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Phenolic Oxidation Using H_2O_2 via in Situ Generated *para*-Quinone Methides for the Preparation of *para*-Spiroepoxydienones

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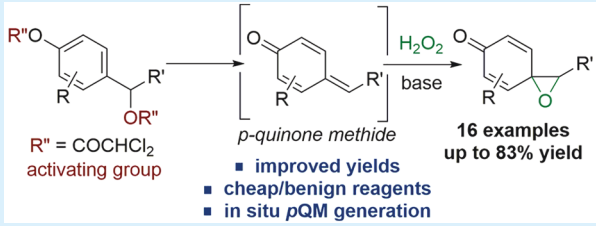
Supporting Information

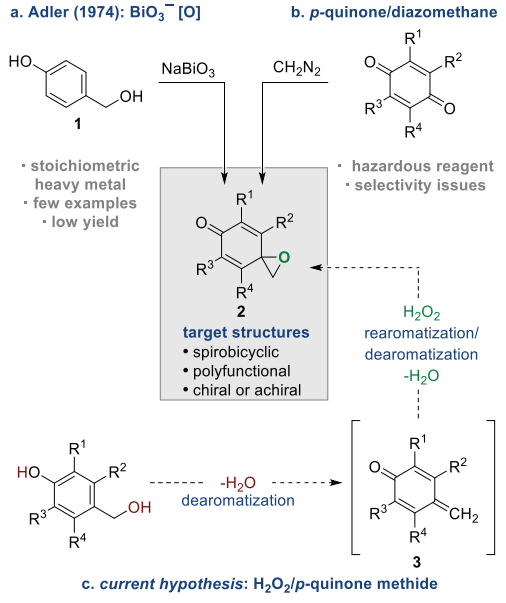
ABSTRACT: Phenols are attractive starting materials for the preparation of highly substituted cyclohexane rings via dearomative processes. Herein we report an efficient preparation of dearomatized 1-oxaspiro[2.5]octa-4,7-dien-6-ones (*para*-spiroepoxydienones) via the nucleophilic epoxidation of in situ generated *para*-quinone methides from 4-(hydroxymethyl)phenols using aqueous H_2O_2. The developed protocol bypasses the need for stoichiometric bismuth reagents or diazomethane, which are frequently deployed for *p*-spiroepoxydienone preparation. The *p*-spiroepoxydienones are further elaborated in numerous downstream complexity-building transformations.



Aromatic feedstock compounds provide an intriguing and economical source for accessing functionalized, complex organic building blocks in a rapid fashion. The latent functionality embedded within these aromatic cores, including phenols, is often unveiled via a wide number of dearomative transformations;[1] however, to overcome the aromatic stabilization energy of the benzenoids, stoichiometric quantities of toxic heavy metals (i.e., lead, silver, and bismuth) have frequently been needed to provide the required thermodynamic driving force.[2] In addition to their inherent toxicity, the use of these metal reagents frequently entails high costs and results in low product yields, ultimately limiting their applicability in industrial settings; therefore, new dearomative methods involving inexpensive and benign oxidants, such as hydrogen peroxide (H_2O_2), are desirable for their favorable byproduct profiles and reactivities.

In 1974, Adler described the preparation of dearomatized 1-oxaspiro[2.5]octa-4,7-dien-6-one (*p*-spiroepoxydienone) **2a** via the oxidation of 4-(hydroxymethyl)phenol **1** with sodium bismuthate ($NaBiO_3$) (Scheme 1a).[3a] While novel, this approach required stoichiometric quantities of $NaBiO_3$ and afforded **2a** in poor yield (20−30%).[3b] Nevertheless, this method for the preparation of *p*-spiroepoxydienones **2** has been employed in the synthesis of bioactive and complex molecules.[4] The low yield obtained with $NaBiO_3$ has resulted in an alternative approach to synthesizing *p*-spiroepoxydienones. The addition of diazomethane (CH_2N_2) into highly substituted *para*-quinone derivatives (Scheme 1b) affords improved yields of the desired product;[5] however, the dual quinone carbonyls present regioselectivity complications, and serious hazards associated with CH_2N_2 prevent its deployment on large scales. $NaIO_4$, an enabling reagent for the analogous oxidation of the ortho-isomer (Adler−Becker oxidation) has not, to the best of our knowledge, been successfully used for the para-isomer, indicating important structural or mechanistic differences.[3]

Scheme 1. Methods for Accessing *p*-Spiroepoxydienones



Because of these limitations to the established methods for *p*-spiroepoxydienone generation as well as the prevalence of naturally occurring bioactive molecules bearing the *p*-spiroepoxide substructure (Figure 1),[6] we were interested in the development of a new approach to these privileged scaffolds.

