First Preparation of Optically Pure Ketals of *p*-Benzoquinone†

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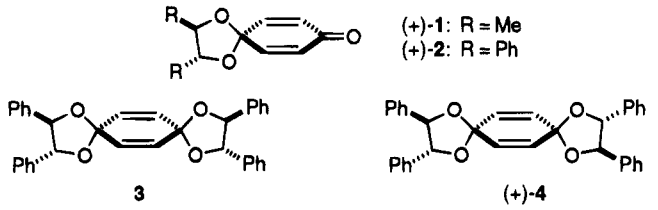
p-Benzoquinone derivatives play an important role in bioorganic redox reactions. This is probably why they have been widely considered as interesting target molecules in the field of organic synthesis.[1] Since quinones are very reactive substrates, the protection of either one or both carbonyl groups can be very useful for synthetic purposes. The formation of ketals is one of the ways more frequently employed to this aim. Ketals of quinones have been shown very effective in synthetic transformations.[2] Quinone monoketals have been employed in a wide variety of strategies for the preparation of many interesting compounds including neolignans,[3] pentaprismanes,[4] anthracyclinones,[5] and aranorosin nuclei[6] among others.

For a carbonyl group that is not close to a stereogenic center, differentiation among the *re* and *si* faces is not possible. The formation of a chiral acetal may allow control of the reactivity and stereoselectivity not only in the acetal function itself, but also in the prochiral vicinal groups. For the protection of quinones, the use of a chiral diol with C_2 axial symmetry would avoid chemoselectivity problems in the subsequent reactions since both double bonds are equivalent. Diols with C_2 axial symmetry have been successfully employed in many systems to perform asymmetric synthesis. They are more selective in relation to other asymmetric diols, since the existence of competitive transition states leading to other products is eliminated.[7] C_2 diols have been used as chiral auxiliaries mainly as ligands for Lewis acid catalysts,[8] but also for acetal formation.[9] Here we report the use of (-)-butane-2,3-diol and (+)-1,2-diphenylethylene glycol for the easy preparation of (1*R*,2*R*)-1,2-dimethyl- and (1*R*,2*R*)-1,2-diphenylethylene monoketals of *p*-benzoquinone (**1** and **2**, respectively), which are the first examples of homochiral monoketals of this quinone.[10]

Chart 1



Results and Discussion

To the best of our knowledge, except for a quite marginal example,[11] until 1992 only one cyclic monoketal of *p*-benzoquinone was known, namely the ethylene monoketal.[12] It had been prepared by monohydrolysis of the corresponding ethylene bisketal or other mixed bisketals, which were generally obtained by electrochemical oxidation of *p*-dialkoxybenzenes.[13] In an isolated example due to Sakaino and Meinwald[14] the preparation of 2,6-dimethyl-*p*-benzoquinone-4,4-ethylene ketal is described by a straightforward procedure from the corresponding quinone and ethylene glycol.

Recently, Pirrung and Nunn[15] described a general method for the preparation of cyclic monoketals of *p*-benzoquinone, through transketalization of 4,4-dimethoxy-2,5-cyclohexadienone with an excess of diol in DME, catalyzed by $BF_3{\cdot}Et_2O$. A reaction mechanism of direct exchange at the dimethyl ketal was proposed, partially based on the absence of bisketals. When trying to reproduce this reaction for the preparation of the optically pure monoketal (+)-**1**, we did isolate the expected product in the reported yield (68%), but we also obtained a considerable amount of the corresponding bisketal. This prompted us to attempt the synthesis of the monoketal by straight reaction of the diol with *p*-benzoquinone, avoiding the previous preparation of the much more expensive dimethyl ketal, accessible only through oxidation of phenol derivatives. Thus, addition of $BF_3{\cdot}Et_2O$ to a solution of *p*-benzoquinone and (2*R*,3*R*)-butane-2,3-diol in DME under argon at room temperature gave the desired monoketal (+)-**1** in 81% yield.

In order to investigate the applicability of the method, we performed the same reaction with several other diols, able to form either five- or six-membered cyclic ketals. Surprisingly, none of the diols tried led to the expected monoketal in good yield. From ethylene glycol, propylene glycol, and 2,4-pentanediol, some monoketals were formed, but they were always accompanied by other unidentified

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products, probably polymeric ketals. With lower temperatures or shorter reaction times unaltered starting materials were recovered. From 1,3-propanediol, *trans*-1,2-cyclohexanediol, L-dimethyl tartrate, and 2-methyl-2,4-pentanediol the corresponding mono- and bisketals were never detected.

When the reaction was performed with (±)-1,2-diphenylethylene glycol, some crystalline material separated from the reaction mixture and, after purification of the remaining crude product by column chromatography, two different fractions were obtained. The less polar fraction happened to be an additional quantity of the former crystalline compound, to which the structure of a bisketal **3** was assigned, according to its spectroscopic properties. This compound was obtained in 35% overall yield. The second fraction was identified as the expected monoketal (±)-**2** (16% yield). Monohydrolysis of the bisketal **3** was accomplished in 85% yield. Therefore the overall yield of (±)-**2** after the two consecutive reactions was at this point 46%. Increasing the number of equivalents of diol to 2.2, the yield of the bisketal **3** obtained through spontaneous crystallization from the reaction mixture rose to 44%. This material was mixed with the remaining neutralized crude product and submitted to hydrolysis to afford the monoketal (±)-**2** in 59% yield from *p*-benzoquinone.

