Hydrolysis of 1,4,6-Trioxaspiro[4.5]decanes to δ-Lactones Using 2,3-Dichloro-5,6-dicyanobenzoquinone in Aqueous Acetone

Sundar Vasudevan and David S. Watt*

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506

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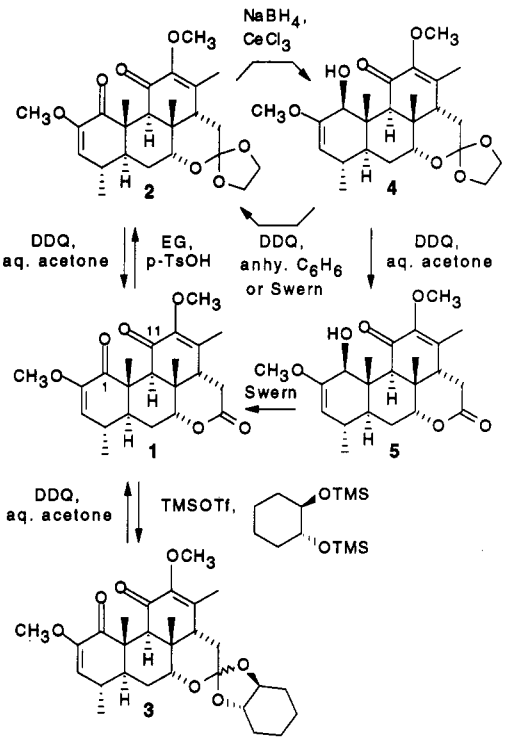
A selective hydrolysis of 1,4,6-trioxaspiro[4.5]decane orthoesters by 2,3-dichloro-5,6-dicyanoquinone (DDQ) in aqueous acetone in the presence of other acid-sensitive ketals is suggested to involve the formation of a charge-transfer complex followed by hydrolysis. A hydride-transfer mechanism for this oxidation was excluded.

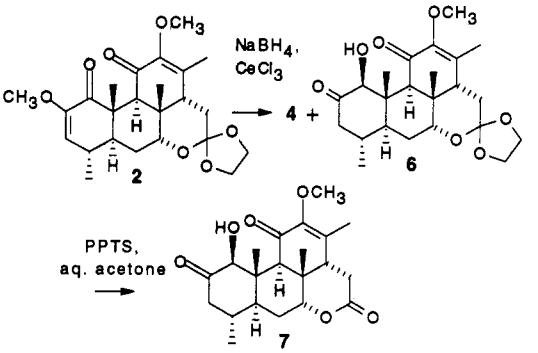
Selective procedures for removing protecting groups[1] in a multifunctional substrate are of current interest.[1] In connection with the preparation of pentacyclic quassinoids from (+)-quassin (1), we had occasion to prepare the orthoesters **2** and **3** in Scheme 1 using ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid or using *trans*-1,2-cyclohexanediol bis(trimethylsilyl) ether in the presence of a catalytic amount of trimethylsilyl triflate.[2] The hindered nature of the C-1 and C-11 carbonyl groups in **1** favored the selective formation of these orthoesters rather than the more typical ketals. Following other planned operations, we anticipated that an acid-catalyzed hydrolysis or oxidative cleavage[1,3] of the 1,4,6-trioxaspiro[4.5]decane would regenerate the δ-lactone functionality. We previously reported[4] that 2,3-dichloro-4,5-dicyanoquinone (DDQ) effected the selective cleavage of an orthoester to a δ-lactone in the presence of an enol ether. We now report studies that suggest this process involves the formation of a charge-transfer complex that undergoes hydrolysis.

In an investigation of the scope and mechanism of this reaction, we prepared a selection of orthoesters, acetals, and thioketals, displayed in Schemes 1–3. As shown in Scheme 1, the "oxidative hydrolysis" of the orthoester **2** with DDQ in aqueous acetone at 25 °C for 45 min led to deprotection to give (+)-quassin (**1**) in 82% yield.[4] Water was essential for the reaction. The exposure of another orthoester (**4**) to DDQ in aqueous acetone gave the δ-lactone **5** under these same conditions[4] but gave the keto orthoester **2** on exposure to DDQ in *anhydrous* benzene. A trace amount of 2,3-dichloro-5,6-dicyano-1,4-hydroquinone (DDQ-H_2) was initially suspected as the agent that promoted a simple, acid-catalyzed hydrolysis of **2** to **1** and **4** to **5**. Even if relatively little DDQ-H_2 were present, the DDQ oxidation of ethylene glycol, liberated in the hydrolysis reaction, might produce sufficient DDQ-H_2 to catalyze efficient hydrolysis. This latter suggestion was eliminated, however, when the oxidation of *meso*-hydrobenzoin with DDQ failed to produce benzoin, and we were left with the hypothesis that the observed hydrolysis was driven solely by the trace amounts of DDQ-H_2 that might be present in commercial samples of DDQ.

