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Synthesis of Resorcinol Derived Spironitronates

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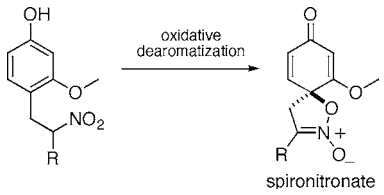
ABSTRACT



Syntheses of several unique spironitronates are reported. The key transformation involves the first known example of an *ipso* oxidative cyclization of nitro functionality. Oxidation proceeds from both *o*- and *p*-phenols. Reductions of these compounds provide novel spiroisoxazoline derivatives.

Natural products isolated from marine sponges come in a variety of exotic forms. Secondary metabolites derived from the oxidation of tyrosine, in particular, halogenated derivatives, have a wide range of biological activity.[1,2] The biosynthesis of these compounds purportedly involves bromination of tyrosine followed by oxidation of the amine to an oxime and concludes by oxidative dearomatization to form the spiroisoxazoline core.[3] The latter scaffold is then further processed by reduction and conversion of the ester moiety into an amide (Figure 1). A number of syntheses of spiroisoxazoline natural products have been reported; most appear to resemble the reported biosynthesis.[4]

Hypervalent iodide reagents (diacetoxyiodo)benzene (PIDA) and bis(trifluoroacetoxyiodo)benzene (PIFA) as well as other chemical oxidants such as thallium(III) nitrate, manganese(III) acetate, and even electrochemical oxidations have all been shown to mimic the postulated biosynthesis.[4a−n] The reaction proceeds by formation of a phenoxonium and concomitant 5-*exo*-*trig* intramolecular nucleophilic attack of the oxygen atom of the oxime to afford a spiroisoxazoline. It occurs with a variety of substituents on the aromatic ring,

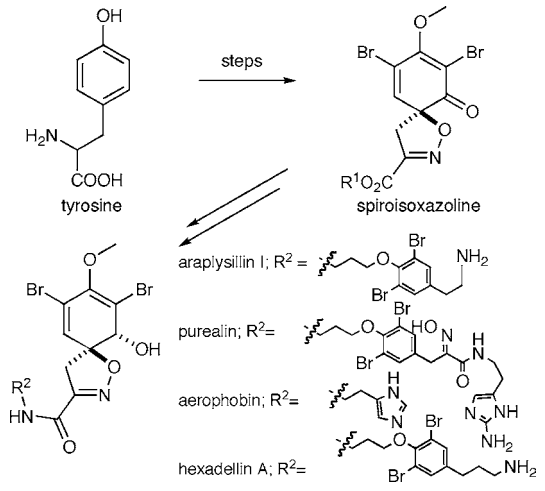


Figure 1. Biosynthesis of spiroisoxazoline derivatives.

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(2) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, *113* and previous reports in this series.

(3) (a) Tymiak, A. A.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 6763. (b) De Rosa, M.; Minale, L.; Sodano, G. *Comput. Biochem. Physiol.* ***1973****, 45B, 883.* (c) Carney, J. R.; Rinehart, K. L. *J. Nat. Prod.* **1995**, *58*, 971.

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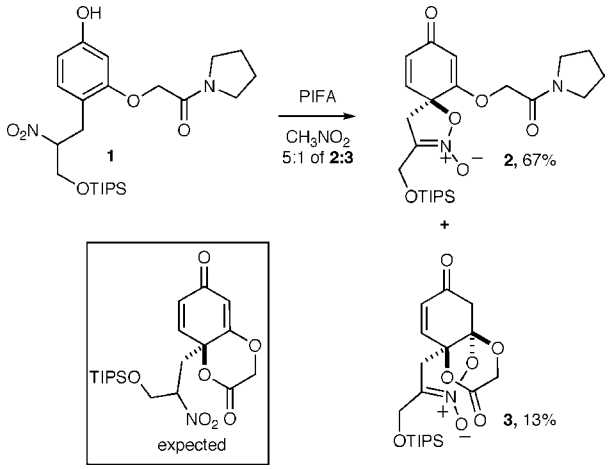
including halogen and methoxy substituents. Our interest was sparked during studies with resorcinol derivatives (Scheme 1).[5] When phenol **1** (0.05 M in CH_3NO_2) is subjected to

