Functionalization of Unactivated C–H Bonds in Steroids via (Salen)manganese(III) Complexes

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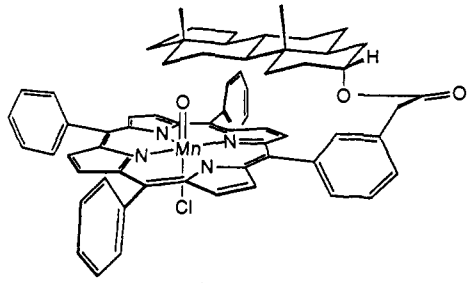
Oxometalloporphinates covalently linked to steroid substrates (cf. **1**) have been shown to introduce hydroxyl groups at specific unactivated carbons on the steroid backbone while maintaining the integrity of the carbon atom undergoing hydroxylation.[2-4]



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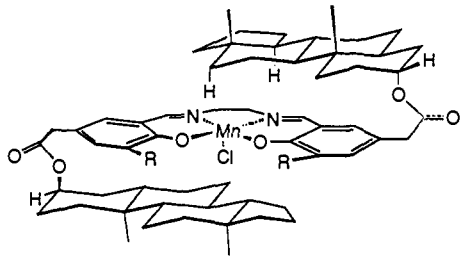
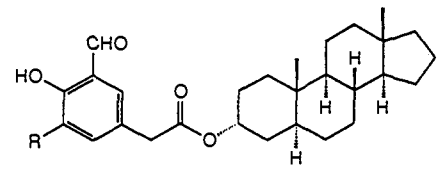


2

The selectivity of these remote hydroxylation reactions is geometrically controlled, being governed by the steroid–porphyrin tether. Serious problems associated with the synthesis of the requisite porphyrins,[5] coupled with the instability of the porphyrin ligands under the oxidative conditions, led us to examine alternate systems. We report that manganese(III) salen (*N,N'*-bis-(salicylideneamino)ethane) complexes attached to steroid substrates (cf. **2**) mediate the hydroxylation of unactivated carbons with iodosylbenzene as the oxygen atom source. Whereas manganese(III) salen complexes have received considerable attention as epoxidation catalysts,[6] they have been only very briefly studied as catalysts for the oxidation of unactivated C–H bonds.[6a,c]

Our initial study centered around the manganese(III) salen **2** (R = H) possessing two covalently linked steroid substrates. The required complex **2** (R = H) was prepared in 90% overall yield via the standard three-step, one-pot sequence[6d] commencing with 5α-androstanyl 3-formyl-4-hydroxyphenylacetate **3** (R = H).[7]



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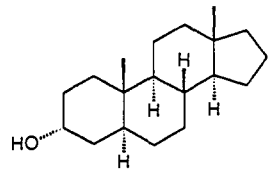
Exposure of a 1.0×10^{-3} M solution of **2** (R = H) in dry methylene chloride under argon to 3.0 equiv of iodosylbenzene for 12 h at ambient temperature followed by hydrolysis (EtOH–10% aqueous KOH–THF, 3:1:1, reflux, 12 h) of the ester linkages gives rise to a 41% isolated yield [57% based on recovered 5α-androstan-3α-ol (**4**)] of 5α-androstane-3α,14α-diol (**5**), mp 141.5–142.5 °C, an 8% isolated yield of 5α-androstane-3α,12α,14α-triol (**6**), mp 225–230 °C dec, and a 2% yield of 12-oxo-5α-androstane-3α,14α-diol (**7**), mp 205.0–206.5 °C (lit.[2a] mp 205.0–206.5 °C) (Table I, entry 1).[9] Use of either a 5.0×10^{-4} M or 1.0×10^{-4} M solution of **2** (R = H) in the above reaction with 3.0 equiv of iodosylbenzene gives rise to comparable yields of **5–7** (Table I, entries 2 and 3). In contrast, when a 1.0×10^{-3} M solution of the phenylacetate of 5α-androstan-3α-ol (**4**) in methylene chloride is exposed to 1.0 equiv of the (salen)manganese(III) complex **8** and treated with iodosylbenzene, the phenylacetate of **4** is recovered after 18 h in 99% yield. The above studies suggest that all of the hydroxylation is intramolecular.



