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The Oxidative Spirocyclization of 2-(ω-(OH)-Alkyl)cyclic Enol Ethers by Rhenium (VII)-oxide

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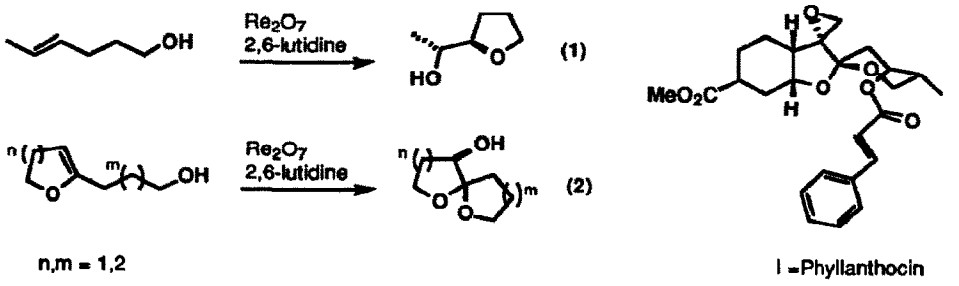
Abstract. : 2-(ω-(OH)-Alkyl)cyclic enol ethers react with rhenium(VII)-oxide to directly provide spiroketal alcohols resulting from an intramolecular *syn* oxidation of the enol ether double bond.

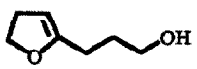
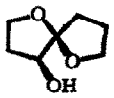
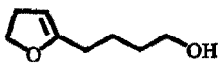
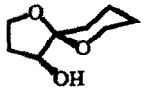
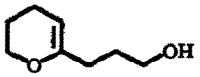
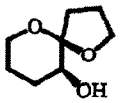
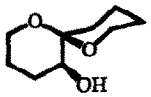
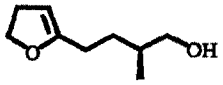
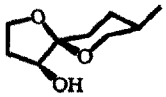
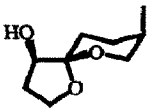
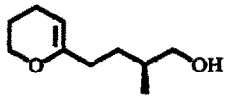
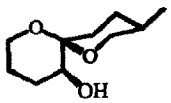
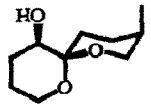
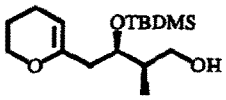
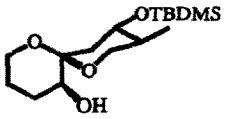
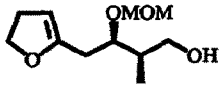
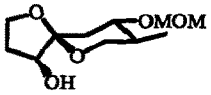
A number of natural products, *e.g.*, phyllanthocin (I), comprise a spirocyclic skeleton with oxygenated stereocenters α to the spirocyclic junction.[1] Although methodology exists for construction of these natural products,[2] none achieves both spirocyclization and stereospecific introduction of the hydroxyl group in a single operation. The ability of rhenium(VII)-oxide to intramolecularly direct oxidation of carbon-carbon double bonds has been used in the synthesis of 2-hydroxymethyl tetrahydrofurans[3] (equation 1). Herein we report the spirocyclization and α-oxidation of 2-(ω-(OH)-alkyl)-cyclic enol ethers in a stereospecific *syn* fashion utilizing the above described reagent (equation 2).



Scheme 1

Substrates **1a** through **8a**, prepared by alkylation of metallated cyclic enol ethers,[7a,b] were treated with rhenium(VII)-oxide[8] and 2,6-lutidine in methylene chloride at room temperature for 12 hours. Rhenium was removed by oxidation with basic hydrogen peroxide, and the product spiroketals **1b** through **8b** were isolated as single diastereomers with the exception of entries **5** and **6**. All products resulted from a *syn* oxidation of the enolic double bond (i.e., the newly formed CO spiro bond and adjacent C-OH bonds were *cis*.) Stereochemistry was verified by a combination of ^{1}H NOE and COSY spectra, and equilibration studies of *cis* and *trans* forms in several products shown in Table 1. In each of entries **5** and **6** two products were formed; the major diastereomers **5b** and **6b** had equatorial methyl groups at C3 and the minor diastereomers **5c** and **6c** had axial methyl groups as determined by ^{1}H NMR spectroscopy. The data in Table 1 shows that cyclizations to six membered rings proceed in higher yield than those leading to five membered rings.

Table 1. Results of Oxidative Spiroketalization

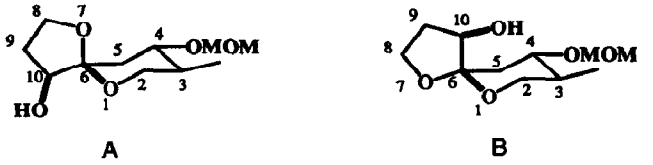
Entry	Substrate (a)	Product (b)	Yield (%)
1)	1a 	1b 	18
2)	2a 	2b 	48 ***
3)	3a 	3b 	56*
4)	4a 	4b 	78
5)	5a 	5b  5c 	63* 5.8:1
6)	6a 	6b  6c 	78* 5.5:1
7)	7a 	7b 	48*
8)	8a 	8b 	25**