Scheme 1. Unanticipated Spironitronate Formation

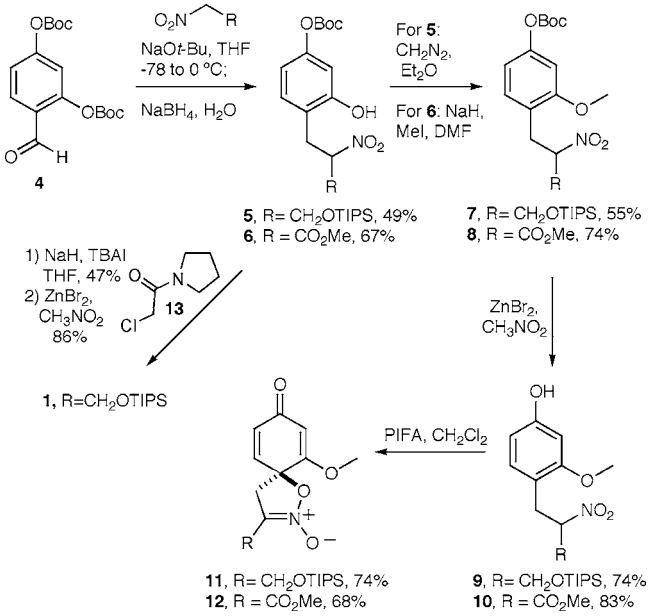


PIFA, the expected lactone (Scheme 1, inset) is not observed. Instead, the spironitronate **2**, arising from nitro attack and subsequent loss of a proton, is produced in 67% yield. In addition, 13% of tricyclic lactone **3** is obtained displaying four AB coupling patterns in the ^{1}H NMR spectrum.

We speculate compound **3** arises from cyclization of the amide carbonyl and after hydrolysis of the iminium intermediate as expected (cf. Scheme 1, inset) undergoes an intramolecular 1,4-addition to the vinylogous ester by an oxygen atom belonging to the nitro group.[6] The facile addition of the electron-deficient nitro group to the phenoxonium as compared with the corresponding addition of the supposedly more nucleophilic amide carbonyl was indeed surprising. Subsequent studies have shown that placement of a substituent between the oxygen atoms of the resorcinol greatly facilitates cyclization of the oxygen atom of the amide carbonyl.[7] However, to the best of our knowledge, this is the first example of an oxidative dearomatization affording a spironitronate and as such deserved some additional investigation.

We decided to probe the scope and generality of this transformation as compared with the complementary oxime oxidative cyclization. We began from the known bis-OBoc benzaldehyde, **4**, which undergoes addition of the sodium salt of TIPS-protected nitroethanol (0.3 M in THF).[8] The intermediate product is reduced in situ with $NaBH_4$. This one-pot transformation proceeds by 1,4-reduction of an *o*-quinone methide (*o*-QM) intermediate generated by an anionic cascade to provide the phenol **5** in 49% yield (Scheme 2).[9] After failing to methylate the resulting phenol

Scheme 2. General Synthesis of *p*-Quinol Spironitronates



under a variety of conditions (AgOTf/MeI; DEAD/MeOH), the necessary methylation of phenol **5** (1.4 M in Et_2O) was eventually accomplished with diazomethane to afford the methyl ether **7** in an acceptable 55% yield. Deprotection of the BOC residue in **7** (0.05 M in CH_3NO_2) with $ZnBr_2$ affords the phenol **9** in 74% yield. This three-step sequence was also carried out using methyl nitroacetate in place of TIPS-protected nitroethanol and thereby provides the phenol **10** under similar conditions. A similar strategy of attachment led to phenol **1**, which prompted this initial study. Oxidative dearomatization of **9** (0.05 M in CH_3NO_2) with PIFA provides the *p*-quinol spironitronate **11** in 74% yield. Similarly, oxidation of phenol **10** provides spironitronate **12** in 68% yield. The timing as to the loss of the nitro α-proton remains unclear. With these results in hand, we set out to probe the reactivity of these novel compounds with respect to reduction and other functional group manipulations.

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(7) (a) Mejorado, L. H.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2006**, *128*, 15625. (b) Mejorado, L.; Hoarau, C.; Pettus, T. R. R. *Org. Lett.* **2004**, *6*, 1535.

