (2.0 g, 16 mmole) and alcohol **1j** (2.5 g, 10 mmole) in 1,2-dichlororoethane (30 ml) was refluxed for 3.5 h, then product **2j** (Table 1) was isolated as described for **2d**.

2 - Bromo - 3,4,5,6 - tetramethoxybenzaldehyde **2k**. To a stirred and ice-salt cooled solution of aldehyde **2c** (22.6 g, 100 mmole), in CF_3COOH (80 ml) 21 g (118 mmole) of NBS was added portionwise during 2.5 h. Stirring was continued for 30 min after the addition. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with water, then with 5% $NaHCO_3$, again with water, and dried over $MgSO_4$. The solvent was evaporated *in vacuo*. Vacuum distillation of a residue afforded **2k** (Table 1).

2 - Bromo - 1 - (1,3 - dioxolanyl) - 3,4,5,6 - tetramethoxybenzene **5**. A solution of aldehyde **2k** (30.5 g, 100 mmole), ethyleneglycol (15 ml), and toluene - p - sulfonic acid (0.1 g) in benzene (200 ml) was refluxed in apparatus equipped with the Dean-Stark trap for 3.5 h. After cooling, the solution was washed with water, sat aq $NaCHO_3$, and again with water. The solvent was evaporated and a residue distilled *in vacou* to give acetal **5** (33.0 g, 95%), b.p. 168–171/0.04 mm, m.p. 50° (from hexane), NMR ($CDCl_3$) δ 4.20, 4.22, 4.27 and 4.30 (12H, s, $-OCH_3$), 4.36–4.66 (4H, m, $-CH_2-$); 6.69 (1H, s, $-CH=$).

2 - Allyl - 3,4,5,6 - tetramethoxybenzaldehyde **2m**. To stirred and cooled to −78° acetal **5** (3.6 g, 10 mmole) in Et_2O (30 ml), 1.6M solution of n-BuLi in hexane (7 ml) was added dropwise under argon and stirring was continued for 30 min. After this period, CuI (2 g) was added and then dimethyl sulfide (2 ml) was added dropwise. The mixture was stirred for additional 2.5 h and then allyl bromide (1.4 g, 12 mhole) in Et_2O (5 ml) was added dropwise during 10 min. The reaction was continued for 1 h at −78° and for 1 h at room temperature. The mixture was poured into water (80 ml), conc HCl (1 ml) was added and stirred magnetically for 17 h at room temp. An additional amount of conc HCl (1 ml) was added after this period and reaction was continued for 2 h. After filtration the organic layer was separated, washed with sat aq $NaHCO_3$, then with water, and dried over $MgSO_4$. Ether was distilled off and crude product was purified through column chromatography on silica gel using hexane–Et_2O (10:3) followed by hexane–Et_2O (10:4) as eluents. Product **2m** was distilled (120–122°/0.1 mm) yielding pure **2m** (Table 1).

3 - Bromo - 2 - (1,3 - dioxolanyl) - 1,4 - dimethoxynaphthalene **6**. A solution of aldehyde **2g** (9.2 g, 31 mmole), ethylene glycol (5 ml) and p-toluenesulfonic acid (0.1 g) in benzene (80 ml) was refluxed in apparatus equipped with the Dean-Stark trap for 3 h. After cooling the solution was washed with water, sat aq $NaHCO_3$ and again with water then dried over $MgSO_4$. The solvent was evaporated and a residue recrystallized from cyclohexane gave **6** (10.2 g, 97%), m.p. 130°, NMR ($CDCl_3$) δ 4.34 (6H, s, $-OCH_3$); 4.32–4.74 (4H, m, $-CH_2-$); 6.90 (1H, s, $-CH=$); 7.86–7.96 (2H, m, ArH); 8.40–8.52 (2H, m, ArH).

3 - Allyl - 1,4 - dimethoxy - 2 - naphthaldehyde **2l**. To a stirred and cooled to −78° acetal **6** (3.4 g, 10 mmole) in THF (30 ml), 1.6 M solution of n-BuLi in hexane (8 ml) was added dropwise

under argon. Stirring was continued for 30 min and solution of CuI (2.6 g) in THF (10 ml) and $(CH_3)_2Se$ (4 ml) were added. The mixture was stirred for 2.5 h, then allyl bromide (1.5 g, 13 mmole) in THF (5 ml) was added dropwise during a 10 min period. The reaction was continued for 1 h at −78° and for 1 h at room temp. The mixture was poured into water (10 ml), conc HCl (2 ml) was added and stirred for 15 h at room temp then diluted with water and extracted with Et_2O. The extract was worked up as reported for **2n**.

