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Ortho-Dearomatization of Phenols Creating All-Carbon Spiro-Bicycles

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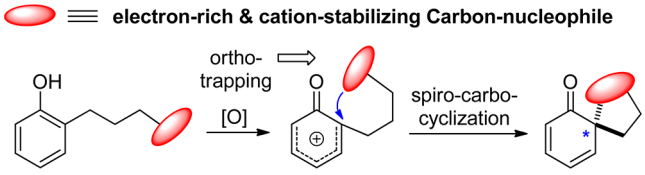
ABSTRACT



A range of alkene-linked phenols are generally and reliably dearomatized specifically at their *ortho*-positions to create all-carbon quaternary stereogenic centers at the corresponding spiro-ring junctions, thus establishing a viable solution to the long-standing synthetic challenge.

Ortho-fused spiro-[6-5]-bicycles and their architectural derivatives, generally summarized as structure ***A*** in Scheme 1, represent some of the most frequently encountered motifs[1] that are present in many interesting bioactive natural products, such as anticardiovascular magellanine,[2a−c] cytotoxic daphnilongeranin C,[2d] neurotrophic tricycloillicinone,[2e] and antitubercular colombiasin A.[2f]

Conceptually, as already hypothesized in relevant retrosynthesis[3] and biosynthesis proposals,[4] these structural motifs could all be directly and atom-economically accessed simply by site-specific dearomatizations of appropriate phenols[5] bearing a pendant olefinic side chain at their corresponding *ortho*-position. The broad range of structural as well as functional diversities conferred by these fascinating *ortho*-fused spiro-[6-5]-bicycles are unusual and attention-demanding. Thus it is surprising to observe that up to the present there is still no generally applicable method available allowing for their facile construction.[3] Indeed, in contrast to the voluminous literature on various methods for dearomatization of phenolic substances,[5] particularly those involving hypervalent iodine reagent[6]-mediated formation of widely useful *ortho*- and *para*-quinone monoketals[5,7] (i.e., dearomatized rings featuring the formed C−O or C−N bonds), very few studies are known to tackle the arguably more difficult problem of site-selective dearomatization of phenols via

(1) (a) Huang, J.; Wang, H.; Wu, C.; Wulff, W. D. *Org. Lett.* **2007**, *9*, 2799. (b) Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 1268. (c) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 404. (d) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184. (e) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4336.

(2) (a) Castillo, M.; Loyola, L. A.; Morales, G.; Singh, I.; Calvo, C.; Holland, H. L.; MacLean, D. B. *Can. J. Chem.* **1976**, *54*, 2893. (b) Castillo, M.; Morales, G.; Loyola, L. A.; Singh, I.; Calvo, C.; Holland, H. L.; McLean, D. B. *Can. J. Chem.* **1976**, *54*, 2900. (c) Loyola, L. A.; Morales, G.; Castillo, M. *Phytochemistry* **1979**, *18*, 1721. (d) Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936. (e) Fukuyama, Y.; Shida, N.; Kodama, M.; Chaki, H.; Yugami, T. *Chem. Pharm. Bull.* **1995**, *43*, 2270. (f) RodrÚguez, A. D.; RamÚrez, C. *Org. Lett.* **2000**, *2*, 507.

(3) (a) Green, J. C.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2011**, *133*, 1603. (b) Rudolph, A.; Bos, P. H.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 5834. (c) Oguma, T.; Katsuki, T. *J. Am. Chem. Soc.* **2012**, *134*, 20017.

(4) Parker, W.; Roberts, J. S.; Ramage, R. *Q. Rev. Chem. Soc.* **1967**, *21*, 331.

(5) Selected reviews on oxidative dearomatizations: (a) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (b) Stéphane, R. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068. (c) Zhuo, C. X.; Zhang, W.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662. (d) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, *4*, 467.

(6) For reviews on hypervalent iodine chemistry: (a) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (c) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123.

