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Synthesis of Spiroacetal Enol Ethers by Oxidative Activation of Furan Derivatives

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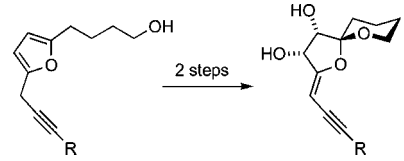
ABSTRACT



Activation of furan by electron transfer combines with the radical stabilizing effect of the alkynyl substituent (R = Ph, MeC≡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 reaction[2] and its aza-counterpart[3] 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. We[4] and others[5] 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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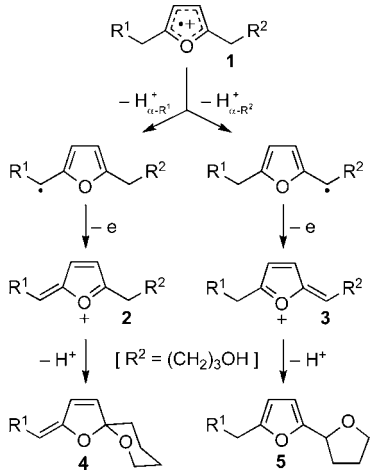
formation precedes reversible electron transfer to the reagent and the resulting delocalized radical-cation **1** (Scheme 1) is

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$^{\bullet}$ (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 R^1 or R^2; for example, if $R^2 = (CH_2)_3OH$, 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 R^1 can stabilize an adjacent radical more effectively than R^2 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

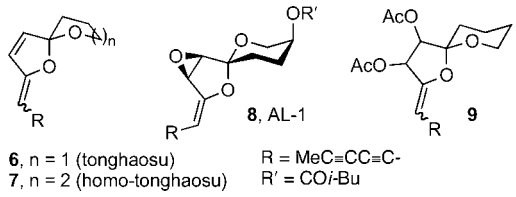
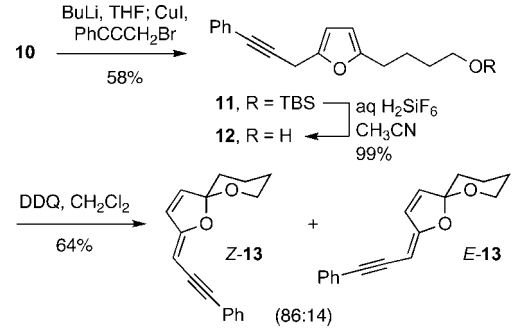


Figure 1. Representative bis(acetylene) enol ether spiroacetals from *Artemisia* and *Chrysanthemum* species.

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

Scheme 2. Preparation and Cyclization of a Model Substrate



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 equiv[13] 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 $CDCl_3$ led to their equilibration, the *Z*/*E* ratio stabilizing after a few days at ca. 2.5:1.

(8) (a) Höfler, C.; Rüchardt, C. *Liebigs Ann. Recl.* **1996**, 183–188. (b) Baciocchi, E.; Giacco, T. D.; Elisei, F.; Lanzalunga, O. *J. Am. Chem. Soc.* **1998**, *120*, 11800–11801. (c) Yamamoto, S.; Sakurai, T.; Yingjin, L.; Sueishi, Y. *Phys. Chem. Chem. Phys.* **1999**, *1*, 833–837. (d) Fukuzumi, S.; Ohkubo, K.; Tokuda, Y.; Suenobu, T. *J. Am. Chem. Soc.* **2000**, *122*, 4286–4294. (e) Wurche, F.; Sicking, W.; Sustmann, R.; Klärner, F.-G.; Rüchardt, C. *Chem.—Eur. J.* **2004**, *10*, 2707–2721.

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(10) (a) Gao, Y.; Wu, W.-L.; Ye, B.; Zhou, R.; Wu, Y.-L. *Tetrahedron Lett.* **1996**, *37*, 893–896. (b) Gao, Y.; Wu, W.-L.; Wu, Y.-L.; Ye, B.; Zhou, R. *Tetrahedron* **1998**, *54*, 12523–12538. (c) Toshima, H.; Aramaki, H.; Ichihara, A. *Tetrahedron Lett.* **1999**, *40*, 3587–3590. (d) Miyakoshi, N.; Mukai, C. *Org. Lett.* **2003**, *5*, 2335–2338. (e) Miyakoshi, N.; Aburano, D.; Mukai, C. *J. Org. Chem.* **2005**, *70*, 6045–6052. (f) Wensley, A. M.; Hardy, A. O.; Gonsalves, K. M.; Koviach, J. L *Tetrahedron Lett.* **2007**, *48*, 2431–2434. See also ref 9c, e, f.