Scheme 1



Scheme 2



The relatively small amounts of DDQ-H_2 likely to be present in the recrystallized DDQ used in our studies made this hypothesis suspect. Furthermore, as shown in Scheme 2, the reduction[4] of **2** using sodium borohydride and cerium trichloride produced not only the enol ether orthoester **4** but also a trace amount of the α-ketol orthoester **6**, presumably as a result of exposure of **4** to aqueous ammonium chloride during the isolation procedure. The structure of α-ketol orthoester **6** was confirmed by a further

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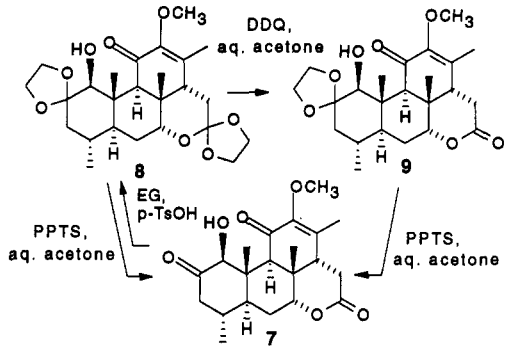
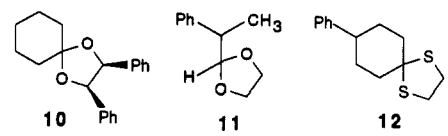
Scheme 3

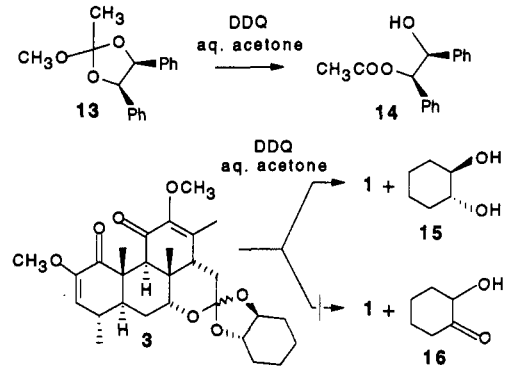


8 9 7



10 11 12

Scheme 4



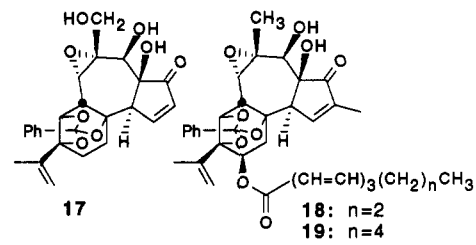
13 14 15 16 3

acid-catalyzed hydrolysis to isopicrasin B[4] (**7**). In contrast to the ammonium chloride-catalyzed hydrolysis of the enol ether in **4** that led to the α-ketol orthoester **6** in Scheme 2, the DDQ-promoted hydrolysis of **4** led exclusively to the enol ether δ-lactone **5** in Scheme 1. No hydrolysis of the enol ether in **4** was noted using DDQ in aqueous acetone. Once again, this evidence suggested that the DDQ-promoted reactions were not simple acid-catalyzed hydrolysis reactions.

The exposure of the ketal orthoester **8** in Scheme 3 to DDQ in aqueous acetone gave selectively the ketal δ-lactone **9** and none of the fully hydrolyzed compound, isopicrasin B[4] (**7**). Finally, the ketal[3] **10**, acetal[5] **11**, and thioketal[6] **12** in Scheme 3 were also unaffected by DDQ in aqueous acetone at 25 °C for 24 h, whereas ketal **10** was hydrolyzed to the expected *meso*-hydrobenzoin with *p*-toluenesulfonic acid in aqueous acetone. These data were also inconsistent with a mechanism for the hydrolysis of the orthoesters that involved a simple acid-catalyzed hydrolysis by DDQ-H_2.

The lack of reactivity of ketal **10** toward DDQ also excluded a hydride-transfer mechanism that was operative in the deprotection of ketals using trityl tetrafluoroborate.[3] This point was further confirmed by two other experiments. The exposure of the orthoester[7] **13** in Scheme 4 to DDQ in aqueous acetone gave selectively the ester[8] **14**.

