Studies on Chromium(0)-Promoted Higher-Order Cycloaddition-Based Benzannulation. Total Synthesis of (+)-Estradiol

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Received March 29, 1999

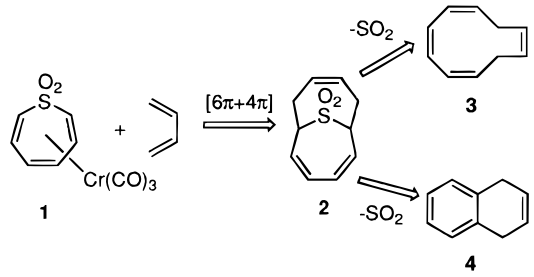
Abstract: A benzannulation sequence featuring [6π + 4π] cycloaddition of (η^6-thiepin 1,1-dioxide)-tricarbonylchromium(0) complexes with highly substituted dienes followed by Ramberg−Bäcklund rearrangement has been developed. Enantiomerically pure (+)-estradiol (estra-1,3,5(10)-triene-3,17β-diol) has been synthesized by employing a higher-order cycloaddition between an appropriately substituted thiepin dioxide chromium(0) complex and a diene partner derived from an enantiomerically pure indandione precursor as the key ring construction event. Subsequent Ramberg−Bäcklund rearrangement of this cycloadduct and routine functional group interchanges afforded the steroid target.

In recent years, higher-order cycloaddition reactions have been shown to be powerful methods for the rapid construction of stereochemically rich and structurally elaborate polycyclic systems in a variety of contexts.[1,2] Certainly, one of the most versatile 6π partners for applications to natural product synthesis is the thiepin dioxide ligand system. Complex **1** has been shown to undergo smooth cycloaddition with a range of 4π partners to afford cycloadducts that are amenable to various postcycloaddition heteroatom extrusion protocols.[3]

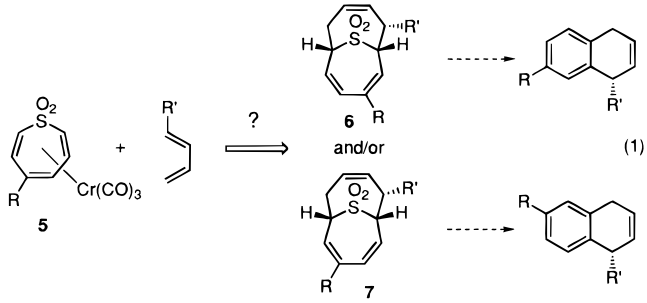
Ten-membered carbocycles, for example, can be quickly accessed via a cycloaddition−cheletropic extrusion sequence **1** → **2** → **3** (Scheme 1). A particularly powerful and complementary application of this cycloaddition−heteroatom extrusion technology is the net benzannulation sequence **1** → **2** → **4** (Scheme 1), wherein SO_2 excision occurs as part of a Ramberg−Bäcklund rearrangement process.[4] Noteworthy features of this protocol include the *simultaneous formation of two rings*, rather than the usual one, and that *all six* of the carbon atoms comprising the incipient benzo ring are delivered by the thiepin dioxide triene moiety.

While these sequences are quite attractive and show much promise in relatively simple applications, several critical issues must be addressed in more complex environments if this methodology is to become a generally useful addition to the synthetic repertoire. Among the most important of these is establishing the regioselectivity profile of the cycloaddition step when unsymmetrically substituted trienes are employed, and

Scheme 1



determining whether structurally elaborate diene partners can, in fact, participate in the process in an efficient fashion (eq 1).



We wish to report that these questions have now been answered within the setting of a total synthesis of enantiomerically pure (+)-estradiol (**8**), one of the most potent estrogens, in which the higher-order cycloaddition−Ramberg−Bäcklund protocol serves as the key strategy level transformation.

Construction of the tetracyclic steroid nucleus has long served as an important forum for illustrating the scope and limitations of new synthetic methods,[5] and developing a novel approach into the estrone ring system was viewed as an excellent opportunity for evaluating several critical aspects of our cycloaddition benzannulation protocol. The salient features of the synthesis strategy are outlined in Scheme 2. In terms of the

(1) For general reviews, see: (a) Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579. (b) Rigby, J. H. In *Advances in Metal−Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1995; Vol. 4, pp 89−127. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (d) Rigby, J. H. *Org. React.* **1997**, *49*, 331.

(2) For some representative applications of Cr(0)-mediated cycloadditions, see: (a) Rigby, J. H.; Sugathapala, P.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 8851. (b) Rigby, J. H.; Niyaz, N. M.; Short, K.; Heeg, M. J. *J. Org. Chem.* **1995**, *60*, 7720. (c) Rigby, J. H.; Pigge, F. C. *J. Org. Chem.* **1995**, *60*, 7392. (d) Rigby, J. H.; Warshakoon, N. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6094. (e) Rigby, J. H.; Niyaz, N. M.; Sugathapala, P. *J. Am. Chem. Soc.* **1996**, *118*, 8178. (f) Rigby, J. H.; Kirova-Snover, M. *Tetrahedron Lett.* **1997**, *38*, 8153. (g) Rigby, J. H.; Hu, J.; Heeg, M. J. *Tetrahedron Lett.* **1998**, *39*, 2265.

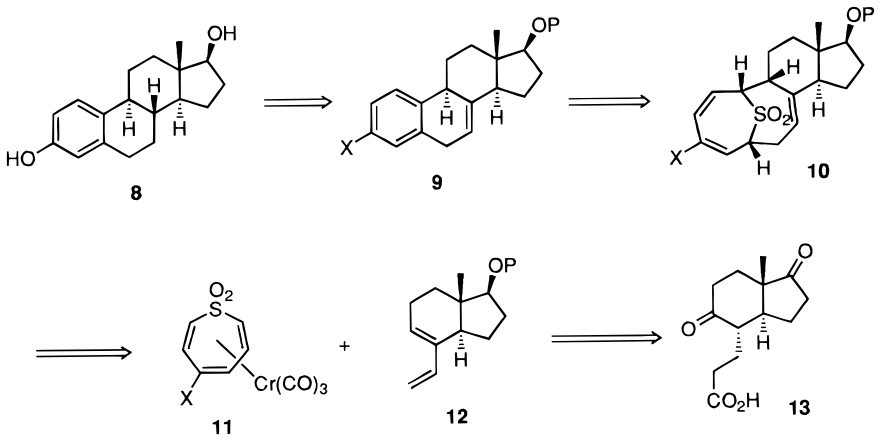
(3) (a) Rigby, J. H.; Ateeq, H. S.; Krueger, A. C. *Tetrahedron Lett.* **1992**, *33*, 5873. (b) Rigby, J. H.; Krueger, A. C. *Synlett*, **1993**, 829.

(4) Rigby, J. H.; Warshakoon, N. C. *J. Org. Chem.* **1996**, *61*, 7644.

(5) For an overview of some recent advances in the synthesis of estrone steroids, see: (a) Zeelen, F. *J. Nat. Prod. Rep.* **1994**, *11*, 607. (b) Tietze, L. F.; Nöbel, T.; Spescha, M. *J. Am. Chem. Soc.* **1998**, *120*, 8971.

