Pergamon

*Tetrahedron Letters*, Vol. 37, No. 11, pp. 1721-1724, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00118-9

# UNPRECEDENTED LOSS OF STEREOCHEMICAL INTEGRITY AT A NEIGHBORING QUATERNARY CARBON DURING OXIDATION OF A HIGHLY SUBSTITUTED CYCLOHEXANOL

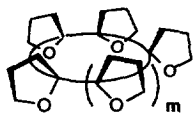
Leo A. Paquette,* Bruce M. Branan, and Marshall Stepanian

*Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210*

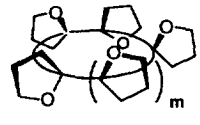
**Abstract:** Whereas the oxidation of alcohol **3** with various types of reagents leads cleanly to ketone **5**, the epimeric alcohol **4** under identical circumstances experiences competitive desymmetrization to provide mixtures of **5** and **6**.

Oxidative processes are of central importance to organic synthesis. The need to transform secondary alcohols into ketones is frequently encountered, and a variety of methods is available for this purpose.[1] Although reactive intermediates of differing structure intervene in these reactions, all share in the capability of removing the carbinol hydrogen and effecting the necessary hybridization change at carbon. For systems that contain a neighboring quaternary center, it is generally assumed that this adjoining site is not affected in either a structural or a stereochemical sense. This conclusion has been borne out in many examples and, to our knowledge, no test case has been reported where stereochemical integrity has been compromised at a fully substituted carbon positioned immediately adjacent to the site of oxidative change. In this communication, we describe the first example of a molecule that exhibits such behavior.

As part of a program designed to access and develop belted spirocyclic tetrahydrofurans of generic formula **1** and **2** as a new class of preorganized ionophoric polyethers,[2,3] the epimeric trans-configured pentaspiro cyclohexanols **3** and **4** have become available. The obvious steric congestion surrounding the hydroxyl-substituted carbon is very substantial in both substrates. The resulting limited accessibility of oxidizing agents to the carbinol center is reflected in the unreactivity



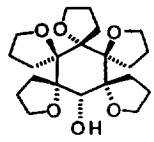
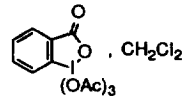
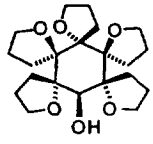
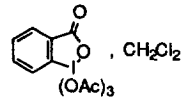
**1**



**2**

of **3** toward Oppenauer oxidation.[4] Under other circumstances involving the exposure of *syn*-**3** to the Dess-Martin,[5] Swern,[6] pyridinium dichromate,[7] and tetrapropylammonium perruthenate reagents,[8] conversion to ketone **5** occurred smoothly and without any detectable erosion of the extensive stereochemical setting (Table I).

**Table I.** Oxidation Results

| alcohol | oxidant | Product distribution, %[a] **5** | **6** |
|---|---|---|---|
|  **3** |  | 100 | — |
| | DMSO, $(COCl)_2$, $Et_3N$, $CH_2Cl_2$ | 77 | — |
| | PDC, 3 Å MS, $CH_2Cl_2$ | 94 | — |
| | TPAP, 4 Å MS, $CH_2Cl_2$–$CH_3CN$ (1:1) | 92 | — |
|  **4** |  | 56 | 39 |
| | DMSO, $(COCl)_2$, $Et_3N$, $CH_2Cl_2$ | 44 | 44 |
| | PDC, 3 Å MS, $CH_2Cl_2$ | 52 | 26 |
| | TPAP, 4 Å MS, $CH_2Cl_2$–$CH_3CN$ (1:1) | 61 | 30 |

[a] The percentages given are based on isolated yields of the ketones.

On the other hand, submission of anti alcohol **4** to the identical four oxidants under essentially duplicative conditions gave rise to both **5** and **6**. Although the distribution of stereoisomeric ketones varies somewhat from reagent to reagent, the proportions of **6** are always substantial and, in one instance, equivalent to the level of **5** produced simultaneously. The distinction between **5** and **6** is readily made since the $C_s$ symmetry of **5** reduces the number of its $^{13}C$ resonances significantly.[9]

Direct competition experiments performed on **3** and **4** show **3** to be consumed 50% faster than **4** versus TPAP. Under these circumstances, the resultant quantities of **5** and **6** conform to the product distribution anticipated from Table I. Further, alcohol **4** and ketone **5** are completely unaltered when stored overnight at 25 °C in $CHCl_3$ solution containing small amounts of *p*-toluenesulfonic acid. For **5**, this stability persists at the reflux temperature (16 h).

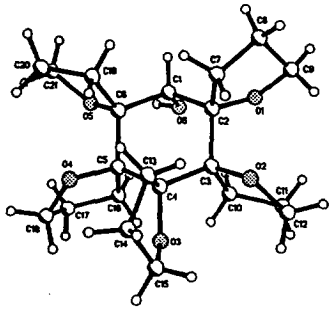
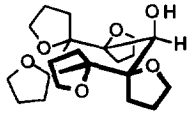


Figure 1. Computer-generated perspective drawing of the final X-ray model of **3**.