3 - *Geranyl* - 1,4 - *dimethoxy* - 2 - *naphthaldehyde* **2m**. Geranyl bromide (2.5 g, 11 mmole) was used instead of allyl bromide by the method for conversion of **6** into **2l**. When reaction was finished, the mixture was poured into water and was extracted with Et_2O. A solution was washed with 5% aq ammonia then with water, and dried over Na_2SO_4. Then ether was distilled off. To a residue, acetone (40 ml), water (10 ml), and 99% formic acid (2 ml) were added. This mixture was allowed to stand for 17 h, diluted with water, extracted with CH_2Cl_2, washed with sat aq $NaHCO_3$ and then with water, dried over $MgSO_4$ and evaporated. A residue was purified by column chromatography on Florosil as for **2n**.

2 - *Bromo* - 3,6 - *dimethoxy* - 4,5 - *dimethylbenzaldehyde* **2o**. Bromide **1o** (10.2 g, 37 mmole), PPS (6.9 g, 30 mmole) dipotassium hydrogen phosphate (5.0 g, 29 mmole), and 18 - crown - 6 (0.5 g) in CH_3CN (90 ml) were refluxed with vigorous stirring for 20 h. Aldehyde **2o** (Table 1) and diphenyl diselenide were isolated as described for **2a**.

2 - *Hydroxy* - 1,4 - *dimethoxynaphthalene* **7**. A solution of **2h** (27.3 g, 126 mmole), and 2-nitrophenylselenic acid (1.5 g) in CH_2Cl_2 (200 ml) was stirred with 30% H_2O_2 (30 ml) for 30 h at room temp. The mixture was filtered and successively washed with water, 10% aq $NaHSO_3$, then water and dried over $MgSO_4$. The solvent was distilled off and to a solid residue, acetone (150 ml) and 10% HCl (50 ml) were added and refluxed for 30 min. This solution was concentrated to a small volume *in vacuo* and crystalline **7** collected and dried *in vacuo*. Recrystallization from cyclohexane gave pure **7** (22.9 g, 93%), m.p. 91° (Ref. 20, 90.5–92.5°).

1,2,4-*Trimethoxynaphthalene* **8**. To a stirred solution of **7** (19.3 g, 95 mmole) and $(CH_3)_2SO_4$ (12 ml, 71 mmole) in DMSO (50 ml) cooled to 0°, a solution of KOH (15 g) in water (20 ml) was added dropwise for 30 min and temperature was maintained below 20°. Then the stirring was continued for 1 h, mixture diluted with water, and product filtered off, washed with water and dried *in vacuo*. Crude **8** was recrystallized from methanol giving pure product (19.3 g, 93%), m.p. 38–40°, NMR ($CDCl_3$) δ 4.22, 4.24 *and* 4.28 (9H, s, $-OCH_3$); 6.90 (1H, s, ArH); 7.52–7.84 (2H, m, ArH); 8.30–8.48 (2H, m, ArH). The elemental analysis and NMR spectrum gave an evidence for purity of **8**, nevertheless m.p. is different from that reported in ref 21 (79–80°).

1,3,4 - *Trimethoxy* - 2 - *naphthaldehyde* **2p**. To a stirred solution of **8** (3.6 g, 16 mmole) in Et_2O (50 ml) cooled on an ice-water bath, 1.6 M n-BuLi in hexane (20 ml) was added and reaction was carried out for 5 h. Then DMF (3 ml, 35 mmole) was added and the reaction was continued for 30 min. The mixture was poured into 10% HCl and stirred for 15 min. After separation, the organic layer was washed with water, dried over $MgSO_4$, and the solvent was distilled off. Solid residue recrystallized from hexane gave **2p** (Table 1).