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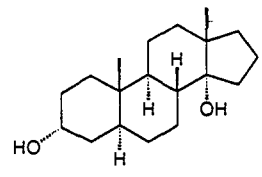

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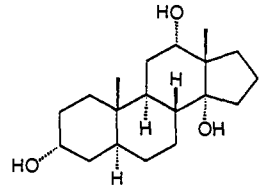

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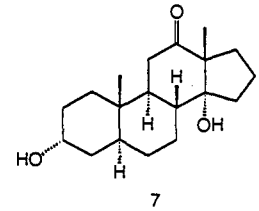

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In an attempt to drive the reaction to completion, the salen complex **2** (R = H) was treated with 8 equiv of iodosylbenzene

(1) Indiana University Graduate School Fellow, 1990–1994.

(2) (a) Grieco, P. A.; Stuk, T. L. *J. Am. Chem. Soc.* **1990**, *112*, 7799. (b) Stuk, T. L.; Grieco, P. A.; Marsh, M. M. *J. Org. Chem.* **1991**, *56*, 2957.

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(5) The hybrid porphyrins could only be prepared in yields of 15–25% following very tedious chromatographic separation.

(6) (a) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309. (b) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (c) Agarwal, D. D.; Bhatnagar, R. P.; Jain, R.; Srivastava, S. *J. Chem. Soc., Perkin Trans. 2* **1990**, 989. (d) Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296. (e) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (f) Lee, N. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 6533. (g) Irie, R.; Noda, K.; Ito, Y.; Katsuki, T. *Tetrahedron Lett.* **1991**, *32*, 1055. (h) Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T. *Synlett* **1991**, 691. (i) Reddy, D. R.; Thornton, E. R. *J. Chem. Soc., Chem. Commun.* **1992**, 172.

(7) 5α-Androstanyl 3-formyl-4-hydroxyphenylacetate **3** (R = H) was prepared in straightforward fashion from methyl 3-formyl-4-hydroxyphenylacetate[8] via a four-step process [(1) MOMCl, DIPEA, CH_2Cl_2, 93%; (2) LiOH, THF–MeOH–H_2O (3:3:1), 99%; (3) DCC, DMAP, **4**, 53%; (4) BBr_3, CH_2Cl_2, –78 °C, 93%].

(8) Jen, T.; Frazee, J. S.; Schwartz, M. S.; Erhard, K. F.; Kaiser, C. *J. Med. Chem.* **1977**, *20*, 1263.

(9) The structures assigned to **5**, **6**, and **11–13** follow from ^1H NMR and ^{13}C NMR data as well as from chemical transformations and single-crystal X-ray analysis.

(10) Salicylaldehyde **3** (R = *t*-Bu) was prepared via a seven-step sequence [(1) *t*-BuOH, H_3PO_4, 75 °C; (2) MeOH, H_2SO_4, reflux, 82% overall; (3) hexamethylenetetramine, TFA, reflux, 71%; (4) MOMCl, DIPEA, CH_2Cl_2, 98%; (5) LiOH, THF–MeOH–H_2O (3:3:1), 96%; (6) DCC, DMAP, **4**, 86%; (7) BBr_3, CH_2Cl_2, –78 °C, 93%] from methyl 4-hydroxyphenylacetate.

