ORGANIC LETTERS

2009
Vol. 11, No. 4
959−961

A Study of the Epoxidation of Cycloolefins by the *t*-BuOH Copper−Permanganate System

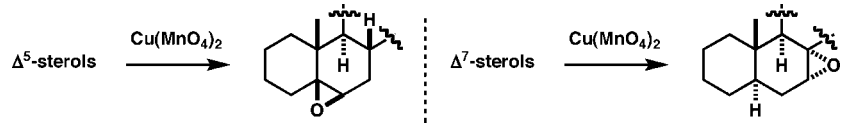
Younis Baqi, Simon Giroux, and E. J. Corey*

Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

corey@chemistry.harvard.edu

Received December 19, 2008

ABSTRACT



Evidence is presented that $Cu(MnO_4)_2$ effectively epoxidizes trisubstituted steroid olefins by a nonconcerted pathway.

It was reported several years ago that the reaction of various steroidal olefins with a mixture of *tert*-butyl alcohol−CH_2Cl_2, powdered $KMnO_4$, and $CuSO_4$ (wet) (Parish reagent) affords good yields of epoxides invariably with the β-orientation of the oxygen, even with substrates that yield predominately α-epoxides with peroxy acids.[1] We became curious about this process for several reasons, including the possible use in projected studies of steroids related to withaferin A (**1**).[2] Compound **1** is of special interest because of its *Ayurvedic* history, antitumor activity, and potent inhibition of angiogenesis (IC_{50} = 12 nM) against human umbilical vein endothelial cell sprouting.[3,4] Specifically, **1** binds covalently to the intermediate filament protein vimentin causing aggregation in vivo so as to block angiogenesis.[4] The action could be synergistic with inhibition of the kinase vascular endothelial growth factor (VEGF).

We found that the oxidation of the Δ^5-olefin cholesteryl benzoate with wet $CuSO_4/KMnO_4$ and 10 equiv of *t*-BuOH in CH_2Cl_2 at reflux produced mainly the 5,6-β-epoxide **2** (ratio β/α = 9:1), as reported.[1] In comparison, we found that epoxidation with *m*-chloroperbenzoic acid gave a modest predominance of 5,6-α-epoxycholesteryl benzoate (ratio β/α = 4:6). During the epoxidations with the Parish oxidizing mixture there is considerable evolution of oxygen, and so an excess of permanganate (ca. 8−9 equiv) must be employed for complete conversion. Without copper(II), little oxygen is evolved and little or no epoxide is formed. There are at least two obvious explanations for the role of copper(II): (1) *t*-BuOO$^{\bullet}$ radical, which has been reported to be formed by metal−ion oxidation of *t*-BuOOH and to effect epoxidation of olefins, is somehow generated, or (2) the effective epoxidation reagent is $Cu(MnO_4)_2$. This matter is addressed below.

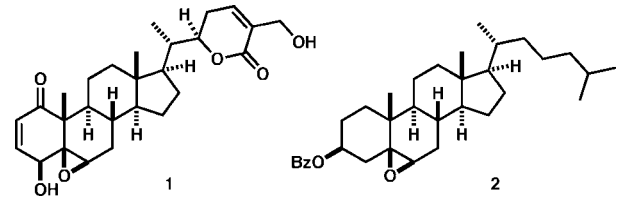


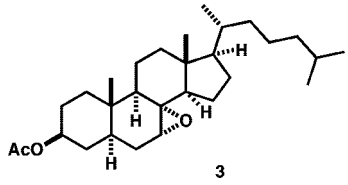
Figure 1. Structures of withaferin A (**1**) and **2**.

