Brief illustrative experimental procedures serve to demonstrate the utility of these methods. First, treatment of 35 mmol of **5** with 50 mmol of LDA in 50 mL of THF for 2 h at 0 °C and hydrolytic workup gave a 96% yield of a 45:55 mixture of the cis and trans isomers of diphenyl-1-propenylamine (**11**). Although stoichiometric amounts of LDA are employed in this case, such isomerizations can be effected by catalytic amounts of LDA as well. Second, treatment of 20 mmol of **5** with 22 mmol of *n*-BuLi in 100 mL of THF at 0 °C for 1 h gave a deep red solution; then, 20 mmol of $PhCH_2Cl$ were added and allowed to react for 6 h at 25 °C; hydrolytic workup and column chromatography of the dried and evaporated organic layer on silica gel (hexane:CH_2Cl_2 = 8:2 as eluent) gave, separately, 4-phenylbutanal (75%) and recovered diphenylamine (95%). Third, treatment of 20 mmol of **5** with 22 mmol of *n*-BuLi in 100 mL of THF at 0 °C for 3 h and the subsequent addition of 20 mmol of benzophenone gave upon the usual hydrolytic workup a crude product that was recrystallized from ethanol to yield 65% of 2-(diphenylamino)-5,5-diphenyltetrahydrofuran, mp 124-125 °C. Treating this with dilute, aqueous HCl eliminates diphenylamine and forms 2,2-diphenyl-2,3-dihydrofuran.

(6) A number of allylic diphenylamines, such as $CH_3CH{=}CHCH_2NPh_2$ and $PhCH{=}CHCH_2NPh_2$, have been prepared in this manner. Eisch, J. J.; Chiu, C. S.; Shah, J. H. Unpublished studies.

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Site-Selective Hydroxylation of Steroids via Oxometalloporphinates Covalently Linked to Ring D: Introduction of Hydroxyl Groups into the C(9) and C(12) Position of 5α-Androstanes

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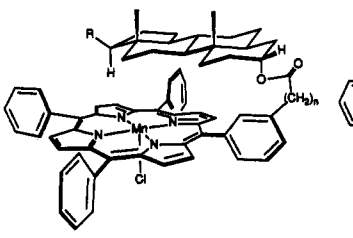
Summary: Oxidation of synthetic manganese(III) porphyrins attached to steroidal substrates at C(17) (cf. **2** and **3**) gives rise to hydrogen atom abstraction at C(9) and/or C(12), thereby leading to hydroxyl incorporation at these sites. The use of more robust metalloporphyrins (cf. **9**) results in substantial increases in the yields of hydroxylated 5α-androstanes.

A recent report[1] from this laboratory described the use of synthetic manganese(III) porphyrins in the remote hydroxylation of steroid substrates.[2] These covalently attached porphyrins, which were oxidized to the corresponding oxomanganese(V) species by iodosylbenzene, were capable of introducing functionality at specific, nonactivated sites on the steroid while maintaining the integrity of the carbon atom undergoing hydroxylation.[3] Herein we wish to report both expansions in the scope of this reaction and improvements in yields through the use of more robust "catalysts".

The site selectivity of these remote oxidation reactions is geometrically controlled, being governed by the steric constraints imposed by the steroid-porphyrin tether. The selectivity can, in principle, be altered by changing the point of attachment to either the porphyrin or steroid, or by adjusting the length and/or composition of the tether itself. Previous efforts in our laboratory focused on the use of "meta"-substituted tetraphenylporphyrins attached to 5α-androstan-3α-ol derivatives (cf. **1**).[1] The present study features the use of "ortho"-substituted porphyrins attached to the C(17) position of 5α-androstane (cf. substrates **2** and **3**) and leads to hydrogen atom abstraction at either C(9) and/or C(12) with hydroxyl incorporation at these sites. In addition, halogens have been incorporated into the 2,6-positions of the phenyl groups located at C(10), C(15), and C(20) on the porphyrin ring that serve to retard oxidative degradation of the porphyrin. We detail below the results of this investigation.