1,4 - *Dimethoxy* - 2,5 - *dioxiranylbenzene* **3a**. A solution of aldehyde **2a** (1.6 g, 8 mmole) in THF (70 ml) was stirred at room temp with $(CH_3)_3SCl$ (2.5 g, 25 mmole), TEBA (0.3 g), and freshly powered NaOH (2 g) for 52 h. After this period the reaction mixture was filtered through Celite under slight overpressure and filtrate evaporated *in vacuo*. Crude product was recrystallized from acetone, then from CCl_4 yielding pure **3a** (Table 2).

1,2,4,5 - *Tetramethoxy* - 3,6 - *dioxiranylbenzene* **3b**. The solution of aldehyde **2b** (1.3 g, 5 mmole) in THF (50 ml) was stirred at room temp with $(CH_3)_3SCl$ (1.5 g, 15 mmole), TEBA (0.2 g) and powdered NaOH (3 g) for 4 h. After this period, the reaction mixture was decanted, a solid washed with THF and the combined solution evaporated *in vacuo*. Crude product was dissolved in benzene (30 ml) and purified by column chromatography using basic Al_2O_3 and light petroleum–diethyl ether (9:1) as eluent. Recrystallization from hexane gave pure **3b** (Table 2).

1,2,3,4 - *Tetramethoxy* - 5 - *oxiranylbenzene* **3c** was obtained as described for **3a**. Aldehyde **2c** (6.8 g, 30 mmole), $(CH_3)_3SCl$ (5.0 g, 50 mmole), freshly powdered NaOH (4.0 g) and TEBA (0.5 g) in THF (100 ml) were stirred for 8 h.

1,4 - *Dimethoxy* - 2,3 - *dimethyl* - 5 - *oxiranylbenzene* **3d** was obtained as described for **3a**, from **2d** (5.3 g, 27 mnole), $(CH_3)_3SCl$ (3.5 g, 35 mmole), NaOH (5.0 g) with TEBA (0.5 g) in THF (80 ml). The reaction time was 5 h. Crude product (oil) was dissolved in benzene–cyclohexane (1:1) (50 ml), filtered and then the solvent was evaporated *in vacuo* and a residue recrystallized twice from hexane.

1,2,4,5 - *Tetramethoxy* - 3 - *oxiranylbenzene* **3e** was obtained as described for **3a**, from **2e** (4.5 g, 20 mmole), $(CH_3)_3SCl$ (2.5 g, 25 mmole), NaOH (4 g) with TEBA (0.2 g) in THF (70 ml) stirred for 6 h. Crude product (oil) was treated with cyclohexane (50 ml) and filtered. From the filtrate the solvent was evaporated *in vacuo* and residue chromatographed like **3b**.

1,4 - *Dimethoxy* - 2,5 - *dimethyl* - 3,6 - *dioxiranylbenzene* **3f**. To sodium dimsylate, prepared from oil-free NaH (0.7 g, 23 mmole) and DMSO under nitrogen (20 ml) THF (20 ml) was added. After cooling to − 5° the solution of $(CH_3)_3SI$ (6 g, 30 mmole) in DMSO (20 ml) was added, with stirring and cooling. Then **2f** (2.2 g, 10 mmole) was added portionwise, the cooling bath was removed and reaction continued for additional 1 h at room temperature. The reaction mixture was poured into ice-water and crystalline product rapidly filtered off, dried *in vacuo* and recrystallized subsequently from hexane, acetone and CCl_4 to give pure product characterized in Table 2.

3 - *Bromo* - 1,4 - *dimethoxy* - 2 - *oxiranylnaphthalene* **3g** was obtained as described for **3a**, from **2g** (4.2 g, 14 mmole), $(CH_3)_3SCl$ (2 g, 20 mmole), NaOH (3 g) with TEBA (0.3 g) in THF (70 ml) stirred for 4 h. A crude product was treated with benzene (50 ml), filtered and benzene removed *in vacuo*. The solid residue was recrystallized from benzene-cyclohexane yielding pure **3g** (Table 2).

1,4 - *Dimethoxy* - 2 - *oxiranylnaphthalene* **3h** was obtained as described for **3a**. Thus **2h** (2.9 g, 14 mmole), $(CH_3)_3SCl$ (2 g, 20 mmole), NaOH (3 g) with TEBA (0.3 g) in THF (70 ml) were stirred for 5 h.

