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1-Substituted 3,6-Dihydroxybenzocyclobutene.
A Versatile Precursor of Naturally Occurring Quinones

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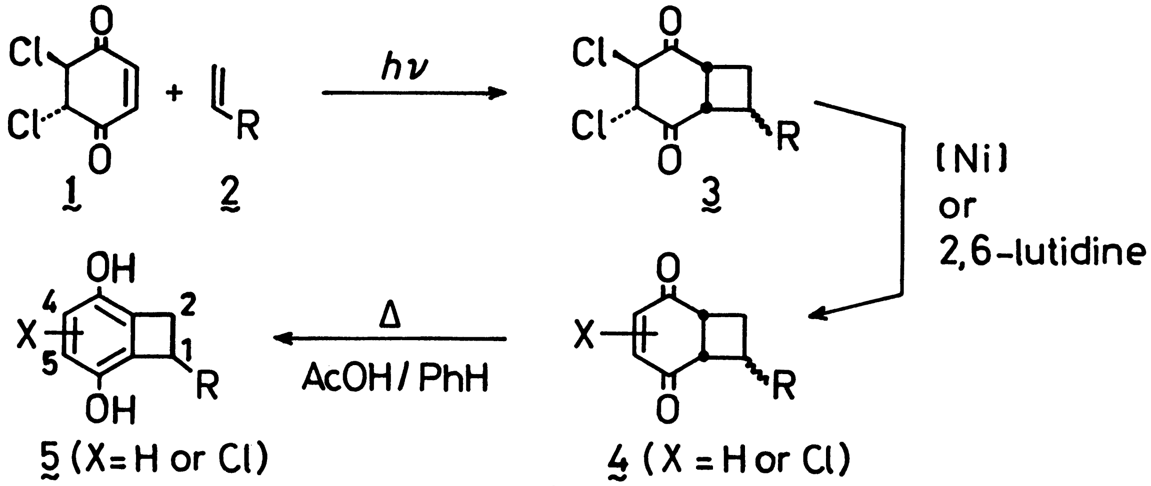
Simple and convenient routes to the title compounds using photoaddition of 5,6-dichloro-2-cyclohexene-1,4-dione to olefins, followed by reduction with a low valent nickel complex or by dehydrochlorination with 2,6-lutidine as key steps are described.

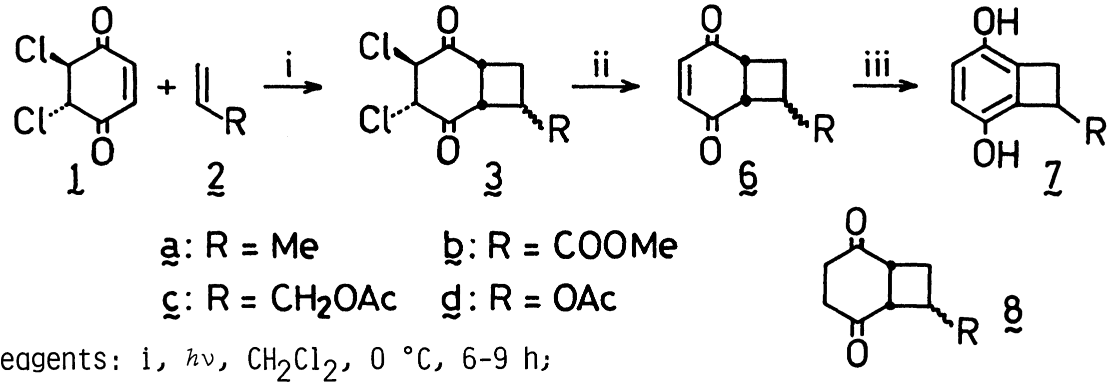
Naturally occurring quinones have attracted considerable interest from the scientific community because of their versatile biological properties. Recently, intra- and intermolecular cycloaddition reactions of o-quinonedimethides have been frequently employed for the synthesis of natural products (i.e., steroids, alkaloids, etc.).[1)] Therefore, similar synthetic method can be expected for 1-substituted 3,6-dihydroxybenzocyclobutenes (5). Thus, thermal electrocyclic ring-opening of 5 followed by the trapping of the resulting o-quinonedimethides with dienophiles[2)] is applicable to the synthesis of naturally occurring quinones.