The oxidative dearomatization of salicyl alcohol derivatives using H_2O_2 was recently reported.[7] The reactions deliver *o*-spiroepoxydienones via a transient *ortho*-quinone methide

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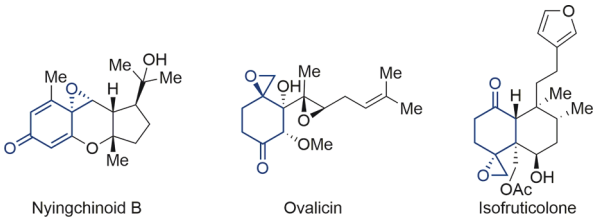
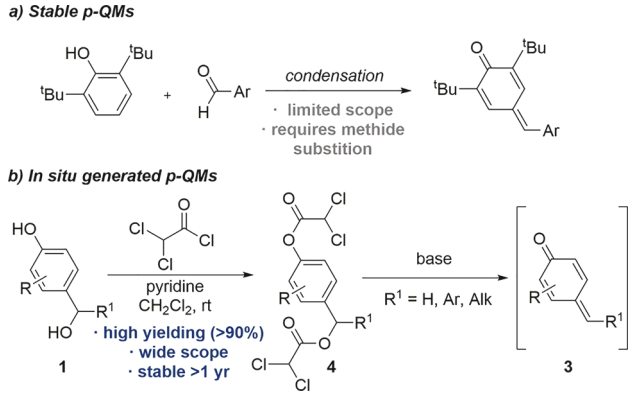


Figure 1. Representative bioactive compounds bearing *p*-spiroepoxide substructure.

intermediate. Encouraged by the success of this approach, we proposed the reaction design outlined in Scheme 1c that accesses *p*-spiroepoxydienone **2** from 4-(hydroxymethyl)-phenol **1** via the intermediacy of a *para*-quinone methide **3**. *para*-Quinone methides **3** (*p*QMs) are highly reactive dearomatized intermediates that have been extensively explored in recent years due to their ability to form complex building blocks.[8] The inherent reactivity exhibited by *p*QMs is governed by the strong aromatic driving force, which has predicated numerous nucleophilic 1,6-conjugate additions to afford derivatized phenolic products.[9] Because of this aromatic driving force, transformations involving *p*QMs resulting in isolable, dearomatized building blocks for further elaboration are limited.[10]

Our working hypothesis, outlined in Scheme 1, required a resolution to a procedural challenge in accessing the transient *p*QMs in situ. Because of the high reactivity of these ephemeral species, a significant majority of methods involving *p*QM intermediates often rely on the prior synthesis of stable derivatives.[11] Because of the ease of preparation and long shelf lives, these stable *p*QMs have been widely employed;[8,9] however, the strict substrate requirements of stable *p*QMs limit the scope of products available to these transformations (Scheme 2a). In contrast, strategies for the preparation of

