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Acid-Induced Rearrangement Reactions of Reduced Benzoquinone Cyclopentadiene Cycloadducts

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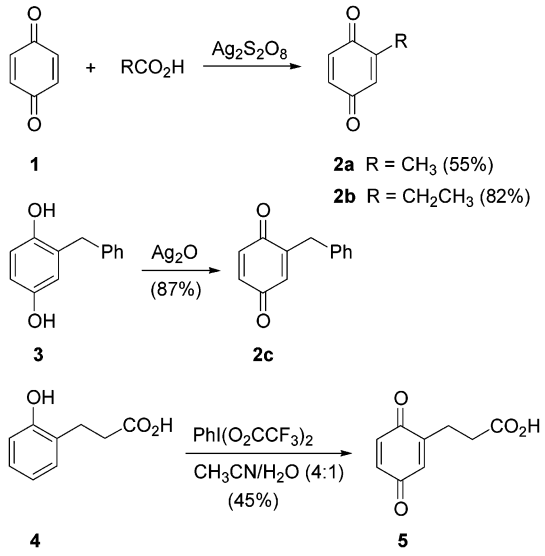
Abstract: Several Diels−Alder adducts between benzoquinones and cyclopentadiene were reduced to the corresponding diols **7a**−**c** and **11**. Treatment of these diols with strong acid triggered a skeletal rearrangement reaction resulting in compounds **8a**−**c** and **12** that contain a 4,8-methanoazulene substructure. In addition, a dyotropic-like rearrangement of the tetracyclic lactone **13** to the spirolactone **18** was observed. Five of the structures were supported by X-ray analysis.

Many natural products, particularly terpenes, illustrate in an impressive way how the combination of cationic cyclization reactions and Wagner−Meerwein shifts can generate a wide range of topologically different structures. Cationic rearrangements are facilitated by several factors such as ring strain, stereoelectronic effects, and proximity. As a case in point, one might quote the skeletal reorganizations that are possible in the camphor system.[1] In connection with work on dearomatized benzene derivatives such as cyclohexadienones and quinone methides, we prepared Diels−Alder adducts from benzoquinones and cyclopentadiene. It was discovered that the diols that were obtained by hydride reduction of the cycloadducts entered into a cascade of cationic rearrangement reactions leading to compounds with a 4,8-methanoazulene-9-ol substructure. In this paper, we present the synthesis, structural elucidation, and a mechanistic proposal for these rearrangements.

For this study, we employed four benzo-1,4-quinones with an alkyl substituent in the 2-position. In addition, benzoquinone was used. Alkylated quinones can be prepared by alkylation of hydroquinonemethyl ethers followed by oxidative ether cleavage. Another common method involves the reaction of radicals with quinones in the presence of an oxidant. Thus, methyl- and ethylbenzoquinones **2a** and **2b** were prepared by oxidative decarboxylation of the corresponding carboxylic acids with silver persulfate in the presence of benzoquinone.[2,3] This way, the monoalkylated quinones were obtained in reasonable yields (Scheme 1). Benzyl-1,4-hydrochinone

SCHEME 1. Synthesis of the Substituted Quinones 2a, 2b, and 5



(**2c**) was prepared by alkylation of hydroquinone with benzyl alcohol in the presence of phosphoric acid, followed by oxidation of the intermediate hydroquinone with silver oxide.[4] The quinone **5** that carries a propionic acid side chain was prepared by oxidation of 3-(2-hydroxyphenyl)-propionic acid (**4**) with bis(trifluoroacetoxy)iodobenzene in an acetonitrile/water mixture. This route is much shorter than the published one.[5,6]

Subsequently, the quinones **2a**, **2b**, and **2c** were subjected to a Diels−Alder reaction with cyclopentadiene that led to the endo cycloadducts **6a**,[7,8] **6b**, and **6c**[4] in good yield (Scheme 2). To solubilize the quinones, the reactions were performed in methanol. Typically, the cycloaddition reactions were performed at room temperature. As is known from related benzoquinone Diels−Alder adducts, the sodium borohydride reduction leads to the *endo*-diols. The diols **7a**,[9,10] **7b**, and **7c** could be isolated, but the acid-induced rearrangement reaction was usually done in the same flask. Thus, after the reduction with sodium borohydride, concentrated sulfuric acid was carefully added to the mixture. After stirring overnight and extractive workup, TLC analysis indicated the formation of several compounds. The most prominent one was isolated by chromatography. Rearrangement of **7a** needed around 30 h to be complete. In contrast, the diols **7b** and **7c** rearranged much faster, being complete after around 9 h.