1,4 - *Dimethoxy* - 3 - *methyl* - 2 - *oxiranylnaphthalene* **3i** was ogtained as described for **3a**. Thus, **2i** (4.6 g, 20 mmole), $(CH_3)_3SCl$ (3.4 g, 34 mmole), NaOH (3 g), with TEBA (0.5 g) in THF (70 ml) were stirred for 5.5 h.

1,4,8 - *Trimethoxy* - 2 - *oxiranylnaphthalene* **3j**. Aldehyde **2j** (1.9 g, 7 mmole), $(CH_3)_3SCl$ (1.2 g, 12 mmole), TEBA (0.3 g) and freshly powdered NaOH (2 g) were stirred for 4 h, then product **3j** (Table 2) was isolated and purified as described for **3b**.

5 - *Bromo* - 1,2,3,4 - *tetramethoxy* - 6 - *oxiranylbenzene* **3k** was obtained as described for **3a**. Thus, **2k** (6.1 g, 20 mmole), $(CH_3)_3SCl$ (2.5 g, 25 mmole), NaOH (2 g) with TEBA (0.5 g) in THF (70 ml) were stirred for 5 h. Crude product was purified as for **3b**.

2 - *Allyl* - 1,4 - *dimethoxy* - 3 - *oxiranylnaphthalene* **3l** was obtained as described for **3a**, from **2l** (2.56 g, 10 mmole), $(CH_3)_3SCl$ (1.5 g, 15 mmole), NaOH (3 g) with TEBA (0.3 g) in THF (70 ml). The reaction time was 4 h. A crude product (an oil) was purified like **3b**.

2 - *Geranyl* - 1,4 - *dimethoxy* - 2 - *oxiranylnaphthalene* **3m** was obtained as described for **3a**, from **2m** (2.1 g, 6 mmole), $(CH_3)_3SCl$ (1.0 g, 10 mmole), NaOH (2 g) with TEBA (0.2 g) in THF (70 ml). The reaction time was 5 h. Crude product was purified as for **3l**.

1 - *Allyl* - 2,3,4,5 - *tetramethoxyoxiranylbenzene* **3n** was obtained in the same way as **3a**, from **2n** (2.1 g, 10 mmole), $(CH_3)_3SCl$ (1.7 g, 17 mmole), NaOH (2 g) with TEBA (0.3 g) in THF (50 ml). The reaction time was 4 h. Crude product was treated with hexane (50 ml) and filtered. From filtrate the solvent was evaporated and residue purified by chromatography using MgO and light petroleum as eluent.

5 - *Bromo* - 1,4 - *dimethoxy* - 2,3 - *dimethyl* - 5 - *oxiranylbenzene* **3o** was obtained as described for **3b**, from **2o** (4.1 g,

15 mmole), $(CH_3)_3SCl$ (2 g, 20 mmole), NaOH (3 g) with TEBA (0.3 g) in THF (70 ml). The reaction time was 4 h.

1,3,4 - *Trimethoxy* - 2 - *oxiranylnaphthalene* **3p** was obtained as described for **3b**, from **2p** (3.7 g, 15 mmole), $(CH_3)_3SCl$ (2 g, 20 mmole), NaOH (3 g) in THF (70 ml). The reaction time was 4 h.

Bromomethyl - 2,3,5,6 - *tetramethoxybenzene* (**1e**). To 1,2,4,5-tetramethoxybenzene (12.5 g, 63 mmole) dissolved in CF_3COOH (25 ml), bromomethyl methyl ether (11.0 g, 88 mmole) was added and the mixture was allowed to stand for 45 h at 10°. The crystalline solid was filtered off and dried *in vacuo* to give pure **1b** (3.3 g, 16%). The filtrate was poured into water and solid filtered off and dried *in vacuo*. Recrystallization of crude product from ethanol and then from cyclohexane gave **1e** (7.4 g, 40%), m.p. 116°, NMR ($CDCl_3$) δ 4.23 and 4.30 (12H, s, $-OCH_3$); 5.00 (2H, s, $-CH_2Br$); 6.90 (1H, s, ArH).