Scheme 2. Methods for *p*-Quinone Methide Generation

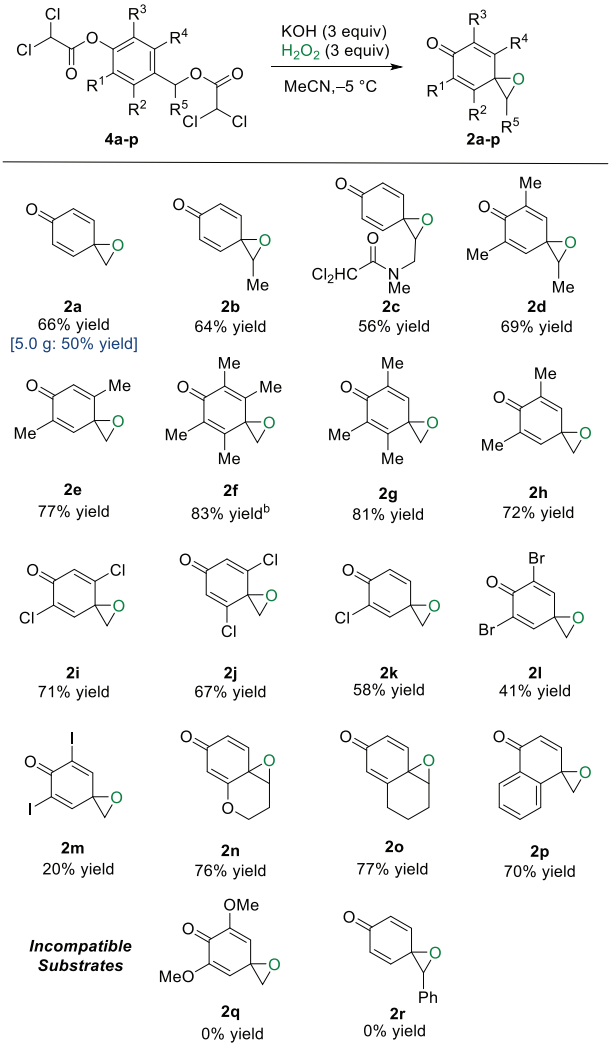


transient *p*QMs in situ using basic conditions have been reported.[12] These approaches are usually restricted to benzylic aryl substitution, a characteristic that is often incompatible with the stability of *p*-spiroepoxydienones **2** due to rapid decomposition.[13]

Bis(dichloroacetate) esters of phenolic *o*-benzylic alcohols are appropriately activated for *o*QM formation in the presence of $^{(-)}$OOH.[7] This cheap and stable activating group exhibited a wide substrate scope, and *o*QM formation could be easily achieved via base-promoted phenolic deprotection, followed by the expulsion of the benzylic acetate. Considering the known differences in spiroepoxide synthesis from *ortho*- and *para*-benzylic alcohol phenols, it was an open question as to whether our previous method could be extended to the para-series. To test this hypothesis, we prepared a variety of 4-(hydroxymethyl)phenols **1** and activated them for projected *p*QM formation via the single-step preparation of heretofore unknown bis(dichloroacetates) **4** in high yield (>90%) (Scheme 2b).

Using optimized conditions,[14] the bis(dichloroacetates) **4** were evaluated as suitable reaction partners in the one-pot *p*QM formation and subsequent homo-Weitz–Scheffer epoxidation (Scheme 3).[15] Bis(dichloroacetate) **4a** afforded the

Scheme 3. Scope of Oxidative Dearomatization Using Bis(dichloroacetates) of 4-(Hydroxymethyl)phenols



[a]Reactions performed with 1.0 equiv of **4** and 3.0 equiv of H_2O_2 and KOH in MeCN ($[4]_0$ = 0.05 M). Isolated yields. [b]Four equiv of KOH was used.

achiral *p*-spiroepoxide **2a** in 66% yield, a significant improvement over the $NaBiO_3$-based methodology.[3] Scaling up this dearomatization afforded 5.0 g of **2a** while maintaining practical yields. Benzylic alkyl substitution (R^5) (**2b–d**) was tolerated, a trend that held true when employing (±)-synephrine as the phenolic precursor (**2c**).

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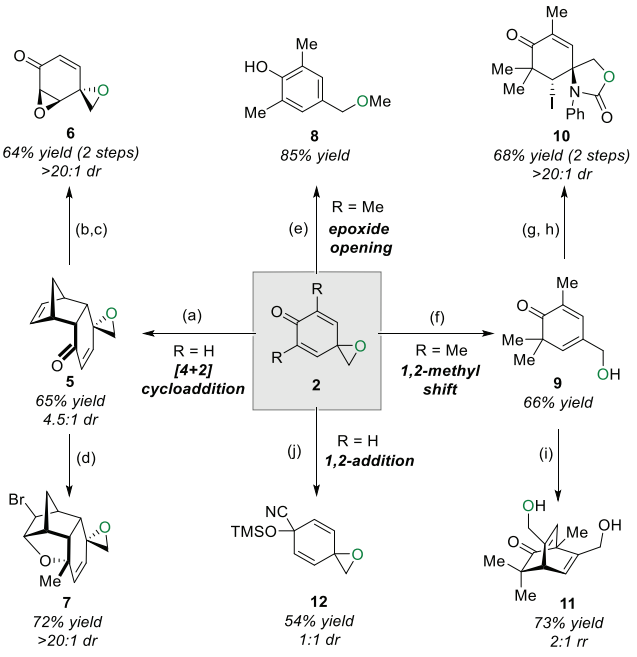
Alkyl substitution (**2e**−**h**) provided for the highest yields due to the increased stability of the *p*QM intermediate.[16] Turning our attention to halogenated substrates, we found that similarly good yields could be obtained with chlorine substitution (**2i**−**k**); however, bromine and iodine were less tolerated under the optimized reaction conditions (**2l,m**). Tricyclic spiroepoxides (**2n**−**p**) were obtained in high yield.