In order to prepare optically pure monoketal **2**, *p*-benzoquinone was treated with 2.2 equiv of (+)-(1*R*,2*R*)-1,2-diphenylethylene glycol under the same conditions. In this case no crystalline material precipitated from the reaction mixture, but purification of the crude product by column chromatography afforded two different fractions. In the more polar one the homochiral monoketal (+)-**2** was collected in 22% yield. The less polar fraction contained one compound that showed identical spectroscopic characteristics to those previously observed for the bisketal **3** isolated from the reaction between *p*-benzoquinone and (±)-1,2-diphenylethylene glycol, but its melting point was much lower than that determined for the former bisketal **3** (196–99 °C *vs* 289–92 °C). The compound depicted in (+)-**4** (41% yield) is the only bisketal that can be obtained starting from (1*R*,2*R*)-1,2-diphenylethylene glycol.

X-ray crystallographic studies confirmed that both compounds **3** and **4** have the assigned bisketal structure.[16] These studies revealed also that the relative configuration of bisketal **3** is different to that of **4**, namely it is a *meso* diastereoisomer and not the racemate. Compound **3** adopts in the crystal a centrosymmetric conformation very close to C_{2h} (the highest symmetry possible for this molecule). The bisketal **4** adopts in the crystal a conformation having a 2-fold symmetry, and the dyad axis passes by the midpoints of the two cyclohexadiene double bonds (the highest symmetry possible for this molecule is D_2). The distinct relative configurations of **3** and **4** produces different crystal packings (space groups are $P2_1/n$ and $P3_121$, respectively) and therefore some of their physical properties differ notably. Thus, crystals of **3** have higher density and melting point and a poorer solubility than crystals of **4**.

The monohydrolysis of the optically pure bisketal **4** was carried out as above to produce the optically pure monoketal (+)-**2** in 85% yield. Therefore the overall yield of (+)-**2** after the two consecutive reactions was at this point 57%. In all the hydrolysis reactions, the chiral auxiliary diol was recovered quantitatively.

The overall yield of monoketal (+)-**2** could be improved to 76% performing the bisketalization with a 2-fold excess of diol (4:1 molar ratio) and conducting the monohydrolysis of the crude product without previous isolation of the bisketal intermediate.

Access to both *p*-benzoquinone (1*R*,2*R*)-1,2-dimethyl- and (1*R*,2*R*)-1,2-diphenylethylene monoketals (**1** and **2**) has therefore been accomplished in good yield, through a simple method and by using the inexpensive *p*-benzoquinone as starting material. These homochiral monoketals open new interesting possibilities for asymmetric organic synthesis, since they contain various functional groups suitable for a plethora of useful synthetic chemical transformations.[2c]

Experimental Section

General. The NMR spectra were recorded at 250 MHz for ^{1}H and 62.5 MHz for ^{13}C from $CDCl_3$ solutions. Chemical shifts are reported in δ relative to residual $CHCl_3$ (7.24 ppm) for ^{1}H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR.

(+)-(1*R*,2*R*)-1,2-Dimethylethylene Monoketal of *p*-Benzoquinone ((+)-1). (2*R*,3*R*)-Butane-2,3-diol (2.3 mL, 25.6 mmol) was added to a solution of *p*-benzoquinone (2.0 g, 18.5 mmol) in anhydrous DME (5 mL) at room temperature under argon. Then, under vigorous stirring, a DME 1.5 M solution of $BF_3{\cdot}Et_2O$ (13 mL, 19.5 mmol) was added dropwise. After stirring the mixture for 1.5 h, it was diluted with ether (10 mL) and neutralized with solid $NaHCO_3$. Subsequent addition of water (5 mL) and extraction with ether (3 × 8 mL) gave, after drying over anhydrous $MgSO_4$ and removal of the solvent, 2.90 g of a deep red oil. Flash column chromatography through silica gel using hexane/ether 9/1 as eluent afforded the following fractions: 0.20 g (10%) of *p*-benzoquinone and 2.70 g (15.0 mmol, 81%) of (+)-**1** as a pale yellow solid: mp 43–45 °C (ether/pentane); IR (KBr) 1685, 1631, 1195, 1103, 1068 cm^{-1}; ^{1}H NMR 6.63 (d, J = 10.2 Hz, 1H), 6.13 (d, J = 10.2 Hz, 1H), 3.80 (m, 1H), 1.30 (d, J = 5.5 Hz, 3H); ^{13}C NMR 185.3, 144.4, 128.4, 97.1, 79.6, 16.4; $[\alpha]^{20}_D$ = 58.7 (c = 2.1 in $CHCl_3$). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.64; H, 6.72. Found: C, 66.55; H, 6.72.

