Synthesis of Spiroacetal Enol Ethers by Oxidative Activation of Furan Derivatives

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Jeremy Robertson* and Sébastien Naud

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K.

jeremy.robertson@chem.ox.ac.uk

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ABSTRACT



Activation of furan by electron transfer combines with the radical stabilizing effect of the alkynyl substituent (R = Ph, $MeC \equiv C-$) to achieve site-selective cation formation. A tethered hydroxy group acts as a probe of this site-selectivity to produce the ring system present in spirocyclic natural products found in *Artemisia* and *Chrysanthemum* species. *cis*-Dihydroxylation proceeds with high *anti*-stereoselectivity with respect to the tetrahydropyranyl ring oxygen.

Furan can be easily incorporated into synthetic intermediates and subsequently converted into a variety of heterocycles and other structural units, usually by oxidation.¹ For example, the Achmatowicz reaction² and its aza-counterpart³ result in the conversion of α -hydroxymethyl- and α -aminomethyl furans into hydroxypyrones and hydroxypyridones, respectively, by interception of an ene-dione intermediate by the appended hydroxy or amino nucleophile. We⁴ and others⁵ have shown that, under conditions similar to those used for the Achmatowicz reaction, substrates bearing more remote nucleophiles are converted into spirocyclic products that have wide application in natural product synthesis.

Treatment of furan derivatives with oxidizing agents that induce overall loss of hydride, such as 2,3-dichloro-5,6-dicyanobenzo-1,4-quinone (DDQ),⁶ can initiate nucleophilic attack α to the ring and return an intact furan derivative.⁷ In the early stages of this process, rapid charge-transfer complex

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formation precedes reversible electron transfer to the reagent and the resulting delocalized radical-cation **1** (Scheme 1) is

Scheme 1. 4-Hydroxybutyl Group as a Probe of Regioselective Proton Abstraction from a Furan-Centered Radical Cation



then activated toward overall loss of H[•] (by sequential H⁺ and electron transfers) to generate cations **2** or **3**.⁸ In principle, the preferred site of deprotonation, which dictates the regiochemistry of cation formation, could be probed by a nucleophile present in either R¹ or R²; for example, if R² = (CH₂)₃OH, two cyclization products **4** or **5** could result. Reported cases of this type of oxidative cyclization afford products of the second type (e.g., **5**)^{7a} but if R¹ can stabilize an adjacent radical more effectively than R² then deprotonation from its α -position should ensue, generating spirocyclic products preferentially. This paper presents a realization of this predicted pathway and provides preliminary results for its application in natural product synthesis.

Spirocycle **4** bears close structural resemblance to a group of natural products (examples, Figure 1) that occur widely



Figure 1. Representative bis(acetylene) enol ether spiroacetals from *Artemisia* and *Chrysanthemum* species.

in *Artemisia* and *Chrysanthemum* species and for which antifeedant, antifungal, and tumor growth inhibitory activities have been reported. Following Bohlmann's extensive investigations,⁹ over 30 examples have now been characterized, and some have been synthesized.¹⁰ Because the penta-1,3-diynyl side chain is a characteristic feature

in these natural products, we set out to establish whether such functionality could direct the course of oxidation toward spirocyclization.

A model substrate (**12**, Scheme 2) was prepared from 2-(4-*tert*-butyldimethylsilanyloxy)butylfuran (**10**),¹¹ and a range





of oxidants was screened for the spirocyclization. Of these,¹² only DDQ resulted in an acceptable reaction; reproducible results, applicable on a reasonable scale, were achieved with addition of 2.2 equiv¹³ of DDQ to a solution of the substrate at -95 °C followed by warming to -78 °C. The formation of over-oxidation products was minimized by performing an inverse quench of the cold reaction mixture into dilute aqueous sodium thiosulfate solution. Under these conditions the spiroacetal **13**¹⁴ was isolated in acceptable yield, typically as a ca. 6:1 ratio of *Z/E* diastereomers. Treatment of the separated diastereomers with a catalytic quantity of camphorsulfonic acid (CSA) in CDCl₃ led to their equilibration, the *Z/E* ratio stabilizing after a few days at ca. 2.5:1.

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(12) E.g., ferrocenium hexafluorophosphate, iron(III) nitrate, tetracyanoethylene, bis(acetoxy)iodobenzene, bis(trifluoroacetoxy)iodobenzene, cerium(IV) ammonium nitrate.

(13) As the reaction progresses, the forming DDQH⁻ consumes DDQ to form DDQH[•] + DDQ^{•-}, the DDQH[•] disproportionating to DDQH₂ + DDQ; overall, 1.5 equiv of DDQ is theoretically required: 2 substr + 3 DDQ \rightarrow 2 substr⁺ + 2 DDQ^{•-} + DDQH₂.^{8c}

Application of this method to the synthesis of natural product **7** ("homo-tonghaosu") (Figure 1) required access to a hexa-2,4-diynyl electrophile for the furan alkylation. Our method for the synthesis of this side chain was based on Tykwinski's protocol for oligo(acetylene) synthesis.¹⁵ Commercially available alkynone **14** (Scheme 3) was converted



into *gem*-dibromide **15** and the TMS group removed to provide the Fritsch–Buttenberg–Wiechell substrate **16**. Lithiation, rearrangement, and alkylation in situ with paraform-aldehyde gave alcohol 17^{16} which was converted into bromide 18^{17} without complication.