1,4 - *Bis(bromomethyl)* - 2,3,5,6 - *tetramethoxybenzene* (**1b**). To 1,2,4,5-tetramethoxybenzene (8.0 g, 40 mmole) dissolved in CF_3COOH (25 ml), bromomethyl methyl ether (11.0 g, 88 mmole) was added and the mixture was allowed to stand for 22 h at room temp. The crystalline product was filtered off, dried *in vacuo* and crystallized from ethanol-ethyl acetate to give pure **1b** (8.6 g, 55%), m.p. 142°, NMR ($CDCl_3$) δ 4.36 (12H, s, $-OCH_3$); 4.97 (4H, s, $-CH_2Br$). The filtrate was poured into water, the solid was collected, dried and recrystallized from hexane and then from ethanol to give **1e** (1.7 g, 14%).

1,4 - *Bis(chloromethyl)* - 2,5 - *dimethoxy* - 3,6 - *dimethylbenzene* (**1f**). The solution of 1,4 - dimethoxy - 2,5 - dimethylbenzene (16.6 g, 100 mmole) in chloromethyl methyl ether (100 ml) was added dropwise to stirred mixture of anhydrous $ZnCl_2$ (28 g) in chloromethylmethyl ether (50 ml) at room temperature for 80 min. The reaction was continued for additional 2 h. Then 5% aq HCl (150 ml) was added the mixture was stirred for additional 1 h. Solid was filtered off, washed with water, dried and recrystallized from heptane–toluene to give pure **1f** (25.6 g, 97%), m.p. 173°, NMR ($CDCl_3$) δ 2.65 (6H, s, $-CH_3$); 4.16 (6H, s, $-OCH_3$); 5.04 (4H, s, $-CH_2Cl$)

1,4 - *Bis(bromomethyl)* - 2,5 - *dimethoxybenzene* (**1a**. To a stirred mixture of 1,4-dimethoxybenzene (70 g, 0.5 mmole), paraformaldehyde (30 g, 1.0 mmole) and glacial acetic (300 ml) acid kept at 15–20°, a solution of HBr in glacial acetic acid (200 ml, 45% w/v) was added dropwise for 1 h. The reaction was continued at room temp. for additional 2 h and the mixture was left for 17 h. After this period the mixture was heated to 65° for 1 h, then cooled and diluted with water (500 ml). Precipitated solid was filtered off and washed with water. Crude **1a** was dried *in vacuo* and recrystallized from chloroform to give pure **1a** (124.6 g, 77%), m.p. 206°, NMR ($CDCl_3$) δ 4.24 (6H, s, $-OCH_3$); 4.86 (4H, s, $-CH_2Br$); 7.11 (2H, s, ArH).

1 - *Bromomethyl* - 2,5 - *dimethoxy* - 3,4 - *dimethylbenzene* **1d**. To a stirred mixture of 1,4 - dimethoxy - 2,3 - dimethylbenzene (16.6 g, 100 mmole), paraformaldehyde (3.1 g, 103 mmole) and glacial acetic acid (80 ml) kept at 15°, a solution of HBr in glacial acetic acid (20 ml, 45% w/v) was added dropwise for 30 min. The stirring was continued at this temperature for additional 4 h and the mixture was left at room temp for 16 h. After this period the mixture was diluted with water (200 ml) and precipitated solid was filtered off, then dissolved in chloroform and solution dried over $MgSO_4$. The solvent was evaporated and crude product was recrystallized from hexane to give **1d** (21.4 g, 86%) m.p. 74°, NMR ($CDCl_3$) δ 2.46 and 2.54 (6H, s, $-CH_3$); 4.14 (6H, s, $-OCH_3$); 4.92 (2H, s, $-CH_2Br$); 7.02 (1H, s, ArH).

2 - *Bromomethyl* - 1,4 - *dimethoxynaphthalene* **1h**. To a stirred mixture of 1,4-dimethoxynaphthalene (26 g, 137 mmole) and paraformaldehyde (4.2 g, 140 mmole) and glacial acetic acid (150 ml) kept at 15°, a soln of HBr in glacial acetic acid (30 ml, 45% w/v) was added dropwise for 50 min. The reaction was continued at room temp for additional 3 h and the mixture was left for 16 h, then worked up as in the case of **1a**. Crude product recrystallized from hexane gave **1h** in 85% yield (32.7 g), m.p. 102°, NMR ($CDCl_3$), δ 4.30 and 4.34 (6H, s, $-OCH_3$); 5.90 (2H, s, $-CH_2Br$); 7.02 (1H, s, ArH); 7.76–7.90 (2H, m, ArH); 8.32–8.60 (2H, m, ArH).

