Synthesis of 2,19-Bridged Androstenediones

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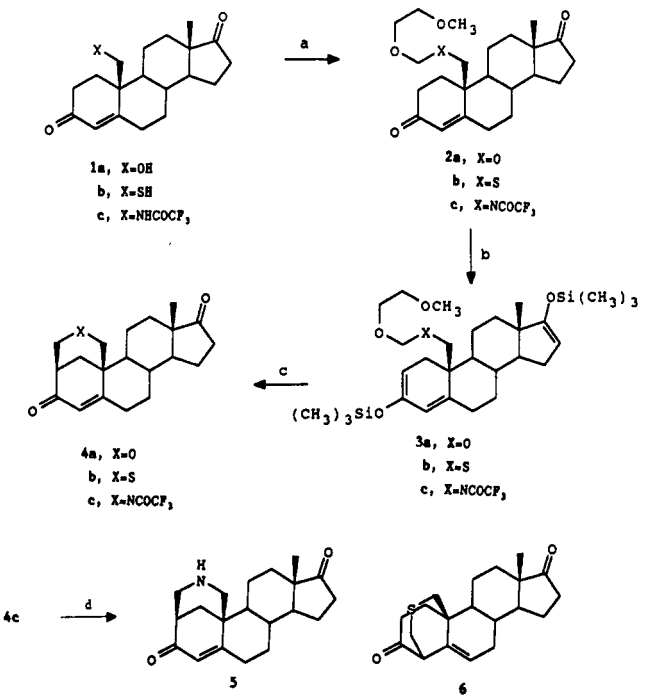
The syntheses of 2,19-(methyleneoxy)androst-4-ene-3,17-dione (**4a**), a potent, time-dependent inhibitor of human placental aromatase, and its thio (**4b**), amino (**5**), and methylene (**14**) analogs are described. The key step in the construction of **4a**, **4b**, and **5** is a Lewis acid-mediated intramolecular alkylation of an A-ring *O*-trimethylsilyl dienol ether.

We have recently described A-ring bridged androstenediones as inhibitors of human placental aromatase. Hydroxylated 2,19-methylene-bridged androst-4-ene-3,17-diones were designed as stable mimics of a presumed intermediate in the aromatase-mediated oxidation of androst-4-ene-3,17-dione, and they are competitive inhibitors of aromatase.[1a] 2,19-(Methyleneoxy)androst-4-ene-3,17-dione (**4a**) and the isomeric 6,19-bridged compound **8** were designed as potential mechanism-based inhibitors of aromatase. Compound **4a** proved to be a potent, time-dependent inhibitor in vitro.[1b] The novelty of **4a**[2] coupled with its potential utility in treating estrogen-dependent breast cancer led us to prepare additional compounds. This report describes the synthesis of **4a** and the thio (**4b**), amino (**5**), and methylene (**14**) analogs.

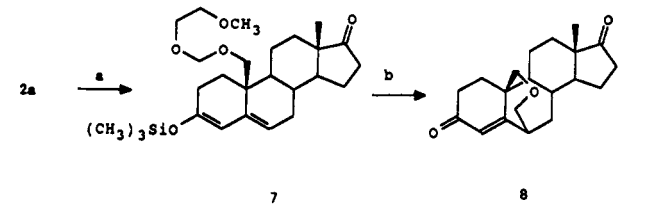
Scheme I shows syntheses of the 2,19-bridged androstenediones with heteroatoms in the bridge. Thus, the commercially available 19-hydroxy- and known 19-mercaptoandrostenediones[3] were treated with (2-methoxyethoxy)methyl chloride (MEM chloride) and diisopropylethylamine[4] to give the MEM ether **2a** (76%) and thioether **2b** (79%), respectively. The known 19-[(trifluoroacetyl)amino]androstenedione[5] was converted to **2c** using a procedure developed by Nordlander and coworkers[6] for the alkylation of N-substituted trifluoroacetamides. Introduction of the MEM group was based upon previous reports[7a,b] which indicated that this group, upon treatment with a Lewis acid, could be expected to generate the desired reactive intermediate necessary for productive ring cyclization. Treatment of MEM derivatives **2a–c** with lithium diisopropylamide (LDA) and trimethylsilyl chloride (TMSCl)[8] gave bis-TMS ethers **3a–c** in which the kinetic A-ring enolates were trapped, in nearly quantitative yield. Titanium tetrachloride-mediated[7c] cyclization of MEM derivatives **3a–c** in methylene chloride at −20 °C gave the 2,19-bridged androstenediones **4a–c**, respectively. Coproduced with **4b** under these conditions was the interesting 4,19-bridged sulfide **6**. The ^{1}H NMR spectrum of **6** clearly showed a vinyl proton whose shift

Scheme I[a]



[a] Reagents and conditions: (a) MEMCl, $(i\text{-Pr})_2$NEt, CH_2Cl_2 for **2a**, **2b** and KH, 18-c-6, MEMCl, THF for **2c**; (b) LDA, TMSCl, THF; (c) $TiCl_4$, CH_2Cl_2; (d) K_2CO_3, MeOH, H_2O.

Scheme II[a]



[a] Reagents and conditions: (a) Et_3N, DMAP, DMF, TMSCl; (b) $TiCl_4$, CH_2Cl_2.

position, relative to the enone systems of **4a–c**, and multiplicity (dd) was consistent with its assigned $\Delta^{5,6}$ position. The IR spectrum of **6** also indicated a nonconjugated C3 ketone (1714 cm^{-1} vs 1666 cm^{-1} for **4b**). We surmise that some rearrangement to the thermodynamic enolate occurred under the reaction conditions to produce **6**. Removal of the trifluoroacetyl group from **4c** was accomplished with potassium carbonate in aqueous methanol.[9]

Treatment of MEM ether **2a** with triethylamine, 4-(dimethylamino)pyridine (DMAP), and trimethylsilyl chloride afforded the *O*-trimethylsilyl dienol **7** (Scheme II). Interestingly, when **7** was treated with titanium tet-

(1) (a) Burkhart, J. P.; Peet, N. P.; Wright, C. L.; Johnston, J. O. *J. Med. Chem.* **1991**, *34*, 1748. (b) Peet, N. P.; Burkhart, J. P.; Wright, C. L.; Johnston, J. O. *J. Med. Chem.* **1992**, *35*, 3303–3306.