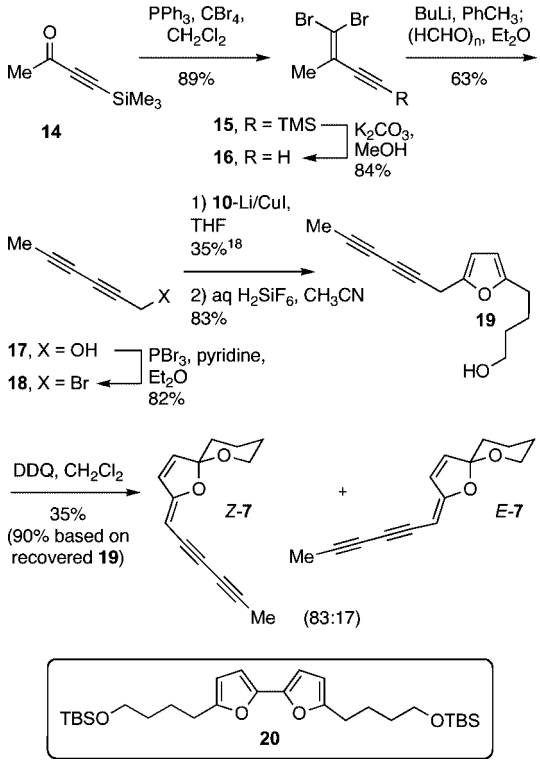
(11) Sun, M.; Deng, Y.; Batyreva, E.; Sha, W.; Salomon, R. G. *J. Org. Chem.* **2002**, *67*, 3575–3584.

(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$^{\bullet}$ + $DDQ^{\bullet-}$, the DDQH$^{\bullet}$ disproportionating to $DDQH_2$ + DDQ; overall, 1.5 equiv of DDQ is theoretically required: 2 substr + 3 DDQ → 2 $substr^+$ + 2 $DDQ^{\bullet-}$ + $DDQH_2$.[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 paraformaldehyde gave alcohol **17**[16] which was converted into bromide **18**[17] without complication.

Scheme 3. Synthesis of *E*- and *Z*-Homo-tonghaosu (**7**)



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 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.

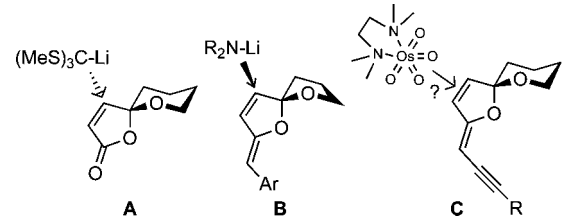


Figure 2. Stereochemical control in conjugate addition to spirocetal-butenolides (**A**) and -alkylidene dihydrofurans (**B**) and the question of diastereoselective dihydroxylation of spirocycles **7** and **13** (**C**).

For the dihydroxylation of spirocycle *Z*-**13**, the combination of OsO_4 and TMEDA in dichloromethane at low-temperature[22] 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 ^{1}H NMR data (for *cis*-*Z*-**9**) and those reported for the natural product.[25] Furthermore, the coupling constants

(14) Chen, L.; Xu, H.-H.; Yin, B.-L.; Xiao, C.; Hu, T.-S.; Wu, Y.-L. *J. Agric. Food Chem.* **2004**, *52*, 6719–6723.

(15) Luu, T.; Morisaki, Y.; Cunningham, N.; Tykwinski, R. R. *J. Org. Chem.* **2007**, *72*, 9622–9629.

(16) First preparation: Armitage, J. B.; Cook, C. L.; Entwistle, N.; Jones, E. R. H.; Whiting, M. C *J. Chem. Soc.* **1952**, 1998–2005.

(17) Bohlmann, F.; Seyberlich, A. *Chem. Ber.* **1965**, *98*, 3015–3019.

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

(19) Robertson, J.; Dallimore, J. W. P. *Org. Lett.* **2005**, *7*, 5007–5010.