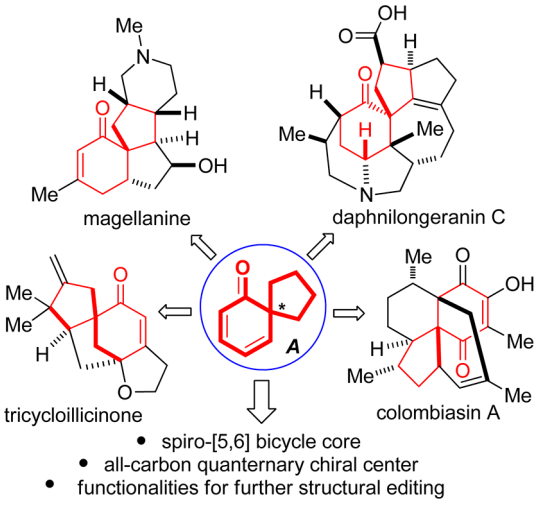
(7) (a) Swenton, J. S. Chemistry of Quinone Bis- and Monoketals. In *The Chemistry of Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1988; Vol. II, Part 2, pp 899−962 and references cited therein. *Ortho*-dearomatized rings featuring the formed C−O bond: (b) Pouységu, L.; Chassaing, S.; Dejugnac, D.; Lamidey, A.-M.; Miqueu, K.; Sotiropoulos, J.-M.; Quideau, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3552. (c) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175.

(8) Selected examples of the uses of carbon nucleophiles in the oxidative dearomatization of phenols; see: (a) Guérard, K. C.; Chapelle, C.; Giroux, M.-A.; Sabot, C.; Beaulieu, M.-A.; Achache, N.; Canesi, S. *Org. Lett.* **2009**, *11*, 4756. (b) Desjardins, S.; Andrez, J.-C.; Canesi, S. *Org. Lett.* **2011**, *13*, 3406. (c) Hempel, C.; Weckenmann, N. M.; Maichle-Moessmer, C.; Nachtsheim, B. J. *Org. Biomol. Chem.* **2012**, *10*, 9325.

(9) Of considerable relevance is the recently discovered enantioselective dearomatizations of phenols involving C−F bond formations; see: Phipps, R. J.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 1268.

10.1021/ol401863k

Scheme 1. Biologically Active Natural Products Featuring Functionalized *Ortho*-Spiro-[6-5]-bicyclic Cores



concomitant C−C bond construction,[8,9] particularly in an *ortho*- rather than *para*-selective manner.[10] The challenge escalates in the fact that such fully C−C bond formation-enabled phenol dearomatization inevitably incurs the emergence of so-called all-carbon quaternary stereogenic centers[11] that situate exactly at the corresponding spiro-ring junctions.[12] To the best of our knowledge, there appears to be only two studies by Pettus[3a] and Feringa[3b] and co-workers, respectively, both reported in 2011, that have successfully realized selective *ortho*-dearomatization of phenols and naphthols with strategic C−C bonds formation for the targeted construction of spiro-carbocycles. The substrate scopes they examined appeared to be limited, and phenols have proven to be more challenging motifs than naphthols for the events of oxidative dearomatizations.[3b,c] Thus it remains to be seen if a more generally applicable *ortho*-oxidative phenol dearomatization protocol can be established to enable the facile construction of all-carbon quaternary spiro-carbocycles, and ideally with more readily commercially available and user-friendly oxidants such as $PhI(OAc)_2$.[6]

Stimulated by this challenge, we initiated a program that attempts to explore a potentially general solution. Our design concept was sketched in Scheme 2. We envisioned that a phenolic substrate ***B*** tethered with a carbon-based nucleophile, preferably a C=C double bond moiety, at its *ortho*-position would likely undergo *ortho*-oxidative dearomative spiro-carbocyclization under appropriate oxidation stimulation to directly yield the desired spirocyclohexadienone skeleton ***A***, which would subsequently serve as a shared facile entry point to other derived spiro-[6-5]-bicycles. Although it might initially be conceived that simple alkene-substituted phenols structured as ***B1*** would function as reasonable substrates, our own experiments and literature reviews[5,8] had in fact unanimously pointed to the lesson that it is very difficult to obtain generally efficient and reproducible *ortho*-dearomatization events on this type of substrates. This may in fact explain the extreme scarcity of literature disclosures on ***B1***-type phenols. Our failure-inspired recognition is thus that a reliable ***B***-to-***A*** conversion would require new types of phenolic substrates in which the incorporated electron-rich double bond is capable of not only initiating *ortho*-nucleophilic trapping toward the dearomatized cationic ring but also stabilizing thus the formed carbocation against competing decompositions. Guided by this recognition, we decided to focus on phenols that are *ortho*-substituted by either a pendant allylsilane (***B2***) or vinyl ether (***B3***). It is important to note that oxidative dearomatization of an allylsilane-functionalized phenol[13] had previously been reported by Nicolaou et al. under the influence of $PhI(OAc)_2$ oxidation, albeit in the *para*- rather than *ortho*-spiroannulation manner.[10a,b]