(2) A few 2,19-bridged steroids with oxygen atoms in the bridge connected directly to the 2-position have been reported: Kocovsky, P.; Pour, M. *J. Org. Chem.* **1990**, *55*, 5580 and references cited therein. Kocovsky, P. *J. Org. Chem.* **1988**, *53*, 5816. Njar, V. C. O.; Spiteller, G.; Wicha, J.; Caspi, E. *Heterocycles* **1989**, *28*, 1051. de Armas, P.; Concepcion, J. I.; Francisco, C. G.; Hernandez, R.; Salazar, J. A.; Suarez, E. *J. Chem. Soc., Perkin Trans. 1* **1989**, 405.

(3) Bednarski, P. J.; Porubek, D. J.; Nelson, D. J. *J. Med. Chem.* **1985**, *28*, 775.

(4) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

(5) Lovett, J. A.; Darby, M. V.; Counsell, R. E. *J. Med. Chem.* **1984**, *27*, 734.

(6) Nordlander, J. E.; Catalano, D. B.; Eberlein, T. H.; Farkas, L. V.; Howe, R. S.; Stevens, R. M.; Tripoulas, N. A.; Stansfield, R. E.; Cox, J. L.; Payne, M. J.; Viehbeck, A. *Tetrahedron Lett.* **1978**, 4987.

(7) (a) Walker, D. M.; Logusch, E. W. *Tetrahedron Lett.* **1989**, 1181. (b) Nishiyama, H.; Itoh, K. *J. Org. Chem.* **1982**, *47*, 2496. (c) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043.

(8) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, 495.

(9) Newman, H. *J. Org. Chem.* **1965**, *30*, 1287.

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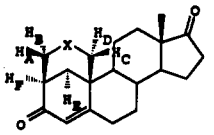
Table I. ^{1}H NMR Chemical Shifts and Coupling Constants for Selected Protons of 2,19-Bridged Androstenediones



compd no.	X	chem shift (ppm)[a]				coupling constants (Hz)						
		H_A	H_B	H_C	H_D	J_{AB}	J_{AC}	J_{AE}	J_{AF}	J_{BF}	J_{CD}	J_{CE}
4a	O	3.89	3.50	3.78	3.60	11.2	–	1.8	1.8	2.5	10.8	2.6
4b	S	2.48[b]	2.82	2.35[b]	3.04	13.1	–[c]	–[c]	–[c]	3.5	13.2	–[c]
5	NH	2.98	2.73	2.78	2.90	13.5	–	1.9	1.9	3.4	13.0	2.4
4c	$NCOCF_3$	4.05	3.28	4.62	2.92	14.0	2.2	–[c]	–[c]	3.2	12.8	2.2

[a] 300 MHz in $CDCl_3$. [b] Chemical shift position is estimated from COSY experiments; exact value could not be obtained due to overlapping signals. [c] Coupling was observed in COSY experiments but J value could not be determined.

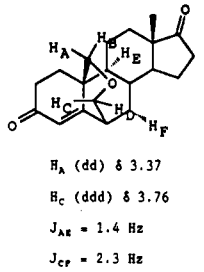


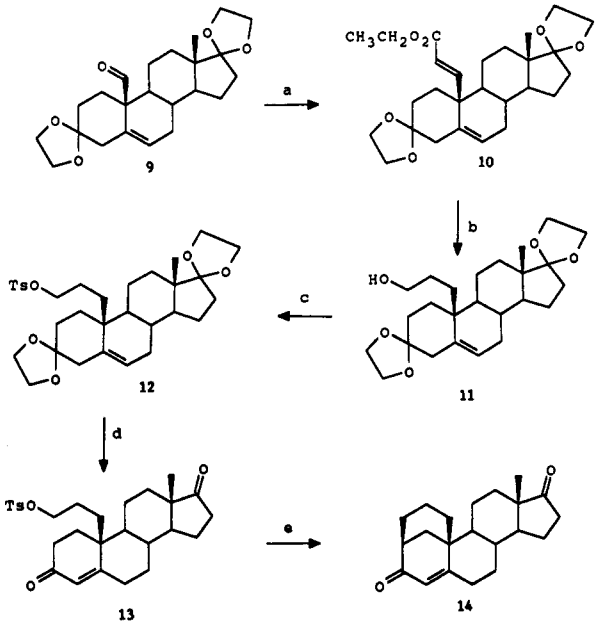
Figure 1. Chemical shift positions and W coupling constants observed from the ^{1}H NMR ($CDCl_3$) spectrum of 6,19-(methyleneoxy)androstenedione (8).

rachloride in methylene chloride, 6,19-(methyleneoxy)-androstenedione (8) was produced. ^{1}H NMR, ^{13}C NMR, and IR spectral data for the enone system of 8 were directly analogous to those of enones **4a–c** and **5**. Although we did not attempt to prepare and cyclize the thermodynamic *O*-trimethylsilyl dienol of thioether **2b**, it is noteworthy that 4,19-bridged thioether **6** was isolated from the cyclization of **3b**, presumably arising from partial isomerization of the kinetic to the thermodynamic dienolate prior to ring closure, whereas 6,19-bridged ether **8** was the product isolated from the cyclization of **7**.

Analysis of the ^{1}H NMR spectra of bridged compounds **4a–c** and **5** clearly showed the 6-membered ring containing the bridge exists in solution as a chair conformation. Coupling constants and field positions for hydrogen atoms in the bridge ring are displayed in Table I. Geminal coupling constants (J_{AB} and J_{CD}) fell into the 10–15 Hz range as expected. The equatorial–equatorial couplings (J_{AF}) were similar to the axial–equatorial coupling (J_{BF}) as expected[10] and as predicted by inspection of dihedral angles from molecular models of these rigid systems. However, the presence of long range W coupling between H_A and H_E, and H_C and H_E was strikingly diagnostic for the chair conformations. From an inspection of molecular models, it was clear that W arrangements could exist only in the chair, and not the boat, conformations of these molecules. Additionally, long-range W coupling between H_A and H_C was observed for **4b** (X = S) and **4c** (X = $NCOCF_3$) but not for **4a** (X = O) or **5** (X = NH).

