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From *p*-benzoquinone to useful chiral cyclohexane building blocks

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Abstract—A straightforward and efficient access to 12 new cyclohexane chirons from an easily available enantiopure monoketal of *p*-benzoquinone is described. These chirons possess a variety of functional groups which render them useful for further synthetic elaboration.

1. Introduction

There are many natural products which contain a densely functionalised, stereogenic cyclohexane unit in their structure. In particular, there exists a variety of polyoxygenated cyclohexanes which have interesting anti-cancer activity. Some examples of such compounds are bromoxone, **1**, the antitumour antibiotic LL-C10037α, **2**, the manumycins, **3** and fumagillin, **4**, among others (Fig. 1). Because of the biological activity of these substances, during the last decade many efforts have been devoted to the development of efficient methodologies for the preparation of enantiomerically pure cyclohexane building blocks. For instance, Hudlicky[1] has reported the synthesis of a large number of enantiopure cyclohexadienediols, **5** (Fig. 2); Ogasawara[2] has described several Diels–Alder adducts derived from *p*-benzoquinone, **6**; the cyclohexenone **7** has been described by Sato;[3] Enders[4] has recently achieved the asymmetric synthesis of several substituted 1,4-cyclohexanedione derivative, **8**; and Taber has demonstrated the utility of the cyclohexenone **9**,[5] by using it as an intermediate in a synthesis of **4**.[6] Most of these authors have already demonstrated the versatility of these cyclohexane chirons as building blocks by performing the syntheses of several natural products in enantiopure form.

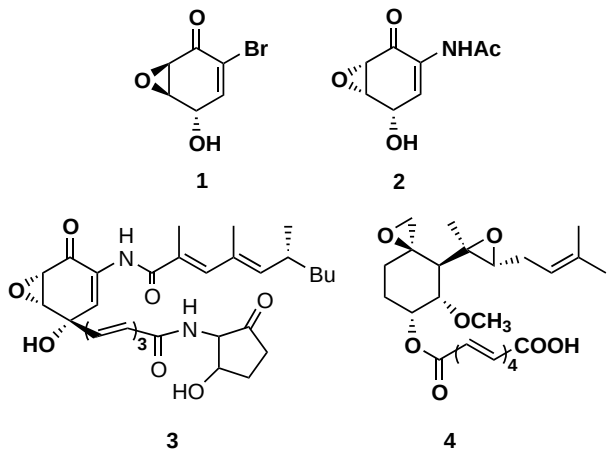

Figure 1.

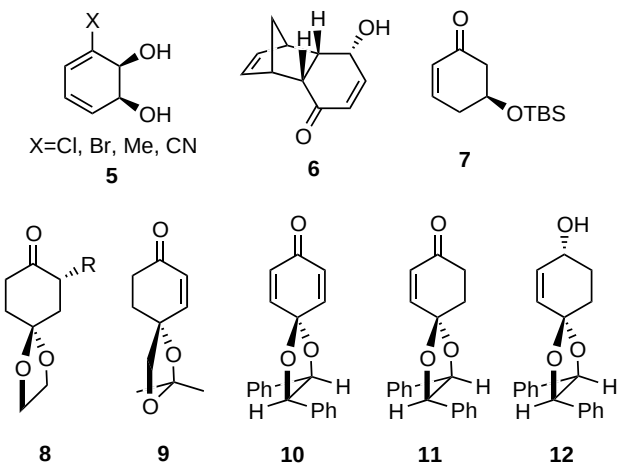

Figure 2.

