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Catalytic hydroxylation of steroids by cytochrome P-450 mimics. Hydroxylation at C-9 with novel catalysts and steroid substrates

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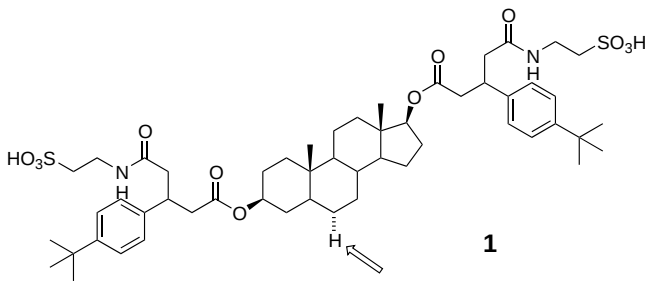
Abstract—Double binding of a steroid substrate to our previously described mimic of the cytochrome P-450 enzymes hydroxylates carbon 9 of the steroid, but with a second significant product. The geometry has been adjusted with new catalysts that show high selectivity and excellent turnover for the C-9 hydroxylation.

We have described the hydroxylation of steroids by a mimic of cytochrome P-450 in which we attach β-cyclodextrin to a manganese–porphyrin core.[1–6] Our original catalyst had phenyl linkers holding the cyclodextrin to the porphyrin, and gave selective hydroxylation of a steroid substrate **1** at carbon 6, but with only 4 turnovers.[1–3] A later improvement **2** has fluorinated phenyls, and affords the same C-6 α-hydroxysteroid product with 187 turnovers.[4] An even better catalyst is **3**, whose nitrophenyl group decreases the destructive oxidation of the porphyrin ring and raises the turnovers to 3000.[5]



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With substrate **4** we saw that we could selectively hydroxylate C-9 of the steroid in the triply bound complex.[6] This was an important achievement since this affords entry into the 9(11) unsaturated steroid from which 9-fluorocorticosteroids can be produced.[7] Such hydroxylation at C-9 has previously been possible only with biological fermentation. The new hydroxylation at C-9 in substrate **4**, which we had not seen in substrate **1**, is consistent with computer models—with substrate **1** the steroid can rotate in the substrate/catalyst complex so as to present its C-6 edge to the Mn=O hydroxylating species, but with the triple binding of substrate **4** the steroid now presents its alpha face to the catalyst, specifically the hydrogen at C-9.[6] However, it seemed likely that such triple binding would not be needed for hydroxylation at C-9 if we simply bound the substrate at positions 3 and 6, omitting the binding at C-17. This proves to be true.

In our first experiments, we prepared substrate **5** from the corresponding diol (the 6-OH group was introduced by hydroboration of the 5,6 double bond) using our standard procedure.[1–3] We then submitted **5** to hydroxylation in water with catalyst **2** and iodosobenzene oxidant. We indeed saw the formation of the 9-hydroxylated species **6**, but an almost equal amount of a second product was formed, apparently the C-15 hydroxylated alcohol **7** (Scheme 1). Thus it was clear that we had to move the steroid in the complex, specifically so that the Mn=O group would be closer to ring A of the steroid. Molecular models indicated that this would occur if we had an analog of catalyst **2** in which the cyclodextrins were attached on the *meta* positions of the phenyls, not the *para* positions.

We synthesized catalyst **8** by reacting the porphyrin carrying SH groups on the *meta* position of unfluorinated phenyls with 6-deoxy-6-iodo-β-cyclodextrin, according to the method previously developed for our original catalyst.[1] Indeed we saw that now the product **6** was essentially free of other products (Scheme 2). However, there were only 2.5 turnovers before the