Salient data from the ^{1}H NMR spectrum of 6,19-bridged compound **8** are shown in Figure 1. Hydrogen atoms H_A and H_C were clearly discerned at δ 3.37 (dd) and δ 3.76 (ddd), respectively. Remarkably, W couplings were observed for these hydrogen atoms to two different B-ring hydrogen atoms, H_E and H_F, respectively. Again, an inspection of molecular models clearly showed that these W arrangements were present in the chair conformation of the 6-membered ring containing the bridge and not in the boat conformation.

Scheme III[a]



[a] Reagents and conditions: (a) $(EtO)_2POCH_2CO_2Et$, *n*-BuLi, THF; (b) Li, NH_3, EtOH, Et_2O; (c) TsCl, pyridine, $CHCl_3$; (d) $TsOH{\cdot}H_2O$, acetone; (e) LHMDS, THF.

Synthesis of the 2,19-ethylene-bridged androstenedione is shown in Scheme III. Treatment of aldehyde **9**[5,11,12] with the anion of triethyl phosphonoacetate,[13] as shown in Scheme III, gave the α,β-unsaturated ester **10** (89%) which was reduced with lithium in ammonia[14] to afford alcohol **11** (63%). The direct reduction of **10** to **11** was preferable to another method we investigated wherein **10** was treated with magnesium in methanol[15] to provide the corre-

(10) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*; John Wiley and Sons: New York, 1981; p 209.

(11) We have previously used aldehyde **9** in the preparation of 10-[1-hydroxy-2-(trimethylsilyl)ethyl]estr-4-ene-3,17-dione, a weak, competitive aromatase inhibitor. See: Burkhart, J. P.; Weintraub, P. M.; Wright, C. L.; Johnston, J. O. *Steroids* **1985**, *45*, 357.

(12) While the PDC oxidation of the alcohol precursor to **9** gave yields (72–90%) comparable to that reported in ref 5, several alternative methods of oxidation were investigated. The reagents and respective yields are as follows: PCC/4-Å molecular sieves/CH_2Cl_2 (84%); ClCO-COCl/DMSO/CH_2Cl_2, then Et_3N (85%); 6 mol % $(n\text{-Pr})_4NRuO_4$/NMMO/3-Å molecular sieves/10% CH_3CN–CH_2Cl_2 (78%).

(13) Arai, Y.; Yamamoto, M.; Koizumi, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 467.

(14) Mirrington, R. N.; Schmalzl, K. J. *J. Org. Chem.* **1972**, *37*, 2871.

(15) Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409.

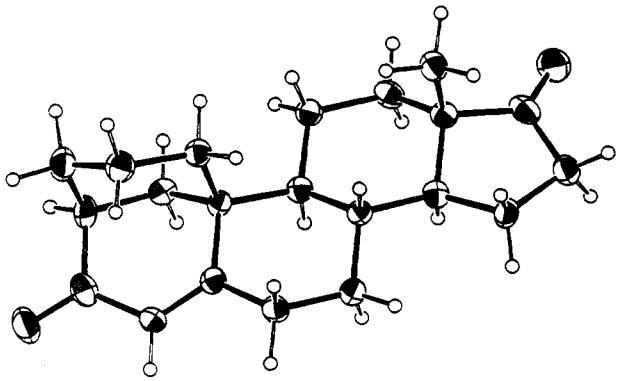


Figure 2. ORTEP drawing for (4α,10α)-4,19-cyclo-*A*-dihomoandrost-4b-ene-4a,17-dione (**14**).

sponding saturated ester which was then reduced to **11** with lithium aluminum hydride in ether. Tosylation of alcohol **11** using conditions which minimized the formation of chloroalkane[16] gave tosylate **12** which was deprotected with *p*-toluenesulfonic acid monohydrate in acetone to provide diketone **13** in 73% overall yield from **11**. The kinetic enolate of **13** was generated with lithium hexamethyldisilazane (LHMDS), and this enolate underwent intramolecular alkylation[17] to provide (4α,10α)-4,19-cyclo-*A*-dihomoandrost-4b-ene-13,17-dione (**14**) in 62% yield after chromatographic purification. The structure of **14** was confirmed by X-ray analysis. The ORTEP drawing (Figure 2) for **14** clearly shows the 6-membered ring containing the bridge in a chair conformation.

The preparation of bridged compounds **4a**, **4b**, **5**, and **8** using Lewis acid-catalyzed cyclization of A-ring dienol silyl ethers demonstrates the utility and generality of this synthetic methodology. Bridged compounds **4a**, **4b**, **5**, and **14** are time-dependent inhibitors of human placental aromatase. Enzyme kinetic data for these compounds will be the subject of a forthcoming report.

Experimental Section

General Methods and Materials. Melting points were determined in open capillary tubes and are uncorrected. TLC analyses were performed with Merck DC-F_{254} or Analtech GHLF silica gel plates, with visualization by alkaline permanganate and UV irradiation. Flash chromatography was performed with Merck silica gel 60 (0.040–0.063 mm). NMR spectra were recorded at 75 MHz for ^{13}C, 282 MHz for ^{19}F, and at 300 MHz for ^{1}H in $CDCl_3$ unless otherwise indicated; ^{19}F NMR signals are reported in ppm from $CFCl_3$. MS and HRMS data were recorded at 70 eV using computerized peak matching with perfluorokerosene as the HRMS reference. All reactions were run under an inert atmosphere. The organic extracts were dried over anhydrous $MgSO_4$ or Na_2SO_4 prior to solvent removal on a rotary evaporator.