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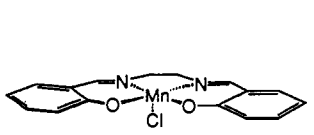
Table I. Oxidation of (Salen)manganese(III) Complexes Derived from 5α-Androstan-3α-ol (**4**)[a]

entry	substrate **2** R	equiv of oxidant	solvent (concn, M)	time, h	products[b] (% yield)	recovered **4**[b] (% yield)
1	H	3	CH_2Cl_2 (1.0×10^{-3})	12	**5** (41), **6** (8), **7** (2)	28
2	H	3	CH_2Cl_2 (5.0×10^{-4})	24	**5** (41), **6** (8), **7** (3)	25
3	H	3	CH_2Cl_2 (1.0×10^{-4})	36	**5** (42), **6** (7), **7** (2)	28
4	H	8	CH_2Cl_2 (1.0×10^{-3})	12	**5** (30), **6** (14), **7** (7)	15
5	H	8	CH_2Cl_2 (5.0×10^{-4})	24	**5** (29), **6** (15), **7** (5)	14
6	*t*-Bu	2	$ClCH_2CH_2Cl$ (1.0×10^{-3})	24	**5** (28), **6** (11), **7** (1), **9** (3)	42
7	*t*-Bu	2	$ClCH_2CH_2Cl$ (5.0×10^{-4})	24	**5** (35), **6** (12), **7** (1), **9** (2)	45
8	*t*-Bu	8	$ClCH_2CH_2Cl$ (1.0×10^{-3})	12	**5** (18), **6** (38), **7** (7), **9** (1)	9
9	*t*-Bu	8	CH_2Cl_2 (1.0×10^{-3})	12	**5** (25), **6** (18), **7** (7)	31

[a] All reactions were carried out in the indicated solvent employing iodosylbenzene as the oxidant. [b] Yields are based on isolated crystalline materials.

(Table I, entry 4). After hydrolysis of the ester linkages, only 15% of the starting 5α-androstan-3α-ol (**4**) was isolated. However, the isolated yield of the 3α,14α-diol **5** changed significantly, decreasing to 30%. The additional equivalents of oxidant gave rise to increases in the yields of **6** and **7**. Use of greater than 8 equiv of iodosylbenzene did not result in more complete consumption of **4**.



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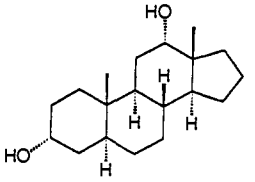

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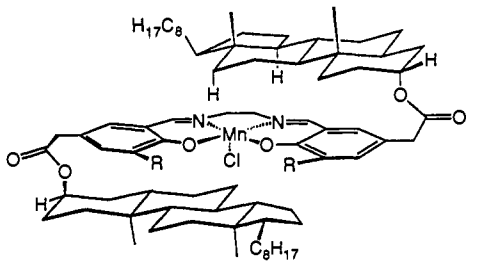
Assuming that oxidative degradation of the salen catalyst was responsible for incomplete conversion of the steroid substrate, the more "robust" *tert*-butyl-substituted complex **2** (R = *t*-Bu)[6d] was prepared from salicylaldehyde **3** (R = *t*-Bu)[10] as detailed above. Interestingly, greater steroid conversion was obtained with complex **2** (R = *t*-Bu) when 1,2-dichloroethane was employed as the solvent. Thus treatment of a 1.0×10^{-3} M solution of salen **2** (R = *t*-Bu) in 1,2-dichloroethane under argon with 2 equiv of iodosylbenzene for 24 h at ambient temperature, followed by hydrolysis of the ester linkages, as described above, gives rise to a 28% yield of **5**, a 11% yield of **6**, a 3% yield of 5α-androstane-3α,12α-diol (**9**), mp 162–164 °C (lit.[2a] mp 162–164 °C), and only a trace (ca. 1%) of keto diol **7** (Table I, entry 6). When substrate **2** (R = *t*-Bu) was exposed to 8 equiv of iodosylbenzene in 1,2-dichloroethane followed by hydrolysis, the ratio of products changed (Table I, entry 8), with triol **6** being isolated in 38% yield as the major product and only 9% recovery of starting 5α-androstan-3α-ol. Use of methylene chloride as solvent (Table I, entry 9) resulted in less complete conversion, with a reversal in the preference for diol **5** over triol **6**.