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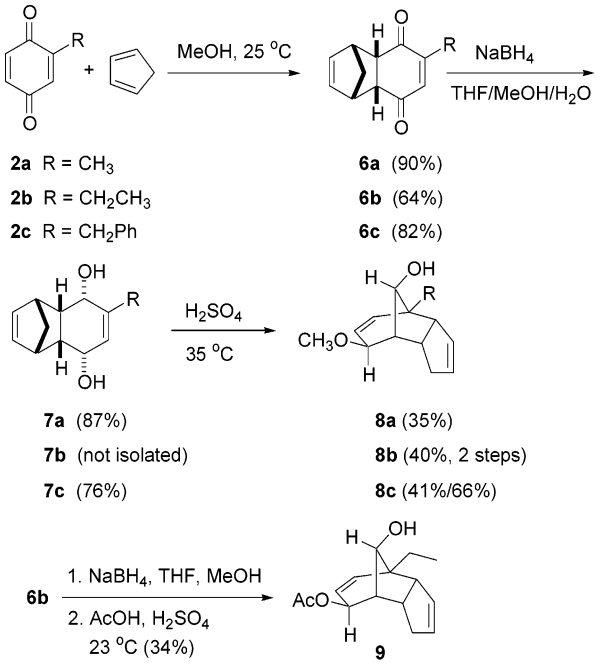
SCHEME 2. Diels–Alder Reaction of the Quinones 2a–c with Cyclopentadiene Followed by Reduction and Acid-Induced Rearrangement of the Cycloadducts



The structure of **8a** was supported by spectroscopic data, particularly the 2D NMR spectra. In a similar manner, the ethyl-substituted quinone cyclopentadiene cycloadduct **6b** was reduced and the resulting diol **7b** subjected to the rearrangement. If sulfuric acid was used for the quenching of the sodium borohydride, the allylic ether **8b** was produced in about 40% yield after 9 h at room temperature. With an excess of acetic acid and sulfuric acid, a mixture of the acetate **9** and the ether **8b** was obtained. Likewise, the benzyl-substituted tricyclic diol **7c** was rearranged to compound **8c**. Performing the reaction with HBr resulted in a 66% yield of **8c**. The X-ray structure of **9** is shown in Figure 1. Surprisingly, the diol obtained by reduction of the parent cyclopentadiene–benzoquinone cycloadduct did not enter into the rearrangement cascade.

In the case of the quinone **5**, the Diels–Alder reaction was done at 0 °C. Due to the carboxylic group, some of the subsequent reactions are characterized by participation of the carboxylic group. For example, reduction of the quinone **10** led to the diol **11** (Scheme 3). The diol **11** was not isolated, but as before, the acid-induced rearrangement reaction was done in the same flask. The rearrangement reaction of **11** proceeded along similar pathways. In this case, the carboxylic function participated in the termination of the rearrangement cascade yielding the lactone **12**. The structure of **12** was unambiguously assigned by X-ray analysis. A Chem3D rendering of **12** is depicted in Figure 1.

Compound **12** was subjected to further transformations. Thus, silylation of the secondary hydroxyl group furnished the silyl ether **13** as a quite stable entity that could be chromatographed on silica gel. Treatment of **13** with 1 equiv of *m*-chloroperbenzoic acid led to a stereoselective epoxidation of the cyclopentene double bond

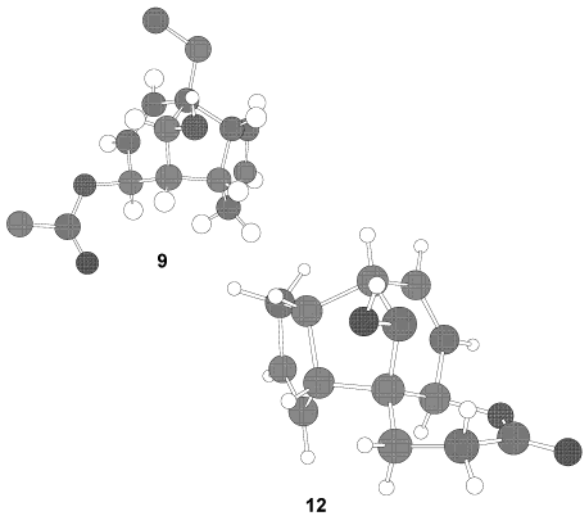


FIGURE 1. Chem3D rendering of the crystal structure of **9** and **12**.

providing epoxide **14**. The structure of **14** was assigned on the basis of X-ray analysis (see Figure S1 of the Supporting Information).

