**Novel Analysis for Unexpected Reactions: Understanding the Enol Ether Epoxidation in Spiroketals**

**Chris Lorenz, Josep Sauri, Arvin Moser, Alexei V. Buevich, Antony J. Williams, R. Thomas Williamson, Gary E. Martin, Mark W. Peczuh, Patrick D. Wheeler, Steve J. Hayward**

1. Department of Chemistry, University of Connecticut, 55 N. Eagleville Road, U3060, Storrs, CT 06269. 2. Process & Analytical Chemistry, NMR Structure Elucidation, Merck Research Laboratories, Rahway, NJ 07065. 3. Advanced Chemistry Development, Toronto Department, 8 King Street E. Suite 107, M5C 1B5, Ontario, Canada. 4. ChemiConnect Inc. 513 Chestnut Grove Ct, Wake Forest, NC 27587

---

**Introduction**

Spiroketals organize small molecule structures into well-defined, three-dimensional configurations that make them good ligands for proteins. We have discovered a tandem cyclosimerization-dimerization reaction of alkynyl hemiketals that delivered polycyclic, enol-ether-containing spiroketals. Here we describe rearrangements of these compounds, triggered by epoxidation of their enol ethers that completely remodel their structures, essentially turning them “inside out.”[1] Due to the high level of substitution on the carbon skeletons of the substrates and products, we employed Computer-Assisted Structure Elucidation (CASE) coupled with a new proton-detected ADEQUATE NMR experiment (1,1-HD-ADEQUATE), to unequivocally assign the carbon skeleton of one of the new compounds.[1] Both the rearrangement and the methods used for structural determination of the products are valuable tools for the preparation and characterization of new small molecule compounds.

**Synthetic Method**

We recently reported the discovery of a phosphine-mediated cycloisomerization of alkynyl hemiketals (e.g., structure 1 to 2 in Figure 1). For terminal alkynes, the enone intermediate 2 rapidly dimerized to give a spiroketal product, 3.[2] The reaction led to relatively complex spiroketals from starting materials that were readily accessible. With Diversity-Oriented Synthesis (DOS) in mind,[3] we took the opportunity to further diversify these small molecules through subsequent reactions. One obvious choice was to cleave the carbon-carbon double bond through oxidation to produce new macrocycles.[4] Conversion of spiroketal 3 to macrocycle 4 under various oxidation conditions (O3, NaOCl) proceeded in modest (23–44%) yields. With an eye toward a step-wise oxidative cleavage of the bond, reaction of 3 and the related structure 5 with m-chloro peroxycarboxylic acid (mCPBA) gave unexpected, rearranged products. Whereas the product of reaction of 3 was a crystalline solid whose structure was solved by X-ray diffraction (not shown), the product of reaction with 5 was not. The fact that the reaction product was not crystalline, and the intricacies of its spectra, prompted us to solve its structure by alternative means.

---

**Analytical Method—Application of CASE & ADEQUATE**

For this example, when CASE methods were employed, the appropriate structure was determined based on the initial data (Figure 3). This structure (6) was so novel and unexpected that further certainty was sought by utilizing LR-HSQMBC [6] and 1,1-ADEQUATE spectra to unequivocally define the carbon skeleton (Figure 4). To facilitate the acquisition of the ADEQUATE data, we utilized a newly developed, partially homodecoupled 1,1-ADEQUATE (1,1-HD-ADEQUATE) experiment optimized for JCC=40 Hz.[7] Utilizing these data and beginning from the hydroxyl-bearing methine (see Figure 4), the constitution of the series of rings suggested in the calculations of ACD/Structure Elucidator Suite was confirmed.

---

**Analytical Method—Application of CASE**

Initially, the 1H, 13C, 1H-1H COSY, 1H-13C HSQC, and 1H-13C HMBC experiments and the molecular formula were employed to assist in the characterization of reaction products with manual analysis of the data. The compact nature of the product structure and the indeterminate nature of the correlations in the HMBC spectrum, coupled with incorrect expectations from the expected synthetic mechanisms, created challenges in the structure determination. In order to address these challenges, we chose to employ CASE methods, in which connectivities drawn from NMR correlation data are used to automatically generate the side of all possible matching isomers (Figures 2 and 3).[5] These candidates can then be ranked based on various criteria, including deviation between the predicted and experimental chemical shifts.

---

**Conclusion**

A new mechanism for an oxidative rearrangement of spiroketalolefins was described. This “inside-out” rearrangement provided structural diversity and complexity, allowing for the synthesis of natural product-like molecules. CASE methods were invaluable in bringing better understanding of the structures created. Utilization of a newly developed partially homodecoupled 1,1-HD-ADEQUATE experiment provided the means to further confirm the carbon skeleton.

**References**

1. Lorenz, C; Sauri, J; Moser, A; Buevich, A; Williams, A; Williamson, R; Martin, G; and Peczuh, M. W. Chemistry Open, 2015, 4, 577-580.

**Acknowledgements**

We recognize NSF CHE-0957626 for supporting work at the University of Connecticut.

---

**CASE Attempts**

<table>
<thead>
<tr>
<th>Unique Structures Generated</th>
<th>Original</th>
<th>ADEQUATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Taken</td>
<td>148 sec.</td>
<td>8 sec.</td>
</tr>
</tbody>
</table>

Table 1. The original data were sufficient to support the generation of the correct structure when used in ACD/Structure Elucidator Suite. However, the availability of correlation data form the 1,1-HD-ADEQUATE substantially hastened the CASE protocol.