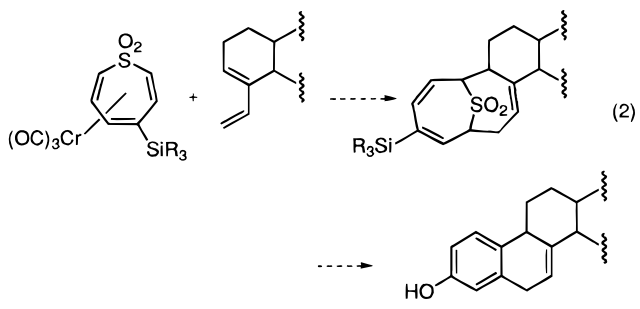
10.1021/ja991016w CCC: $18.00
Published on Web 08/31/1999

Scheme 2



synthesis end-game, it was envisioned that the $\Delta^{7,8}$-intermediate **9** derived directly from Ramberg−Bäcklund rearrangement of key cycloadduct **10** could be processed without much difficulty to deliver the requisite trans-BC fusion in **8**. However, at the outset of this investigation crucial questions remained regarding regiocontrol during the cycloaddition between 4-substituted thiepin dioxide complex **11** and the structurally complex diene **12**. A key feature of the synthesis was the expectation that diene **12** could be easily prepared from the enantiomerically pure indandione **13**,[6] which is readily available from microbial degradation of the abundant soya sterols sitosterol and campesterol.[7]

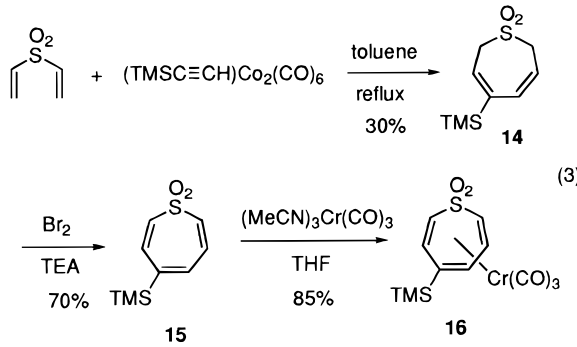
With a viable strategy delineated, attention was initially directed toward establishing the regiochemical preferences for the photocycloaddition of substituted thiepin dioxide complexes with various dienes. This aspect of the strategy design was a source of some concern, since earlier studies in our laboratory on the regioselectivity of metal-mediated [$6\pi + 4\pi$] cycloadditions with substituted cycloheptatriene complexes revealed a mixed set of results in which no clear selectivity trends could be discerned when electronic effects were considered.[8] This situation is in stark contrast to the Diels−Alder and other cycloaddition reactions in which electronic effects strongly and predictably influence the regiochemical course of reaction. On the basis of our view of the mechanistic pathway followed by Cr(0)-promoted cycloadditions,[8] it was reasoned that properly designed and positioned substituents of sufficient steric hindrance might offer a reliable regiocontrol strategy. Silicon-based substituents were selected for initial study since they are frequently effective steric control elements, and there exists a number of methods by which they can be transformed, after cycloaddition, into oxygen substituents as required in the steroid target molecule.[9,10] A search for preparative methods for these complexes was then initiated.



(2)

(6) We are grateful to Pharmacia & Upjohn for providing very generous supplies of this compound for our studies.

As studies on making substituted thiepin dioxide ligands moved forward, it became clear that convenient access to these 6π partners was quite difficult, if not impossible to achieve, using conventional preparative methods. However, an intriguing and somewhat obscure report a number of years ago by Khand and Pauson[11] on a cobalt-mediated cycloaddition between phenylacetylene and divinyl sulfone to give 4-phenyldihydrothiepin dioxide presented a possible solution to our problem, if the reaction could be successfully extended to include bulkier silicon-substituted alkynes. Thus, the corresponding trimethylsilylacetylenedicobalt hexacarbonyl complex was prepared and exposed to divinyl sulfone in refluxing toluene. To our delight, this afforded the heterocycle **14** in modest, but serviceable yields. Although the yield was relatively low, the reaction proved to be amenable to scale-up so sufficient quantities of material could be secured in this fashion. Subsequent oxidation to the triene via the usual halogenation−dehydrohalogenation protocol and metalation under standard conditions provided the well-behaved complex **16** in good yield.



(3)

A brief examination of this unusual Co-mediated cycloaddition process to assess its generality for preparing a range of substituted dihydrothiepin dioxides revealed that bis(trimeth-

(7) (a) Biggs, C. B.; Pyke, T. R.; Wovcha, M. G. U.S. Patent 4,062,729, 1977; *Chem. Abstr.* **1978**, *88*, P188129t. (b) Cooper, G. F.; Van Horn, A. R. *Tetrahedron Lett.* **1981**, *22*, 1479.

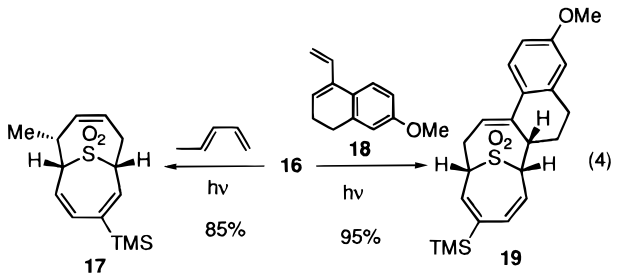
(8) Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Cuisiat, S. V.; Ferguson, M. D.; Henshilwood, J. A.; Krueger, A. C.; Ogbu, C. O.; Short, K. M.; Heeg, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 1382.

(9) (a) Partch, R. E. *J. Am. Chem. Soc.* **1967**, *89*, 3662. (b) Kalman, J. R.; Pinhey, J. T.; Sternhell, S. *Tetrahedron Lett.* **1972**, 5369.

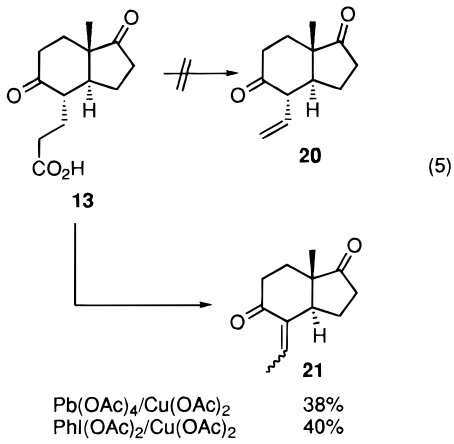
(10) (a) Kumada, M.; Tamao, K.; Yoshida, J. *J. Organomet. Chem.* **1982**, *239*, 115. (b) Fleming, I. In *Organosilicon and Bioorganosilicon Chemistry*; Sakurai, H., Ed.; Ellis Horwood: Chichester, 1985; p 197.

(11) Khand, I. U.; Pauson, P. L. *Heterocycles* **1978**, *11*, 59.

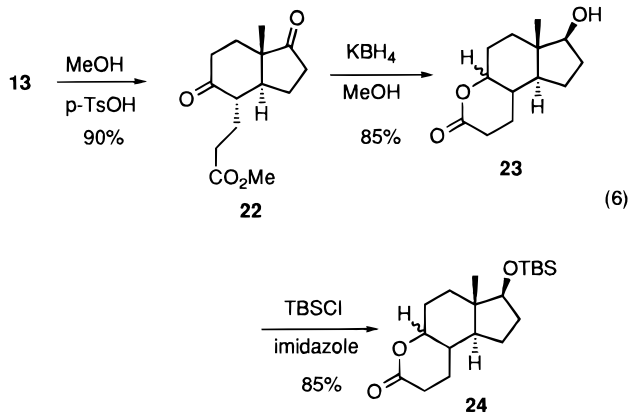
ylsilyl)acetylene did not undergo cycloaddition under these conditions, although diphenylacetylene did. A thorough appraisal of this reaction is now underway in our laboratory.



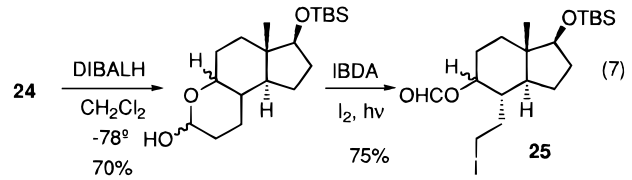
With the key TMS-substituted complex **16** in hand, attention turned to exploring its cycloaddition chemistry to evaluate regioselection trends. Thus, irradiating **16** in the presence of piperylene afforded cycloadduct **17** *as a single stereo- and regioisomer*. As anticipated, the reaction proceeded through an endo transition state and the diene approached the triene from what would appear to be the least hindered orientation. A more revealing result was obtained by reacting complex **16** with the structurally elaborate diene **18**,[12] which provided tetracyclic adduct **19** in nearly quantitative yield, once again, as a single isomer. It was gratifying that both cycloaddition events proceeded with high regioselectivity in the sense required for the projected synthesis of estradiol.