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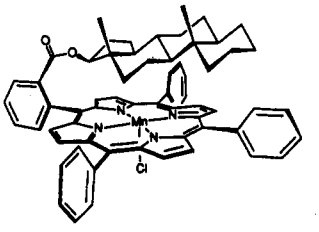

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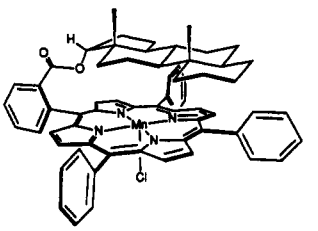

3

Our initial study centered around the manganese(III) (*o*-((androstanyloxy)carbonyl)phenyl)triphenylporphyrin **2**, which was prepared by a minor modification[4] of the Lindsey method[5] employing 5α-androstanyl formylbenzoate **4**[6] followed by metalation in the usual fashion.[8]

(1) Grieco, P. A.; Stuk, T. L. *J. Am. Chem. Soc.* **1990**, *112*, 7799.

(2) For other approaches to remote functionalization of steroids, see: (a) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170. (b) Mazur, Y., *Pure Appl. Chem.* **1975**, *51*, 145. (c) Barton, D. H. R.; Göktük, A. K.; Morzycki, J. W.; Motherwell, W. B. *J. Chem. Soc., Perkin Trans 1* **1985**, 583. Also see: Rozen, S.; Brand, M.; Kol, M. *J. Am. Chem. Soc.* **1989**, *111*, 8325.

(3) For model systems that mimic the hydroxylation of cytochrome P-450, see: (a) Chang, C. K.; Kuo, M.-S., *J. Am. Chem. Soc.* **1979**, *101*, 3413. (b) Hill, C. L.; Schardt, B. C., *Ibid.* **1980**, *102*, 6375. (c) Groves, J. T.; Nemo, T. E. *Ibid.* **1983**, *105*, 6243. (d) Dolphin, D.; James, B. R.; Leung, T. *Inorganica Chim. Acta.* **1983**, *79*, 25. (e) Battioni, P.; Renaud, J. P.; Bartoli, J. F.; Reina-Artiles, M.; Fort, M.; Mansuy, D. *J. Am. Chem. Soc.* **1988**, *110*, 8462. (f) Cook, B. R.; Reinert, T. J.; Suslick, K. S. *Ibid.* **1986**, *108*, 7281.

(4) An 8:1 ratio of benzaldehyde to substituted *o*-formylbenzoate **4** was employed.

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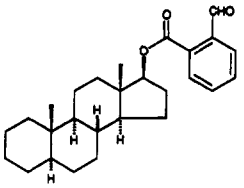

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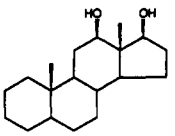

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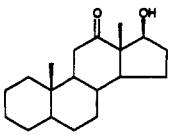
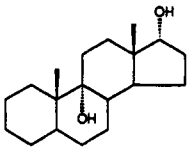


6

Exposure of a 2×10^{-3} M solution (degassed) of **2** in dry methylene chloride under argon to 10.0 equiv of iodosylbenzene for 4 h at ambient temperature provided, after removal of the solvent in vacuo and hydrolysis (MeOH:8% aqueous KOH:THF = 4:1:1; reflux, 6 h) of the ester linkage, 5α-androstane-12β,17β-diol (**5**), mp 160–161 °C (lit.[9] mp 159–160 °C), in 13% yield (46% based on recovered 5α-androstan-17β-ol) and 12-oxo-5α-androstan-17β-ol (**6**),[10] mp 184–186 °C in 10% yield (36% based on recovered 5α-androstan-17β-ol).[11] The surprising preference for secondary hydrogen atom abstraction at C(12) observed with substrate **2** undoubtedly stems from the severe directive constraints imposed on the porphyrin by the tether despite the intrinsic 10:1 preference[12] for tertiary hydrogen atom abstraction over secondary hydrogen atom abstraction. Note that the intermediate oxomanganese(V) species is incapable of a direct $4e^-$ oxidation;[13] thus, androstanone **6** must arise from **5** via α-hydrogen atom abstraction at C(12).

Interestingly, when a 1.5×10^{-3} M solution of metalloporphyrin **3**[14a] in methylene chloride (degassed) was exposed to 8.0 equiv of iodosylbenzene[14b] for 4 h and subsequently hydrolyzed using the standard conditions, there was obtained a 16% yield (30%) of 5α-androstane-9α,17α-diol (**7**), mp 203–204 °C, and a 27% (50%) of 5α-androstane-12β,17α-diol (**8**),[10] mp 188.5–190.5 °C. It is



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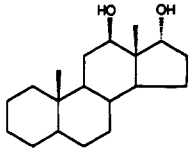
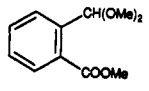


8

(5) Lindsey, J. S.; Schreiman, I. C.; Hsu, H.-C.; Kearney, P. C.; Marguerettaz, A. M. *J. Org. Chem.* **1987**, *52*, 827.