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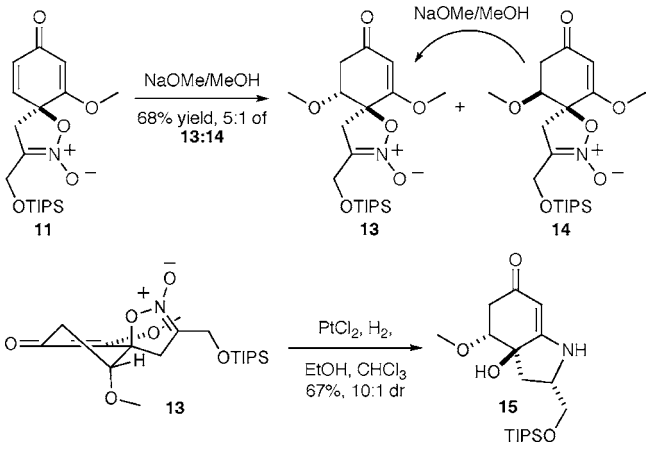
(9) (a) Jones, R. M.; Selenski, C.; Pettus, T. R. R. *J. Org. Chem.* **2002**, *67*, 6911. (b) Jones, R. M.; Van De Water, R. W.; Lindsey, C. C.; Hoarau, C.; Ung, T.; Pettus, T. R. R. *J. Org. Chem.* **2001**, *66*, 3435. (c) Van De Water, R. W.; Magdziak, D. J.; Chau, J. N.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2000**, *122*, 6502.

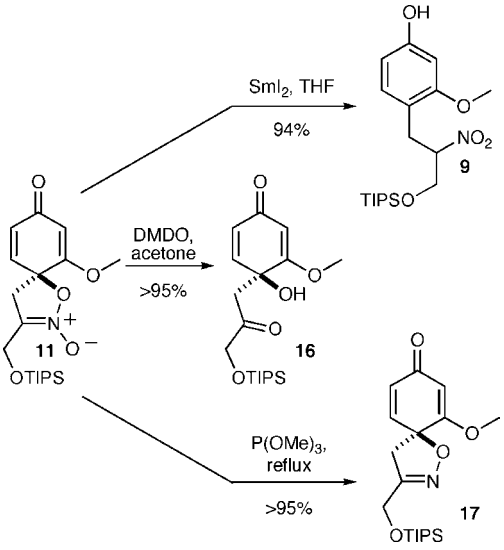
Attempts to reduce the spironitronate **11** were unsuccessful. Exposure of **11** to metal catalysts and an H_2 atmosphere resulted in decomposition, presumably by single electron transfer and rearomatization as is the case with cyclohexadienone *p*-quinols.[10] To circumvent this problem, 1,4-addition of methanol to the enone moiety of **11** was examined (Scheme 3). Treatment of **11** with catalytic sodium methoxide (0.1 M in MeOH) at 0 °C affords a 5:1 mixture of spironitronates **13** and **14** in a combined 68% yield. The major diastereomer **13** reflects addition to the more congested face of the enone **11**. Monte Carlo conformational analysis with Macromodel using MM3 parameters predicts a 0.5 kcal/mol energy difference between diastereomers **13** and **14**, favoring the former isomer.[11] Furthermore, after purification, resubmission of the minor diastereomer **14**, which arose from addition to the least congested face of the cyclohexadienone of the spironitronate **11**, to the earlier conditions provides the same 5:1 ratio of **13**:**14**. With the cyclohexadienone partially reduced, reduction of the spironitronate moiety was reexamined. Hydrogenation of **13** (0.1 M in EtOH, 1 equiv $CHCl_3$) with platinum(II) oxide[12] under an H_2 atmosphere affords the vinylogous amide **15** in 67% yield with 10:1 dr. While the relative stereochemistry of the major diastereomer could not be determined by NOE with absolute certainty, it is likely that reduction occurs from the less congested *Re* face of the spironitronate **13** as the *Si* face is blocked by the vinyl methoxy residue. This result illustrates the steric and electronic difference between the two faces of the nitronate moiety and might suggest application of the reverse strategy: use of a chiral α-carbon substituent to direct oxidative dearomatization in a diastereoselective manner.