2 - *Bromomethyl* - 1,4 - *dimethoxy* - 3 - *methylnaphthalene* **1i**. To a stirred mixture of 1,4 - dimethoxy - 2 - methylnaphthalene (10.0 g, 50 mmole) and paraformaldehyde (3.2 g, 107 mmole) and glacial acetic acid (100 ml) kept at room temp, a soln of HBr in glacial acetic acid (24 ml, 45% w/v) was added dropwise for 30 min. The reaction was continued for additional 2h and the mixture was left for 40 h, then worked up as **1a**. Recrystallized from hexane, pure **1i** was obtained in 85% yield (12.5 g), m.p. 82°, NMR ($CDCl_3$) δ 4.34 and 4.44 (6H, s, $-OCH_3$); 5.28 (2H, s, $-CH_2Br$); 7.72–7.92 (2H, m, ArH); 8.36–8.48 (2H, m, ArH).

3 - *Bromo* - 2 - *bromomethyl* - 1,4 - *dimethoxynaphthalene* **1g**. To **1h** (20.8 g, 75 mmole) suspended in CCl_4, solution of bromine (12 g, 75 mmole) in CCl_4 (30 ml) was added dropwise and the solution was allowed to stand for a week. After this time the solution was washed successively with water, 10% aq $NaHSO_3$ and again with water, and dried over $MgSO_4$. The solvent was evaporated and residue recrystallized from hexane to give **1g** (25.0 g, 94%), m.p. 95° (ref. 22 88°).

3 - *Bromo* - 2 - *bromomethyl* - 1,4 - *dimethoxy* - 5,6 - *dimethylbenzene* **1o** was obtained as for **1g** from **1d** (17.0 g, 66 mmole) and Br_2 (15.5 g, 97 mmole). Yield 87% (19.4 g) m.p. 73°, NMR ($CDCl_3$) δ 2.56 and 2.64 (6H, s, $-CH_3$); 4.16 and 4.24 (6H, s, $-OCH_3$); 5.13 (2H, s, $-CH_2Br$).

1 - *Hydroxy* - 4,8 - *dimethoxynaphthalene* **10**. 4,8 - Dimethoxy - 1 - naphthaldehyde **9** (34.1 g, 158 mmole) (prepared according to ref. 23) and o-nitrophenylselenic acid (2.0 g, 8.5 mmole) were added to CH_2Cl_2 (200 ml) and 30% H_2O_2 (45 ml). This mixture was stirred for 26 h at room temp then o-nitrophenylselenic acid was removed by filtration and the filtrate was washed with water, 10% aq $NaHSO_3$ and again with water, and then dried over $MgSO_4$. The solvent was removed *in vacuo* and a solid residue was dissolved in acetone (200 ml) and 10% aq HCl (60 ml) and heated for 30 min under reflux. After cooling to 0° crystalline **10** precipitated and was filtered off, washed with acetone–water (1:1) and dried to give pure product (25.8 g, 83%), m.p. 158° (ref. 22 155–156°).

2 - *Phenyl* - 4H - 1,3,2 - *naphthodioxaborin* **11**. To a solution of **10** (10.2 g, 50 mmole) and phenylboric acid (6.5 g, 53 mmole) in benzene (100 ml), refluxed under a Dean–Stark trap, paraformaldehyde (9.0 g, 300 mmole) was added portionwise. After cooling to room temp the mixture was filtered and from filtrate the solvent was removed *in vacuo*. The residue, recrystallized from cyclohexane–benzene, gave **11** (12.8 g, 83%), m.p. 141°, NMR ($CDCl_3$) δ 4.14 and 4.32 (6H, s, $-OCH_3$); 5.48 (2H, s, $-CH_2-$); 6.46 (1H, s, Ar–H); 7.14 (1H, dd, 8 Hz and 1 Hz Ar–H); 7.50–7.80 (4 Hz, m, ArH); 8.06 (1 Hz, dd, 8 Hz and 1 Hz, ArH); 8.32–8.42 (2H, m, ArH).