(6) 5α-Androstanyl formylbenzoate **4** was available in 84% overall yield by trans esterification[7] of 5α-androstan-17β-ol with methyl ester **i** and subsequent hydrolysis of the acetal.



i

(7) Meth-Cohn, O. *Org. Synth.* **1989**, *68*, 155.

(8) Jones, R. D.; Summerville, D. A.; Basolo, F. *J. Am. Chem. Soc.* **1978**, *100*, 4416.

(9) Clegg, A. S.; Denny, W. A.; Jones, R.; Kumar, V.; Meakins, G.; Thomas, V. *J. Chem. Soc., Perkin Trans. 1* **1972**, 492.

(10) Compounds **6** and **8**, upon Jones oxidation, gave rise to 5α-androstane-12,17-dione, mp 184–185 °C (lit.[9] mp 182.5–184.0 °C).

(11) New compounds have been characterized by IR, ^{1}H NMR, and mass spectroscopy, combustion analysis, and, where appropriate, UV–vis spectroscopy.

(12) Groves, J. T.; Kruper, W. J.; Haushalter, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 6375.

(13) Collman, J. P.; Tanaka, H.; Hembre, R. T.; Brauman, J. I. *J. Am. Chem. Soc.* **1990**, *112*, 3689.

(14) (a) Metalloporphyrin **3** was prepared from 5α-androstan-17α-ol in the manner described previously for the preparation of **2**. 5α-Androstan-17α-ol was prepared from 5α-androstan-17β-ol via a Mitsunobu reaction, see: Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1977**, *60*, 417. (b) Note that 8.0 equiv of iodosylbenzene is preferred over 10 equiv since at the higher concentration of oxidizing agent one observes increased oxidative degradation of the porphyrin ring.

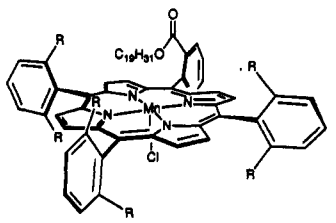
Table I. Manganese(III) Porphyrin–Iodosylbenzene Oxidation of 5α-Androstan-17-ol

substrate[a]	products[b] (% yield)
2[c]	**5** (13), **6** (10)
9a (C(17)β)	**5** (18), **6** (4)
9b (C(17)β)	**5** (9), **6** (35)
3[d]	**7** (16), **8** (27)
9b (C(17)α)	**7** (25), **8** (38)

[a] All reactions were conducted at 1.0×10^{-3} M in methylene chloride in the presence of 8.0 equiv of iodosylbenzene unless stated otherwise. [b] Yields are based on isolated crystalline material. Due to oxidative degradation of the porphyrins encountered in these reactions, particularly in the nonhalogenated examples, no attempt was made to recover and/or recycle in the porphyrin. [c] Reaction carried out at 2.0×10^{-3} M in methylene chloride containing 10 equiv of iodosylbenzene. [d] Reaction carried out at 1.5×10^{-3} M in methylene chloride containing 8 equiv of iodosylbenzene.

of interest to note that CPK models reveal that the 9α and 12β hydrogens of **3** are readily accessible to the reactive oxomanganese(V) center; however, attempts to sterically refine the reactive conformations leading to the respective products according to the model proposed by Groves and Nemo[3c] were successful only for the 12β hydrogen. Using computer-generated ground-state conformations,[15] a low-energy structure[16] placing the 12β hydrogen within reactive range and in the plane of the oxygen reactive orbitals could be easily generated. This was not the case, however, for the 9α hydrogen; its most favorable position was directly over the oxygen and well out of the reactive orbital plane. The inability to model the abstraction of the 9α hydrogen atom according to the Groves model suggested that the formation of **7** may arise via an intermolecular reaction or that a head-on model, in which the 9α hydrogen atom is in line with the manganese–oxygen bond, may be operational. Dilution experiments clearly reveal that the formation of **7** involves an intramolecular process. For example, exposure of a 1.0×10^{-4} M solution of **3** in methylene chloride to 8.0 equiv of iodosylbenzene gave rise, after hydrolysis, to **7** and **8** in a ratio of 1:1.5 (note that when the reaction was conducted at 1.5×10^{-3} M in CH_2Cl_2, the ratio of **7** to **8** was 1:1.7).