In the course of our studies on quinones and hydroquinones annelated by 4-membered rings,[3)] we have studied new synthetic reactions using 5,6-dichloro-2-cyclohexene-1,4-diones (1)[4)] as a synthetic building block.[5)] In this paper, we report that 1-substituted 3,6-dihydroxybenzocyclobutenes (5) can be easily prepared in a 3 step sequence which involves photoaddition of 1 to olefins, reduction with a low valent nickel complex or dehydrochlorination with 2,6-lutidine, and enolization with acetic acid (Scheme 1).



Scheme 1.

In a previous paper,[5a)] we have reported the reductive dechlorination of 3,4-dichlorobicyclo[4.2.0]octane-2,5-dione to bicyclo[4.2.0]oct-3-ene-2,5-dione using an active nickel complex [i.e., $NiX_2(PPh_3)_2$-Zn-Et_4NI]. This dechlorination can be applied satisfactorily to the conversion of the photoadducts (**3a**-**c**) into the corresponding enediones (**6a**-**c**). Thus, the photoaddition of **1** to propene (**2a**), methyl acrylate (**2b**) and allyl acetate (**2c**), followed by treatment with the active nickel complex, afforded **6a**-**c** in 38-54% yields based on **1** (Table 1). In the case of the adduct (**3d**), however, the reaction of **3d** with the active nickel complex gave only the fully saturated dione (**8d**), which can be also prepared by reduction of **3d** with zinc in the presence of acetic acid.[5c)] The enediones (**6a**-**c**), consisting of the endo- and exo-isomer (1:9), can be easily converted into the hydroquinones (**7a**,[3a)] **7b**,[6)] and **7c**[6)]) in refluxing acetic acid-benzene (1:10).



Reagents: i, $h\nu$, CH_2Cl_2, 0 °C, 6-9 h; ii, $NiBr_2(PPh_3)_2$ (0.05 equiv.), Zn (4 molar equiv.), Et_4NI (2 equiv.), THF, rt, 2 h; iii, AcOH-benzene (1:10), reflux, 2-3 days.

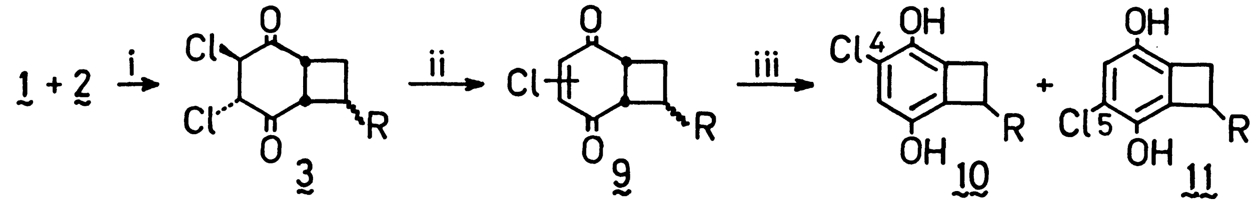
Table 1. Synthesis of 1-substituted 3,6-dihydroxybenzocyclobutenes (**7**) from **1**

1[a)] →	**3** →	**6**	**6** → **7**
Entry	R	Yield of **6** / %	Yield / %
1	Me	54	82
2	CO_2Me	38	88
3	CH_2OAc	39	88
4	OAc	0[b)]	-

a) Irradiations were carried out using 0.2 M solution of **1**, 2 equiv. of olefins and Pyrex filter.

b) **8d** was obtained in 56% yield.