TMSCl was distilled from BaO prior to use. $TiCl_4$ (Aldrich, 1.0 M in CH_2Cl_2) was used from a freshly opened bottle, and anhydrous CH_2Cl_2 (Aldrich) was used without further drying. 19-Hydroxyandrost-4-ene-3,17-dione (**1a**) was purchased from Diosynth. 19-Mercaptoandrost-4-ene-3,17-dione (**1b**),[4] 19-(trifluoroacetamido)androst-4-ene-3,17-dione (**1c**),[5] and 3,17-bis-[1,2-ethanediylbis(oxy)]-androst-5-ene-19-carboxyaldehyde (**9**)[5] were prepared as previously described. TsCl was purified by distillation under reduced pressure. All other reagents were obtained from commercial sources and used without further purification.

19-[(2-Methoxyethoxy)methoxy]androst-4-ene-3,17-dione (2a). A solution of **1** (4.54 g, 15.0 mmol), diisopropylethylamine (5.23 mL, 30.0 mmol), and MEMCl (2.57 mL, 22.5 mmol) in CH_2Cl_2 (40 mL) was stirred for 20 h. The reaction mixture was diluted with CH_2Cl_2 (60 mL), and the organics were washed with H_2O (75 mL), 0.5 N HCl (2 × 75 mL), saturated aqueous $NaHCO_3$ (35 mL), and brine (75 mL). The resulting oil was chromatographed (65% EtOAc/hexane) to provide **2a** (4.44 g, 76%) as a pale yellow, viscous oil: ^{1}H NMR δ 5.89 (d, 1 H, J = 1.3 Hz, vinyl), 4.71 and 4.66 (pr d, 2 H, J = 6.9 Hz, OCH_2O), 3.93 (dd, 1 H, J = 9.6, 0.8 Hz, $^{1}/_{2}CH_2O$), 3.80 (d, 1 H, J = 9.6 Hz, $^{1}/_{2}CH_2O$), 3.68–3.52 (m, 4 H, OCH_2CH_2O), 3.39 (s, 3 H, OCH_3), 0.91 (s, 3 H, 18-CH_3); IR (KBr) 1738, 1670 cm^{-1}; MS (DCI/CH_4) m/z (rel intensity) 391 (MH^+, 100), 315 (70), 89 (86); HRMS m/z (M^+) calcd 390.2406, obsd 390.2401.

19-[[(2-Methoxyethoxy)methyl]thio]androst-4-ene-3,17-dione (2b). MEM ether **2b** was prepared using the same procedure described for the preparation of **2a**. Purification by chromatography (75% EtOAc/hexane) gave **2b** (1.83 g, 79%) as a colorless, viscous oil: ^{1}H NMR δ 5.90 (d, 1 H, J = 1.3 Hz, vinyl), 4.72 and 4.68 (pr d, 2 H, J = 11.7 Hz, OCH_2S), 3.74–3.54 (m, 4 H, OCH_2CH_2O), 3.39 (s, 3 H, OCH_3), 3.17 (dd, J = 12.0, 0.7 Hz, $^{1}/_{2}CH_2S$), 2.96 (d, 1 H, J = 12.0 Hz, $^{1}/_{2}CH_2S$), 0.93 (s, 3 H, 18-CH_3); MS (DCI/CH_4) m/z (rel intensity) 407 (MH^+, 38), 331 (100), 89 (24).

Anal. Calcd for $C_{26}H_{34}O_4S$: C, 67.94; H, 8.43. Found: C, 68.08; H, 8.37.

***N*-(3,17-Dioxoandrost-4-en-19-yl)-2,2,2-trifluoro-*N*-[(2-methoxyethoxy)methyl]acetamide (2c).** To a stirred suspension of KH (0.95 g, 8.30 mmol) in THF (40 mL) was added a solution of **1c** (3.00 g, 7.55 mmol) in THF (40 mL). After cessation of H_2 gas evolution, 18-crown-6 (2.99 g, 11.3 mmol) was added followed by MEMCl (1.21 mL, 10.6 mmol). After 1 h at rt, the reaction was refluxed for 25 h. Concentration to one-fourth the original reaction volume was followed by dilution with Et_2O (100 mL)/CH_2Cl_2 (50 mL). The organic layer was washed with saturated aqueous KCl (4 × 100 mL), dried, and concentrated. Chromatography (65% EtOAc/hexane) gave **2c** (1.09 g, 30%) as an oily, yellow foam: ^{1}H NMR δ 5.96 (s, 1 H, vinyl), 4.87 and 4.72 (pr d, 2 H, J = 11 Hz, NCH_2O), 4.32 and 3.91 (pr d, 2 H, J = 14 Hz, CH_2N), 3.57 (br s, 4 H, OCH_2CH_2O), 3.39 (s, 3 H, OCH_3), 0.94 (s, 3 H, 18-CH_3); IR ($CHCl_3$) 1736, 1700, 1670 cm^{-1}; MS (DCI/CH_4) m/z (rel intensity) 486 (MH^+, 100), 410 (65), 392 (12), 89 (19); HRMS m/z (MH^+) calcd 486.2467, obsd 486.2445.

[[19-[(2-Methoxyethoxy)methoxy]androsta-2,4,16-triene-3,17-diyl]bis(oxy)]bis[trimethylsilane] (3a). To a stirred solution of LDA, generated from diisopropylamine (1.21 mL, 8.60 mmol) and *n*-BuLi (3.33 mL of a 2.42 M solution in hexane, 8.07 mmol) in THF (25 mL) cooled to −20 °C was rapidly added a precooled (−20 °C) solution of TMSCl (2.39 mL, 18.82 mmol) in THF (3 mL). After 3 min, a precooled (−20 °C) solution of **2a** (1.05 g, 2.69 mmol) in THF (7 mL) was added dropwise, and the reaction was maintained at −20 °C for 30 min and then allowed to warm slowly to rt. After 30 min at rt, Et_3N (3 mL) was added, the reaction was diluted with Et_2O (150 mL), and the organics were washed with saturated aqueous $NaHCO_3$ (2 × 50 mL) followed by 20 mL of brine/saturated aqueous $NaHCO_3$ (3:1). The organics were dried and concentrated. Hexane was added to the residue and the mixture concentrated to remove any remaining Et_3N and give **3a**[18] in nearly quantitative yield as a colorless oil: ^{1}H NMR δ 5.46–5.43 (m, 1 H, vinyl), 4.71–4.63 and 4.66 (m and s, 3 H, vinyl and OCH_2O), 4.50–4.46 (m, 1 H, vinyl), 3.79–3.50 (m, 6 H, OCH_2CH_2O and CH_2O), 3.40 (s, 3 H, OCH_3), 0.88 (s, 3 H, 18-CH_3), 0.19 [s, 9 H, $Si(CH_3)_3$], 0.16 [s, 9 H, $Si(CH_3)_3$].