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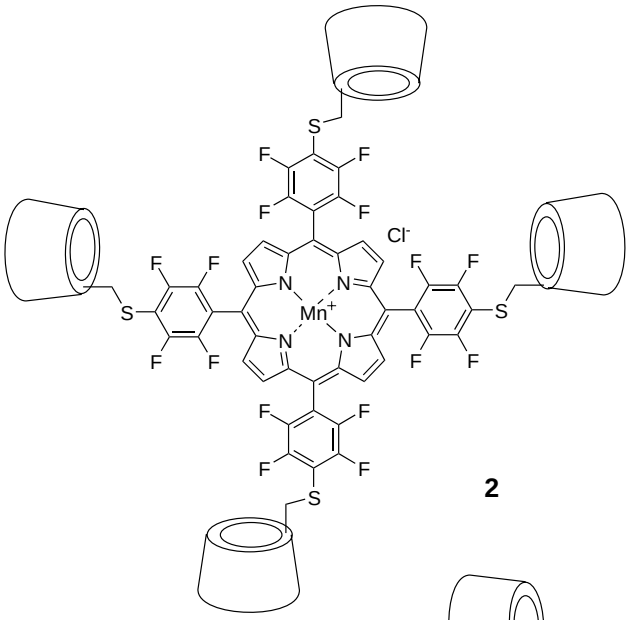
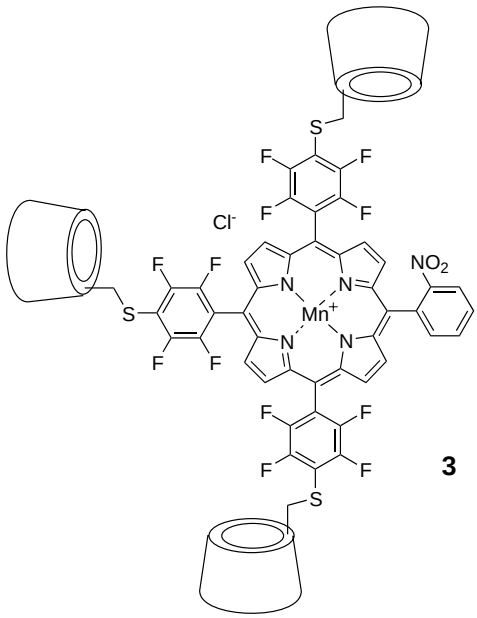
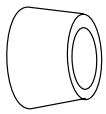
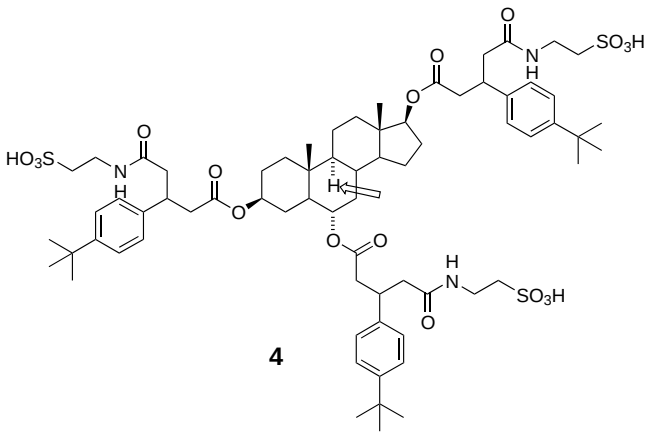