The major factor limiting the yields of these hydroxylations is the ease with which tetraphenylporphyrin is oxidatively degraded. In recent years, several substituted tetraphenylporphyrins[17] bearing electron-withdrawing substituents on the phenyl rings have been designed that greatly reduce the extent of oxidation. In order to examine whether or not these oxidation-resistant porphyrins would increase the yields in our remote hydroxylations, 2,6-disubstituted hybrid manganese(III) porphyrins (cf. **9**) were



9a (R=Cl)
9b (R=F)

synthesized[4] and subjected to the oxidation/hydrolysis protocol described previously. The details are summarized

(15) Molecular Graphics displays were implemented on an Evans and Sutherland PS340 Picture System, using Version 2.5 of MACROMODEL as described by: Mohamadi, F.; Richards, N.; Guida, W.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467.

in Table I. The use of a chlorinated porphyrin resulted in no increase in yield, possibly due to the increased steric bulk shielding the face of the porphyrin. However, the much less sterically demanding fluorinated porphyrins gave rise to substantial increases in the yields of hydroxylated 5α-androstanes. For example, incorporation of fluorine atoms in the 2,6-positions of the C(10), C(15), and C(20) phenyl groups of metalloporphyrin **2** dramatically increases the isolated yield of 12-oxo-5α-androstan-17β-ol from 10 to 35%. Similarly, substantial increases in isolated yields were also realized when fluorine atoms were incorporated into **3** (see Table I).[18] The oxometalloporphinate-based methodology described previously appears to be the most efficient nonenzymatic procedure reported to date for the remote hydroxylation of unactivated C–H bonds at C(9)[19] and C(12)[20] steroid systems.

Acknowledgment. This investigation was supported by Public Health Service Research Grant CA 28865 from the National Cancer Institute.

(16) Conformational energies were calculated and minimized for the structures using Molecular Mechanics: Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982. For these computations, the four pyrrole nitrogens and the hydrogen atom to be abstracted were constrained not to move during the energy minimization procedure. The results were compared to those obtained from various fully relaxed conformations.

(17) Chang, C. K.; Ebina, F. *J. Chem. Soc., Chem. Commun.* **1981**, 778. Traylor, P. S.; Dolphin, D.; Traylor, T. G. *Ibid.* **1984**, 279. Lee, W. A.; Calderwood, T. S.; Bruice, T. C. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 4301.

(18) The following experimental employing metalloporphyrin **9b** serves as a general procedure. A solution of 176 mg (156 μmol) of metalloporphyrin **9b** in 80 mL of dry $CHCl_2$ was cooled to −78 °C and was evacuated in vacuo and flushed with Ar three times. The flask was warmed to ambient temperature, and 275 mg (1.25 mmol) of iodosylbenzene was added in one portion. After 4 h, 1.0 mL of a saturated aqueous Na_2SO_3 was added. After 5 min, the reaction was concentrated in vacuo. The residue was dissolved in 100 mL of a solution comprised of ethanol/THF/8% aqueous KOH solution (3:1:1). The solution was heated at reflux for 12 h. The cooled reaction mixture was concentrated in vacuo. The residue was diluted with 100 mL of CH_2Cl_2. The resultant solution was washed with 100 mL of water and 2 × 100 mL of brine and was dried ($MgSO_4$). The solvent was removed under reduced pressure. The residue was purified on 25 g of silica gel. Elution with hexanes/ethyl acetate (5:1) afforded 10 mg (24%) of the starting steroid, 5α-androstane-17α-ol. Continued elution with hexanes/ethyl acetate (3:1) provided 11 mg (25%) of crystalline 5α-androstane-9α,17α-diol, mp 203–204 °C. Further elution with hexanes/ethyl acetate (1:1) afforded 17 mg (38%) of crystalline 5α-androstane-12β,17α-diol, mp 188.5–190.5 °C.

(19) Remote functionalization at C(9) has been limited previously to chlorination[2a] and fluorination.[21]

(20) Remote hydroxylation at C(12) has been achieved with only limited success.[2a,22]

(21) Barton, D. H. R.; Hesse, R. H.; Merkwell, R. E., Pechet, M. M.; Rozen, S. *J. Am. Chem. Soc.* **1976**, *98*, 3036.

(22) Orito, K.; Ohto, M.; Sugawara, N.; Suginome, H. *Tetrahedron Lett.* **1990**, *41*, 5921.