Reduction of the lactone **13** with lithium aluminum hydride provided the diol **15**. If this compound was treated with borontrifluoride etherate ($BF_3 \cdot Et_2O$), the rearranged polycyclic alcohol **16** was formed (Scheme 3). The structure of **16** was secured by X-ray analysis (see Figure S2 of the Supporting Information). A chemical proof for the presence a hydroxyl group came from Swern oxidation of **12** to the ketone **17**.

The formation of the rearranged compounds can be explained by invoking formation of an initial allylic carbocation **A** followed by a 1,2-shift and formation of a double bond with formation of another allylic cation **B**. The allylic cation **B** reacts to the tricyclic carbocation **C** with the positive charge in the central cyclopentane ring. Addition of a nucleophile, such as methanol leads to the tricyclic compound **8b** (Scheme 4).

Under the influence of the Lewis acid $BF_3 \cdot Et_2O$, the lactone **13** underwent a further rearrangement to the spiro lactone **18**. This reaction, which is formulated in Scheme 5 as a stepwise ionic rearrangement, can also be viewed as a dyotropic rearrangement.[11–13] Oxidation of the secondary hydroxyl group of **18** provided ketone **19** (Scheme 5). The structure of **18** was solved by X-ray analysis (see Figure S3 of the Supporting Information).

The structures that were formed by these rearrangements (**8a–c**, **9**, **12–14**, **16**, and **17**) feature a bicyclo[3.2.1]octane substructure. This type of substructure is found in several natural products, such as the sesquiterpenoids drechslerine D (**20**),[14] the trichothecene sambucinic acid (**21**),[15] the neolignan puberulin C (**22**),[16] and gymnomitrane sesquiterpenoids, such as gymnomitrene

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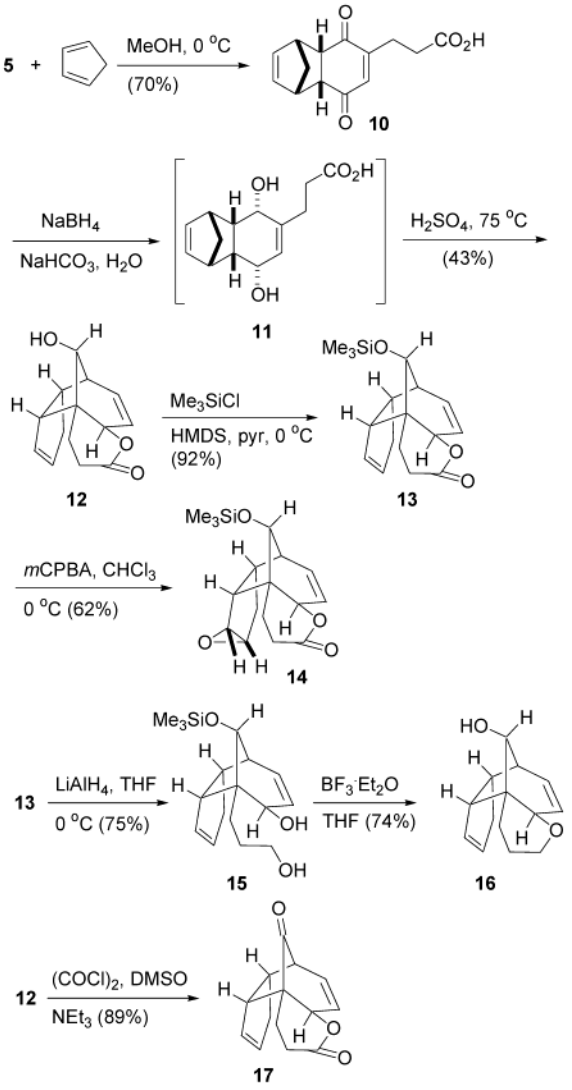
SCHEME 3. Diels−Alder Reaction of the Quinone 5 with Cyclopentadiene Followed by Reduction and Acid-Induced Rearrangement of the Diol 11 Together with Some Derivatization Reactions



(**23**)[17] (Figure 2). Thus, these natural products or analogues thereof might be available using this kind of rearrangement strategy.