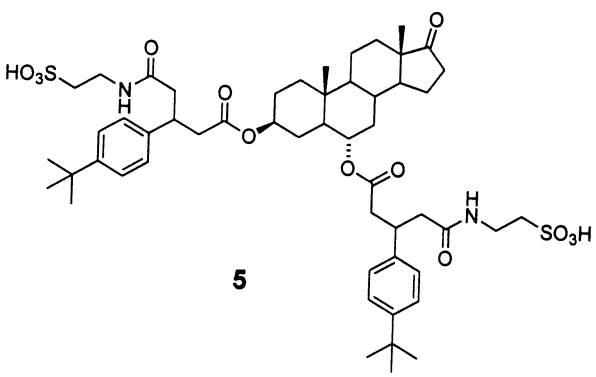
= beta-cyclodextrin

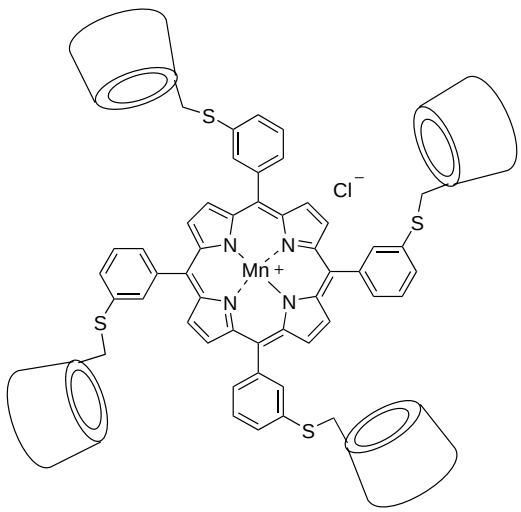


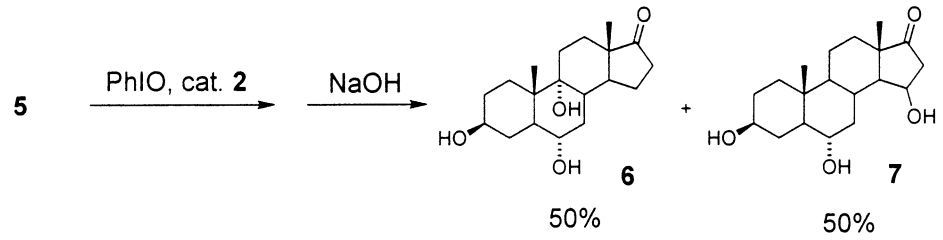
With iodosobenzene **11** performed the hydroxylation of substrate **5** to produce triol **6** after hydrolysis, with 90 turnovers and again with essentially complete selectivity for hydroxylation at C-9.

Molecular models indicate that the binding of **5** into **8** and **11** uses only two neighboring cyclodextrin rings, so the other two may be changed to make yet more robust catalysts. However, even with only 90 turnovers the current system makes the C-9 hydroxylation an appealing process. It will be interesting to see whether such selective hydroxylations, and the geometric control that they permit, will replace fermentation processes in the manufacture of useful medicinal compounds.[8]

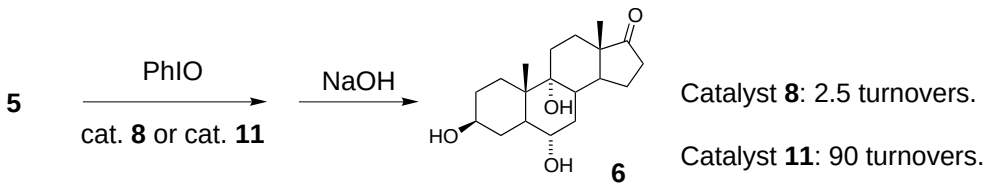
catalyst was destroyed by oxidation. We needed a more robust catalyst with the same geometric characteristics as **8**. This was achieved by the synthesis of porphyrin **9** from pyrrole and tetrafluoropyridine-4-carboxaldehyde. When this reacted with thiol **10**, then $MnCl_2$ and air, the product **11** was our needed catalyst (Scheme 3).



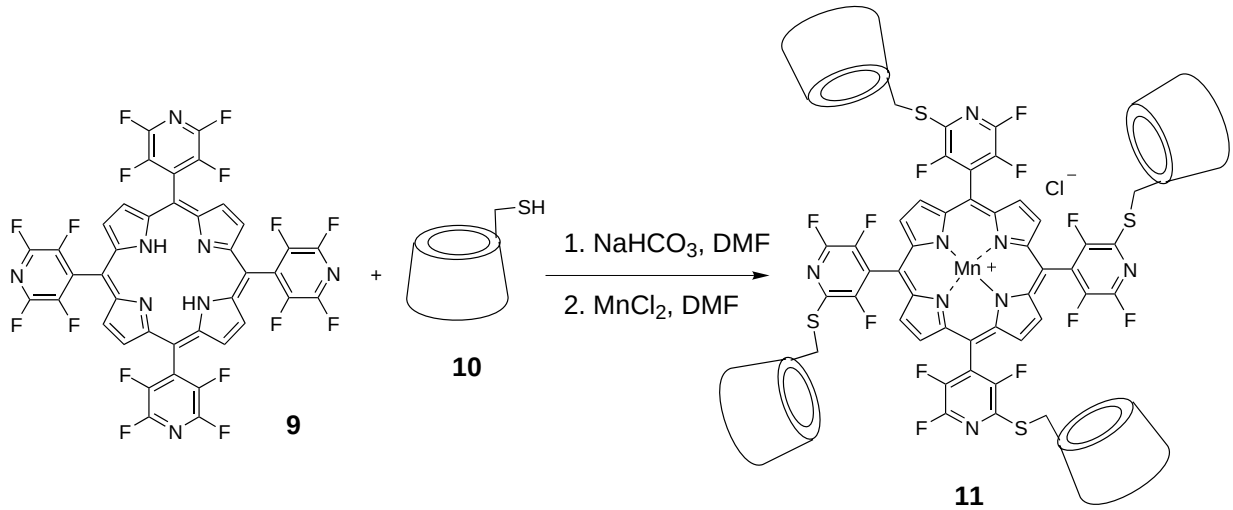




Scheme 1.



Scheme 2.



Scheme 3.

Acknowledgements

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8. All new compounds were characterized by proton (and where relevant fluorine) NMR and mass spectroscopy. The steroid hydroxylation positions were confirmed by the characteristic NMR shifts of the angular methyl groups.