Direct 10β-Alkylation of β-Estradiol: Osmium(II) as a Dearomatization Agent

Michael E. Kopach, Laurie P. Kelsh, Kevin C. Stork, and W. D. Harman*,[1]

Department of Chemistry
University of Virginia
Charlottesville, Virginia 22901

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A central pathway of steroidogenesis in humans involves the conversion of androgens to estrogens by cytochrome P-450 aromatase. C(19)-alkylated testosterones and androstenediones have been found to be potent aromatase inhibitors and are currently of interest as therapeutic agents for breast cancer, due to their ability to block estrogen biosynthesis.[2,3] We wish to report here an efficient synthesis of C(19)-alkylated-Δ^1-testosterones resulting directly from an unprecedented conjugate addition to C(10) of β-estradiol mediated by Os(II) complexation.

The powerful π-donor pentaammineosmium(II) forms stable complexes with phenols in which the metal binds across C(2)–C(3).[4] This action partially *dearomatizes* the arene ligand and, as a consequence, activates it toward electrophilic addition.[5] In particular, the complex $[Os(NH_3)_5(\eta^2\text{-phenol})]^{2+}$ was observed to undergo conjugate addition preferentially at the para position, yielding a stable 2,5-dienone complex. Upon oxidation, the organic ligand rearomatizes to the 4-substituted phenol. Since our initial report, we have discovered that conjugate addition can be directed to C(4) even in cases where this position is more sterically hindered than C(2).[6] Addition followed by oxidative decomplexation provides a general route to 4,4-dialkylated 2,5-dienones directly from phenols.[7] Extending this dearomatization technology to estrone derivatives provides the means to convert an aromatic steroid to a testosterone derivative by the *direct alkylation of C(10)*.

Introduction of the $\{Os(NH_3)_5\}^{2+}$ fragment to the α face of estradiol (*vide infra*) is accomplished by reduction of $Os(NH_3)_5(OTf)_3$,[8] with Mg^0 powder in the presence of an excess of β-estradiol.[9] Spectral and electrochemical data indicate that the reaction mixture contains two steroidal osmium(II) complexes (**1**, **2**, (67%) and unidentified paramagnetic materials, which are readily removed by ion-exchange chromatography.[10] ^{13}C and ^1H NMR data[11] support the assignment of **1** as an η^2-arene complex whose carbon resonances closely parallel those observed for model systems $[Os(NH_3)_5(\eta^2\text{-L})]^{2+}$, where L = 3,4-dimethylphenol[4] or 5,6,7,8-tetrahydro-2-napthol.[6] By similar comparison, **2** is assigned to be the 1,2-η^2-1,5(10)-dien-3-one tautomer shown in Figure 1. When the tautomeric mixture is placed in acidic methanol and reprecipitated, a 3:1 equilibrium ratio of the phenolic (**1**) and dienone (**2**) tautomers is obtained, consistent with that found for other 3,4-dialkylated phenol ligands.[4,6]

Addition at C(10) is accomplished with greatest regioselectivity when an acetonitrile solution of the crude complexed steroid mixture (**1**,**2**) and 1.0 equiv of MVK is cooled to −35 °C and then treated with 0.1 equiv of $(i\text{-Pr})_2NEt$.[12] After 15 h at −35 °C, addition of the reaction mixture to ether produces a tan precipitate **3** (97% yield). ^1H and ^{13}C NMR and cyclic voltammetry data[13] support the assignment of **3** as a 1,2-η^2-1,4-dien-3-one species.[4] Additionally, ^{13}C DEPT data reveal eight sets of methylene protons and seven methine protons consistent with the formation of $[Os(NH_3)_5(1,2\text{-}\eta^2\text{-}19\text{-}(2\text{-oxopropyl})\text{-}\Delta^1\text{-testosterone})]^{2+}$ (Figure 1). A similar addition occurs at C(10) when 3-butyn-2-one is utilized as the Michael acceptor, but bulkier electrophiles such as *N*-methylmaleimide add only to C(4).