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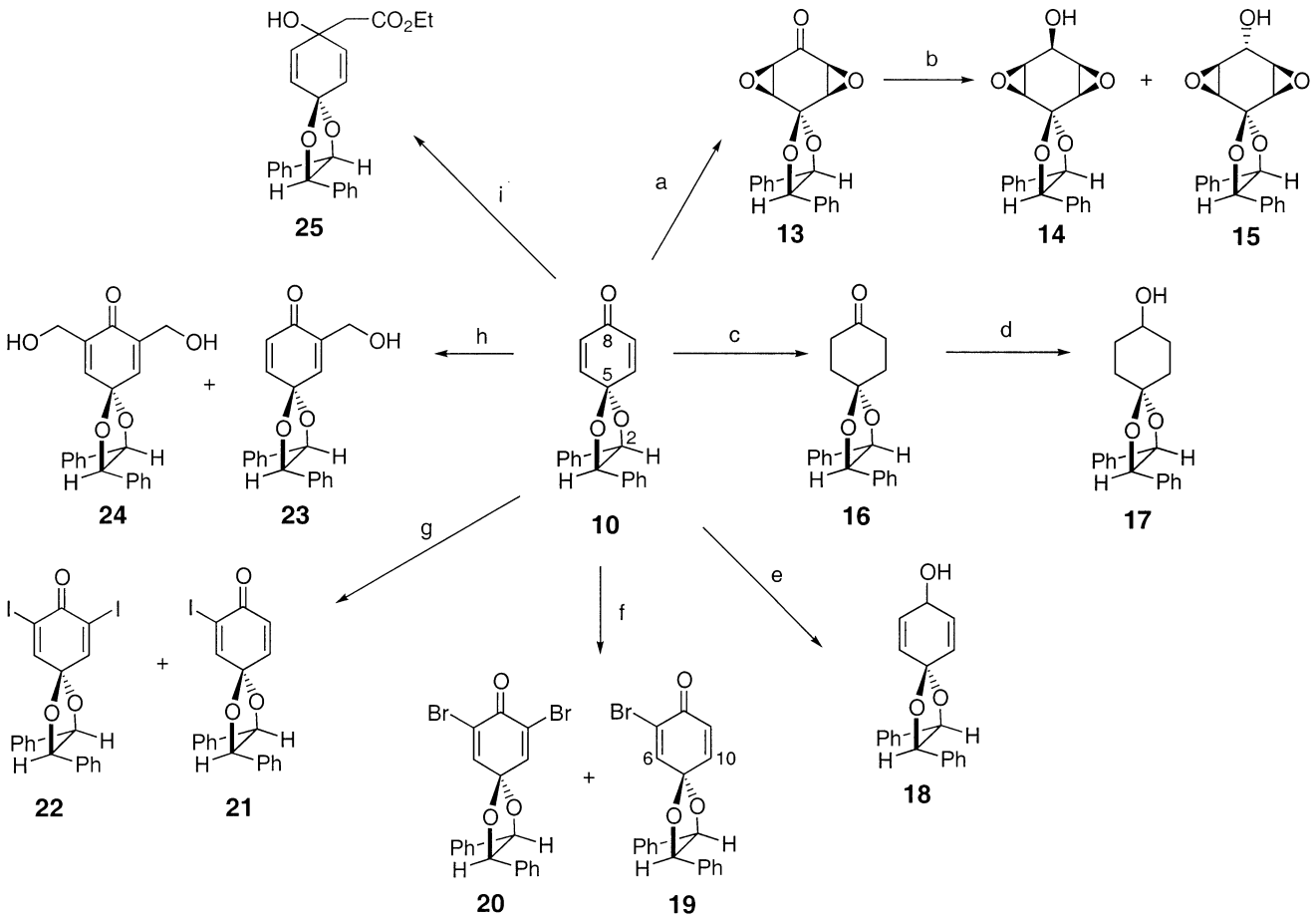
A few years ago, we described the preparation of the first enantiopure monoketals of *p*-benzoquinone derived from C_2-symmetric 1,2-diols, e.g. **10**,[7] and since then we have investigated the utility of these enantiopure substrates in several diastereoselective transformations.[8] An advantage of these ketals,[9] owing to their C_2-symmetry, is that both faces of the remaining carbonyl group and both carbon–carbon double bonds are equivalent. The other important feature is that all six carbon atoms of the cyclohexane ring are functionalised. Monoketal (+)-**10** can be prepared in gram-scale from *p*-benzoquinone and (*R*,*R*)-hydrobenzoin in a single step. It seems therefore that **10** is a very attractive precursor for the preparation of a new set of useful and accessible cyclohexane chirons presenting a wide variety of functional groups. Thus, we have developed a new, highly efficient synthesis of (*S*)-4-hydroxy-2-cyclohexen-1-one,[10] which illustrates the use of compound **10** and, in connection with this synthesis, the conjugated enone **11** and the allylic alcohol **12** have already been prepared.