The implementations of ***B2***- and ***B3***-type substrates in the intended *ortho*-dearomative spirocarbocyclizations, however, turned out to be nontrivial. With **S1** and **S2** as the standard substrates (Scheme 2), it was only through the repeated interactions of purposeful screening and fortunate serendipity that we eventually were able to identify optimal conditions capable of bringing about the desired transformations on each of them (see Supporting Information for details of substrate syntheses and experimental screening). Both cases employed $PhI(OAc)_2$ as the oxidant, thereby significantly enhancing the method's practicality and ease in implementation. For **S1**, the standard condition **I** recruited a mixture of CF_3CH_2OH (TFE) and CH_2Cl_2 (volume ratio 1/1) as the reaction solvent and 0.02 M substrate concentration; for **S2** (in 1/1 geometric *E*/*Z* mixtures), the standard condition **II** utilized pure TFE as the solvent and maintained the 0.02 M substrate concentration. The additive effect in both conditions had proved to be remarkable: while the 4 é molecular sieve was selected for the former case, $MgSO_4$ was chosen in the latter. Under those defined conditions, the reactions proceeded quickly even at a very low temperature of −40 °C, delivering the desired *ortho*-spirobicyclic products **P1** and **P2** in 57% and 66% isolated yield, respectively. These yields are respectable,

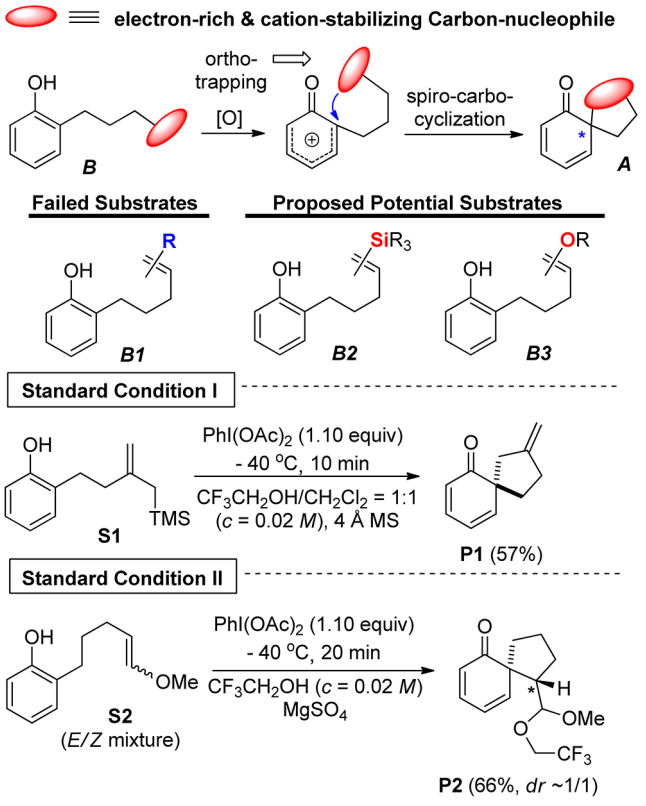
(10) Selected dearomatizations of phenols leading to *para*-selective all-carbon spiro-cycles; see: (a) Nicolaou, K. C.; Edmonds, D. J.; Li, A.; Tria, G. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 3942. (b) Nicolaou, K. C.; Li, A.; Edmonds, D. J.; Tria, G. S.; Ellery, S. P. *J. Am. Chem. Soc.* **2009**, *131*, 16905. (c) Honda, T.; Shigehisa, H. *Org. Lett.* **2006**, *8*, 657. (d) Beaulieu, M.-A.; Guérard, K. C.; Maertens, G.; Sabot, C.; Canesi, S. *J. Org. Chem.* **2011**, *76*, 9460. (e) Andrez, J.-C.; Giroux, M.-A.; Lucien, J.; Canesi, S. *Org. Lett.* **2010**, *12*, 4368. (f) Nemoto, T.; Zhao, Z.; Yokosaka, T.; Suzuki, Y.; Wu, R.; Hamada, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 2217. (g) Rousseaux, S.; GarcÚa-Fortanet, J.; Angel Del Aguila Sanchez, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 9282. (h) Dohi, Y.; Minamitsuji, Y.; Maruyama, A.; Hirose, S.; Kita, Y. *Org. Lett.* **2008**, *10*, 3559. (i) Dohi, T.; Nakae, T.; Ishikado, T.; Kato, D.; Kita, Y. *Org. Biomol. Chem.* **2011**, *9*, 6899.