The steroid ligand **4** is removed from the metal by treatment of the complex **3** with 1.0 equiv of ceric ammonium nitrate (82%).[14] After extraction of the product from aqueous solution and passage through silica, a yellow oil (**4**) is obtained (overall isolated yield from the mixture of **1** and **2**: 69%). High field NOESY, COSY, and ^1H–^{13}C correlation spectroscopy data unambiguously establish the stereochemistry of **4** as the β isomer (*vide infra*) and indicate that the osmium coordinates to the less hindered α steroid face, as has been found for several $\{RuCp\}^+$ and $\{RuCp^*\}^+$ complexes of estrogen ligands.[15]

Confirmation that conjugate addition occurs from the β-face of the steroid was unambiguously obtained by the observation of a nuclear Overhauser effect (NOE) between H19a and H8 (Figure 1). H8 is unambiguously assigned by coupling to H7α,β and by observance of strong trans coupling to H9 and H14; this assignment is confirmed by the lack of NOE between H8-H14 and H8-H9 and by the presence of an NOE between H9–H14. The β-face is also identified by NOEs between the angular methyl group at C(13) (H18) and H8 (supplementary material).[16]

When the synthesis of **3** is attempted as before but in the presence of 1 equiv of $Zn(OTf)_2$, a complete reversal of

(1) 1992 Camille and Henry Dreyfus Teacher-Scholar.

(2) For a recent review on the inhibition of cytochrome P-450 aromatase, see: Cole, P. A.; Robinson, C. H. *J. Med. Chem.* **1990**, *33*, 2933. Van Wauwe, J. P.; Janssen, P. A. J. *J. Med. Chem.* **1989**, *32*, 2331.

(3) Childers, W. E.; Silverton, J. V.; Kellis, J. T.; Vickery, L. E.; Robinson, C. H. *J. Med. Chem.* **1991**, *34*, 1344. Beusen, D. D.; Carrell, H. L.; Covey, D. F. *Biochemistry* **1987**, *26*, 7833.

(4) Kopach, M. E.; Hipple, W. G.; Harman, W. D. *J. Am. Chem. Soc.* **1992**, *114*, 1736.

(5) Kopach, M. E.; Gonzalez, J.; Harman, W. D. *J. Am. Chem. Soc.* **1991**, *113*, 8972.

(6) Typically, conjugate addition reactions with phenols (including those without para substitution) occur at oxygen under basic conditions; under acidic conditions, electrophilic *substitution* occurs at C4 (phenol/MVK), but there are no reports of C(4) conjugate addition with *p*-alkylated phenols.

(7) Kopach, M. E.; Harman, W. D., manuscript in preparation. The conjugate addition with $[Os(NH_3)_5(\eta^2\text{-phenol})]^{2+}$ works for acrylonitrile, methyl acrylate, acrolein, cyclopentenone, and various maleimides in addition to MVK. With MVK, successful para conjugate additions also can be carried out with *p*-cresol and 5,6,7,8-tetrahydro-2-naphthol.

(8) Lay, P. A.; Taube, H.; Magnuson, R. H. *Inorg. Synth.* **1986**, *24*, 269.

(9) $Os(NH_3)_5OTf_3$ (683 mg) was reduced in 11 mL of a 7:4 (v/v) 1,2-dimethoxyethane/*N*,*N*-dimethylacetamide solution with an excess of Mg^0 powder and β-estradiol (2.90 g, 10.7 mmol). Subsequent treatment with ether resulted in the precipitation of osmium salts. Approximate recovery of osmium: 85%.

(10) A mixture of the cations **1** and **2** was eluted with NaCl(aq) down a Sephadex SP C-25 ion-exchange column and precipitated as BPh_4^- salts. Anal. Calcd for $C_{66}H_{79}N_5O_2B_2Os\cdot H_2O$: C, H, N.