Halo-substituted quinones have been extensively employed for regioselective cycloaddition.[7)] Therefore, we investigated the synthesis of the chloro-substituted hydroquinones (**10** and/or **11**), which might be transformed into anthraquinone derivatives by the cycloaddition reaction of o-quinonedimethide generated from **10** and/or **11**, followed by oxidation and Diels-Alder reaction of the resultant quinone with dienes. Thus, the above-mentioned photoadduct (**3**) was treated with 3 equiv. of 2,6-lutidine in CH_2Cl_2 at 0 °C overnight to give enedione (**9**). Separation of the two isomers of **9** was difficult owing to the instability of these compounds for slow column chromatography on silica gel. Therefore, **9** was converted into the hydroquinones (**10** and **11**) without separation. The results of this conversion and the ratio of the two isomers (**10** and **11**) are shown in Table 2.



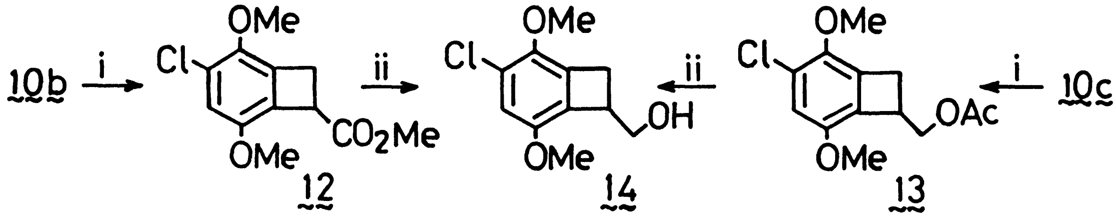
a: R = Me **b**: R = COOMe **c**: R = CH_2OAc **d**: R = OAc

Reagents: i, $h\nu$, CH_2Cl_2, 0 °C, 6-10 h; ii, 2,6-lutidine, CH_2Cl_2, 0 °C, overnight; iii, AcOH-benzene (1:10), reflux, 2-3 days.

Table 2. Synthesis of 1-substituted 4- and 5-chloro-3,6-dihydroxybenzocyclobutenes (**10** and **11**)[6] from **1**

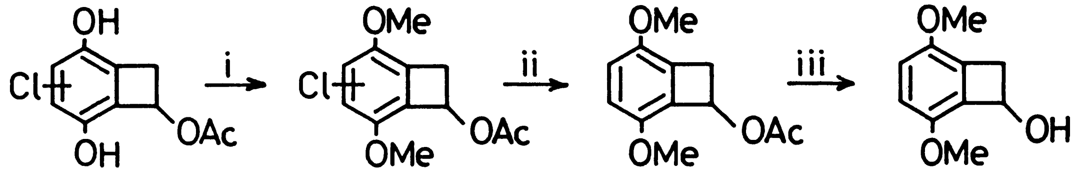
1 →	**3** →	**9**	**9** → **10** +	**11**
Entry	R	Yield of **9** / %	Yield of **10** and **11** / %	Ratio (**10** : **11**)
5	Me	42	79	3 : 1
6	CO_2Me	65	81	3 : 1
7	CH_2OAc	80	80	3 : 1
8	OAc	84	88	3 : 2

Dehydrochlorination of **3a**-**c** with 2,6-lutidine showed regioselectivity to some extent and produced after enolization the 4-chlorobenzocyclobutene derivatives (**10a**-**c**) as major isomers (entries 5-7). However, similar treatment of **3d** revealed a rather little selectivity and gave 4- and 5-chlorobenzocyclobutenes (**10d** and **11d**) in the ratio of 3:2. The two isomers (**10** and **11**) are assigned on the basis of their NMR chemical shift comparisons together with $Eu(fod)_3$ induced shifts and confirmed by chemical correlation between **10b** and **10c**. Thus, methylation of **10b** with $(CH_3)_2SO_4$-K_2CO_3 (94%), followed by reduction of **12** with $LiAlH_4$ (89%) gave the alcohol (**14**), which is also prepared by a two-step sequence [$(CH_3)_2SO_4$-K_2CO_3 (93%) and $LiAlH_4$ (97%)].



Reagents: i, $(CH_3)_2SO_4$, K_2CO_3, acetone, reflux, 2 h; ii, $LiAlH_4$, THF, 0 °C, 30 min.