(11) For a review on constructions of all-carbon quaternary stereocenters, see: Trost, B. M.; Jiang, C. H. *Synthesis* **2006**, *3*, 369.

(12) For general synthesis methods on spiro compounds, see: (a) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060. (b) Asaoka, M.; Takenouchi, K.; Takei, H. *Chem. Lett.* **1988**, *17*, 1225. (c) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007. (d) Zhang, E.; Fan, C.-A.; Tu, Y.-Q.; Zhang, F.-M.; Song, Y.-L. *J. Am. Chem. Soc.* **2009**, *131*, 14626. (e) Trost, B. M.; Chen, D. W. C. *J. Am. Chem. Soc.* **1996**, *118*, 12541.

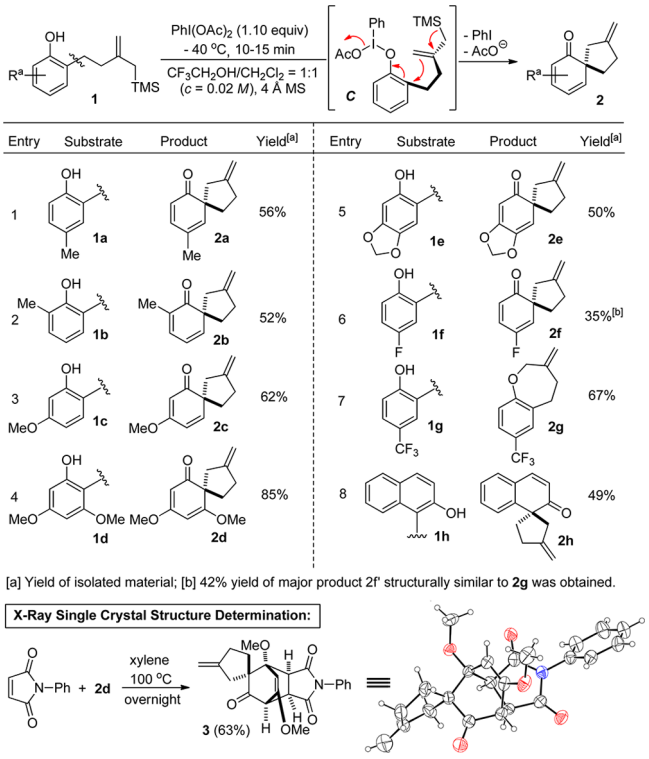
(13) For examples of the oxidative Hosomi−Sakurai-type dearomatizations, see: (a) Guérard, K. C.; Sabot, C.; Beaulieu, M.-A.; Giroux, M.-A.; Canesi, S. *Tetrahedron* **2010**, *66*, 5893. (b) Quideau, S.; Pouységu, L.; Oxoby, M.; Looney, M. A. *Tetrahedron* **2001**, *57*, 319. (c) Quideau, S.; Looney, M. A.; Pouységu, L. *Org. Lett.* **1999**, *1*, 1651. (d) Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun.* **2009**, 2941.

Scheme 2. Design Concept on Potential Substrates for *Ortho*-Dearomative Spiro-carbocyclization of Phenols



given the high degrees of unsaturations in the structures of **P1** and **P2** and occurrences of many possible side reactions on such inherently reactive skeletal identities. The proposed key intermediates were illustrated in ***C*** and ***D***,[5] respectively (Schemes 3 and 4). The use of pure TFE as the solvent in the standard condition **II** for **S2** apparently secures an advantage in that TFE itself engages on cationic stabilization toward ***D*** to furnish the product **P2** in its acetal-protected form. With the above identified standard condition **I**, a range of ***B2***-type allyltrimethylsilane (TMS)-linked phenols **1** were subsequently examined and the results are compiled in Scheme 3. In each case except **1g** the desired *ortho*-spirobicyclic product **2** was obtained in moderate to good isolated yield and, perhaps more significantly, in excellent reproducibility over multiple runnings. In general, phenols bearing electron-donating ring substituents (**1a**−**1e**), presumably due to their beneficial carbocationic stabilization effects, tend to give higher yields as compared to those with electron-withdrawing groups (**1f**−**1g**). The highest yield (85%) was obtained on phenol **1d** with two methoxyl substituents, while for **1g** having the strongly electron-withdrawing trifluoromethyl group the spiroannulation was practically inhibited, and the obtained product **2g** was formally the result of the Hosomi−Sakurai-type process.[13] For 2-naphthol **1h**, the protocol is equally competent, leading to the product **2h** in 49% isolated yield. Although these dearomatized spiro-carbocycles evidently possess high reactivities, when isolated pure, they could be routinely