Scheme 5



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The *meso*-hydrobenzoin portion of the ester **14** was not oxidized, and this finding excluded a hydride-transfer mechanism. In addition, the oxidation of the orthoester **3** with DDQ in aqueous acetone gave (+)-quassin (**1**) and *trans*-1,2-cyanohexanediol (**15**) but not the α-ketol 2-hydroxycyclohexanone (**16**).

Having discounted a hydride-transfer mechanism, we suggested that the hydrolysis reactions promoted by DDQ in aqueous medium involved the formation of a charge-transfer complex that intercepted water to form the observed products. A similar suggestion[9] was made for the photoinduced hydrolysis of acetals by 1,2,4,5-tetracyanobenzene (TCNB). The greater oxidation potential for DDQ ($E_{1/2}$ = +0.51 V) relative to TCNB ($E_{1/2}$ = −0.70 V) presumably permitted electron transfer from the ground state of the orthoesters in the DDQ oxidations noted here.

The benzylic oxidation[10-13] of various hydrocarbons by DDQ is a well-known reaction that serves particularly well in the deprotection[14] of (*p*-methoxyphenoxy)methyl (MPM) and (3,4-dimethoxyphenoxy)methyl (DMPM) ethers to the corresponding alcohols. The initial step proposed in these deprotection reactions is suggested to involve the formation of a charge-transfer (CT) complex between DDQ and the electron-rich MPM and DMPM ethers. Since an orthoester is a more electron-rich species than an acetal,[15] a charge-transfer–hydrolysis mechanism accounts for our observations. The acetals **10** and **11** as well as the thioketal **12** in Scheme 3 were not deprotected by treatment with DDQ in aqueous acetone at 25 °C for 24 h, consistent with the hypothesis that only the electron-rich orthoester would afford a CT complex with DDQ. Orthoester functionality occurs in some antineoplastic agents such as daphnetoxin[16a] (**17**), gniditrin[16b] (**18**), and gnididin[16b] (**19**), shown in Scheme 5. It is interesting to speculate whether *in vivo* oxidation by naturally occurring

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(15) The ionization potentials are directly related to $\Delta H°_f$: methyl vinyl ether, 179 kcal/mol; 2-methoxypropene, 164 kcal/mol; dimethoxymethane, ca. 137 kcal/mol; trimethoxymethane, 90–95 kcal/mol; and trimethyl orthoacetate, *ca.* 86 kcal/mol. Holmes, J. L.; Lossing, F. P. *Can. J. Chem.* **1982**, *60*, 2365.
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quinones and subsequent interception by nucleophiles might account for the cytotoxic properties of these natural products.

Experimental Section

(+)-Quassin (1) from 2. To a solution of 50 mg (0.115 mmol, 1 equiv) of **2** in 1.25 mL of 1:20 water–acetone was added dropwise 31 mg (0.138 mmol, 1.2 equiv) of DDQ in 1.25 mL of 1:20 water–acetone. The mixture was stirred at 25 °C for 45 min. The product was chromatographed on neutral alumina using acetone to afford 37 mg (82%) of (+)-quassin (1) that was identical with the authentic sample by TLC and NMR.

(+)-Quassin (1) from 3. The procedure described for the preparation of **1** from **2** was repeated using 20 mg (0.041 mmol) of **3** and 11 mg (0.048 mmol, 1.2 equiv) of DDQ in 840 μL of 1:20 water–acetone to afford, after chromatography on neutral alumina using acetone, 12 mg (75%) of (+)-qaussin (1) and 3 mg (60%) of *trans*-1,2-cyclohexanendiol (**15**).

(+)-Quassin (1) from 5. To a solution of 48 mg (0.61 mmol, 12 equiv) of DMSO in 225 μL of anhydrous CH_2Cl_2 was added 58 mg (0.46 mmol, 9 equiv) of oxalyl chloride at −78 °C under a N_2 atmosphere. The mixtture was stirred for 10 min, and a white precipitate formed. To this mixture was added 20 mg (0.05 mmol, 1 equiv) of **5**[4] in 225 μL of anhydrous CH_2Cl_2. The mixture was stirred at −78 °C for 1 h, and 140 μL (103 mg, 1.02 mmol, 20 equiv) of Et_3N was added. The mixture was warmed to 25 °C over a 1-h period, diluted with CH_2Cl_2, and washed with brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to afford a crude product that was purified by preparative layer silica gel chromatography using EtOAc to afford 17 mg (86%) of (+)-quassin (1) that was identical with an authentic sample.