It has been reported that the reaction of Δ^7-unstaturated steroids with the Parish reagent leads selectively to the 7,8-

(1) Parish, E. J.; Li, H.; Li, S. *Synth. Commun.* **1995**, *25*, 927–940.
(2) Kupchan, S. M.; Doskotch, R. W.; Bollinger, P.; McPhail, A. T.; Sim, G. A.; Renauld, J. A. S. *J. Am. Chem. Soc.* **1965**, *87*, 5805–5806.
(3) Mohan, R.; Hammers, H. J.; Bargagna-Mohan, P.; Zhan, X. H.; Herbstritt, C. J.; Ruiz, A.; Zhang, L.; Hanson, A. D.; Conner, B. P.; Rougas, J.; Pribluda, V. S. *Angiogenesis* **2004**, *7*, 115–122.
(4) Bargagna-Mohan, P.; Hamza, A.; Kim, Y.; Ho, Y. K.; Mor-Vaknin, N.; Wendschlag, N.; Liu, J.; Evans, R. M.; Markovitz, D. M.; Zhan, C.-G.; Kim, K. B.; Mohan, R. *Chem. Biol.* **2007**, *14*, 623–634.

10.1021/ol802923n CCC: $40.75
Published on Web 01/30/2009

β-epoxide.[1] We have reevaluated this claim using 3β-acetoxy-Δ^7-cholestene and the Parish reagent under the recommended conditions[1] since it seemed difficult to rationalize the β-selectivity with this substrate. We found, as we had suspected, that the product was the 7,8-α-epoxide (**3**, 7:1 selectivity) and was identical to that obtained by epoxidation of the Δ^7-linkage by *m*-chloroperbenzoic acid. The 7,8-α and 7,8-β-epoxides are readily identified by ^{1}H NMR analysis.[6]



3

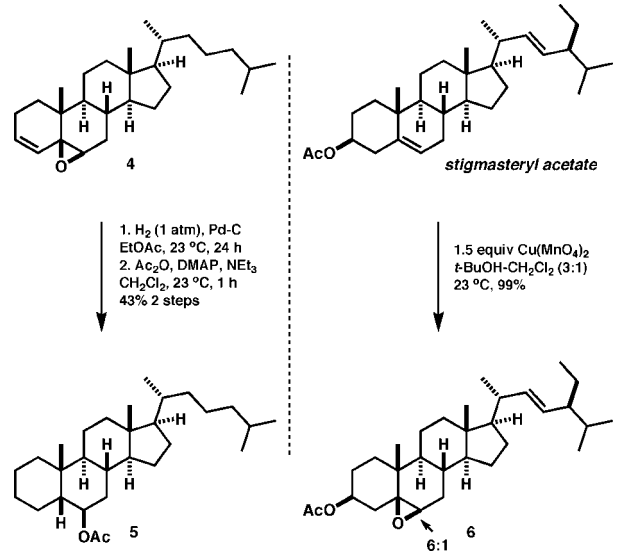
Figure 2. 7,8-α-Epoxide **3**.

To follow up on these results, we prepared $Cu(MnO_4)_2$ by a new and convenient procedure from aqueous $Cu(BF_4)_2$ and $KMnO_4$ in concentrated solution. Filtration of the precipitate of KBF_4 and removal of water under reduced pressure gave a hydrate of $Cu(MnO_4)_2$ as a dark solid, soluble not only in H_2O, but also in mixtures of CH_2Cl_2, *t*-BuOH, and HOAc. Although stable in aqueous or acetic acid solution, the reagent decomposes fairly rapidly in CH_3CN or *t*-BuOH−CH_2Cl_2 solution. We found that a solution in CH_2Cl_2−HOAc (98:2) decomposes at 23 °C in about 20 min to yield approximately 1.2 equiv of O_2 and a copious precipitate of MnO_2. Some $Cu(MnO_4)_2$ is entrained by the precipitating MnO_2 and thus removed from solution. The instability of copper permanganate and its tendency to coprecipitate with MnO_2 explains the need to use a substantial excess of permanganate in the oxidations described by Parish et al.[1] It is also possible that the manganese dioxide just formed catalyzes the decomposition of $Cu(MnO_4)_2$.

The reaction of cholesteryl benzoate with 1.5 equiv of $Cu(MnO_4)_2$ in 3:1 *t*-BuOH−CH_2Cl_2 solution at 23 °C for 1 h gave clean epoxidation of the double bond (>99% yield) and mainly the β-epoxide (β/α = 6:1). The reaction proceeded much faster upon addition of HOAc, but the β/α ratio was markedly diminished. In 2:1 HOAc−CH_2Cl_2 at −20 °C, the reaction went to completion in 15 min and gave a 1.5:1 mixture of β/α epoxides in >98% yield. It is possible that the acceleration of the epoxidation by HOAc is due to its H-bonding interaction with MnO_4^-.