(11) Characterization of **1**: ^1H NMR (CD_3CN) δ 5.42 (d, 1H, CH, J = 8.1 Hz), 5.40 (s, 1H, CH), 4.91 (d, 1H, CH, J = 8.1 Hz), 4.04 (br s, 3H, *t*-NH_3), 2.96 (br s, 12H, *c*-NH_3), 0.723 (s, 3H); ^{13}C NMR (300 MHz, CD_3CN) δ 164, 133, 128, 99.5, 81.3, 60.7, 56.6, 50.1, 46.8, 43.7, 40.7, 37.4, 30.6, 29.9, 27.0, 26.0, 23.4, 11.4. Partial Characterization of **2**: ^1H NMR (CD_3CN) δ 5.15 (d, 1H, CH, J = 7.5 Hz), 4.40 (d, 1H, CH, J = 7.5 Hz), 4.60 (br s, 3H, *t*-NH_3), 3.25 (br s, 12H, *c*-NH_3), 0.78 (s, 3H, CH_3) Mixture of **1** and **2** as BPh_4^- salt: Anal. Calcd for $C_{66}H_{79}N_5O_2B_2Os\cdot H_2O$: C, H, N.

(12) All manipulations of organometallic compounds were carried out under nitrogen. All compounds are triflate salts unless otherwise noted.

(13) Characterization of **3**: ^1H NMR (CD_3CN) δ 5.70 (s, 1H), 4.38 (br s, 3H, *t*-NH_3), 4.32 (d, 1H), 4.25 (d, 1H), 3.35 (br s, 12H, *c*-NH_3), 2.04 (s, 3H, CH_3), 0.80 (s, 3H, CH_3); ^{13}C NMR (300 MHz CD_3CN) δ 209, 198, 166, 127, 80.8, 55.3, 54.6, 51.6, 50.2, 47.9, 43.6, 38.3, 37.3, 35.7, 33.2, 31.0, 30.15, 30.12, 29.9, 23.8, 23.3, 11.7). BPh_4^- salt anal. Calcd for $C_{70}H_{85}B_2N_5O_3Os\cdot 3/2\ H_2O$: C, H, N.

(14) Heating a solution of **3** in CH_3CN at 70 °C for 2 h effected a retro-Michael reaction. Characterization of **4**: selected ^1H NMR data ($CDCl_3$) δ 6.95 (1H, d, J = 10.2 Hz), 6.32 (1H, d, J = 10.2 Hz), 6.17 (1H, s), 0.82 (3H, s); ^{13}C NMR ($CDCl_3$) δ 154.9 (C1), 130.2 (C2), 186.76 (C3), 126.6 (C4), 167.6 (C5), 33.2 (C6), 33.8 (C7), 35.7 (C8), 53.8 (C9), 47.0 (C10), 22.9 (C11), 36.9 (C12), 43.6 (C13), 50.4 (C14), 30.8 (C15), 23.9 (C16), 81.5 (C17), 11.7 (C18), 24.6 (C19), 38.0 (C20), 208.2 (C21), 30.65 (C22); IR $\nu_{C=O}$ 1716.7 (C21), $\nu_{C=O}$ 1658.9 (C3). Anal. Calcd for $C_{22}H_3O_3$: C, H.

(15) Vichard, D.; Gruselle, M.; Amouri, H. E. Jaouen, G., Vaissermann, J. *Organometallics* **1992**, *11*, 976 and references within. For examples of $Co(CO)_3$ analogs, see: Top, S.; Jaouen, G.; Vessiéres, A.; Abjean, J.-P.; Davoust, D.; Rodger, C. A.; Sayer, B. G.; McGlinchey, M. J. *Organometallics* **1985**, *4*, 2143.

(16) H14 and H9 were distinguished on the basis of scalar coupling to ring D and ring B protons, respectively. Once the ring protons were assigned, the H19a,b protons were assigned to the remaining nonequivalent proton pair from the HMQC spectrum; this is confirmed by the lack of scalar connectivity to any ring protons.