(±)-**1** was also prepared following the same procedure: mp 38–40 °C (ether/pentane).

(+)-(1*R*,2*R*)-1,2-Diphenylethylene Monoketal of *p*-Benzoquinone ((+)-2) and (+)-(1*R*,2*R*)-1,2-Diphenylethylene Bisketal of *p*-Benzoquinone ((+)-4). To a stirred solution of *p*-benzoquinone (35 mg, 0.32 mmol) and (2*R*,3*R*)-diphenylethylene glycol (153 mg, 0.71 mmol) in anhydrous DME (1.0 mL) at room temperature under nitrogen was added dropwise a DME 1.5 M solution of $BF_3{\cdot}Et_2O$ (0.50 mL, 0.75 mmol. After stirring for 3 h, the mixture was diluted with ether (2 mL) and neutralized with saturated $NaHCO_3$ solution. Subsequent extraction with ether (3 × 1 mL) gave, after drying over anhydrous $MgSO_4$ and removal of the solvent, 164 mg of an orange oil. Flash column chromatography through silica gel using hexane/ether 9/1 as eluent afforded the following fractions: 65 mg (0.13 mmol, 41%) of (+)-**4**, and 21 mg (0.069 mmol, 22%) of (+)-**2**. A solution of (+)-**4** (17 mg, 0.034 mmol) in dioxane/acetonitrile/3% HCl (5.0/0.5/0.5 mL) was heated at 75 °C for 1 h. After neutralization with saturated $NaHCO_3$ solution, extraction with ether, drying over anhydrous $MgSO_4$, and removal of the solvent, 16 mg of crude material was obtained. Purification by flash column chromatography through silica gel using hexane/ether 9/1 as eluent afforded 9 mg (0.03 mmol, 85%) of (+)-**2** and 7 mg (0.03 mmol, 97%) of (2*R*,3*R*)-2,3-diphenylethylene glycol.

In another run, from 23 mg (0.21 mmol) of *p*-benzoquinone, 178 mg (0.83 mmol) of (2*R*,3*R*)-2,3-diphenylethylene glycol and 2.0 mL of DME 1.5 M solution of $BF_3{\cdot}Et_2O$ (0.35 mL, 0.52 mmol), following the same procedure, 200 mg of crude bisketal was obtained. This material was exposed to the hydrolysis conditions as above. Purification through flash column chromatography

(16) The author has deposited atomic coordinates for **3** and **4** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(hexane/ether 9/1), followed by washing of the fraction containing **2** (62 mg) with hexane, afforded 48 mg (0.16 mmol, 75%) of pure (+)-**2** as colorless crystals: mp 153–156 °C (CH_2Cl_2/hexane); IR (KBr) 1680, 1638, 1181, 1114, 1019 cm^{-1}; ^1H NMR 7.28 (m, 5H), 6.94 (d, J = 10.0 Hz, 1H), 6.27 (d, J = 10.0 Hz, 1H), 4.93 (s, 1H); ^{13}C NMR 185.2, 143.5, 135.0, 129.1, 128.9, 128.7, 126.5, 98.5, 85.9; $[\alpha]^{20}_D$ = 52.0 (c = 0.50 in $CHCl_3$). Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.92; H, 5.30. Found: C, 78.71; H, 5.13. (+)-**4**: mp 196–199 °C ($CHCl_3$/pentane); IR (KBr) 1124, 1012, 977 cm^{-1}; ^1H NMR 7.28 (m, 5H), 6.34 (s, 1H), 4.87 (s, 1H); ^{13}C NMR 136.0, 131.2, 128.4, 126.6, 98.9, 85.6; $[\alpha]^{20}_D$ = 32.6 (c = 0.95 in $CHCl_3$). Anal. Calcd for $C_{34}H_{28}O_4$: C, 81.57; H, 5.64. Found: C, 81.53; H, 5.63.

(1*RS*,2*RS*)-1,2-Diphenylethylene Monoketal of *p*-Benzoquinone ((±)-2) and (1*RS*,2*RS*)-1,2-Diphenylethylene Bisketal of *p*-Benzoquinone (3). The reaction between *p*-benzoquinone and racemic diphenylethylene glycol was run under the same conditions described above, but after stirring for 3 h, the precipitate was filtered off to afford 44% yield of bisketal **3**. The solution was neutralized and extracted as described before. When the mixture of this crude material and compound **3** was submitted to hydrolysis a 59% yield of racemic **2** was obtained. (±)-**2** : mp 145–147 °C (CH_2Cl_2/hexane); IR (KBr) 1680, 1638, 1173, 1117, 1068, 1012 cm^{-1}. Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.92; H, 5.30. Found: C, 78.98; H, 5.21. **3**: mp 289–292 °C (DME); IR (KBr) 1124, 1019, 977 cm^{-1}; ^1H NMR 7.28 (m, 5H), 6.34 (s, 1H), 4.87 (s, 1H); ^{13}C NMR 136.0, 131.2, 128.4, 126.6, 98.9, 85.6. Anal. Calcd for $C_{34}H_{28}O_4$: C, 81.57; H, 5.64. Found: C, 81.52; H, 5.66.

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