With the successful synthesis and cycloaddition chemistry of complex **16** established, construction of enantiomerically pure diene **12** from indandione **13** became our principal focus (see Scheme 2). Compound **13** is, in principle, a very attractive steroid CD ring building block and has been employed for that purpose on several previous occasions;[7a,13] however, it had never been modified in a fashion that provided useful precedent to support our projected processing into the diene. Initially, it was envisioned that oxidative decarboxylation of the proprionate side chain in **13** using one of several Pb(IV)- or I(III)-based methods should lead to vinyl dione **20**, which could then be further converted to the desired diene **12** in straightforward fashion. Unfortunately, subjecting the dione acid to either $Pb(OAc)_4$/$Cu(OAc)_2$[14] or $PhI(OAc)_2$/$Cu(OAc)_2$[15] led only to the conjugated enone **21** as a mixture of isomers in modest yields.



In an effort to install functionality that would preclude the undesired isomerization process, **13** was efficiently converted by a series of routine reactions into the protected hydroxy lactone **24** as a mixture of isomers (eq 6). This material was then further transformed into iodoformate **25** via treatment of the corresponding lactol with iodobenzene diacetate (IBDA) and I_2.[16] It was anticipated that dehydrohalogenation to the vinyl group could be achieved in **25** without concomitant isomerization, since the ethylidene isomer would no longer benefit from conjugation with a carbonyl group.



The success of this trial cleavage prompted a more detailed examination of the preparation of the lactol precursor in an effort to effectively control the stereochemistry of the ketone reduction step. To our delight, it was found that L-Selectride (Aldrich) at −78 °C converted diketo ester **22** directly into keto lactol **26** in excellent yield with complete control of stereochemistry. It is noteworthy that reduction of the cyclopentanone did not occur under these conditions. This material was then subjected to the IBDA/I_2 fragmentation conditions, which afforded the stereochemically homogeneous iodoformate **27** in good yield. Unfortunately, attempted dehydrohalogenation of this material using a variety of bases gave the desired vinyl formate in no better than 30% yield (eq 8). Clearly, an alternative entry into the diene was required.

Based on our own earlier experience with oxidative decarboxylation using $Pb(OAc)_4$/$Cu(OAc)_2$ and recognizing that related lactol cleavages can be effected with $FeSO_4$[17] and $Mn(OAc)_2$,[18] both in the presence of catalytic $Cu(OAc)_2$, we elected to explore modified cleavage conditions that incorporated $Cu(OAc)_2$ as an electron-transfer agent. It was hoped that these modified reaction conditions could produce the requisite alkene directly during the ring-opening step. In the event, we were most

(12) Woski, S. A.; Koreeda, M. *J. Org. Chem.* **1992**, *57*, 5736.

(13) (a) Guarna, A.; Occhiato, E. G.; Machetti, F.; Scarpi, D. *J. Org. Chem.* **1998**, *63*, 4111. (b) Stork, G.; Clark, G.; Weller, T. *Tetrahedron Lett.* **1984**, *25*, 5367. (c) Stork, G.; Clark, G.; Shiner, C. S. *J. Am. Chem. Soc.* **1981**, *103*, 4948.

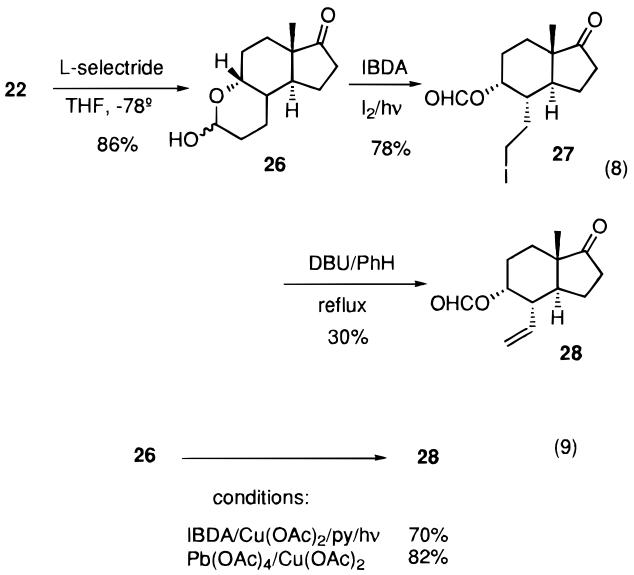
(14) (a) Sheldon, R. A.; Kochi, J. K. *Org. React.* **1972**, *19*, 279. (b) Kochi, J. K. *J. Am. Chem. Soc.* **1965**, *87*, 1811. (c) Kochi, J. K.; Bacha, J. D.; Bethea, T. W. *J. Am. Chem. Soc.* **1967**, *89*, 6538. (d) Kochi, J. K.; Bacha, J. D. *J. Org. Chem.* **1968**, *33*, 2746. (e) Ogibin, Y. N.; Katzin, M. I.; Nikishin, G. I. *Synthesis* **1974**, 889.

(15) Concepcion, J. I.; Francisco, C. G.; Freire, R.; Hernandez, R.; Salazar, J. A.; Suarez, E. *J. Org. Chem.* **1986**, *51*, 402.

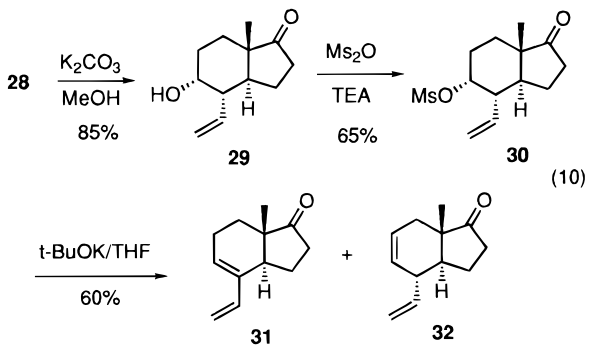
(16) Francisco, C. G.; Freire, R.; Rodriguez, M. S.; Suarez, E. *Tetrahedron Lett.* **1987**, *28*, 3397.

(17) Schreiber, S. L.; Hulin, B.; Liew, W. F. *Tetrahedron* **1986**, *42*, 2945.

(18) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 524.

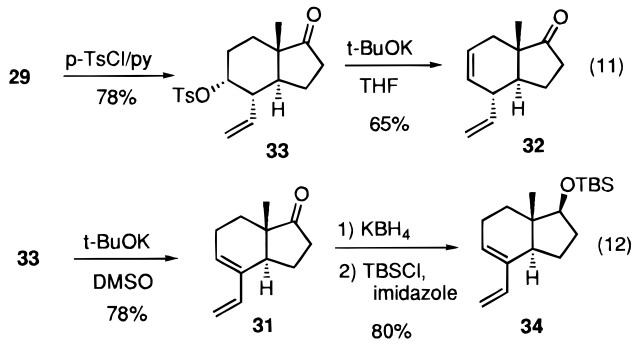


pleased to find that irradiating lactol **26** with a mixture of IBDA/cat. $Cu(OAc)_2$ and pyridine in cyclohexane afforded **28** in 70% yield. Even more encouraging for our purposes, a $Pb(OAc)_4$/$Cu(OAc)_2$ combination provided 82% of the desired vinyl formate **28**. It appears that these novel fragmentation conditions offer certain advantages over existing methods, and a detailed study of their scope and limitations is currently underway in our laboratory.

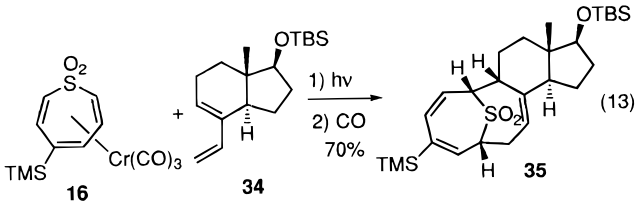


With a new and reliable fragmentation protocol at our disposal, the next task in this segment of the synthesis became the completion of the diene preparation via a trans-diaxial elimination of the alcohol resulting from the aforementioned cleavage process. Routine saponification of **28** yielded **29**, which was treated with Ms_2O/TEA to give the corresponding mesylate. Subsequent exposure of this compound to *t*-BuOK in THF at 0 °C gave a 60% yield of an inseparable mixture of the desired diene **31** and a regioisomeric diene **32** in a 1:2 ratio. This was a disappointing result, but it suggested that subtle modification of the reaction conditions could shift the product ratio in a more favorable direction.