The salen complexes **2** (R = H, *t*-Bu) mediate the oxygen atom insertion into the same C–H bonds as does the oxometalloporphinate **1**, but with complementary selectivity. Whereas the 12α-H and 14α-H atoms are both 6.5 Å from the C(3) oxygen atoms, salens **2** (R = H, *t*-Bu) give rise to selective hydrogen atom abstraction at C(14). In contrast, oxometalloporphinate **1** oxidizes C(12) preferentially, oxidizing C(14) only after both C(12) hydrogens have been abstracted in sequential oxidations. Apparently, the nonplanar surface of the tetraphenylporphyrin in **1** makes approach of the active oxomanganese(V) species to the C(14) hydrogen atom virtually impossible until the axial steric hindrance at C(12) is removed. In contrast, the surface of salens **2** (R = H, *t*-Bu) is relatively planar and the selectivity in the initial hydrogen abstraction is governed by the intrinsic preference for tertiary hydrogen atom abstraction at C(14) over secondary hydrogen atom abstraction at C(12). However, in the presence of excess oxidant, further oxidation at C(12) takes place, most notably with **2** (R = *t*-Bu).

Selective functionalization at C(14) is also observed with the cholestanol-derived (salen)manganese(III) complexes **10** (R = H, *t*-Bu). Analogous to the androstane-derived salen **2** (R = H), treatment of a 1.0×10^{-3} M solution of **10** (R = H) in methylene chloride with 3.0 equiv of iodosylbenzene followed by hydrolysis of the ester linkages gives rise to a 39% isolated yield of 5α-cholestane-3α,14α-diol (**12**), mp 187.5–188.5 °C, an 8% yield of 5α-cholestane-3α,12α,14α-triol (**11**), mp 209–211 °C dec, and a 2% yield of 12-oxo-5α-cholestane-3α,14α-diol (**13**), mp 199.5–201.0 °C, along with 32% recovered 5α-cholestan-3α-ol.[9] In contrast, when the more robust complex **10** (R = *t*-Bu) is exposed to excess oxidant, the triol **11** is isolated as the major product [cf. androstane-derived salen **2** (R = *t*-Bu) (Table I, entry 8)]. Thus, exposure of a 1.0×10^{-3} M solution of **10** (R = *t*-Bu) in 1,2-dichloroethane to 8.0 equiv of iodosylbenzene affords, after ester hydrolysis, a 44% isolated yield of **11** along with a 14% yield of **12**, a 3% yield of **13**, and 11% of recovered cholestanol.



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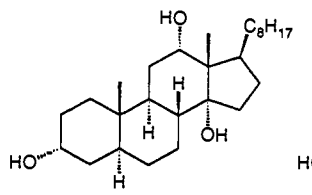

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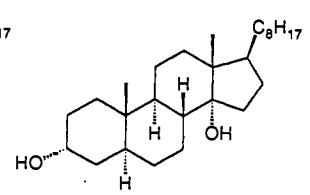

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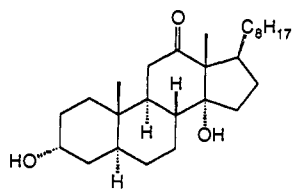

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In summary, the salen complexes **2** and **10** mediate the remote hydroxylation at C(14) in the presence of 2–3 equiv of oxidant, which stands in sharp contrast to the results obtained with oxometalloporphinate **1**. In the presence of excess oxidant, hydroxylation occurs at both C(12) and C(14). The ease of synthesis of the salen complexes makes their use attractive in organic synthesis. Further exploration of the scope of this metallosalen-based hydroxylation process will be reported in due course.

Acknowledgment. This investigation was supported by Public Health Service Research Grant CA28865 from the National Cancer Institute.