Pergamon

Tetrahedron Letters 39 (1998) 2887–2890

TETRAHEDRON LETTERS

Geometrically Directed Selective Steroid Hydroxylation with High Turnover by a Fluorinated Artificial Cytochrome P-450

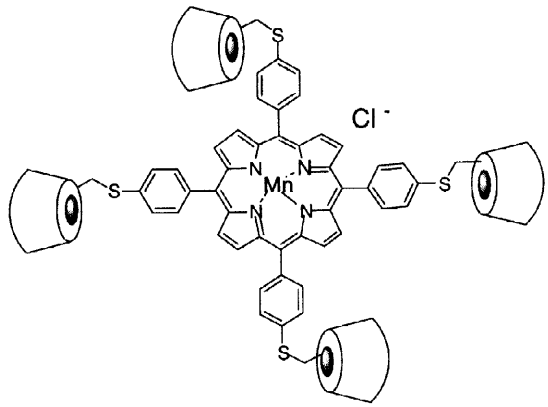
Ronald Breslow*, Bartolo Gabriele#, and Jerry Yang

Department of Chemistry, Columbia University, New York, New York 10027

Received 29 January 1998; revised 13 February 1998; accepted 16 February 1998

Abstract: A metalloporphyrin has been synthesized carrying a beta-cyclodextrin group on tetrafluorophenyl rings at the four meso positions of the porphyrin. It performs the selective hydroxylation of an androstanediol derivative with complete positional selectivity and 187 turnovers.

The ability of enzymes such as the cytochrome P-450 group to perform chemical reactions independent of the intrinsic reactivity of the substrate is a challenge for biomimetic chemistry. For example, in the biosynthesis of cholesterol such enzymes oxidize methyl groups on saturated carbons in the presence of carbon-carbon double bonds that are not attacked. This is the result of the geometry of the enzyme-substrate complex, that holds the substrate next to an iron atom in a porphyrin ring of the enzyme. We have recently described[1-3] the synthesis of a tetraphenylporphyrin derivative whose Mn(III) complex **1** can bind and hydroxylate substrates with two ends that bind diagonally into cyclodextrins in water so as to place a particular carbon atom directly above the Mn(III) atom (Fig. 1). With iodosobenzene as oxidant our catalyst **1** was able to achieve the hydroxylation of a dihydrostilbene **2** to product **3**[2] with 650 turnovers,[3] and also to hydroxylate the derivative **5** of androstanediol **4** with complete selectivity for the formation of the 6α hydroxy derivative **6**, hydrolyzed to androstantriol **7** (Scheme 1). This



1 = beta-cyclodextrin

0040-4039/98/$19.00
PII: S0040-4039(98)00425-0

selective hydroxylation is directed by the geometry of the catalyst-substrate complex, as in the enzyme. However, the hydroxylation of **5** proceeded with only 3-5 turnovers before the catalyst **1** was oxidatively destroyed.[4]