[[19-[[(2-Methoxyethoxy)methyl]thio]androsta-2,4,16-triene-3,17-diyl]bis(oxy)]bis[trimethylsilane] (3b). Using the same procedure described for the preparation of **3a**, except that the reaction was stirred for 1.5 h at rt and 5 mL of Et_3N were added prior to workup, **2b** (1.78 g, 4.38 mmol) was converted in nearly quantitative yield to **3b**[18] (oil): ^{1}H NMR (90 MHz) δ 5.50–5.37 (m, 1 H, vinyl), 4.78–4.57 and 4.63 (m and s, 3 H, vinyl and OCH_2S), 4.52–4.40 (m, 1 H, vinyl), 3.77–3.43 (m, 4 H, OCH_2CH_2O), 3.36 (s, 3 H, OCH_3), 2.86 (s, 2 H, CH_2S), 0.89 (s, 3 H, 18-CH_3), 0.19 [s, 18 H, $2Si(CH_3)_3$].

(16) Kabalka, G. W.; Varma, M.; Varma, R. S. *J. Org. Chem.* **1986**, *51*, 2386.

(17) A similar intramolecular alkylation has been reported by: Lan-Hargest, H.-L.; Elliot, J. D.; Eggleston, D. S.; Holt, D. A.; Levy, M. A.; Metcalf, B. W. *Tetrahedron Lett.* **1987**, *28*, 6117.

(18) This trimethylsilyl dienol ether was not stable upon attempted purification or storage and was used immediately in the subsequent transformation.

N-[3,17-Bis[(trimethylsilyl)oxy]androsta-2,4,16-trien-19-yl]-2,2,2-trifluoro-N-[(2-methoxyethoxy)methyl]acetamide (3c). Using the same procedure described for the preparation of **3a**, except that 10 equiv of TMSCl and 10 mL of Et_3N were used, **2c** (1.08 g, 2.22 mmol) was converted in nearly quantitative yield to **3c**[18] (pale yellow, viscous oil): ^1H NMR δ 5.49–5.45 (m, 1 H, vinyl), 4.94 and 4.86 (pr d, 2 H, J = 11 Hz, OCH_2N), 4.60–4.52 (m, 1 H, vinyl), 4.52–4.46 (m, 1 H, vinyl), 3.84 and 3.78 (pr d, 2 H, J = 15 Hz, CH_2N), 3.55 (s, 4 H, OCH_2CH_2O), 3.38 (s, 3 H, OCH_3), 0.84 (s, 3 H, 18-CH_3), 0.19 [s, 18 H, $2Si(CH_3)_3$].

(4α,10α)-4,19-Cyclo-A-dihomo-2-oxaandrost-4b-ene-4a,17-dione (4a).[19] To a rapidly stirred solution of $TiCl_4$ (8.1 mL of a 1.0 M solution in CH_2Cl_2, 8.1 mmol) in additional CH_2Cl_2 (30 mL) at −20 °C was slowly added a precooled (−20 °C) solution of **3a** (ca. 2.69 mmol) in CH_2Cl_2 (4 mL). The resultant suspension was stirred at −20 °C for 30 min and then poured into saturated aqueous $NaHCO_3$ (75 mL). Additional CH_2Cl_2 (200 mL), saturated aqueous $NaHCO_3$ (150 mL), and H_2O (150 mL) were added, the layers were separated, and the aqueous layer was extracted with additional CH_2Cl_2 (2 × 35 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (75 mL), 0.5 N HCl (150 mL), and brine (50 mL). Chromatography (65% EtOAc/hexane) followed by trituration of the resultant solid with 8 mL of Et_2O/hexane (3:1) gave **4a** (0.30 g, 35% from **2a**) as a white solid: mp 214–217 °C (ethanol); ^1H NMR δ 6.11 (s, 1 H, vinyl), 3.89 (ddd, 1 H, J = 11.2, 1.8, 1.8 Hz, $^1/_4CH_2OCH_2$), 3.78 (dd, 1 H, J = 10.8, 2.6 Hz, $^1/_4CH_2OCH_2$), 3.60 (d, 1 H, J = 10.8 Hz, $^1/_4CH_2OCH_2$), 3.50 (dd, 1 H, J = 11.2, 2.5 Hz, $^1/_4CH_2OCH_2$), 0.91 (s, 3 H, 18-CH_3); ^{13}C NMR ($CDCl_3$) δ 219.8, 200.5, 165.5, 129.2, 68.8, 67.5, 51.2, 50.7, 47.3, 44.2, 40.4, 36.6, 35.6, 35.4, 32.1, 31.6, 29.4, 21.6, 20.7, 13.6; IR (KBr) 1734, 1658 cm^{-1}; MS (DCI/CH_4) m/z (rel intensity) 315 (MH^+, 100), 297 (10).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.14; H, 8.48.

(4α,10α)-4,19-Cyclo-A-dihomo-2-thiaandrost-4b-ene-4a,17-dione (4b). Thioether **4b** was prepared using the procedure described for the preparation of **4a**. Purification by consecutive chromatographies (50% EtOAc/hexane followed by 45% EtOAc/hexane) followed by crystallization from Et_2O gave **4b** (59 mg, 4% from **2b**) as a white solid, mp 183–189 °C: ^1H NMR δ 6.23 (d, 1 H, J = 2.1 Hz, vinyl), 3.04 (d, 1 H, J = 13.2 Hz, $^1/_4CH_2SCH_2$), 2.82 (dd, 1 H, J = 13.1, 3.5 Hz, $^1/_4CH_2SCH_2$), 2.71–2.65 (m, 1 H), 0.91 (s, 3 H, 18-CH_3); ^{13}C NMR ($CDCl_3$) δ 219.9, 199.5, 164.6, 130.3, 53.1, 51.0, 47.3, 42.1, 39.3, 38.1, 35.7, 34.5, 32.1, 31.4, 29.9, 28.9, 28.6, 21.7, 20.2, 13.6; IR (KBr) 1738, 1666 cm^{-1}; MS (EI) m/z (rel intensity) 330 (M^+, 32), 261 (100), 97 (27), 91 (18), 61 (60), 55 (12), 41 (20); HRMS m/z (MH^+) calcd 331.1732, obsd 331.1720.