Alkylation of furan derivative **10** with this electrophile was somewhat low yielding, and dimer **20** was also produced;¹⁸ however, while this step remains unoptimized, sufficient material was prepared after desilylation to assess the DDQ oxidation. With this substrate (**19**), the formation of products of over-oxidation was more problematic but maintaining the reaction mixture at -95 °C gave a very clean reaction, and a 90% yield of spirocyclic product **7** was obtained based on a 39% conversion of starting material. Again, the *Z*- isomer predominated (*Z/E* ratio, ca. 5:1). This

kinetic isomer distribution was converted into a ca. 1:1 ratio upon exposure to catalytic CSA, as before.

During our work on the synthesis of the lituarines, we reported that conjugate additions to certain spiroacetal butenolides proceed with high *anti*-stereoselectivity with respect to the tetrahydropyranyl (THP) oxygen (**A**, Figure 2).^{4,19} Conversely, in conjugate additions of lithium amides



Figure 2. Stereochemical control in conjugate addition to spirocetalbutenolides (A) and -alkylidene dihydrofurans (B) and the question of diastereoselective dihydroxylation of spirocycles 7 and 13 (C).

to analogous enol ethers, a high *syn*-stereoselectivity was reported (**B**), the authors attributing this to chelation control.²⁰ Although dihydroxylation is expected to be regioselective for the endocyclic alkene in these systems^{9a} (**C**), the sense and level of stereocontrol imparted by the THP oxygen is not known. Knowledge of this aspect would allow us to complete a synthesis of diacetate *cis-Z-9* (Figure 1) isolated from *Chrysanthemum boreale*,²¹ and determine the relative stereochemistry at its spiro center.

For the dihydroxylation of spirocycle Z-13, the combination of OsO₄ and TMEDA in dichloromethane at lowtemperature²² gave complete conversion to essentially one stereoisomer of an osmate complex (*cis*-Z-22, Scheme 4) that could be isolated in 81% yield. Although this complex could not be crystallized, its stereochemistry was inferred by X-ray analysis of the derived diacetate (*cis*-Z-21) which revealed that dihydroxylation had proceeded from the face *opposite* to the THP oxygen.²³ Application of the same conditions to bis(acetylene) variant Z-7 was also successful, and the diacetate *cis*-Z-9 could also be crystallized for X-ray confirmation of the *anti*-disposition of the acetoxy groups relative to the THP oxygen (Figure 3).²⁴

We found significant chemical shift deviations between our ¹H NMR data (for *cis-Z-9*) and those reported for the natural product.²⁵ Furthermore, the coupling constants

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(18) In the ¹H NMR spectrum of the crude product, the components **10**, **19**-OTBS, and **20** were present in a ratio of 50:40:10.

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Figure 3. ORTEP diagram of diacetate cis-Z-9.

between the CH(OAc) protons in both *cis-Z*-**21** and *cis-Z*-**9** are 4.8 ± 0.2 Hz (in C₆D₆, CDCl₃ and CCl₄), whereas the value reported²¹ for the natural product is 7.5 Hz (in CCl₄). This is significant because this value²⁶ led to the authors'

cis assignment in the original report. While we cannot rule out the possibility that the natural product is the spirodiastereomer of our *cis-Z-9*, it is more likely to be the *trans* isomer.²⁷ Indeed, the corresponding coupling constant reported²⁸ for *trans-E-9* is 7.5 Hz and a *trans-1,2-*dioxygenation pattern would also be expected on the basis of a biosynthetic epoxide ring-opening.

It remains, of course, to establish the correct identity of the natural product by independent synthesis. We will describe our efforts toward that end in a full account of this work, along with the DDQ-mediated reactions of furans bearing a variety of non-acetylenic conjugating substituents, and molecular modeling studies that shed light on the stereochemical aspects of our results. In closing, we note that substituent-controlled oxidative activation processes of this type should not be limited to furan derivatives and broader applications are envisaged.

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Supporting Information Available: Experimental details and copies of ¹H and ¹³C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) I.e., one of the two *trans-Z-9* isomers that differ in the configuration at the spiro center. The Z-stereochemical assignment for the side chain enol ether in the natural product was secured²¹ by conversion of the diacetate into the corresponding alkene (i.e., Z-7) and comparison of data with those from an authentic sample.

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⁽²⁵⁾ In the following listings, significant deviations are evident in the marked (*) resonances. Reported data for *cis-Z*-9^{,21} ¹H NMR (CCl₄) 1.50–1.90 (6 H, m), 1.97 (3 H, d, *J* 1.0 Hz), 2.08 and 2.10 (2 × 3 H, 2 × s), 3.73 (2 H, t, *J* 5.0 Hz), 4.99* (1 H, d, *J* 7.5 Hz), 5.03* (1 H, dq, *J* 2.0, 1.0 Hz), 6.07* (1 H, dd, *J* 7.5, 2.0 Hz). Data for *cis-Z*-9[:] ¹H NMR (500 MHz, CCl₄) 1.45–1.70 and 1.84–2.00 (6 H, 2 × m), 1.90, 1.93 and 1.98 (3 × 3 H, 3 × s), 3.63–3.69 and 3.81–3.88 (2 × 1 H, 2 × m), 4.42* (1 H, 4, *J* 4.7 Hz), 5.82* (1 H, poorly resolved dd, *J* 4.7, 1.8 Hz).