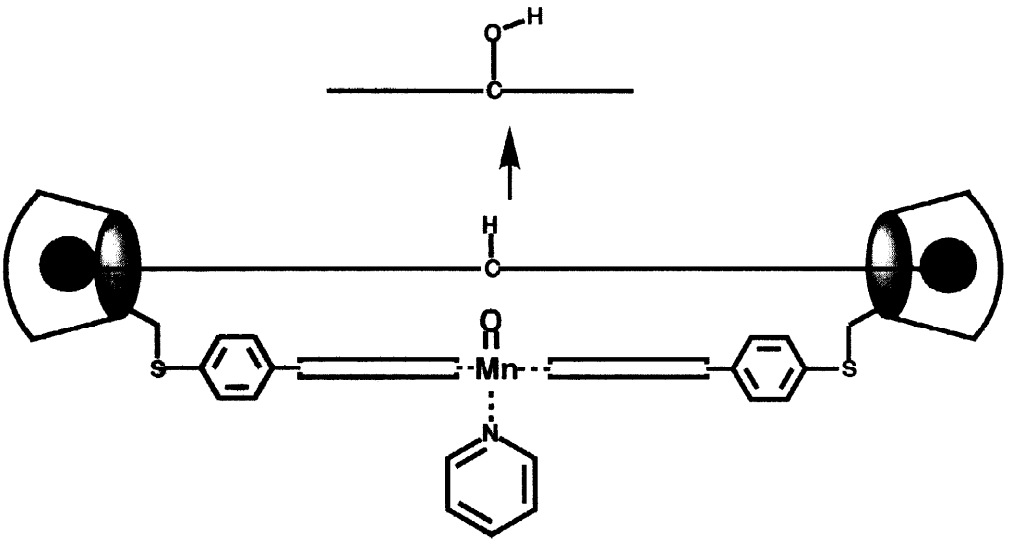
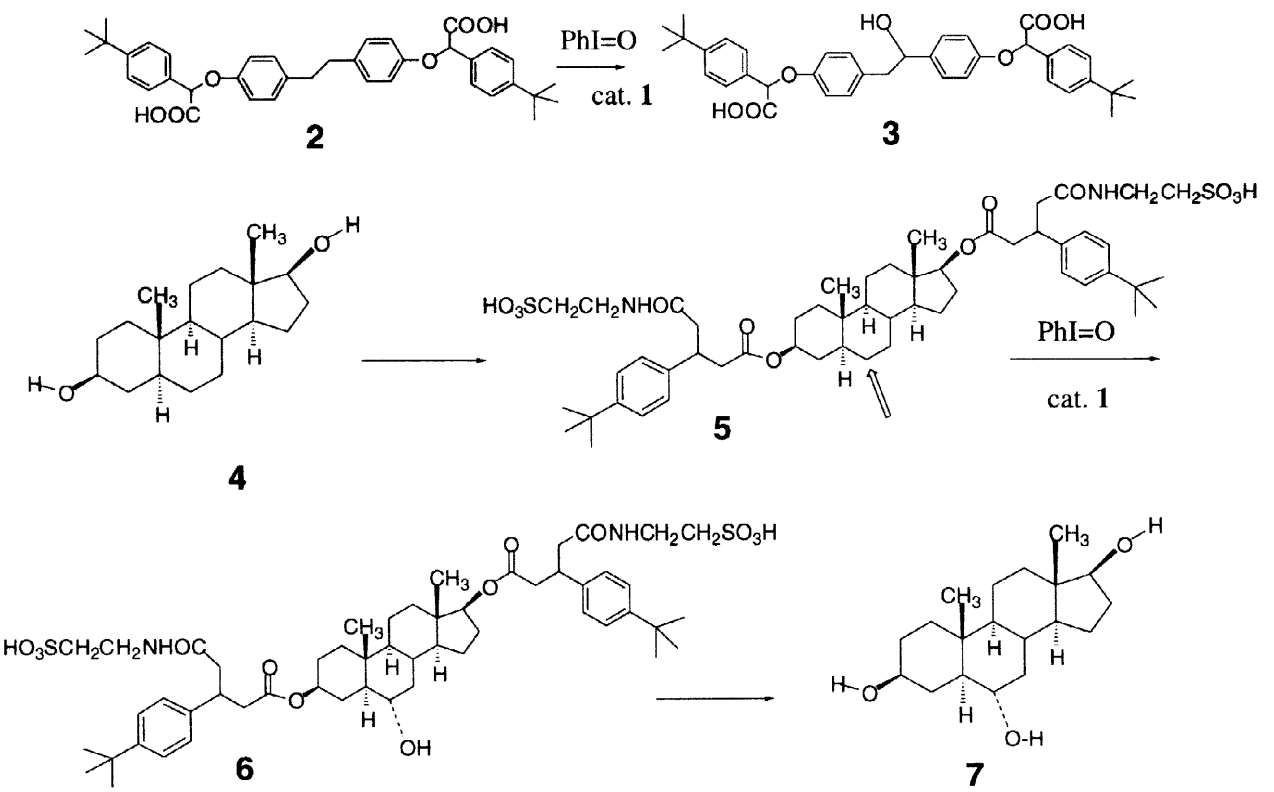