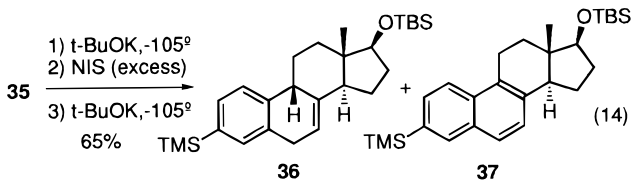
Toward this end, a second attempt to control this elimination process was carried out. Thus, alcohol **29** was converted to the tosylate **33** and again treated with *t*-BuOK/THF. Unfortunately, these conditions provided only the undesired diene **32** in 65% yield. We were quite pleased, however, when it was found that by performing the elimination in DMSO instead of THF the desired diene **31** was produced exclusively in a very respectable 78% yield. One final manipulation of this substrate was required prior to attempting the key cycloaddition step. The need for this particular operation was prompted by results from previous



cycloaddition studies in our laboratory that suggested the projected Cr(0)-promoted [$6\pi + 4\pi$] cycloaddition would proceed more efficiently and with greater selectivity if the ketone in **31** was reduced to the β-oriented alcohol and protected.[19] Therefore, **31** was reduced to the corresponding β-alcohol as a single isomer with KBH_4 and protected as the TBS ether in excellent overall yield for the two steps.



The stage was now set to carry out the crucial higher-order cycloaddition step to assemble the tetracyclic target system, and based on the preliminary studies described above, it was expected that this operation would proceed as required. In the event, a mixture of complex **16** and excess diene **34** were irradiated through a uranium glass filter[20] for several hours at which time the original 1,2-dichloroethane solvent was replaced with MeOH and the solution stirred under a blanket of CO for 15 h.[21] As anticipated, a single regio- and stereoisomer was isolated from this reaction. The previous model studies with complex **16** (vide supra) correctly predicted the regiochemical outcome of the current reaction, and the normal endo-selective cycloaddition pathway once again prevailed to deliver compound **35** in quite good yield. At this stage of the synthesis, it becomes important to note that the endo transition state that dominates these reactions delivers an adduct possessing the *unnatural* stereogenicity at C-9 (steroid numbering). We were, of course, well aware of this situation from the outset of this investigation, but assumed that subsequent manipulations of the substrate would afford the natural stereochemistry at this center as precedented in the steroid literature.

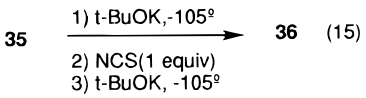


(19) Rigby, J. H.; Ateeq, H. S. *J. Am. Chem. Soc.* **1990**, *112*, 6442.

(20) It has been determined that cycloadditions involving thiepin dioxide complexes proceed best when irradiated through a uranium glass filter: ref 3a.

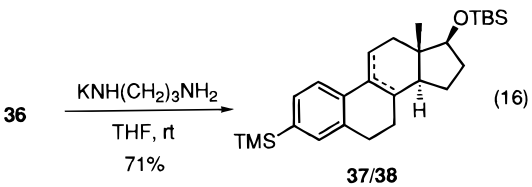
(21) Stirring under CO often enhances yields by collapsing intermediates and facilitating decomplexation: Rigby, J. H.; Krueger, A. C. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI: Greenwich, CT, 1995; Vol. 4, pp 1−40.

The projected end-game of the synthesis involved Ramberg−Bäcklund conversion of **35** into the benzo-fused tetracycle.[22] Following the sequence of steps that had proven most effective during previous studies,[4] **35** was treated sequentially with *t*-BuOK/THF at −105 °C, then excess NIS, and, finally, a second equivalent of *t*-BuOK/THF at −105 °C. This set of steps afforded a 65% yield of a mixture of the desired tetracycle **36** and an overoxidized, equilenin-type product, **37**. It was reasoned that the presence of excess NIS was responsible for the oxidation to **37**, so the reaction conditions were modified accordingly. Employing only 1 equiv of NIS did indeed suppress the formation of **37**, but it also had the undesired effect of depressing the yield of **36** to only 30%. After considerable experimentation it was found that the cleanest conversion to **36** could be achieved using 1 equiv of NCS as the halogen source (eq 15). It is interesting to note that in previous studies on this type of rearrangement, NCS was often the least effective electrophilic reagent.[4]



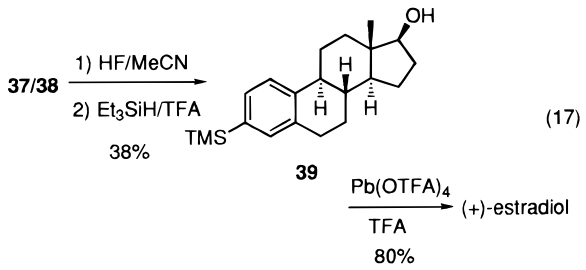
(15)

With **36** in hand, the final assault on the estrogen target required only reduction to the trans-fused tetracycle. To set the stage for this reduction, it was assumed that equilibration of the $\Delta^{7,8}$ unsaturation into conjugation with the A ring would be routine. Indeed, in the natural series, it is quite difficult to avoid this migration.[23] However, as pointed out above, compound **36** is epimeric to the natural series at C9, and as it turned out, this minor difference contributed significantly to the difficulties experienced in trying to move this alkene into conjugation with the A-ring. For example, no reaction occurred when **36** was treated with *t*-BuOK at room temperature in various solvents, and decomposition ensued under more forcing conditions. A number of other conditions were explored to no avail. Finally, potassium 3-aminopropylamide (KAPA), an exceptional base for effecting prototropic reactions, was examined.[24] To our disappointment, exposing **36** to KAPA in 3-aminopropylamine (APA) under standard conditions reported in the literature resulted only in recovered starting material. Replacing APA with THF, however, resulted in the disappearance of **36** to give an inseparable mixture of two new tetracycles tentatively assigned structures **37** and **38** in 71% yield. The replacement of the vinylic signal at δ 5.67 in the starting material with a new signal at δ 5.44 confirmed the complete disappearance of **36** and the appearance of a new isomer during this reaction. Both of the new compounds were considered to be useful for subsequent reduction to the requisite trans BC ring fusion.[25]



(16)

The mixture of **37** and **38** was first treated with HF/MeCN to remove the hydroxyl group protection, and the resultant alcohols were then exposed to Et_3SiH/TFA in benzene[25a,b] to provide the requisite trans-fused tetracycle **39** in 45% yield. The synthesis of (+)-estradiol was completed by transforming the trimethylsilyl substituent on the arene ring into the corresponding phenol using the well-known $Pb(OTFA)_4$/TFA procedure.[26] The resultant synthetic sample was shown to be identical in all regards with authentic (+)-estradiol.



(17)

This study has revealed a number of important attributes of thiepin dioxide as a 6π participant in the Cr(0)-promoted higher-order cycloaddition process. Structurally elaborate dienes react with good efficiency and high levels of regiocontrol are frequently obtained when sterically hindered substituents are present on the triene. These capabilities have been illustrated in an efficiently total synthesis of (+)-estradiol, and the success in this endeavor points to the utility of this chemistry in evermore challenging syntheses. In addition, a novel radical-based lactol fragmentation has been developed in conjunction with these studies, which may provide advantages over existing technology in this area.

Experimental Section[27]

General Procedure for the Preparation of Alkynecobalt Complexes. Dicobalt octacarbonyl (5.0 g, 14.62 mmol) was dissolved in CH_2Cl_2 (20 mL), and to this mixture was added a neat solution of the alkyne (1.2 equiv) at room temperature. A rapid evolution of CO gas resulted, and the color of the solution changed from purple to dark red. At the completion of the reaction as indicated by TLC analysis (10−15 min), the solvent was removed in vacuo and the crude residue was chromatographed on silica gel with 100% hexane as the eluant to afford the corresponding alkynecobalt complexes as viscous oils or solids.