Scheme 3. Reaction Scope of *Ortho*-Spiro-carbocyclization of ***B2***-Type Phenol Substrates



spectroscopically characterized and stored under an inert atmosphere for a prolonged time. We were also able to grow single crystals of the Diels−Alder adduct **3** which was prepared in 63% yield by heating **2d** with *N*-phenylmaleimide in xylene, thereby confirming unambiguously its spiro-structural identity by X-ray crystallographic analysis.[14]

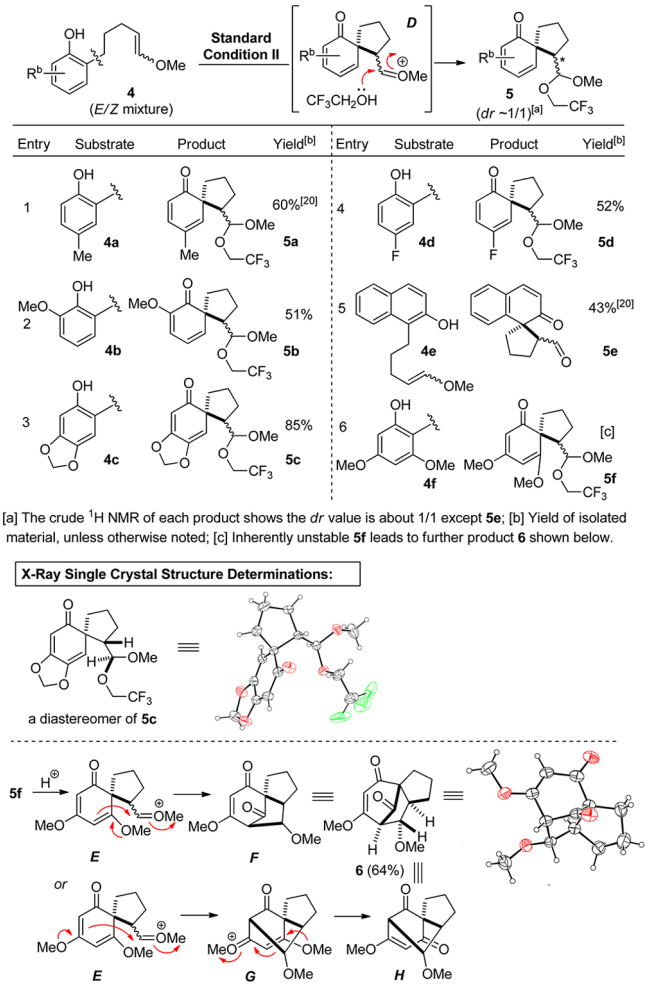
The applications of the standard condition **II** on several vinyl methyl ether functionalized phenols **4** are summarized in Scheme 4. In complete analogy to the transformation of **S2** to **P2**, these *ortho*-oxidative dearomatizations progressed uneventfully to give their corresponding acetal-terminated spiro-carbocyclization products **5** in nearly 1/1 diastereomeric ratios relative to the star-labeled stereogenic centers.[15] Once again, the phenols possessing either electron-donating (**4a**−**4c**) or electron-withdrawing (**4d**) substituents are suitable substrates. 2-Naphthol **4e** worked in comparable efficiency to that of allylsilane-modified counterpart **1h** (entry 8, Scheme 3), producing the desired spiro-tricycle **5e** in 43% yield. Single crystals of a diastereomer of product **5c** were fortunately obtained and then analyzed by X-ray crystallography, thus confirming directly its structure and stereochemistry.[16] A very interesting observation made on **4f** was that, apparently owing to the inherent instability of its product **5f**, tricyclic enone **6**

(14) The crystal structure of **3** was deposited at the Cambridge Crystallographic Data Centre (tracking number: 922541).

(15) As an illustrative example, mild acidic hydrolysis of each diastereomer of **5c** with 2 M HCl was shown to give accordingly their diastereomeric aldehydes (see Supporting Information for details).