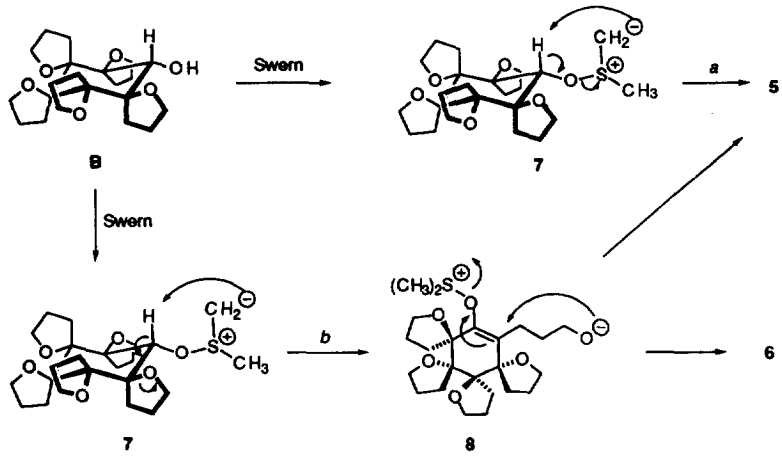


**A**

An X-ray crystallographic analysis performed on **3** (Figure 1)[10] indicates the conformation adopted in the solid to be that shown in **A**. It is noteworthy that all five of the tetrahydrofuranyl oxygens are projected equatorially, an option that is frequently exercised in functionalized poly(spirotetrahydrofuranyl)cyclohexyl systems.[11] On this basis, it would appear entirely plausible to formulate **4** as in **B**, where the only alteration is the repositioning of an axial hydroxyl into equatorial space (Scheme 1). Consequently, the oxidation of **4**, illustrated for the Swern reagent, requires abstraction of an axial hydrogen atom. Evidently, this structural feature allows for the operation of two competitive reaction pathways. The *a* option is the conventional oxidative route that leads directly from **7** without stereochemical scrambling to ketone **5**. The second option consists of C-H bond cleavage accompanied by β-elimination of an oxygen atom with scission of either neighboring tetrahydrofuranyl ring (path *b*). Once **8** has been formed, the inference can be made that ring closure to both **5** and **6** becomes possible, although the formation of **5** need not be operative to rationalize the experimental observations.

The product distributions recorded in Table I are the end result of several competitive reactions. Regardless of how close the suggestion offered in Scheme 1 comes to the actual operative mechanism, the contrasting behavior of **3** and **4**, and the innate propensity of **4** to desym-

**Scheme 1**




metrize during oxidation are noteworthy. Further explicit investigation of this matter in greater depth should be pursued.[12]

## References and Notes

(1) *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A., Ed. John Wiley and Sons, Chichester, 1995.

(2) (a) Negri, J. T.; Rogers, R. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 5073. (b) Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3947.

(3) (a) Paquette, L. A.; Branan, B. M.; Friedrich, D.; Edmondson, S. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1994**, *116*, 506. (b) Branan, B. M.; Paquette, L. A. *J. Am. Chem. Soc.* **1994**, *116*, 7658. (c) Paquette, L. A.; Branan, B. M.; Rogers, R. D. *J. Org. Chem.* **1995**, *60*, 1852.

(4) Paquette, L. A.; Meehan, G. V.; Marshall, S. J. *J. Am. Chem. Soc.* **1969**, *91*, 6779.

(5) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(6) Review: Tidwell, T. T. *Org. React.* **1990**, *39*, 297.

(7) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(8) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13.

(9) For **5**: mp 115 °C; $^1$H NMR (300 MHz, $C_6D_6$) δ 4.06-3.99 (m, 2 H), 3.79-3.69 (m, 4 H), 3.65-3.53 (m, 4 H), 2.54-2.37 (m, 6 H), 2.16-1.94 (m, 6 H), 1.71-1.46 (m, 8 H); $^{13}$C NMR (75 MHz, $C_6D_6$) ppm 209.3, 93.3, 90.5, 90.0, 69.1, 68.1, 67.5, 32.9, 30.8, 30.6, 29.2, 28.9, 26.2; HRMS *m/z* ($M^+$) calcd 378.2042, obsd 378.2027.

For **6**: mp 203 °C; $^1$H NMR (300 MHz, $C_6D_6$) δ 3.99 (ddd, *J* = 7.8, 7.8, 4.7 Hz, 1H), 3.82 (ddd, *J* = 7.8, 7.8, 2.3 Hz, 1 H), 3.78-3.51 (m, 7 H), 3.50-3.45 (m, 1 H), 3.25 (ddd, *J* = 12.5, 8.1, 6.7 Hz, 1 H), 2.78-2.71 (m, 1 H), 2.70-2.60 (m, 2 H), 2.55-2.39 (m, 3 H), 2.31-2.15 (m, 1 H), 2.11-1.91 (m, 3 H), 1.77-1.45 (m, 8 H), 1.12 (ddd, *J* = 12.6, 8.6, 2.8 Hz, 1 H); $^{13}$C NMR (75 MHz, $C_6D_6$) ppm 207.4, 94.9, 93.2, 92.2, 90.5, 88.8, 69.6, 69.3, 68.9, 68.1, 67.3, 32.5, 31.1, 30.7, 30.5, 29.3, 28.9, 28.2, 27.1, 26.4, 25.4; HRMS *m/z* ($M^+$) calcd 378.2042, obsd 378.2030.

(10) We thank Prof. Robin Rogers (Northern Illinois University) for the crystallographic determination.

(11) Paquette, L. A.; Stepanian, M.; Branan, B. M.; Bauer, C. B.; Rogers, R. D. submitted for publication.

(12) We thank the National Science Foundation and Hoechst Marion Roussel for their support of this research.

(*Received in USA* 30 *November* 1995; *revised* 2 *January* 1996; *accepted* 11 *January* 1996)