4-Trimethylsilyl-2,7-dihydrothiepin-1,1-dioxide (14). A mixture of trimethylsilylacetylene complex (1.56 g, 4.77 mmol) and divinyl sulfone (0.77 mL, 6.96 mmol) was heated in dry toluene (100 mL) at reflux until the completion of the reaction as indicated by TLC analysis. At this time, the mixture was filtered through a thin pad of Celite, the filtrate was concentrated, and the residue was purified by column chromatography (silica gel; 1:6 ethyl acetate/hexane) to afford sulfone **14**, 0.30 g (30%), as a yellow oil: IR (neat) ν 3023, 2956, 1408, 1309, 1249, 1126, 1068 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 9H), 3.60 (d, J = 7.0 Hz, 2H), 3.72 (d, J = 6.5 Hz, 2H), 5.97 (m, 1H), 6.18

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(t, J = 6.5 Hz, 1H), 6.62 (d, J = 9.5 Hz, 1H): ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.3, 56.8, 55.1, 120.1, 127.9, 137.3, 150.4; MS *m*/*e* (rel int) 137 (38), 78 (22), 77 (20), 73 (100), 59 (23); HRMS calcd for $C_9H_{16}SO_2Si$ (M^+) 216.0640, found 216.0639.

4-Trimethylsilylthiepin-1,1-dioxide (15). A solution of sulfone **14** (0.20 g, 0.92 mmol) in CH_2Cl_2 (5 mL) was treated with a solution of Br_2 (0.056 mL, 1.08 mmol), in CH_2Cl_2 (1 mL) at room temperature. The progress of the reaction was monitored by TLC, and at the completion of the reaction, the solvent and excess bromine were removed in vacuo to afford a viscous oil. Methylene chloride (10 mL) was added, the mixture was cooled to 0 °C, and triethylamine (0.28 mL, 2.01 mmol) was added dropwise. At the completion of the reaction as indicated by TLC, the solvent was removed in vacuo to afford a solid residue. This material was dissolved in EtOAc (20 mL), filtered, and concentrated in vacuo, and the residue was purified via column chromatography (silica gel; 4:1 hexane/ethyl acetate) to afford sulfone **15**, 0.14 g (70%), as a white solid: mp 132−133 °C (CH_2Cl_2); IR (CH_2Cl_2) ν 3943, 3756, 3692, 3067, 2975, 2685, 2410 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.25 (s, 9H), 6.65 (t, J = 8.5 Hz, 2H), 6.89 (m, 2H), 6.97 (d, J = 10.5 Hz, 1H); ^{13}C NMR (125 Hz, $CDCl_3$) δ −1.8, 132.4, 132.5, 133.5, 135.8, 138.8, 150.6; MS *m*/*e* (rel int) 136 (14), 135 (100), 73 (37); HRMS calcd for $C_9H_{14}SO_2Si$ (M^+) 214.0483, found 214.0478. Anal. Calcd For $C_9H_{14}SO_2Si$: C, 50.45; H, 6.50. Found: C, 49.93; H, 6.50.

(η^6-4-Trimethylsilylthiepin-1,1-dioxide)tricarbonylchromium-(0) (16). A mixture of tris(acetonitrile)tricarbonylchromium(0) [from $Cr(CO)_6$ (2.0 g, 9.08 mmol)] and 4-trimethylsilylthiepin-1,1-dioxide **15** (0.97 g, 4.54 mmol) was stirred in dry THF (20 mL) under argon atmosphere for 15 min. At this time, the solvent was removed in vacuo, and the crude residue was dissolved in CH_2Cl_2, filtered through Celite, and concentrated in vacuo. The residue was dissolved in a small amount of CH_2Cl_2 and charged onto a column of silica gel. The yellow intermediate complex was removed by continuous washing with hexanes and subsequent elution with 100% CH_2Cl_2 to afford the complex 1.34 g (85%) as a red solid: mp 188−189 °C (CH_2Cl_2/hexanes); IR (Nujol) ν 3035, 2020, 1974, 1920, 1280, 1164, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.42 (s, 9H), 4.88 (m, 1H), 5.08 (m, 1H), 5.33 (m, 2H), 6.03 (d, J = 7.8 Hz, 1H): ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.3, 94.6, 95.9, 104.3, 216.1; MS *m*/*e* (rel int) 202 (15), 135 (67); HRMS calcd for $C_{12}H_{14}SO_5SiCr$ (M^+) 349.9736, found 349.9738. Anal. Calcd for $C_{12}H_{14}SO_5SiCr$: C, 41.14; H, 4.03. Found: C, 41.35; H, 4.15.

[1*Hβ*,6H*β*]-7α-Methyl-3-trimethylsilyl-11-thiabicyclo[4.4.1]undeca-2,4,8-triene-11,11-dioxide (17). A mixture of chromium complex **16** (0.20 g, 0.57 mmol) and piperylene (0.22 mL, 2.28 mmol) in 1,2-dichloroethane (20 mL) was irradiated under standard photochemical conditions (medium-pressure Hg lamp, uranium glass filter) until disappearance of the starting materials as indicated by TLC analysis. The solvent was removed in vacuo and the residue dissolved in MeOH and stirred under a blanket of CO gas (balloon) for 12 h. The solvent was removed, and the residue was purified via column chromatography (silica gel; 6:1 hexanes/ethyl acetate) to afford cycloadduct **17**, 0.14 g (85%), as a white solid: mp 142−143 °C (CH_2Cl_2/pentane); IR (CH_2Cl_2) ν 3154, 3007, 1726, 1291, 1120 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 9H), 1.32 (d, J = 7.5 Hz, 3H), 2.61 (m, 1H), 2.94−2.98 (m, 1H), 3.30 (m, 1H), 3.63 (m, 1H), 3.89 (m, 1H), 5.45 (m, 1H), 5.55 (dd, J = 13, 8 Hz, 1H), 5.66 (m, 2H), 6.04 (d, J = 12.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.8, 20.6, 26.5, 32.1, 66.06, 71.0, 119.7, 127.8, 129.4, 130.4, 138.1, 141.3; MS *m*/*e* (rel int) 145 913), 144 (19), 135 (12), 73 (100); HRMS calcd for $C_{14}H_{22}SO_2Si$ (M^+) 282.1109, found 282.1107.

[1*Hβ*,14*Hβ*]-13(S)-8-Methoxy-17-trimethylsilyl-19-thiatetracyclo-[12.4.1.0.^{4,13}0^{5,10}]nonadeca-3,5,7,9,15,17-hexaene-19,19-dioxide (19). A mixture of chromium complex **16** 9.20 g, 0.57 mmol) and diene **18**[12] (0.42 g, 2.28 mmol) in 1,2-dichloroethane (20 mL) was irradiated under standard photochemical conditions (medium-pressure Hg lamp, uranium glass filter) until the disappearance of the starting materials as indicated by TLC analysis. Standard workup procedure (see above) followed by purification via column chromatography (silica gel 6:1 hexanes/ethyl acetate) afforded cycloadduct **120**, 0.21 g (95%), as a white solid: mp 165−166 °C (CH_2Cl_2/pentane); IR (CH_2Cl_2) ν 3147, 3110, 2667, 2550, 1260, 1120 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 9H), 1.24 (m, 1H), 1.57 (m, 1H), 2.28 (m, 1H), 2.48 (m, 1H), 2.61 (m, 1H), 2.84 (m, 1H), 3.06−3.14 (m, 1H), 3.70 (m, 1H), 3.78 (s, 3H), 3.93 (m, 1H), 5.38 (m, 1H), 5.75 (d, J = 12.5 Hz, 1H), 5.89 (m, 2H), 6.62 (bs, H1), 6.68 (m, 1H), 7.10 (d, J = 14 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.8, 27.4, 29.5, 37.2, 55.2, 65.4, 69.3, 112.0, 112.4, 119.4, 122.4, 125.9, 129.6, 130.1, 130.3, 139.7, 140.7, 141.1, 159.0; MS *m*/*e* (rel int) 335 (31), 336 (24), 263 (22), 210 (32), 187 (16); HRMS calcd for $C_{22}H_{28}SO_3Si$ (M^+) 400.1528, found 400.1526.