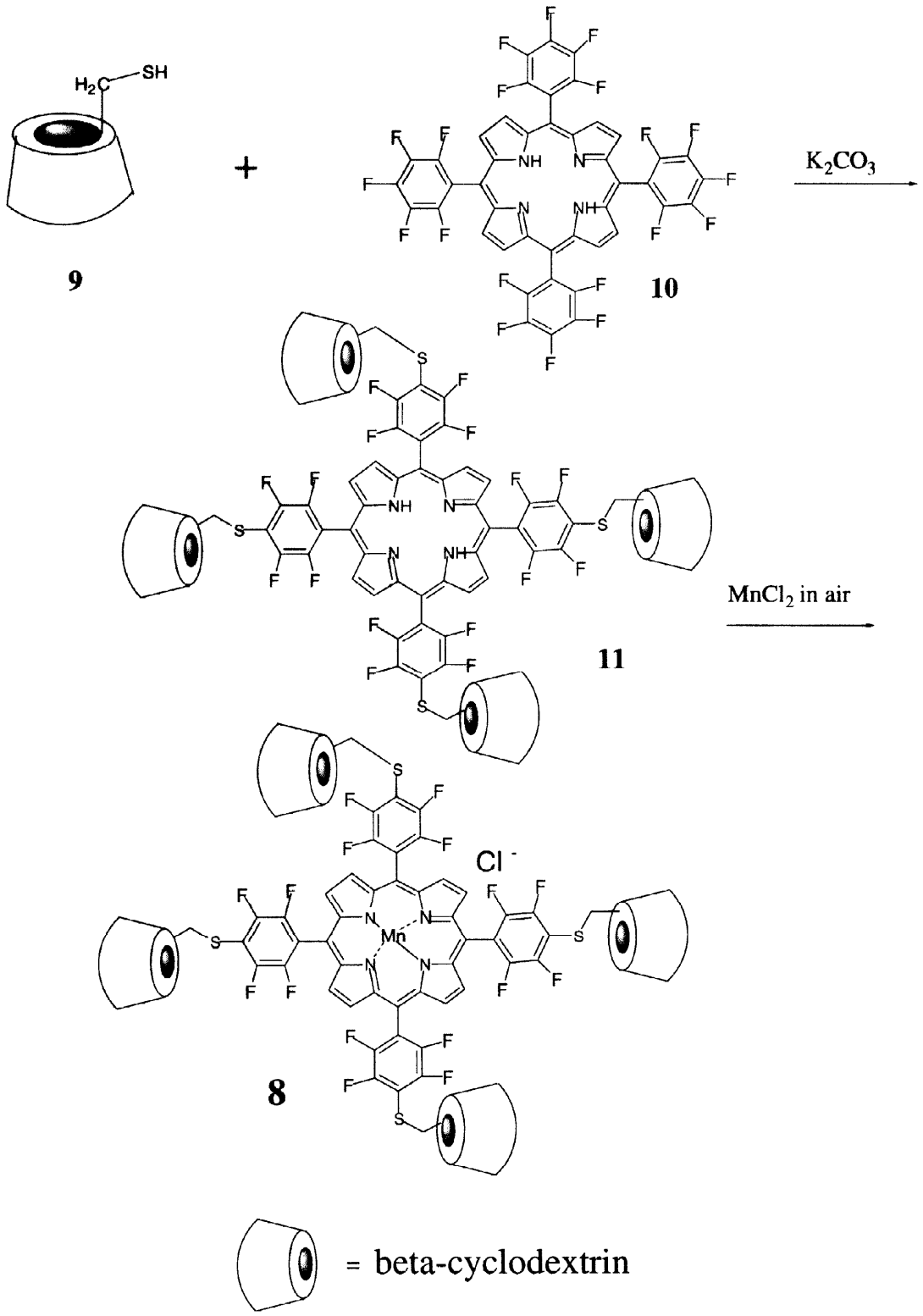