It is known that Ni(0)-complex generated from Ni(II)-complex and zinc in aq. DMF is a mild and selective reducing agent of p-chloroanisole to anisole.[8] This method can be successfully employed for the preparation of 1-hydroxy-3,6-dimethoxybenzocyclobutene (**17**), which has been reported by Wallace as a versatile building block.[9] Methylation of a mixture of **10d** and **11d** with $(CH_3)_2SO_4$-K_2CO_3 produced dimethoxybenzocyclobutene (**15**) in 95% yield, which was treated with Ni(0)-complex to afford **16** in 92% yield. Removal of the acetoxy group in **16** gave the desired **17** in 85% yield. Therefore, this route to **17** has been carried out in six steps with an overall yield of 55%.



10d + **11d** **15** **16** **17**

Reagents: i, $(CH_3)_2SO_4$, K_2CO_3, acetone, reflux, 2 h; ii, $NiCl_2(PPh_3)_2$ (0.5 equiv.), PPh_3 (1 equiv.), NaI (1.8 equiv.), Zn (7.5 equiv.), DMF-H_2O (25:1), 60 °C, 17 h; iii, $LiAlH_4$, THF, 0 °C, 30 min.

In summary, our method has permitted a relatively simple synthesis of 1-substituted 3,6-dihydroxybenzocyclobutenes, new benzocyclobutene derivatives, and in principle should provide access to a variety of versatile precursors of quinones.

References

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6) All new compounds were characterized by IR, NMR, UV, and Mass spectra. The selected spectral data are as follows; **7b**, mp 151.5-153 °C, Mass (m/z) 194 (M^+); ^{1}H-NMR ($CDCl_3$) δ 3.42 (m, 2H), 3.81 (s, 3H), 4.32 (m, 1H), 6.64 (s, 2H); IR (KBr) 3360, 1710 cm^{-1}; **7c**, mp 119-119.5 °C, Mass (m/z) 208 (M^+); ^{1}H-NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.78 (dd, J = 2, 14Hz, 1H), 3.26 (dd, J = 5, 14, 1H), 3.68 (m, 1H), 4.14 (dd, J = 9, 11, 1H), 4.56 (dd, J = 6, 11, 1H), 4.70 (br s, 1H), 5.37 (br s, 1H), 6.56 (s, 2H); IR (KBr) 3350, 1707 cm^{-1}; **10b**, mp 140-142 °C, Mass (m/z) 228 (M^+); ^{1}H-NMR ($CDCl_3$) δ 3.44 (m, 2H), 3.80 (s, 3H), 4.30 (m, 1H), 5.19 (br s, 1H), 5.73 (br s, 1H), 6.80 (s, 1H); IR (KBr) 3375, 1715 cm^{-1}; **10d**, mp 154-155.5 °C, Mass (m/z) 228 (M^+); ^{1}H-NMR ($CDCl_3$) δ 2.17 (s, 3H), 3.25 (dd, J = 2, 14, 1H), 3.54 (dd, J = 4.5, 14, 1H), 5.13 (s, 1H), 5.20 (dd, J = 2, 4.5, 1H), 6.72 (s, 1H), 7.46 (s, 1H); IR (KBr) 3330, 1715 cm^{-1}; **11d**, mp 52-54 °C; Mass (m/z) 228 (M^+); ^{1}H-NMR ($CDCl_3$) δ 2.19 (s, 3H), 3.22 (dd, J = 2, 14, 1H), 3.51 (dd, J = 4, 14, 1H), 4.94 (br s, 1H), 5.50 (dd, J = 2, 4, 1H), 6.88 (s, 1H), 7.86 (br s, 1H); IR (KBr) 3350, 1726 cm^{-1}; **17**, mp 81-81.5 °C,[9] Mass (m/z) 180 (M^+); ^{1}H-NMR ($CDCl_3$) δ 3.08 (dd, J = 2, 14, 1H), 3.70 (dd, J = 5, 14, 1H), 3.79 (s, 3H), 3.90 (s, 3H), 5.32 (m, 1H), 6.62 (d, J = 9, 1H), 6.73 (d, J = 9, 1H); IR (KBr) 3425, 1490, 1265 cm^{-1}.

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