(16) The crystal structure of **5c** was deposited at the Cambridge Crystallographic Data Centre (tracking number: 945361).

Scheme 4. Reaction Scope of *Ortho*-Spiro-carbocyclization of ***B3***-Type Phenol Substrates



was isolated (64% yield) whose structure was again unambiguously established by X-ray crystallographic analysis.[17] The formation of **6** should have originated from cationic rearrangements[18] on the initially formed **5f**. The vinyl methyl ether moiety-triggered cationic cascade trapping may occur either through intermediates ***E*** and ***F*** to give **6** or, alternatively, through the sequence ***E-G-H*** to complete the rearrangement. It is interesting to note that **6** represents a common [6-5-5] fused tricyclic skeleton found in many useful natural products.[19]

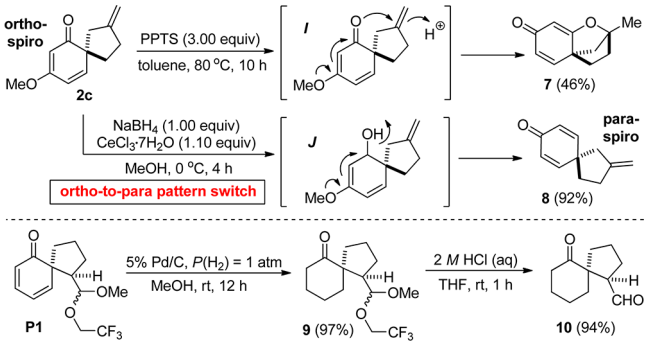
(17) The crystal structure of **6** was deposited at the Cambridge Crystallographic Data Centre (tracking number: 921696).

(18) For a recent review on carbocationic rearrangements, see: Tantillo, D. J. *Chem. Soc. Rev.* **2010**, *39*, 2847.

(19) For selected natural products containing such fused [6-5-5] tricyclic rings, see: (a) Singh, I. P.; Bharate, S. B. *Nat. Prod. Rep.* **2006**, *23*, 558. (b) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963. (c) George, J. H.; Hesse, M. D.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2010**, *12*, 3532. (d) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *J. Nat. Prod.* **2000**, *63*, 104. For dearomatization annulation: (e) Zhang, Q.; Mitasev, B.; Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2010**, *132*, 14212.

(20) Under the standard condition II, compound **4a** was transformed to diastereomeric acetals and quinine monoketal (see Supporting Information for details), and subsequent acidic hydrolysis of the mixture produced the desired aldehydes. Similar reactivities were observed for compound **4e**.

Scheme 5. Representative Reactions on Spiro-dearomatized Products



The reactivities unlocked by such *ortho*-oxidative dearomatization technology are highly diverse, and it must await further studies to define its full scope. Outlined in Scheme 5 are some initial illustrative results. When activated by acidic PPTS in heated toluene, *ortho*-spiro-bicycle **2c** rearranges to the fused tricyclic cyclohexadienone **7** in 46% isolated yield; upon reduction of **2c** by the Luche reagent, the *in situ* generated intermediate ***J*** undergoes efficient dehydration to give a new spiro-bicycle **8** in 92% yield. It merits attention that in this straightforward conversion an important *ortho*-to-*para* pattern switch was accomplished. This discovery demonstrated that, by the simple introduction of an alkoxyl (i.e., OMe) substituent onto the *meta*- position of a phenolic substrate, both *ortho*- and *para*-spiro-regioisomeric products could be efficiently obtained from the same starting material, thus significantly enhancing the methodology's synthetic utilities. Finally, spiro-cycle **P1** was subjected to Pd/C-promoted hydrogenation to produce fully saturated spiro-bicyclic ketone **9** in nearly quantitative yield (97%), and its acetal moiety can be easily removed by acidic hydrolysis to furnish ketoaldehyde **10** in 94% yield.

In summary, with well-optimized reaction conditions, we were able to demonstrate here that a range of alkene-linked phenols are reliably dearomatized specifically at their *ortho*-positions to create all-carbon quaternary stereogenic centers at the corresponding spiro-ring junctions, thus establishing a viable solution to the long-standing synthetic challenge. The new reactivities unlocked by breaking aromaticity in such processes are evidently very rich, and we hope to communicate in due course further in-depth investigations on these exciting possibilities.

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Supporting Information Available. Experimental procedures, X-ray crystallographic analysis, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.