(3a*S*,7a*S*)-4-Ethylidene-5,6,7,7a-tetrahydro-7a-methylindan-1,5-dione. Oxidative Decarboxylation of Diketo Acid 13 (Kochi's Procedure).[14a] Lead tetraacetate (3.0 g, 6.72 mmol) was added to a solution of diketo acid **13** (1.0 g, 4.20 mmol), $Cu(OAc)_2$ (0.14 g, 0.76 mmol), and pyridine (0.40 mL, 5.04 mmol) in benzene (120 mL). The mixture was flushed with nitrogen and carefully warmed to avoid rapid and uncontrollable liberation of CO_2. After the initial evolution of gases had subsided, the reaction was refluxed for an additional 2 h. Ethylene glycol and water were then added, and the layers were separated. The organic layer was then washed sequentially with 10% aqueous HNO_3 solution and H_2O. The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo. The residue was then chromatographed (silica gel; 1:7 ethyl acetate/hexane) to afford enone **21**, 0.30 g (38%), as a colorless oil: IR (neat) ν 2134, 1660, 1655, 1460, 1240 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.81 (m, 2H), 1.95−2.06 (m, 5H), 2.31 (m, 1H), 2.44−2.61 (m, 3H), 2.71 (m, 1H), 5.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 15.3, 20.6, 28.9, 36.3, 37.6, 47.8, 49.9, 81.5, 133.3, 136.9, 202.1, 218.5; MS *m*/*e* (rel int) 192 (100), 149 (28), 136 (28), 107(30), 93 (31); HRMS calcd for $C_{12}H_{16}O_2$ (M^+) 192.1150, found 192.1149.

Oxidative Decarboxylation of Diketo Acid 13 (Ogibin's Modification of Kochi's Procedure).[14e] Solid $Pb(OAc)_4$ was gradually added over 3 h to a vigorously stirred, refluxing mixture of diketo acid **13** (2.0 g, 8.40 mmol), $Cu(OAc)_2$ (0.17 g, 0.84 mmol), and pyridine (0.70 mL, 8.40 mmol) in benzene (120 mL). Stirring and refluxing was continued for 1 h, and the reaction mixture was then allowed to cool to room temperature. The resultant precipitate of $Pb(OAc)_4$ was removed by filtration and extracted with ether. The combined ethereal extracts and the benzene solution were washed with 10% HCl, dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue via column chromatography (silica gel; 1:7 ethyl acetate/hexane) afforded enone **21**, 0.56 g (35%).

Oxidative Decarboxylation of Diketoacid 13 with Iodobenzene Diacetate/Cu(OAc)$_2$.[16] A solution of diketo acid **13** (0.30 g, 1.25 mmol) in dry benzene (40 mL) containing $Cu(OAc)_2$ (0.045 g, 0.20 mmol) and pyridine (0.070 mL, 0.87 mmol) was stirred for 15 min under argon. Iodobenzene diacetate (2.01 g, 6.25 mmol) was added to this solution in portions (1 mmol every 90 min), and the mixture was then refluxed for 8 h. The reaction mixture was cooled and washed with 5% aqueous hydrochloric acid solution and water. The aqueous layer was extracted with EtOAc (3 × 10 mL); the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was subjected to column chromatography (silica gel; 1:7 ethyl acetate/hexane) to afford enone **21**, 0.097 g (40%).

(3a*S*,7a*S*)-1,5-Dioxo-4α-methylpropionic-3aα,4,5,6,7,7a-hexahydro-7a-methylindan (22). A mixture of diketo acid **13** (2.0 g, 8.39 mmol) and *p*-toluenesulfonic acid (0.015 g, 0.083 mmol) in methanol was heated at reflux for 2 h. After 2 h, the reaction mixture was cooled to room temperature and diluted with EtOAc (20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ solution, water, and brine. The combined organic extracts were dried (Na_2SO_4), concentrated, and filtered through a silica gel plug to afford 1.90 g (90%) of diketo ester **22** as a colorless oil: IR (neat) ν 3220, 2956, 2800, 1680, 1646, 1200 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.63 (m, 1H), 1.79 (m, 4H), 1.97 (m, 1H), 2.05 (m, 1H), 2.23 (m, 1H), 2.36 (m, 1H), 2.42−2.59 (m, 5H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.4, 21.3, 22.2, 30.3, 31.5, 36.0, 37.3, 48.9, 49.4, 51.5, 173.9, 210.3, 219.1; MS *m*/*e* (rel int) 219 (48), 218 (95), 190 (84), 162 (66), 126 (45), 94 (74), 55 (100); HRMS calcd for $C_{14}H_{20}O_4$ (M^+) 252.1361, found 252.1360. Anal. Calcd for $C_{14}H_{20}O_4$: C, 65.63; H, 7.99. Found: C, 65.98; H, 8.07.

(3a*S*,7a*S*)-1,5-Dihydroxy-4α-*β*-propionolactone-3aα,4,5,6,7,7a-

hexahydro-7a-methylindan (23). To a solution of diketoester **22** (0.50 gm, 1.98 mmol) in methanol at 0 °C was added solid potassium borohydride (0.16 g, 2.98 mmol), and the mixture was allowed to stir at that temperature for a further 30 min. The solvent was removed in vacuo, the residue was dissolved in EtOAc and washed with water, and the aqueous layer was washed with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel; 1:2 ethyl acetate/hexane) to afford **23**, 0.38 g (85%), as a white solid: mp 121−122 °C (CH_2Cl_2/pentane); IR (NaCl, CH_2Cl_2) ν 3220, 2890, 1660, 1220 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.06−2.17 (m, 13H), 2.47−2.58 (m, 1H), 2.66−2.72 (m, 1H), 3.68 (t, J = 8.5 Hz, 1H), 3.86 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.1, 22.2, 24.0, 27.8, 29.5, 30.7, 33.7, 37.2, 43.5, 47.7, 80.7, 84.0, 171.3; MS *m*/*e* (rel int) 224 (30), 206 (28), 180 (85), 165 (50), 147 (60), 133 (59), 107 (100); HRMS calcd for $C_{13}H_{20}O_3$ (M^+) 224.1412, found 224.1412.

(3a*S*,7a*S*)-5-Hydroxy-4α-*β*-propionolactone-1-[(*tert*-butyldimethylsilyl)oxy]-3a,4,5,6,7,7a-hexahydro-7a-methylindan (24). A mixture of hydroxy lactone **23** (0.50 g, 2.23 mmol), imidazole (0.40 g, 5.89 mmol), and *tert*-butyldimethylsilyl chloride (0.47 g, 3.14 mmol) in dimethylformamide (2 mL) was stirred for 18 h at room temperature. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed thoroughly with water (5 × 10 mL) and brine, and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel; 1:10 ethyl acetate/hexane) to afford **24**, 0.64 g (85%), as a colorless oil: IR (neat) ν 3000, 2986, 1680, 1223 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.001 (s, 3H), 0.006 (s, 3H), 0.86 (s, 3H), 0.87 (s, 9H), 1.33−1.99 (m, 12H), 2.50−2.57 (m, 1H), 2.65−2.71 (m, 1H), 3.58 (t, J = 8.5 Hz, 1H), 3.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −4.5, 11.4, 18.0, 21.7, 22.4, 24.0, 25.7, 25.8, 27.9, 29.5, 31.1, 34.1, 37.3, 47.3, 80.6, 84.4, 141.3; MS *m*/*e* (rel int) 281 (100), 205 (22), 147 (28), 75 (65); HRMS calcd for $C_{19}H_{34}O_3Si$ (M^+) 338.2277, found 338.2270.