1 - *Hydroxy* - 2 - *hydroxymethyl* - 4,8 - *dimethoxynaphthalene* **12**. Silica gel (70–230 mesh, 70 g) was placed into column (diameter 3.5 cm), silica gel impregnated with 2,2 - dimethyl - 1,3 - propandiol was placed as a second layer, then silica gel with **11** was added and 2–3 cm layer of silica gel to the top and eluted with benzene (200 ml) and benzene–ethyl acetate (7:3). From this fraction the solvent was evaporated and residue was recrystallized from hexane to give **12**: yield 9.0 g (97%) m.p. 139°, NMR ($CDCl_3$) δ 2.90 (1H, s, $-CH_2OH$); 4.24 and 4.30 (6H, s, $-OCH_3$); 5.15 (2H, s, $-CH_2-$); 7.08 (1H, dd, 8 Hz and 1 Hz, ArH); 7.14 (1H, s, ArH); 7.58 (1H, t, 8 Hz, ArH); 8.14 (1H, dd, 8 Hz and 1 Hz, ArH); 9.50 (1H, s, ArOH).

Silica gel impregnated with 2,2 - dimethyl - 1,3 - propandiol was prepared as follows. To silica gel (Merck Kieselgel 60, 70–230 mesh, 100 g) the solution of 2,2 - dimethyl - 1,3 - propanediol (15 g, 144 mmole) in ethyl acetate (30 ml) was added portionwise with vigorous shaking and the solvent was removed on rotatory evaporator *in vacuo* at 50°. Similarly, silica gel impregnated with **11** was prepared from solution of **11** (12.8 g, 42 mmole) in $CHCl_3$ (30 ml) and silica gel (30 g).

2 - *Hydroxymethyl* - 1,4,8 - *trimethoxynaphthalene* **1j**. The solution of **12** (2.3 g, 10 mmole) in CH_2Cl_2 was stirred with 10% aq KOH (25 ml) and TEBA (0.5 g) for 5 min at room temp. To this mixture $(CH_3)_2SO_4$ (1.5 ml, 16 mmole) was added and the stirring was continued for 40 min. Then the organic layer was separated, washed with water and dried over $MgSO_4$. Evaporation of the solution gave crude **1j** which was recrystallized from cyclohexane–benzene and methanol. Yield (1.7 g, 77%), m.p.

139°, NMR ($CDCl_3$) δ 3.22 (1H, s, OH); 4.13, 4.23 and 4.32 (9H, s, $-OCH_3$); 5.18 (2H, s, $-CH_2-$); 7.14 (1H, s, ArH); 7.22 (1H, dd, 8 Hz and 1 Hz, ArH); 7.68 (1H, t, 8 Hz, ArH); 8.16 (1H, dd, 8 Hz and 1 Hz, ArH).

Oxiranylquinones **4**; *General procedure.* To a 1,4-dimethoxyarene **3** (5.0 mmole) in benzene (100 ml), water was added (100 ml) and silver(II) dipicolinate (10.3 g, 25 mmole) was added portionwise under vigorous stirring at room temp. When reaction was almost complete, the black oxidant turned into a white silver(I) salt. The reaction progress was controlled by TLC (on silica gel). The reaction time dependent on the substrate used and varied from 2.5–25 h. Solid product was filtered off and washed with benzene. The layers of the filtrate were separated and the water layer was extracted with benzene. The extracts were combined with the benzenic layer, washed with water and dried over $MgSO_4$. The solvent was evaporated off to give crude product in 90–100% yields. The crude products recrystallized from suitable solvents gave pure quinones **4** (Table 3).

Silver(II) dipicolinate. To fine pulverized dipicolinic acid (33.4 g, 200 mmole) suspended in the solution of silver nitrate (16.9 g, 100 mmole) in water (5 l), potassium persulfate (135 g, 500 mmole) was added portionwise within 2 h with vigorous stirring. Then the mixture was stirred till the white crystals of dipicolinic acid vanished (about 24 h). The black precipitate was filtered off, washed with cold water, and dried in the air to give pure silver dipicolinate in quantitative yield.

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