(20) (a) Yin, B.-L.; Hu, T.-S.; Wu, Y.-L. *Tetrahedron Lett.* **2004**, *45*, 2017–2021. (b) Yin, B.-L.; Li, C.; Xu, H.-H.; Hu, T.-S.; Wu, Y.-L. *Chin. J. Chem.* **2006**, *24*, 240–246.

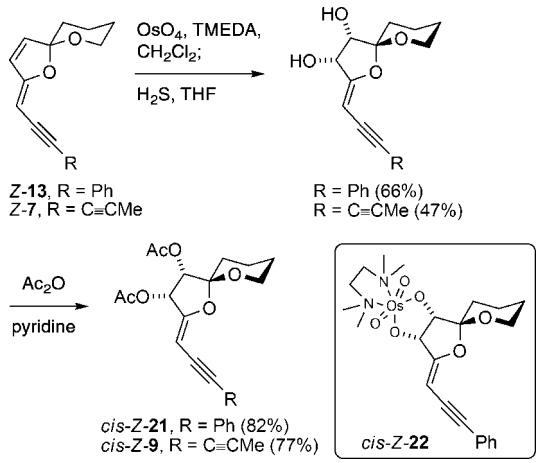
(21) Matsuo, A.; Uchio, Y.; Nakayama, M.; Hayashi, S. *Tetrahedron Lett.* **1974**, 1885–1888.

(22) Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027–5030.

(23) The influence of allylic alkoxy groups on the stereoselectivity of alkene dihydroxylation is reviewed in: Cha, J. K.; Kim, N.-S. *Chem. Rev.* **1995**, *95*, 1761–1795.

(24) CCDC 697832 and 697833 contain crystallographic data for this paper (for compounds *cis*-*Z*-**9** and *cis*-*Z*-**21**, respectively). These can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 4. Regio- and Stereoselective Dihydroxylation of Acetylenic Spiroacetal Enol Ethers **13** and **7**.



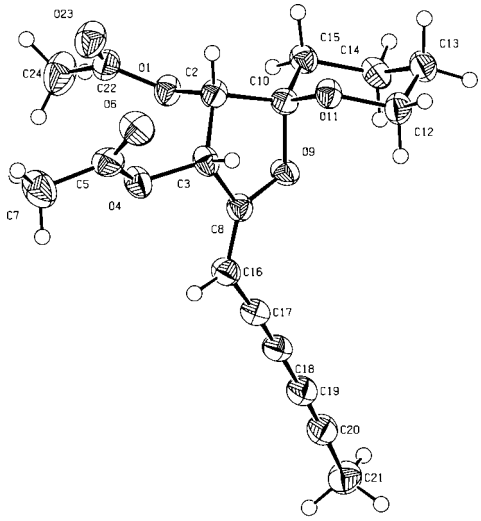


Figure 3. ORTEP diagram of diacetate *cis*-*Z*-**9**.

between the CH(OAc) protons in both *cis*-*Z*-**21** and *cis*-*Z*-**9** are 4.8 ± 0.2 Hz (in C_6D_6, $CDCl_3$ and CCl_4), whereas the value reported[21] for the natural product is 7.5 Hz (in CCl_4). This is significant because this value[26] 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 reported[28] 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.

Acknowledgment. We thank the EU (MEIF CT2006-039126 to SN) for financial support, Andrew Tyrrell, University of Oxford, for X-ray analysis of compounds *cis*-*Z*-**9** and *cis*-*Z*-**21**, and Drs. Tim Claridge and Barbara Odell, University of Oxford, for supporting NMR studies.

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

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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 (CCl_4) 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, CCl_4) 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, app. s), 4.98* (1 H, d, *J* 4.7 Hz), 5.82* (1 H, poorly resolved dd, *J* 4.7, 1.8 Hz).

(26) For a discussion of the magnitude of geminal $^1H-^1H$ coupling constants in cyclopentanes, see: Constantino, M. G.; da Silva, G. V. J. *Tetrahedron* **1998**, *54*, 11363–11374.

(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 secured[21] by conversion of the diacetate into the corresponding alkene (i.e., *Z*-**7**) and comparison of data with those from an authentic sample.

(28) (a) Marco, J. A.; Sanz, J. F.; Jakupovic, J.; Huneck, S. *Tetrahedron* **1990**, *46*, 6931–6938. (b) Wurz, G.; Hofer, O.; Sanz-Cervera, J. F.; Marco, J. A. *Liebigs. Ann. Chem.* **1993**, 99–101.