Other synthetic approaches to bicyclo[3.2.1]octane derivatives include palladium-catalyzed isomerization of 2-vinylhexahydro-2,3-benzofurans,[18] Lewis-acid-catalyzed cycloaddition of benzoquinones with alkenes,[19] 1,3-photocycloaddition between alkenes and anisole derivatives,[20] intramolecular aldol reaction[21] or Claisen condensation[22] to close the 3-carbon bridge, intramolecular

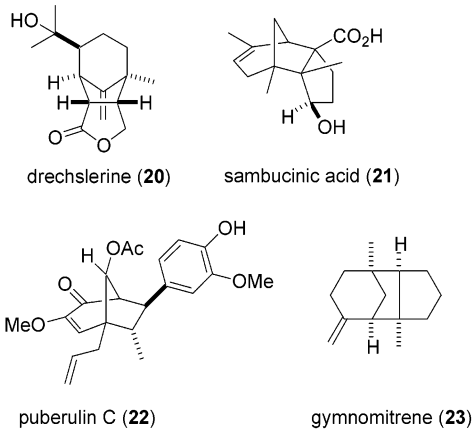
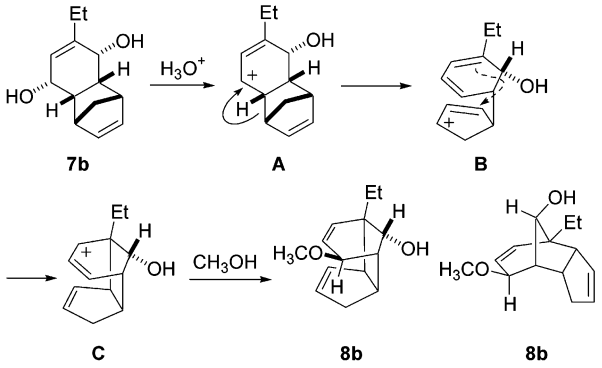
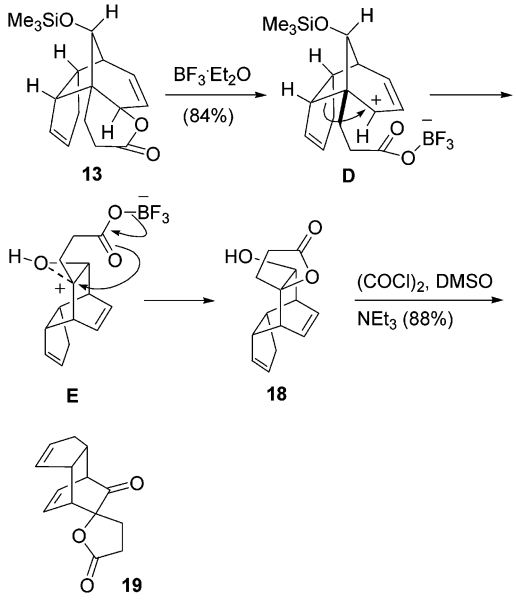


FIGURE 2. Structures of some representative natural products containing a bicyclo[3.2.1]octane substructure.

SCHEME 4. Postulated Mechanism for the Cascade of Rearrangements Illustrated for the Transformation of 7b to 8b



SCHEME 5. Postulated Mechanism for the Rearrangement of the Lactone 13 to the Spiro Lactone 18



ene reaction,[23] radical cyclization of alkynyl cyclopentanones[24] or cyclic triene precursors,[25] and acid-induced rearrangement of bicyclo[2.2.2]octenones.[26]

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In conclusion, we show that Diels−Alder adducts between benzoquinones and cyclopentadiene can enter into skeletal rearrangement reactions after ketone reduction and acid treatment. Structures of this type are otherwise not easily accessible. This way, natural products with a bicyclo[3.2.1]octane substructure might be prepared by this rearrangement strategy.

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Supporting Information Available: Experimental procedures for all new compounds and copies of NMR spectra for important compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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