Scheme 3. Stereoselective 1,4-Addition and Reduction of **11**



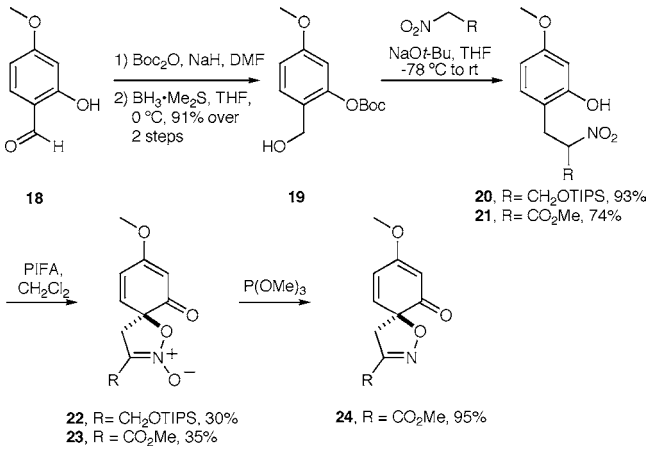
Reductive rearomatization of **11** proceeds via single-electron transfer with samarium diiodide (0.1 M in THF) and affords the phenol **9** in 94% yield (Scheme 4). The addition of dimethyldioxirane (DMDO, 0.08 M in acetone) to **11** cleanly affords the *p*-quinol **16** in >95% yield. Further epoxidation of **16** (0.5 M in CH_2Cl_2) with *m*-CPBA at 0 °C affords a single diastereomer of an epoxide of the vinylogous ester. However, the decomposition of this product thwarted rigorous identification. On the other hand, reduction of the nitronate moiety of **11** with refluxing trimethylphosphite (0.13 M) affords spiroisoxazoline **17** in quantitative yield.

Scheme 4. Other Transformations of **11**



Next, we set out to synthesize the corresponding *o*-quinol spironitronates, which in principle enables access to spiroisoxazoline natural products. Boc-protection and subsequent reduction of commercially available 2-hydroxy-4-methoxybenzaldehyde **18** affords the known benzyl alcohol **19** in 91% yield over two steps (Scheme 5).[13] Sodium *tert*-butoxide was added to generate an *o*-QM intermediate, which is then trapped by the anion of TIPS-protected nitroethanol to

Scheme 5. General Synthesis of *o*-Quinol Spironitronates



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(11) Since the nitro functionality is not tolerated in Macromodel, these calculations were performed using the hemiaminals of **13** and **14**.

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(13) Lindsey, C. C.; Pettus, T. R. R. *Tetrahedron Lett.* **2006**, *47*, 201.

provide phenol **20** in 93% yield. Similarly, the addition of methyl nitroacetate to the generated *o*-QM affords phenol **21** in 74% yield. Oxidative dearomatization of **20** (0.05 M in CH_2Cl_2) with PIFA provides the TIPS-protected *o*-quinol spironitronate **22** in 30% yield. Likewise, oxidation of **21** provides *o*-quinol spironitronate **23** in 35% yield. Reduction of **23** with trimethylphosphite affords the desired spiroisoxazoline **20** in 95% yield. The lower yields for oxidation as compared with the corresponding *p*-quinol derivatives were disappointing. We speculate that the difference may reflect the instability of the *o*-phenoxonium cation as compared with the corresponding para cation. To further probe the scope of this *nitro* cyclization with *o*-quinol precursors, the dibromo analogues of **21** and **22** were synthesized. Unfortunately, all attempts to cause formation of the corresponding spironitronates from these materials failed with a variety of oxidants. Instead of producing the desired dibromospironitronates, small amounts of several *p*-quinones and dihydrofuran products were isolated.

In conclusion, the first synthesis of quinol spironitronates has been illustrated and some of their reactivity examined. Oxidative dearomatization of nitro phenols proceeds for both *o*-quinol and *p*-quinol precursors. The *p*-quinol derivatives are versatile intermediates that undergo a variety of high yielding and stereoselective transformations. While the yields for ortho cyclization are lower than desired compared to cyclization of the corresponding para derivatives, this transformation provides access to spiroisoxazoline scaffolds resembling natural products in short order. We speculate the incorporation of a chiral ester or amide residue might enable enantioselective access to these spironitronates as previously seen for oxime substrates.[14] Furthermore, nitronates are known to be versatile partners in [3 + 2] cycloadditions and therefore oxidative dearomatization may offer entry into a variety of complex molecular architectures.[15] Research into this hypothesis is in progress and will be reported in due course.

Acknowledgment. A substantial portion of this work was performed in the period of 2001−2003 and can be found in the thesis of R.W.V.D.W. We are grateful for past financial support from the National Institutes of Health (NIH GM-64831-06) for our oxidative dearomatization chemistry and for past support by the National Science Foundation (NSF CHE-9971211) for our *o*-quinone methide chemistry. We also thank Daniel Haacke for technical assistance with starting intermediates, as well as UCSB for current TA support given the current funding climate.

Supporting Information Available: Full experimental procedures for each reaction sequence, as well as select spectroscopic data (^{1}H NMR, ^{13}C NMR, FT-IR, MS) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0710257

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