Also isolated was **6** (43 mg, 3%) as a white solid, mp 198–210 °C: ^1H δ 5.65 (dd, 1 H, J = 5.9, 1.5 Hz, vinyl), 3.08 (t, 1 H, J = 3.5 Hz, C-4 methine), 2.97 (d, 1 H, J = 12.3 Hz, $^1/_4CH_2SCH_2$), 2.86 (d, 2 H, J = 3.5 Hz, $^1/_2CH_2SCH_2$), 0.91 (s, 3 H, 18-CH_3); ^{13}C NMR δ 220.5, 214.2, 140.2, 122.6, 55.6, 51.9, 47.9, 40.5, 38.7, 38.5, 36.0, 34.1, 32.8, 32.6, 31.7, 30.4, 22.0, 20.3, 13.9; IR (KBR) 1738, 1714 cm^{-1}; HRMS m/z (MH^+) calcd 331.1732, obsd 331.1729.

(4α,10α)-2-(Trifluoroacetyl)-2-aza-4,19-cyclo-A-dihomoandrost-4b-ene-4a,17-dione (4c). Trifluoroacetamide **4c** was prepared using the procedure described for the preparation of **4a**, except the reaction was stirred at −20 °C for 1.5 h prior to workup. Chromatography (55% EtOAc/hexane) gave **4c** (86 mg, 9% from **2c**) as a white solid: ^1H NMR δ 6.06–6.01 (m, 1 H, vinyl), 4.62 (ddd, 1 H, J = 12.8, 2.2, 2.2 Hz, $^1/_4CH_2NCH_2$), 4.10–4.00 (m, 1 H, $^1/_4CH_2NCH_2$), 3.28 (dd, 1 H, J = 14.0, 3.2 Hz, $^1/_4CH_2NCH_2$), 2.92 (d, 1 H, J = 12.8 Hz, $^1/_4CH_2NCH_2$), 0.95 (s, 3 H, 18-CH_3); ^{13}C NMR δ 219.8, 197.9, 165.5, 156.9 (q, $COCF_3$), 128.6, 116.2 (q, CF_3), 51.1, 50.6, 47.42, 47.40, 47.3, 44.6, 42.8, 40.6, 37.4, 35.6, 35.0, 32.4, 31.4, 29.3, 21.6, 20.6, 13.7; ^{19}F NMR δ 68.62 (s, CF_3); IR ($CHCl_3$) 1736, 1692, 1666 cm^{-1}; MS (DCI/CH_4) m/z (rel intensity) 410 (MH^+, 100).

Anal. Calcd for $C_{22}H_{26}F_3NO_3$: C, 64.54; H, 6.40; N, 3.42. Found: C, 64.42; H, 6.79; N, 3.21.

(4α,10α)-2-Aza-4,19-cyclo-A-dihomoandrost-4b-ene-4a,17-dione (5). A solution of **4c** (72 mg, 0.18 mmol) in CH_3OH (15 mL) and 10% aqueous K_2CO_3 (2.5 mL) was stirred at rt for 2.5 h, concentrated to one-third the original volume, and poured into 5% aqueous K_2CO_3 (25 mL)/CH_2Cl_2 (35 mL). The aqueous layer was extracted with additional CH_2Cl_2 (2 × 15 mL), and the combined organics were washed with 5% aqueous K_2CO_3 (25 mL) followed by 20 mL of brine/5% aqueous K_2CO_3 (3:1). Chromatography (7% $CH_3OH/CHCl_3$) gave **5** (38 mg, 69%) as a white solid: mp 168–171 °C; ^1H NMR δ 6.15 (d, 1 H, J = 1.9 Hz, vinyl), 2.98 (ddd, 1 H, J = 13.5, 1.9, 1.9 Hz, $^1/_4CH_2NCH_2$), 2.90 (d, 1 H, J = 13.0 Hz, $^1/_4CH_2NCH_2$), 2.78 (dd, 1 H, J = 13.0, 2.4 Hz, $^1/_4CH_2NCH_2$), 2.73 (dd, 1 H, J = 13.5, 3.4 Hz, $^1/_4CH_2NCH_2$), 0.91 (s, 3 H, 18-CH_3); ^{13}C NMR δ 220.1, 201.7, 166.4, 129.4, 51.3, 51.2, 47.4, 47.3, 45.8, 44.0, 40.5, 37.7, 35.7, 35.0, 32.2, 31.5, 29.5, 21.7, 20.3, 13.6; IR ($CHCl_3$) 3328, 1738, 1664 cm^{-1}; HRMS m/z (M^+) calcd 313.2042, obsd 313.2030.

[[19-[(2-Methoxyethoxy)methoxy]-17-oxoandrosta-3,5-dien-3-yl]oxy]trimethylsilane (7). To a solution of **2a** (0.46 g, 1.18 mmol), Et_3N (0.98 mL, 7.06 mmol), and 4-(dimethylamino)pyridine (72 mg, 0.59 mmol) in DMF (6 mL) was added TMSCl (0.75 mL, 5.89 mmol), and the reaction was heated to reflux. After 6.5 h, the reaction was allowed to cool and stirred at rt overnight. The reaction was diluted with hexane (45 mL) and washed with saturated aqueous $NaHCO_3$ (40 mL). The aqueous layer was extracted with additional hexane (20 mL), and the combined organics were washed with saturated aqueous $NaHCO_3$ (30 mL) followed by brine (15 mL). Flash chromatography (45% EtOAc/hexane) gave **7** (0.41 g), which contained some residual hexane, as a pale yellow oil: ^1H NMR (90 MHz) δ 5.29–5.08 (m, 2 H, both vinyl), 4.54 (s, 2 H, OCH_2O), 3.67–3.33 (m, 6 H, 3 CH_2O), 3.27 (s, 3 H, OCH_3), 0.83 (s, 3 H, 18-CH_3), 0.14 [s, 9 H, $Si(CH_3)_3$].