We identified a few limitations for this reaction. Highly electron-rich substrate **4q** was incompatible with the optimized reaction conditions due to the poor electrophilicity of the methide. Additionally, we confirmed the instability of R^5 aryl substitution using our reaction conditions.[13] Subjecting bis(dichloroacetate) **4r** to the reaction conditions resulted in the isolation of hydroquinone and benzaldehyde, byproducts of the rapid decomposition of spiroepoxide **2r**.[3a,13]

1-Oxaspiro[2.5]octa-4,7-dien-6-ones **2** provide an interesting platform for further derivatization into complex organic frameworks. Until now, the reactivity of these compounds has been sparsely evaluated, presumably because of the lack of efficient preparation strategies. Accordingly, we sought to expand the reactivity profile of the dearomatized species (Scheme 4).

Scheme 4. Chemoselective Transformations of *p*-Spiroepoxydienones[a]



[a]Conditions: [a]cyclopentadiene (3.0 equiv), TFE, 35 °C; [b]K_2CO_3 (50 mol %), 30% aq H_2O_2 (3.0 equiv), acetone, rt; [c]Ph_2O, 220 °C; [d]MeLi (1.1 equiv), THF, −78 °C, then NBS (1.1 equiv), CH_2Cl_2, rt; [e]MeMgBr (1.1 equiv), THF, −78 °C; [f]MeLi (1.0 equiv), THF, −78 °C; [g]PhNCO (1.1 equiv), DBU (1.0 equiv), CH_2Cl_2, rt; [h]NIS (4.0 equiv), MeCN, 50 °C; [i]propargyl alcohol (3.0 equiv), Ph_2O, 180 °C; [j]TMSCN (1.5 equiv), KF (10 mol % equiv), MeCN, 0 °C to rt.

Initial attempts at functionalizing *p*-spiroepoxydienones **2** revealed a unique reactivity as compared with *para*-quinols[17] or 1-oxaspiro[4.5]deca-6,9-dien-8-ones.[10b] Namely, *p*-spiroepoxydienone **2** demonstrated a high proclivity toward rearomatization under a variety of reaction conditions, partially ascribable to the highly strained spiroepoxide moiety. Several transformations such as direct epoxidation, 1,4- or 1,2-addition, and hydrogenation resulted in rearomatization to the parent phenolic compound, in agreement with previous literature;[4,5] however, the selective functionalization of **2a** could instead be achieved by accessing Diels−Alder cycloadduct **5**[3b] using **2a** and cyclopentadiene, followed by functionalization of the enone and subsequent retro-Diels−Alder cycloaddition. Using this route, bis-epoxide **6** could be prepared as a single diastereomer. Alternatively, pentacycle **7** could be realized via the reaction of **5** with MeLi, followed by bromonium-promoted cyclization using *N*-bromosuccimide (NBS).[18]

To evaluate the unconventional electrophilic sites of the molecule, various nucleophiles were tested against *p*-spiroepoxydienones **2**. The reaction of spiroepoxide **2h** with MeMgBr resulted in nucleophilic attack on the epoxide oxygen attaching a pendant alkyl group while reestablishing the aromaticity to afford phenol **8**. Conversely, upon exposure to MeLi, spiroepoxide **2h** was converted to dearomatized dienone **9** via carbonyl addition, followed by a 1,2-alkyl shift to vinylogously open the strained spiroepoxide moiety. Taking advantage of the new hydroxymethyl handle, the reaction of dienone **9** with phenyl isocyanate followed by iodolactamization resulted in spirocarbamate **10**. Thermal Diels−Alder cycloaddition between propargyl alcohol and dienone **9** afforded bicyclic diene **11** featuring two primary alcohols. *p*-Spiroepoxide **2a** was highly prone to rearomatization when treated with alkylmetal nucleophiles; however, employing trimethylsilyl cyanide (TMSCN), the 1,2-addition product was isolated as silyl ether **12**, preventing the 1,2-cyano shift to restore aromaticity.

In conclusion, we have developed an efficient preparation for *p*-spiroepoxydienones that proceeds through an in situ generated *p*-quinone methide. This method bypasses the need for stoichiometric bismuth or hazardous diazomethane by using aqueous H_2O_2 as the oxidant while allowing superior yield and substrate scope. The unique reactivity these *p*-spiroepoxydienones exhibit was further explored via a number of complexity-building transformations. This methodology demonstrates the potential for complementary dearomative processes via *p*-quinone methide intermediates, and our laboratory is currently exploring these possibilities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02372.

^{1}H and ^{13}C NMR spectra of all newly synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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