*yield of isolated acetate derivative

** yield of three steps, MOM protection, debenzylation and Re_2O_7 cyclization [7b]

*** known compound[4]

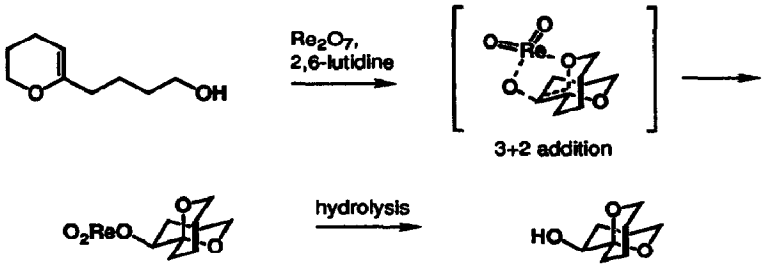
A model for the synthesis of phyllanthocin was constructed[9] and in the event resulted in a single diastereomer **8b** (shown as **A** in Scheme 2), which was again fully characterized. Both substituents on the forming ring were equatorial and the CO spiro bond of the five membered ring was axial to the 6 membered ring. The remote stereocenters at C-3 and C-4 appear to now exert full control[5] over the emergent centers at the spirojunction. Critical to assignment of stereochemistry was the observation in the NOESY spectrum of a cross peak between protons H10 and H5a and H5e. However, none was observed between H10 and H2a or H2e, as would have been expected in the event of formation of isomer B. The anomeric effect and minimization of nonbonded repulsions are expected to account for the observed stereoselectivity.



A B

Scheme 2. The phyllanthocin model

The mechanism of oxidative addition of alkenes to d^0 high valent oxo transition metals such as osmium tetroxide has been the object of recent attention. Both [3+2][6a,b] and [2+2][6c] mechanisms have been proposed. Our earlier work generated data in support of the latter hypothesis in which a metallaoxetane most closely approximated the geometry of the apparently irreversible event. However the observed pattern of stereocontrol here leads to the conclusion that the more electron rich and reactive enol ether double bond effectively shifts the mechanism from a [2+2] configuration toward a [3+2] geometry (Scheme 3).



Scheme 3. Mechanism of oxidative cyclization

We have developed a one step construction of α-hydroxy spiroketals that exploits the ability of rhenium(VII)-oxide to intramolecularly oxidise enol ether double bonds in a stereoselectively *syn* fashion and

with remote stereocontrol. Application of this methodology to the synthesis of phyllanthocin is under way and results will be reported in due course.

References and Notes

1. Spiroketal review; Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617-1661.
2. Phyllanthocin syntheses;
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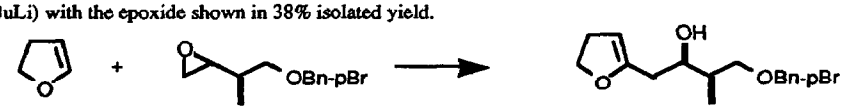
3. (a) Kennedy, R. M. ; Tang, S. *Tetrahedron Lett.* **1992**, *33*, 3729. (b) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5299. (c) Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5303.
4. Kozluk, T.; Cottier, L.; Descotes, G. *Tetrahedron* **1981**, *37*, 1875.
5. For other examples of spiroketalization as a means of asymmetric induction see
   (a) Totah, N. I.; Schreiber, S. L. *J. Org. Chem.* **1991**, *56*, 6255. (b) Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.*, **1985**, *107*, 5303.
6. Mechanism of cycloaddition;
   (a) Jorgensen, K. A.; Hoffman, R. *J. Am. Chem. Soc.* **1986**, *108* ,1867 and references therein. (b) Corey, E. J.; Jardine, P. D.; Virgil, S.; Yuen, P. W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243. (c) Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J. -E. *J. Am. Chem. Soc.* **1977**, *99*, 3120.
7. Syntheses of cyclization substrates in Table 1
   (a) Boeckman, R. K.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997 (b) Kocienski, P.; Yeats, C. *Tetrahedron Lett.* **1983**, *24*, 3905.
8. Typical reaction procedure: To a solution of alcohol **3a** (1.06 mmol) in 5 mL of dry methylene chloride at 0 °C under an atmosphere of argon was added 2,6-lutidine (9 eq) and Re_2O_7 (3 eq). The mixture was stirred for 12 h at room temperature and was worked up by the slow addition of 13 mL 2M of NaO_2H solution with stirring for 1 h at room temperature. The aqueous and organic layers were separated, and the aqueous layer was back extracted with 4x20 mL portions of ethyl acetate. The organic layers were combined and dried over Na_2SO_4. The solvent was removed by evaporation and the crude reaction mixture was redissolved in methylene chloride and subjected to acetylation with acetic anhydride (2eq), Et_3N (4 eq) and DMAP (0.1 eq). The crude solution after saturated bicarbonate workup was dried, concentrated and purified by flash chromatography to yielded 119 mg (0.595 mm, 56%) of pure acetate of **3b**. This acetate was then reduced with 1 eq of $LiAlH_4$ in dry ether to yield 79.3 mg (47%) of **3b**.
9. Substrate **8a** was prepared by the reaction of the cuprate derived from lithiated dihydrofuran (by deprotonation of dihydrofuran with tBuLi) with the epoxide shown in 38% isolated yield.



Secondary alcohol protection as a MOM-ether and dissolving metal debenzylation gave **8a**.

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