1,2,6,7,8,9,11,12,13,14,15,16-Dodecahydro-6,10-(methanoxymethano)-10H-cyclopenta[a]phenanthrene-3,17-dione (8). Bridged compound **8** was prepared using the procedure for the preparation of **4a**, except 1.1 equiv of $TiCl_4$ were used and the reaction was stirred at −20 °C for 1 h prior to workup. Trituration of the resultant oily solid with Et_2O, followed by digestion and filtration, gave **8** (123 mg, 46% from **2a**) as a white solid, mp 189–201 °C: ^1H NMR δ 5.87 (s, 1 H, vinyl), 4.16–4.06 (m, 2 H, $^1/_2CH_2OCH_2$), 3.76 (ddd, 1 H, J = 11.1, 2.3, 2.3 Hz, $^1/_4CH_2OCH_2$), 3.37 (dd, 1 H, J = 11.5, 1.4 Hz, $^1/_4CH_2OCH_2$), 2.92–2.78 (m, 1 H), 0.98 (s, 3 H, 18-CH_3); ^{13}C NMR δ 220.0, 198.4, 169.8, 120.5, 73.6, 73.2, 52.4, 52.2, 48.3, 41.6, 40.7, 37.7, 35.7, 35.4, 33.3, 31.5, 27.2, 21.7, 21.4, 14.4; IR (KBr) 1736, 1670 cm^{-1}; HRMS m/z (MH^+) calcd 315.1960, obsd 315.1939.

3-[3,3:17,17-Bis[1,2-ethanediylbis(oxy)]estr-5-en-10-yl]-2-propenoic Acid Ethyl Ester (10). To a stirred solution of triethyl phosphonoacetate (99.2 mL, 0.50 mol) in THF (500 mL) cooled to −60 °C was added n-BuLi (200 mL of a 2.5 M solution in hexane, 0.50 mol). Upon warming to −30 °C, a solution of **9** (55.4 g, 0.140 mol) in THF (500 mL) was added. The reaction was warmed to reflux, 300 mL of solvent was removed by distillation, and the remaining solution was heated at reflux for 24 h. The reaction was cooled, poured into H_2O (750 mL), and extracted with EtOAc (750 mL and 2 × 250 mL). The combined organics were washed with H_2O (50 mL), dried, and concentrated. Chromatography (50% EtOAc/hexane) gave **10** (57.0 g, 89%) as a white solid: ^1H NMR δ 6.93 and 5.78 (2d, 2 H, J = 15.9 Hz, CH=$CHCO_2Me$), 5.68–5.62 (m, 1 H, vinyl), 4.27–4.16 (m, 2 H, OCH_2), 4.02–3.79 (m, 8 H, 2 OCH_2CH_2O), 1.31 (t, J = 7.2 Hz, CH_3), 0.72 (s, 3 H, 18-CH_3); IR (KBr) 1718 cm^{-1}; MS (DCI/CH_4) m/z (rel intensity) 459 (MH^+, 100), 413 (20), 397 (14), 99 (14).

Anal. Calcd for $C_{27}H_{38}O_6$: C, 70.72; H, 8.35. Found: C, 70.46; H, 8.72.

10-(3-Hydroxypropyl)estr-5-ene-3,17-dione Cyclic Bis(1,2-ethanediyl acetal) (11). To liquid NH_3 (200 mL) was added a solution of **10** (10.1 g, 22.0 mmol) in absolute EtOH (60 mL) and Et_2O (40 mL). Lithium metal (3.5 g, 0.50 mol) was added in portions over 1 h. The NH_3 was then removed, and the residue was treated with H_2O (60 mL) and extracted with Et_2O (3 × 75 mL). The combined organics were washed with H_2O, dried, and concentrated. Chromatography (50% EtOAc/hexane) gave **11**

(19) The name originally assigned to **4a** by Chemical Abstracts was [3*R*-(3α,6aα,6bα,8aβ,11aα,11bβ)]-3,4,6b,7,8,8a,10,11,11a,11b,12,13-dodecahydro-8a-methyl-6*H*-3,6a-methanocyclopenta[5,6]naphth[1,2-*c*]-oxacin-2,9-dione. This name appears for **4a** in the following patent: Peet, N. P.; Johnston, J. O.; Burkhart, J. P. U.S. Patent 5,099,037, Mar 24, 1992.

(5.8 g, 63%) as a white foam: ^{1}H NMR δ 5.57–5.51 (m, 1 H, vinyl), 4.03–3.82 (m, 8 H, $2CH_2CH_2O$), 3.64–3.53 (m, 2 H, CH_2O), 0.90 (s, 3 H, 18-CH_3); ^{13}C NMR δ 137.4, 124.1, 119.5, 109.5, 65.1, 64.5, 64.3, 64.1, 63.8, 51.5, 50.6, 45.9, 41.8, 39.3, 36.7, 34.0, 33.6, 31.0, 30.7, 30.2, 29.8, 27.2, 22.3, 21.1, 14.7; HRMS m/z (MH^+) calcd 419.2797, obsd 419.2775.