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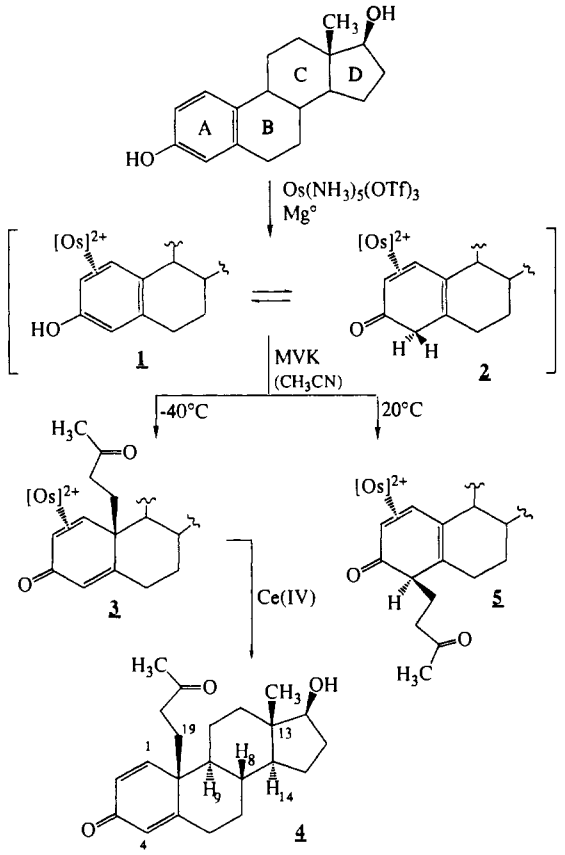

Figure 1. Complexation of β-estradiol by pentaammineosmium(II) and the subsequent conjugate addition of methyl vinyl ketone (MVK). $[Os]^{2+}$ = $[Os(NH_3)_5](OTf)_2$; Ce(IV) = $Ce(NH_4)_2(NO_3)_6$.

regiochemistry is observed.[17] ^1H NMR data for the new product **5** now show only two A-ring proton resonances, and ^{13}C 1D and DEPT NMR data support the assignment of **5** as an 1,2-η^2-1,5-(10)-dien-3-one species resulting from conjugate addition to C(4).[18,19] The stereochemistry at C(4) has not been confirmed, but it is presumed to be that resulting from conjugate addition to the β face, opposite the site of metal coordination (*vide supra*). Attempted synthesis of **3** at room temperature in the absence of Zn^{2+} leads to a 10:1 ratio of ortho (**5**) and para (**3**) addition products.

An intermolecular Michael addition to C(10) of an aromatic steroid is unprecedented. Os(II) serves to activate the phenolic ring toward conjugate addition at either C(4) or C(10), to stabilize the reactive 1,5(10)-dien-3-one intermediate (**5**), and to direct the addition to the β-face of the steroid. A detailed report of conjugate addition of η^2-phenol complexes is forthcoming.[7]

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Supplementary Material Available: Experimental details for synthesis and characterization of compounds **1–5**; stereochemical assignment of **4**; table of ^{13}C and ^1H NMR resonances for **4** (9 pages). Ordering information is given on any current masthead page.

(17) The phenols 5,6,7,8-tetrahydro-2-naphthol and *p*-cresol undergo conjugate addition at oxygen with MVK under basic conditions.

(18) Characterization of **5**: ^1H NMR (CD_3CN) δ 5.04 (d, 1H, J = 7.2 Hz), 4.47 (d, 1 H, J = 7.2 Hz), 2.06 (s, 3H), 0.768 (s, 3H), 3.28 (br s, 12H, *c*-NH_3), 4.54 (br s, 3H, *t*-NH_3); ^{13}C NMR (300 MHz CD_3CN) δ 215.5, 209.1, 135.8, 127.6, 82.0, 51.6, 51.3, 49.5, 48.8, 46.4, 43.6, 40.1, 38.1, 37.0, 29.9, 29.8, 28.6, 26.7, 26.0, 25.2, 23.1, 11.0. BPh_4^- salt, anal. Calcd for $C_{70}H_{85}N_5O_3B_2Os$: C, H, N.

(19) For simple η^2-phenol, η^2-aniline, and η^2-pyrrole complexes of Os(II), we have observed conjugate addition *anti* to metal coordination virtually without exception.