(3a*S*,7a*S*)-5-Formyloxy-4α-(2′-iodoethylene-1-[*tert*-(butyldimethyl)silyloxy]-3a,4,5,6,7,7a-hexahydro-7a-methylindan (25). To a solution of lactone **24** (0.88 g, 2.56 mmol) in dry CH_2Cl_2 (40 mL) at −78 °C was added a solution of diisobutylaluminum hydride (DIBALH) (1.0 M soln in hexane, 2.84 mL, 2.84 mmol). The mixture was stirred at −78 °C for 1 h and then quenched by addition of MeOH (8 mL). Water (20 mL) was added, and the mixture was diluted with CH_2Cl_2 (80 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL). The solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel; 1:8 ethyl acetate/hexane) to afford 0.6 g (70%) of the corresponding hemiacetal. A mixture of this lactol (0.50 g, 1.47 mmol), iodobenzene diacetate (0.52 g, 1.62 mmol), and iodine (0.38 g, 1.47 mmol) in cyclohexane (10 mL) was photolyzed with a 150 W tungsten lamp. The reaction was stopped when the purple color of the solution had disappeared. At this time, no starting material remained in the reaction mixture. The mixture was diluted with CH_2Cl_2 (20 mL) and filtered through a thin pad of Celite. The filtrate was concentrated, and the residue was chromatographed (silica gel; 1:10 ethyl acetate/hexane) to afford iodo formate **25**, 0.53 g (75%), as a colorless oil: IR (neat) ν 2929, 2856, 1724, 1462, 1250, 1175 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ −0.01 (s, 6H), 0.80 (s, 3H), 0.86 (s, 9H), 1.06−1.95 (m, 12H), 3.15 (m, 2H), 3.54 (t, J = 8 Hz, 1H), 4.62 (m, 1H), 8.08 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −4.5, 10.4, 11.1, 23.6, 25.7, 27.5, 30.9, 34.3, 35.2, 42.0, 46.8, 76.6, 80.7, 160.8; MS *m*/*e* (rel int) 409 (23), 341 (22), 297 (16), 161 (28); HRMS calcd for $C_{19}H_{35}O_3I$ (M^+) 466.1398, found (M^+ − 57) 409.0701.

Preparation of Ketolactol 26. To a solution of diketo ester **22** (0.50 g, 1.98 mmol) in dry THF at −78 °C was added a solution of L-Selectride (1.0 M soln in THF, 4.00 mL, 4.00 mmol). The solution was stirred at −78 °C for an additional 30 min, and then a solution of 5% aqueous hydrochloric acid solution (10 mL) was added. EtOAc (20 mL) was added, and the resultant mixture was allowed to stir at room temperature for 2 h. The aqueous layer was extracted with EtOAc (3 × 20 mL), washed with brine, dried (Na_2SO_4), and passed through a plug of silica gel to remove the inorganic byproducts. The solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel; 1:3 ethyl acetate/hexane) to afford lactol **26**, 0.38 g (86%), as a white solid: mp 87−88 °C (CH_2Cl_2/hexane); IR (NaCl, CH_2Cl_2) ν 3408, 2940, 1735, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.43−2.25 (m, 12H), 2.46 (m, 2H), 3.75 (m, 1H), 4.74 (m, 1H), 5.27 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 21.2, 23.5, 26.8, 27.3, 27.6, 33.4, 35.4, 39.7, 73.9, 91.7, 96.8, 220.6; MS *m*/*e* (rel int) 150 (16), 86 (65), 84 (100); HRMS calcd For $C_{13}H_{20}O_3$ (M^+) 224.1412, found 224.1416. Anal. Calcd for $C_{13}H_{20}O_3$: C, 67.60; H, 8.99. Found: C, 67.88; H, 9.07.

(3a*S*,7a*S*)-5-Formyloxy-4α-(2′-iodoethyl)-1-oxo-3a,4,5,6,7,7a-hexahydro-7a-methylindan (27). A mixture of lactol **26** (0.38 g, 1.76 mmol), iodobenzene diacetate (0.68 g, 2.12 mmol), and iodine (0.22 g, 1.76) in cyclohexane (20 mL) was photolyzed with a 150 W tungsten lamp. The reaction was stopped when the violet color disappeared from the reaction mixture. No starting material was detected in the mixture at this time. The reaction was diluted with CH_2Cl_2 (20 mL) and filtered through a thin pad of Celite. The filtrate was concentrated, and the residue was purified by column chromatography (silica gel; 1:5 ethyl acetate/hexane) to afford iodo formate **22**, 0.47 g (78%), as a colorless oil: $[\alpha]^{25}_D$ = +89.0 (c = 1, $CHCl_3$); IR (neat) ν 2940, 2882, 1735, 1456, 1265, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.49−1.99 (m, 8H), 2.12 (m, 2H), 2.46 (m, 1H), 3.11 (m, 1H), 3.22 (m, 1H), 3.22 (m, 1H), 5.27 (m, 1H), 8.06 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 3.6, 2.9, 21.8, 26.4, 26.5, 31.9, 35.2, 39.9, 43.2, 47.8, 69.0, 160.3, 219.4; MS *m*/*e* (rel int) 305 (25), 225 (12), 177 (82), 149 (100), 105 (55), 93 (88); HRMS calcd for $C_{13}H_{19}O_3I$ (M^+) 350.0377, found 350.0375.

(3a*S*,7a*S*)-4α-Ethenyl-5α-formyloxy-1-oxo-3,4,5,6,7,7a-hexahydro-7a-methylindan (28). To a solution of iodo formate **27** (0.20 g, 0.57 mmol) in benzene (1.0 mL) was added a solution of 1,8-diazabicyclo-[5.4.0]undec-7-ene (0.10 mL, 0.68 mmol) in benzene (1 mL). The resultant mixture was heated at reflux while the progress of the reaction was monitored by TLC analysis. At the completion of the reaction as indicated by TLC analysis, the reaction was allowed to cool to room temperature. Water (2.0 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by the column chromatography (silica gel; 1:6 ethyl acetate/hexane) to afford formate **28**, 0.04 g (30%), as a thick, viscous oil: $[\alpha]^{25}_D$ = 78.2° (c = 1, $CHCl_3$); IR (neat) ν 2945, 1721, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (s, 3H), 1.45−2.16 (m, 8H), 2.43 (m, 2H), 5.10−5.20 (m, 3H), 5.67 (m, 1H), 8.05 (s, 1H): ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 22.1, 26.3, 26.4, 35.1, 42.5, 44.7, 72.5, 117.6, 135.9, 160.3, 219.6; MS *m*/*e* (rel int) 176 (68), 148 (22), 133 (45), 119 (67), 105 (83), 79 (100); HRMS calcd for $C_{13}H_{18}O_3$ (M^+) 222.0932, found 222.1259.

Attempted Oxidative Fragmentation of Lactol 26 with Iodobenzene Diacetate/Copper Acetate Mixture. An oven-dried flask equipped with a water reflux condenser was charged with a mixture of lactol **26** (0.95 g, 4.30 mmol), iodobenzene diacetate (1.66 g, 5.16 mmol), and copper acetate (1.20 g, 6.45 mmol) in cyclohexane (20.0 mL) and photolyzed with 150 W tungsten lamp, while the progress of the reaction was monitored by TLC. At the completion of the reaction, the mixture was filtered through a thin pad of Celite, the filtrate was concentrated, and the residue was purified by column chromatography (silica gel; 1:10 ethyl acetate/hexane) to afford formate **28**, 0.66 g (70%).

Oxidative Fragmentation of Lactol 26 with Lead Tetracetate/Copper Acetate. A mixture of lactol **26** (0.55 g, 2.48 mmol), lead tetraacetate (1.76 g, 3.97 mmol), copper acetate (0.08 g, 0.45 mmol), and pyridine (0.24 mL, 2.97 mmol) in benzene (20.0 mL) was heated at reflux while the progress of the reaction was monitored by TLC. At the completion of the reaction as indicated by TLC, the reaction was cooled to room temperature. The mixture was filtered through a thin pad of Celite, the filtrate was concentrated, and the residue was chromatographed (silica gel, 1:10 ethyl acetate/hexane) to afford formate **28**, 0.45 g (82%).