We have undertaken a systematic modification of the C–C double bonds and the carbonyl group of **10** and we have also studied some C–C coupling reactions. As a result, we report herein the straightforward synthesis of several new enantiopure polyfunctionalised cyclohexanes with the structure of 1,4-dioxa[4.5]decane, which may be valuable chirons for bioactive product synthesis.

2. Results and discussion

Reaction of ketal **10** with an excess of hydrogen peroxide in the presence of a catalytic amount of sodium hydroxide at room temperature afforded the *cis*-bisepoxide **13** ($[\alpha]_D^{20}=+44.1$ (*c* 1.2, $CHCl_3$)) as a white solid in 95% yield (Scheme 1). The presence in the ^{13}C NMR spectrum of eight non-aromatic signals reveals the loss of symmetry in the molecule, and hence shows that the epoxides have a *cis*-relationship. This can also be deduced from the ^1H NMR spectrum that presents four different signals for the oxi-



Scheme 1. (a) H_2O_2 excess, NaOH cat., MeOH, rt, 1 day, 95%; (b) $NaBH_4$, MeOH, 0°C, 10 min, 81%; (c) H_2, Pd/C, toluene, 15 min, 95%; (d) $NaBH_4$, MeOH, 0°C, 15 min, 91%; (e) $NaBH_4$, MeOH:CH_2Cl_2 1:1, 0°C, 30 min, 87%; (f) 1.5 equiv. Br_2, CH_2Cl_2, 0°C, 15 min/Et_3N, rt, 1 h, 73% of **19** and 24% of **20**; (g) 2.5 equiv. I_2, CCl_4/py, rt, 3 h, 52% of **21** and 48% of **22**; (h) 3 equiv. HCHO aq., DMAP cat., THF, reflux, 7 days, 25% of **23** and 51% of **24**; (i) 2 equiv. ICH_2CO_2Et, 1.5 equiv. In, DMF, rt, 14 h, 94%.

rane protons. The exclusive formation of the bisepoxides with *cis* relative configuration in the oxidation of *p*-benzoquinone ketals was already documented in the literature.[11] The advantage of using a C_2-symmetric chiral auxiliary is shown here, since a unique diastereoisomer of the *cis*-bisepoxide can be formed. Despite the synthetic potential of the epoxide functionality, to the best of our knowledge, compound **13** is the first enantiopure bisepoxide derived from a monoketal of *p*-benzoquinone.

Reduction of the carbonyl group of **13** with sodium borohydride gave the diastereoisomeric alcohols **14** ($[\alpha]_D^{20}=+20.4$ (*c* 0.8, $CHCl_3$)) and **15** ($[\alpha]_D^{20}=+8.9$ (*c* 0.9, $CHCl_3$)) in 54 and 27% yield, respectively, as solids. The stereochemical assignment of the less polar and major isomer relies on the NOE observed on two of the oxirane protons upon irradiation of C(8)H. The same experiment was negative for the diastereoisomer **15**.

Hydrogenation of **10** using Pd/C as catalyst and toluene as solvent resulted in a 95% yield of **16** ($[\alpha]_D^{20}=+38.4$ (*c* 1.3, $CHCl_3$)). A different preparation of **16**, starting from 1,4-cyclohexanediol, was recently described by Konopelski,[12] in relation with the synthesis of anti-cancer chemotherapeutic agents. Sodium borohydride reduction of the carbonyl group of ketal **16** delivered the alcohol **17** as a solid ($[\alpha]_D^{20}=+44.4$ (*c* 1.2, $CHCl_3$)) in 91% yield. The C_2-symmetry of the chiral auxiliary prevents the formation of a new stereogenic centre at C(8) and hence the existence of diastereoisomeric products.