2,12-Dimethoxy-2,12-picradiene-1,11,16-trione 16-(Ethylene ketal) (2) from 4 Using DDQ in Anhydrous Benzene. To a solution of 24 mg (0.055 mmol, 1 equiv) of **4** in 550 μL of anhydrous benzene was added 15 mg (0.066 mmol, 1.2 equiv) of DDQ in 550 μL of anhydrous benzene dropwise. The mixture was stirred at 25 °C under a N_2 atmosphere for 23 h and passed through a neutral alumina column using acetone. The eluate was collected, concentrated, and purified by chromatography on an analytical silica gel TLC plate using EtOAc to afford 8 mg (34%) of **2** that was identical with authentic material according to TLC and ^1H NMR.

2,12-Dimethoxy-2,12-picradiene-1,11,16-trione 16-(Ethylene ketal) (2) from 4 Using a Swern Oxidation Reaction. To a solution of 52 mg (0.66 mmol, 12 equiv) of DMSO in 240 μL of anhydrous CH_2Cl_2 was added 63 mg (0.50 mmol, 9 equiv) of oxalyl chloride at −78 °C under a N_2 atmosphere. The mixture was stirred for 10 min, and a white precipitate formed. To this mixture was added 24 mg (0.06 mmol, 1 equiv) of **4** in 240 μL of anhydrous CH_2Cl_2. The mixture was stirred at −78 °C for 1 h, and 154 μL (112 mg, 1.11 mmol, 20 equiv) of Et_3N was added. The mixture was warmed to 25 °C over a 1-h period, diluted with CH_2Cl_2, and washed with brine. The organic solution was dried over anhydrous $MgSO_4$ and concentrated to afford a crude product that was purified by preparative layer silica gel chromatography using 2:1 EtOAc–hexane to yield 14 mg (58%) of **2** that was identical with an authentic sample.

2,12-Dimethoxy-2,12-picradiene-1,11-dione 16-(*trans*-1,2-Cyclohexanediyl ketal) (3). To a solution of 118 mg (0.303 mmol, 1 equiv) of (+)-quassin (**1**) and 253 mg (0.969 mmol, 3.2 equiv) of *trans*-1,2-bis((trimethylsilyl)oxy)cyclohexane[2] in 1 mL of anhydrous CH_2Cl_2 at −10 °C under an Ar atmosphere was added 6 μL (7 mg, 0.030 mmol, 0.1 equiv) of trimethylsilyl trifluoromethanesulfonate. The mixture was stirred at 25 °C for 18 h and was quenched with 250 μL of pyridine. The solution was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution. The aqueous layer was extracted twice with CH_2Cl_2. The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography using 2:1 EtOAc–hexane to afford 35 mg and 32 mg, respectively, of two diastereomers (45% combined yield) and 42 mg (36%) of unreacted **1**. The major diastereomer of **3** had the following spectral data: IR (KBr) 1684 (enone C=O), 1636 (C=C) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 12.8, 15.2, 19.3, 21.8, 23.5, 23.6, 25.7, 28.4, 28.9, 31.4, 34.6, 38.0, 43.1, 45.8, 45.9, 47.8, 54.9, 59.1, 75.6, 79.1, 82.0, 116.3 (C-3), 118.7 (C-16), 138.3, 148.1, 148.3, 192.9, 198.2; exact mass spectrum calcd for $C_{28}H_{38}O_7$ 486.2618, found 486.2621. A minor impurity, that could not be removed by recrystallization or chromatography, was noted in the GC-MS of **3**.

12-Methoxy-1β-hydroxy-12-picrasene-2,11,16-trione 16-(Ethylene ketal) (6). Compound **6** was obtained in 9% yield during the reduction of **2** to **4** according to a previously published procedure.[4] Spectral data for **6**: IR (KBr) 3420, 1724 (C-2 C=O), 1654 (enone C=O), 1637 (C=C) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 11.5, 15.1, 19.6, 21.3, 25.0, 31.2, 32.4, 39.3, 42.9, 46.0, 48.2, 48.3, 52.6, 59.5, 63.6, 64.8, 75.2, 86.0, 118.4 (C-16), 142.6, 148.6, 199.1 (C-11), 208.8 (C-2). Anal. Calcd for $C_{23}H_{32}O_7 \cdot H_2O$: C, 63.00; H, 7.81. Found: C, 62.94; H, 8.16.

Isopicrasin B (7) from 4, 6, 8, and 9. A mixture of 29 mg (0.062 mmol, 1 equiv) of **8** and 5 mg (0.02 mmol, 0.3 equiv) of PPTS in 1.54 mL of 1:10 H_2O–acetone was refluxed for 18 h. The mixture was cooled, concentrated, diluted with EtOAc, and washed successively with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to afford 18 mg (75%) of isopicrasin B (**7**). The hydrolysis of **4** and **9** under similar conditions afforded 94%[4] and 59%, respectively, of isopicrasin B (**7**). The hydrolysis of **6** for 3 h afforded 62% of isopicrasin B (**7**).