Figure 1



Scheme 1


H2C
SH
9
+
NH
N
10
K2CO3
S
F
11
MnCl2 in air
Cl -
Mn
8
= beta-cyclodextrin

Scheme 2

It seemed likely that the oxidative destruction of the catalyst involved the porphyrin system of **1**, not the cyclodextrins, and if so prior work indicated how to solve the problem. Tetraphenylporphyrin based catalysts are much more stable with pentafluorophenyl rings, which decrease the oxidizability of the porphyrin meso positions that carry the phenyl groups.[5] Thus we have now synthesized catalyst **8**, with tetrafluorophenyl rings. The synthesis was particularly easy (Scheme 2), since we found that reaction of the readily prepared 6-deoxy-6-mercapto-betacyclodextrin **9**[6] and the pentafluorophenyl porphyrin derivative **10**[7] with K_2CO_3 in dry DMF at RT in the dark afforded dark red porphyrin **11** in 95% yield. The compound showed the expected ^1H and ^{19}F NMR spectra, and in particular the ^{19}F NMR spectrum indicated that the four p-fluorines of **10** had been replaced. The UV-vis spectrum of **11** was typical of a porphyrin, with λ_{max} 412, 510, 582 nm. With $MnCl_2$ compound **11** was converted in 93% yield to catalyst **8**, with LD-MS 5582 (M^+) and λ_{max} 369, 458, 554 nm.

Substrate **5** was oxidized at RT in neutral water with 10 equiv. of PhIO and 10 equiv. of pyridine using varying concentrations of **5** and of catalyst **8**. The products were assayed by hydrolysis to starting androstanediol **4** and to androstanetriol **7**, again the only product, followed by benzoylation and quantitative hplc analysis. Under the conditions used, the benzoylation is known to be quantitative and reliable for such an hplc assay.[8,9] The assays were run in triplicate, and the errors were ca. 0.5%. With 1.46 mM **5** and 0.0146 mM **8** (1 mol%), followed by hydrolysis, the 6α hydroxy derivative **7** was formed in 95% yield, indicating 95 turnovers. With the use of 1.02 mM **5** and 0.00102 mM **8** (0.1 mol%) the product **7** was found in 18.7% yield, along with recovered starting androstanediol **4**. Thus there were 187 turnovers. The lower number of turnovers with high conversion presumably reflects some product inhibition.[2]

These results indicate that with the stabilized fluorocatalyst **8** we can achieve both high conversion and high turnover in the selective hydroxylation of **5** to **6**. As we vary the geometry of such complexes, we expect to achieve other selective hydroxylations of interest, mimicking the selectivities achieved by the enzymes of the cytochrome P-450 group.

Acknowledgment: This work has been supported by the NIH, and by a NATO-CNR postdoctoral fellowship to Bartolo Gabriele#.

On leave from the Department of Chemistry, University of Calabria, Cosenza, Italy.

REFERENCES

1. Breslow, R.; Zhang, X.; Xu, R.; Maletic, M.; Merger, R. *J. Am. Chem. Soc.* **1996**, *118*, 11678.
2. Breslow, R.; Zhang, X.; Huang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4535;
3. Breslow, R.; Huang, Y.; Zhang, X.; Yang, J. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 11156.
4. The hydroxylation of **2** by catalyst **1** was complete is 45 min. at room temp. The hydroxylation of **5** by catalyst **8** was allowed to proceed for 4h; addition of an additional 10 equiv of oxidant and a further 2h standing did not increase the substrate conversion, indicating that catalyst lifetime is the limiting factor.
5. Ellis, P. E.; Lyons, J. E. *Coord. Chem. Rev.* **1990**, *105*, 181-193.
6. Fujita, K.; Ueda, T.; Imoto, T.; Tabushi, I.; Toh, N.; Koga, T. *Bioorg. Chem.* **1982**, *11*, 72.
7. Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C.; Kearney, P. C. Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827.
8. Fitzpatrick, F.; Siggia, S. *Anal. Chem.* **1973**, *45*, 2310-2314.
9. Fillion, L.; Lee, J.; Gosselin, C. *J. Chromatography* **1991**, *547*, 105-112.