10-[3-[[(4-Methylphenyl)sulfonyl]oxy]propyl]estr-4-ene-3,17-dione (13). To a stirred solution of 11 (1.5 g, 35.8 mmol) in $CHCl_3$ (369 mL, EtOH free) cooled to 0 °C was added pyridine (8.7 mL, 107.6 mmol) followed by TsCl (13.7 g, 71.9 mmol) in portions. After 72 h at 0 °C, the reaction was washed with 0.5 N HCl (200 mL) and H_2O (200 mL) followed by saturated aqueous $NaHCO_3$ (200 mL), dried, and concentrated. The resultant crude 12[20] was dissolved in acetone (300 mL), and $TsOH·H_2O$ (1.2 g, 6.3 mmol) was added. After 20 h, the reaction was concentrated and the residue was partitioned between EtOAc (400 mL) and H_2O (150 mL). The organics were washed with H_2O (100 mL), dried, and concentrated. Chromatography (15% EtOAc/$CHCl_3$) gave 13 (12.6 g, 73% from alcohol 11) as a white foam: ^{1}H NMR δ 7.79 and 7.35 (pr d, 4 H, J = 8.1 Hz, aryl), 5.87 (s, 1 H, vinyl), 4.03 (t, 2 H, J = 5.5 Hz, CH_2O), 2.46 (s, 3 H, aryl-CH_3), 0.92 (s, 3 H, 18-CH_3); IR (KBr) 1738, 1670 cm^{-1}; MS (DCI/CH_4) m/z (rel intensity) 485 (MH^+, 100), 331 (17), 313 (17).

(20) Compound 12 was initially purified by chromatography (35% EtOAc/hexane) but was used crude in subsequent runs to improve the overall yield for the conversion of 11 to 13, and because of the relative instability of 12. For 12: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 and 7.36 (pr d, 4 H, aryl), 5.53–5.49 (m, 1 H, vinyl), 4.03–3.81 (m, 10 H, $2OCH_2CH_2O$ and CH_2O), 2.46 (s, 3 H, aryl-CH_3), 0.83 (s, 3 H, 18-CH_3); MS (DCI/CH_4) m/z (rel intensity) 574 (22), 573 (MH^+, 60), 419 (21), 402 (26), 401 (100), 400 (16), 399 (28), 357 (21), 339 (21), 217 (23), 173 (43), 93 (17). Anal. Calcd for $C_{32}H_{44}O_7S$: C, 67.11; H, 7.74. Found: C, 67.19; H, 7.96.

Anal. Calcd for $C_{28}H_{36}O_5S$: C, 69.39; H, 7.49. Found: C, 69.05; H, 7.83.

(4α,10α)-4,19-Cyclo-*A*-dihomoandrost-4b-ene-4a,17-dione (14). To a stirred solution of LHMDS (1.50 mL of a 1.0 M solution in THF, 1.50 mmol) in additional THF (15 mL) cooled to −78 °C was added a precooled (−78 °C) solution of 13 (242 mg, 0.50 mmol) in THF (10 mL), dropwise. After 40 min, the reaction was allowed to warm slowly to rt. After 1 h at rt, the reaction was poured into 0.5 N HCl (60 mL) and extracted with CH_2Cl_2 (60 mL and 30 mL). The combined organics were washed with 0.5 N HCl (60 mL) and saturated aqueous $NaHCO_3$ (60 mL) followed by brine (50 mL). Chromatography (45% EtOAc/hexane) gave 14 (96 mg, 62%) as a white solid: mp 180–183 °C; ^{1}H NMR δ 6.02 (s, 1 H, vinyl), 0.91 (s, 3 H, 18-CH_3); ^{13}C NMR δ 220.4, 202.6, 167.1, 128.1, 52.1, 51.1, 47.4, 43.1, 40.3, 38.8, 35.7, 34.6, 32.2, 31.4, 29.9, 27.3, 25.3, 21.7, 20.1, 18.8, 13.6; IR (KBr) 1740, 1658 cm^{-1}; MS (DCI/CH_4) m/z (rel intensity) 313 (MH^+, 100), 295 (18).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.63; H, 9.33.

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Supplementary Material Available: NMR spectra and X-ray data for 14 (43 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Medium-Sized Cyclophanes. 21.[1] Preparation and Reduction of *syn*- and *anti*-[3.2]Metacyclophanequinone and *anti*-[4.2]Metacyclophanequinone

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The title compounds, *anti*- and *syn*-[3.2]metacyclophanequinone (**12a**) and (**12b**), were prepared by oxidation of the corresponding *anti*- and *syn*-9,17-dihydroxy-6,14-di-*tert*-butyl[3.2]metacyclophanes (**10a**) and (**10b**) with $Tl(OCOCF_3)_3$ in CF_3COOH. When *anti*-[3.2]quinonophane (**12a**) was reduced with Zn powder in acetic acid, the corresponding tetrahydroxy derivative **14a** was obtained, which was converted to the quinhydrone **13a** by treatment with an equimolar amount of quinonophane **12a** in refluxing THF. The electronic spectrum of **13a** shows a band due to a charge-transfer complex at 400 nm (log ε 2.45). In contrast, attempted reduction of *syn*-quinonophane (**12b**) with Zn powder in acetic acid yielded only a complex mixture of products. It was also found that *syn*-quinonophane was easily converted to the corresponding [2 + 2] cycloadducts **16** and **17** by irradiation with sunlight or tungsten lamp. When oxidation of *anti*- and *syn*-10,18-dihydroxy-7,15-di-*tert*-butyl[4.2]-metacyclophanes (**11a**) and (**11b**) with $Tl(OCOCF_3)_3$ in CF_3COOH was carried out under the same conditions as [3.2]metacyclophanes, both compounds gave *anti*-metacyclophanequinone (**18a**). This finding suggests that the ring inversion to the thermodynamically more stable anti conformation is possible in the [4.2]metacyclophanequinone. While *anti*-[4.2]metacyclophanequinone (**18a**) was reduced with Zn powder in acetic acid, the color change of reaction mixture from pale yellow to reddish brown was observed due to the formation of the corresponding quinhydrone **19**. However, the attempted isolation of the quinhydrone **19** was unsuccessful. Rather, the fully reduced tetrahydroxy derivative **20** was obtained in 91% yield.

Introduction

The first charge-transfer bridged aromatic compound, [2.2]paracyclophanequinone (1) was prepared from [2.2]-paracyclophane by Cram[2] in 1966. Subsequently, the chemistry of the charge-transfer cyclophanes has been extensively studied.[3-8] Staab and Rebafka[5,9] reported that

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