When the carbonyl group of the original ketal **10** was subjected to $NaBH_4$ reduction in a 1:1 mixture of methylene chloride:methanol solution, the new bisallylic alcohol **18** was isolated in 87% yield as a white solid ($[\alpha]_D^{20}=+24.4$ (*c* 2.1, $CHCl_3$)). The absorptions at δ 99.4 and 62.4 in its ^{13}C NMR spectrum demonstrate the presence of the ketal group and the allylic alcohol, respectively.

Next, we explored the introduction of halogen atoms attached to the cyclohexane moiety of ketal **10** for two reasons. Firstly, because some bioactive compounds present a vinylic halogen atom in their structure and, secondly, because a vinylic halide is an appropriate precursor for further synthetic elaborations, as the introduction of side chains through well established C–C coupling reactions like the Stille,[13] Suzuki[14] or Sonogashira[15] methodologies. Treatment of **10** with a slight excess of bromine in methylene chloride followed by addition of triethylamine afforded the bromo derivatives **19** ($[\alpha]_D^{20}=+49.2$ (*c* 1.0, CH_2Cl_2)) and **20** ($[\alpha]_D^{20}=+36.0$ (*c* 1.3, CH_2Cl_2)) as white solids in 73 and 24% yield, respectively. The NMR spectra of **20** were very simple, as is consistent with the high symmetry of the molecule, while the ^1H NMR spectrum of **19** showed three absorptions at δ 7.39, 6.97 and 6.40, corresponding to C(6)H, C(10)H and C(9)H, respectively. The iodination reaction was performed with an excess of iodine in carbon tetrachloride as solvent and in the presence of pyridine. The mono- and direction products, **21** ($[\alpha]_D^{20}=+45.0$ (*c* 1.7, $CHCl_3$)) and **22** ($[\alpha]_D^{20}=+28.3$ (*c* 0.6, $CHCl_3$)), respectively, were each isolated as white solids in ca 50% yield.

Once the reduction and oxidation of the dienone system of **10** had been successfully explored, our next goal was the attachment of carbon chains to the cyclohexane skeleton. To this end, ketal **10** was allowed to react with an excess of aqueous formaldehyde in the presence of 4-dimethylaminopyridine (DMAP),[16] delivering the mono- and dihydroxymethyl derivatives, **23** ($[\alpha]_D^{20}=+56.0$ (*c* 2.0, $CHCl_3$)) and **24** ($[\alpha]_D^{20}=+65.2$ (*c* 0.7, THF)), in 25 and 51% isolated yield, respectively. The ^1H NMR spectrum of **24** displays a unique olefinic proton signal as a singlet at δ 6.95, while the spectrum of **23** discloses two deshielded protons at δ 6.90–7.00 (C(6)H and C(10)H) and a third one at δ 6.26 (C(9)H). The presence of the hydroxymethyl group is revealed by the absorptions at δ 60.2 and 57.1 in the ^{13}C NMR spectra of **23** and **24**, respectively.

Efforts were also directed to link a carbon chain to the ring at the carbon atom of the carbonyl group of **10**. Wittig-type reactions were originally investigated, but all attempts to condense **10** with phosphonates derived from ethyl acetate or acetic acid failed. However, treatment of **10** with ethyl iodoacetate in the presence of indium powder[17] led to the isolation of the new ester **25** ($[\alpha]_D^{20}=+11.8$ (*c* 3.7, $CHCl_3$)) in 94% yield as a colourless oil. The olefinic protons resonate at δ 6.1–6.3, according to the loss of conjugation and the presence of a saturated ester is shown by the absorption at 1731 cm^{-1} in the IR spectrum.

In summary, we have described herein a straightforward and efficient access to 12 new enantiopure cyclohexane synthons, compounds **13**, **14**, **15** and **17**–**25**, along with a new synthesis of the previously known ketone **16**. The complete series displays a wide variety of functional groups useful for further synthetic elaborations. Considering the low cost of the starting materials, *p*-benzoquinone and enantiopure hydrobenzoin, we believe that this set of enantiopure cyclohexane compounds will become valuable chirons for bioactive product synthesis.[18] Work is still in progress in our laboratories to further increase the number of available cyclohexane chirons.

Acknowledgements

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