The formation of the 5,6-β-epoxide from cholesteryl benzoate (or acetate) using copper permanganate clearly supports the possibility that this is the actual oxidant in the Parish reagent. Further evidence is provided by additional examples. First, we found that the epoxidation of $\Delta^{3,5}$ cholestadiene using the Parish reagent produced the corresponding 5,6-β-epoxide (**4**) with a β/α selectivity of 9:1, consistent with the β-preference for epoxidation of the Δ^5-linkage of cholesteryl benzoate. The structure of the epoxide **4** was confirmed by hydrogenation to the 6-β-alcohol which was identified by acetylation and comparison with the previously reported acetate **5**.[7] Using either $Cu(MnO_4)_2$ or the Parish mixture, the epoxidation of stigmasteryl acetate was also position selective for the Δ^5-olefinic linkage and afforded mainly the corresponding 5,6-β-epoxide (**6**) (6:1 5,6-β/5,6-α, 99% yield) (Scheme 1). The oxidation of 3-β-acetoxy-Δ^7-cholestene with 1.5 equiv of $Cu(MnO_4)_2$ in 3:1 *t*-BuOH/CH_2Cl_2 at 23 °C for 1 h gave predominantly (4.4:1) the 7,8-α-epoxide **3**, as was the case when the Parish reagent was employed.

Scheme 1



It is probably not a coincidence in the several examples outlined above that the Parish reagent and $Cu(MnO_4)_2$ led to the same predominating diastereomeric epoxide. In addition, there did not seem to be significant amounts of 1,2-diol, despite the fact that vicinal dioxygenation is the customary pathway for olefin oxygenation by sodium or potassium permanganate in water-containing reaction mixtures.

The epoxidation reactions of $Cu(MnO_4)_2$ appear to differ mechanistically from the much-studied epoxidation of olefins with peroxycarboxylic acids, which clearly are concerted 1,2-cycloaddition processes. One argument in support of this surmise is the opposite stereochemical course observed with

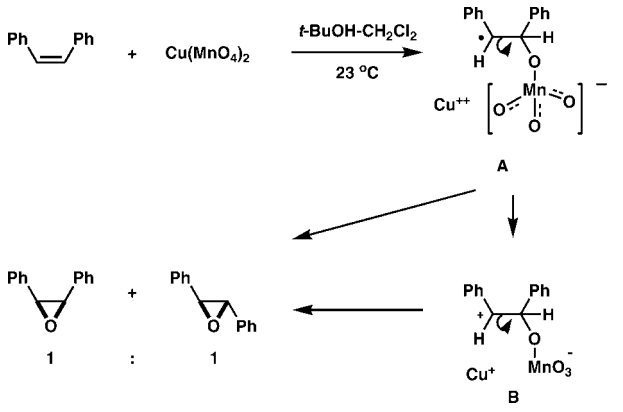
(5) (a) Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3233–3233. (b) Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727–2729. (c) Bartlett, P. D.; Günther, P. *J. Am. Chem. Soc.* **1966**, *88*, 3288–3294. (d) Barlett, P. D.; Guaraldi, G. *J. Am. Chem. Soc.* **1967**, *89*, 4799–4801. For the oxidative formation of peroxy radicals from hydroperoxides, see: (e) Haynes, R. K.; Vonwiller, S. C. *J. Chem. Soc., Chem. Commun.* **1990**, 1102–1104. (f) Kharasch, M. S.; Pauson, P.; Nudenberg, W. *J. Org. Chem.* **1953**, *18*, 322–327. (g) Araneo, S.; Fontana, F.; Minisci, F.; Recupero, F.; Serri, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1399–1400.

(6) Eguchi, S.; Yamaguchi, S.; Furuya, M.; Morisaki, M. *Chem. Pharm. Bull.* **1988**, *36*, 2813–2818.