12-Methoxy-1β-hydroxy-12-picrasene-2,11,16-trione 2,16-Bis(ethylene ketal) (8). To a solution of 76 mg (0.20 mmol, 1 equiv) of isopicrasin B (**7**) in 4 mL of anhydrous benzene were added 251 mg (4.04 mmol, 20 equiv) of ethylene glycol and 1.9 mg (0.01 mmol, 0.05 equiv) of *p*-toluenesulfonic acid monohydrate. The mixture was refluxed under a N_2 atmosphere using a Dean–Stark trap for 5 h. The mixture was cooled to room temperature, diluted with EtOAc, and washed successively with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to afford a crude product that was purified by preparative layer silica gel chromatography using 2:1 EtOAc–hexane to yield 66 mg (70%) of **8**: IR (KBr) 3364, 1663 (enone C=O) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 10.8, 15.4, 19.4, 22.4, 25.0, 27.4, 32.6, 39.6, 43.0, 44.0, 44.7, 49.0, 55.1, 59.4, 63.6, 64.8, 65.0, 67.0, 75.8, 83.7, 109.8 (C-2), 118.3 (C-16), 142.1, 148.4, 199 .9 (C-11). Anal. Calcd for $C_{25}H_{36}O_8 \cdot {}^1/_2H_2O$: C, 63.41; H, 7.87. Found: C, 63.42; H, 8.20.

12-Methoxy-1β-hydroxy-12-picrasene-2,11,16-trione 2-(Ethylene ketal) (9). To a solution of 55 mg (0.12 mmol, 1 equiv) of **8** in 1.2 mL of 1:20 H_2O–acetone was added dropwise 32 mg (0.14 mmol, 1.2 equiv) of DDQ in 1.2 mL of 1:20 H_2O–acetone. The mixture was stirred at 25 °C for 60 min and passed through a short column of neutral alumina using acetone. The eluate was collected, concentrated, and chromatographed on a preparative layer silica gel plate using 1:20 acetone–benzene to afford 49 mg (99%) of **9**. An analytical sample was obtained by crystallization from CH_2Cl_2–hexane: mp 131–133 °C; IR (KBr) 3345, 1728 (lactone C=O), 1664 (enone C=O), 1641 (C=C) cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 10.5, 15.5, 19.3, 23.0, 25.1, 27.3, 31.2, 38.4, 43.2, 43.8, 44.5, 47.2, 55.6, 59.6, 65.0, 66.9, 83.1, 83.4, 109.3 (C-2), 144.4, 148.5, 168.7 (C-16), 197.8 (C-11). Anal. Calcd for $C_{23}H_{32}O_7 \cdot {}^1/_2H_2O$: C, 64.32; H, 7.74. Found: C, 64.14; H, 7.78.

***meso*-2-Acetoxy-1-hydroxydibenzyl (14).** To a solution of 35 mg (0.128 mmol, 1 equiv) of **13**[7] in 1.3 mL of 1:20 H_2O–acetone was added dropwise 35 mg (0.153 mmol, 1.2 equiv) of DDQ in 1.3 mL of 1:20 H_2O–acetone. The mixture was stirred at 25 °C for 60 min and passed through a neutral alumina column using acetone. The eluate on concentration gave 31 mg (94%) of **14**. An analytical sample was obtained by crystallization from EtOAc–hexane: mp 84–86 °C (lit.[8] mp 84–86 °C); IR (KBr) 3363 (br OH), 1738 (C=O), 1456, 1374 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 20.7 (CH_3), 76.2, 78.8, 127.1, 127.9, 128.3, 128.4, 128.6, 136.6, 139.8, 170.2 (C=O). Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.08; H, 6.34.

A mixture of 38 mg (0.142 mmol, 1 equiv) of **13** and 11 mg (0.043 mmol, 0.3 equiv) of PPTS in 2.75 mL of 1:10 H_2O–acetone was refluxed under a N_2 atmosphere for 3 h. The mixture was cooled, concentrated, diluted with EtOAc, and washed successively with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to afford

36 mg (100%) of 14 that was identical with the material obtained by hydrolysis of 13 using DDQ in aqueous acetone.

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Supplementary Material Available: ^{1}H NMR data for compounds 3, 6, 8, 9, and 14 (2 pages). This material is contained in libraries on microfiche, immediately following this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.