(7) Jones, D. N.; Shoppee, C. W.; Summers, G. H. R. *J. Chem. Soc.* **1955**, 2876–2887.

the Δ^5-steroid substrates: strong 5,6-β preference for $Cu(MnO_4)_2$ vs 5,6-α preference for peroxy acids. An important difference was shown with the substrate *cis*-stilbene. Although this olefin affords the *cis*-epoxide with peroxyacids, a 1:1 mixture of *cis*- and *trans*-epoxides was observed with $Cu(MnO_4)_2$. This result argues that $Cu(MnO_4)_2$ behaves more like an oxy radical reagent than a peroxy acid and that it adds to olefins to form a carbon radical that cyclizes to epoxide in a distinct, later step. Such a pathway is depicted in Scheme 2 for the reaction of *cis*-stilbene with

Scheme 2. Oxidation of *cis*-Stilbene by $Cu(MnO_4)_2$



$Cu(MnO_4)_2$. Another possibility is that $Cu(MnO_4)_2$ attacks the olefin electrophilically so that a cationic intermediate such as **B** (Scheme 2) is formed directly.

As depicted, it is also possible that Cu(II) plays a role in the epoxidation by converting the intermediate benzylic radical **A** to a cation **B**, which might facilitate ring closure to form the epoxide. Obviously, since rapid rotation is possible around the central single bond, the observed mixture of *cis*- and *trans*-epoxides would be expected for the oxidation mechanism shown in Scheme 2. Another reason why the intermediate **A** might be favored with $Cu(MnO_4)_2$ is the possibility that the negative charges spread out over the three oxygens of the $OMnO_3^-$ moiety of **A** might be stabilized by interaction with associated Cu(II).

The two-step pathway also provides a simple explanation for the stereochemical preference in $Cu(MnO_4)_2$ epoxidation. For Δ^5-steroid epoxidation, a radical-like $Cu(MnO_4)_2$ would be expected to attach to C(6) by an axial bond to form the intermediate **7** (radical or cationic form) which can be

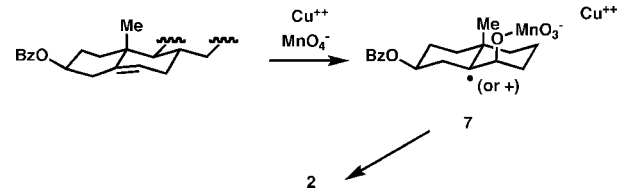


Figure 3. Intermediate **7** stabilized by hyperconjugation.

stabilized by hyperconjugation of MnO_4^- (stereoelectronically preferred axial attack).[8] The same argument can account for 7,8-α-epoxidation of Δ^7-sterol derivatives. The epoxidation by $Cu(MnO_4)_2$ that is described herein is either very slow or negligible with 1,2-disubstituted or monosubstituted olefins, a result that is consistent with the mechanistic pathway outlined in Scheme 2 and that also indicates a modest level of reactivity for this form of permanganate. In contrast, quaternary ammonium permanganate reagents rapidly react with most olefins by a vicinal dioxygenation pathway which can involve concomitant C−C cleavage.[9]

In conclusion, the data in this paper support the view that: (1) epoxidations with the Parish reagent probably involve $Cu(MnO)_4$ as the reactive species; (2) the epoxidation of Δ^7-unsaturated sterol systems leads predominately to 7-α-epoxidation rather than 7-β-epoxidation as claimed in the literature;[1] (3) the pathway of epoxidation by $Cu(MnO_4)_2$ occurs in two or possibly three steps and is nonconcerted; (4) the stereochemical preferences for the oxidation of unsaturated steroids can be explained by the operation of stereoelectronic effects (axial attack by O) and a nonconcerted pathway.

Acknowledgment. Y.B. is indebted to Deutscher Akademischer Austausch Dienst (DAAD) and Deutsche Forschungsgemeinschaft (DFG, GRK804) for fellowship support; S.G. is grateful to NSERC (Canada) for a postdoctoral fellowship.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802923N

(8) (a) Corey, E. J. *Experientia* **1953**, *9*, 329–331. (b) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269–6278.
(9) Sala, T.; Sargent, M. V. *Chem. Commun.* **1978**, 253–254.