(3a*S*,7a*S*)-4α-Ethenyl-5α-hydroxy-1-oxo-3a,4,5,6,7,7a-hexahydro-7a-methylindan (29). To a solution of formate **28** (0.20 g, 0.90 mmol) in methanol (5 mL) was added potassium carbonate (K_2CO_3) (0.14 g, 0.99 mmol) at room temperature. The resultant mixture was allowed

to stir while the progress of the reaction was monitored by TLC. At the completion of the reaction, the solvent was removed, and the residue was dissolved in water (10 mL) and acidified with 5% aqueous hydrochloric acid solution. The resultant mixture was extracted with EtOAc (3 × 10 mL), washed with brine, and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel; 1:6 ethyl acetate/hexane) to afford alcohol **29**, 0.15 g (85%), as a white solid: $[\alpha]^{25}_D = +6.5$ ($c = 1$, $CHCl_3$); mp 81−82 °C (EtOAc/hexane); IR (NaCl, CH_2Cl_2) ν 3471, 2939, 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (s, 3H), 1.42−1.89 (m, 7H), 2.06 (m, 2H), 2.39 (m, 1H), 2.39 (m, 1H), 3.89 (m, 1H), 5.16 (m, 2H), 5.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.7, 22.1, 25.8, 28.6, 35.2, 40.8, 45.9, 69.3, 116.9, 137.6, 220.5; MS *m*/*e* (rel int) 194 (49), 139 (44), 109 (73), 97 (100), 81 (74), 79 (91); HRMS calcd For $C_{12}H_{18}O_2$ (M^+) 194.1306, found 194.1303. Anal. Calcd For $C_{12}H_{18}O_2$: C, 74.18; H, 9.34. Found: C, 73.97; H, 9.31.

(3a*S*,7a*S*)-4α-Ethenyl-5α-methanesulfonyl-1-oxo-3a,4,5,6,7,7a-hexahydro-7a-methylindan (30). To a solution of alcohol **29** (0.20 g, 1.03 mmol) in CH_2Cl_2 (5.0 mL) was added triethylamine (0.20 mL, 1.44 mmol) followed by methanesulfonic anhydride (0.25 g, 1.44 mmol) at 0 °C. The resultant mixture was stirred at 0 °C for 2 h and then quenched by the addition of water (2.0 mL). The mixture was extracted by CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (silica gel; 1:6 ethyl acetate/hexane) to afford mesylate **30**, 0.18 g (65%), as a colorless oil: IR (neat ν 2930, 2846, 1465, 1221 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 3H), 1.00 (m, 1H), 1.47 (m, 1H), 1.65 (m, 1H), 1.82 (m, 2H), 1.94 (m, 2H), 2.08 (m, 1H), 2.16−2.21 (m, 2H), 2.97 (s, 3H), 4.82 (m, 1H), 5.20 (m, 2H), 5.76 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 21.9, 25.9, 27.5, 31.5, 35.0, 38.5, 41.9, 43.1, 45.4, 47.0, 82.2, 118.3, 135.6; MS *m*/*e* (rel int) 256 (67), 155 (45), 73 (100); HRMS calcd for $C_{13}H_{20}SO_4$ (M^+) 272.1028, found 272.1023.

(3a*S*,7a*S*)-4α-Ethenyl-1-oxo-5-(4′-methylbenzenesulfonyl)-3a,4,5,6,7,7a-hexahydro-7a-methylindan (33). A solution of alcohol **29** (0.79 g, 4.08 mmol), *p*-toluenesulfonyl chloride (2.40 g, 12.25 mmol), and 4-(dimethylamino)pyridine (4.50 mg, 0.04 mmol) was stirred at room temperature for 3 days. At this time, a solution of 5% aqueous hydrochloric acid solution was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed thoroughly with water (3 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel; 1:10 ethyl acetate/hexane) to afford tosylate **33**, 1.10 g (78%), as a white solid: $[\alpha]^{25}_D = +78.1°$ ($c = 1$, $CHCl_3$); mp 146−147 °C (EtOAc/hexane); IR (NaCl, CH_2Cl_2) ν 3079, 2685, 2410, 2305, 1737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.37−2.37 (m, 10H), 2.43 (s, 3H), 4.72 (m, 1H), 4.89−5.04 (m, 2H), 5.53 (m, 1H), 7.30 (d, $J = 8.1$ Hz, 2H), 7.74 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 21.5, 22.0, 26.0, 27.0, 35.0, 41.9, 45.7, 47.0, 82.2, 117.5, 127.7, 129.7, 134.3, 135.4, 144.6, 219.1; MS *m*/*e* (rel int) 176 (49), 105 (25), 91 (100), 79 (29); HRMS calcd for $C_{19}H_{24}SO_4$ (M^+) 348.1395, found 348.1395. Anal. Calcd for $C_{19}H_{24}SO_4$: C, 65.59; H, 6.95. Found: C, 65.59; H, 7.07.

(3a*S*,7a*S*)-4-Ethenyl-1-[(*tert*-butyldimethylsilyl)oxy]-3a-methyl-3a,6,7,7a-tetrahydro-4-indene (34). To a solution of tosylate **33** (1 g, 2.8 mmol) in DMSO (15 mL) was added a solution of potassium *tert*-butoxide (1.0 M soln in THF, 6.0 mL, 5.9 mmol) at 0 °C. The solution was stirred at 0 °C for 1 h and quenched by addition of water (20 mL). The solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed thoroughly with water (3 × 50 mL), dried (Na_2SO_4), and concentrated. The residue was purified (silica gel; 1:20 ethyl acetate/hexane) to afford diene **31**, 0.40 g (78%) as a colorless oil: $[\alpha]^{25}_D = +54.2$ ($c = 1$, $CHCl_3$); IR (neat) ν 2933, 1739, 1625, 1458, 1369, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.10−2.75 (m, 9H), 4.84 (m, 1H), 5.16 (m, 1H), 5.64 (m, 1H), 6.21 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.1, 22.8, 28.2, 33.3, 35.7, 46.5, 115.5, 125.8, 129.5, 139.7, 221.4; MS *m*/*e* 155 (45), 100 (43), 99 (100), 73 (55); HRMS calcd for $C_{12}H_{16}O$ (M^+) 176.1201, found 176.1109. This diene (0.38 g, 2.18 mmol) was dissolved in methanol (5.0 mL) and cooled to 0 °C. To this was added solid potassium borohydride (0.09 g, 1.74 mmol), and the resultant mixture was stirred at 0 °C for 1 h. Acetone (1.0 mL) was added, the solvent was removed in vacuo, and the residue was dissolved in EtOAc (20 mL). The mixture was washed with water (2 × 10 mL), dried (Na_2SO_4), and concentrated. The resultant crude alcohol was dissolved in dimethylformamide (DMF) (1.0 mL), *tert*-butyldimethylsilyl chloride (0.29 g, 1.90 mmol) and imidazole (0.24 g, 3.56 mmol) were added at room temperature, and the resultant mixture was stirred at room temperature for 18 h. At this time, a saturated solution of $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (5 × 10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (silica gel; hexanes) to afford diene **34**, 0.50 g (80%): $[\alpha]^{25}_D = +36.1°$ ($c = 1$, $CHCl_3$); IR (neat) ν 2928, 2857, 1462, 1361, 1256, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.88 (s, 3H), 0.90 (s, 9H), 1.25 (m, 1H), 1.58 (m, 2H), 1.74 (m, 1H), 1.98 (m, 2H), 2.22 (m, 3H), 3.68 (t, $J = 8.5$ Hz, 1H), 4.85 (d, $J = 11.5$ Hz, 1H), 5.17 (d, $J = 18.0$ Hz, 1H), 5.66 (m, 1H), 6.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.8, −4.5, 10.9, 18.1, 23.8, 24.5, 25.7, 25.8, 31.2, 33.3, 43.6, 43.7, 80.0, 111.5, 126.8, 137.8, 138.7; MS *m*/*e* (rel int) 235 (55), 159 (32), 117 (51); HRMS calcd For $C_{18}H_{32}OSi$ (M^+) 292.222, found 292.2220.

(1*S*,2*S*,5*S*,9*S*,13*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-5-methyl-15-trimethylsilyl-18-thiatetracyclo[11.4.1.0^{2,10}0^{5,9}]-10,14,16-triene-18,18-dioxide (35). A mixture of (η^6-4-trimethylsilylthiepin-1,1-dioxide)-chromium(0) complex **16** (0.25 g, 0.72 mmol) and the diene **34** (0.83 g, 2.88 mmol) in 1,2-dichloroethane was irradiated under standard conditions (medium-pressure mercury lamp, uranium glass filter) until the disappearance of the starting material as indicated by the TLC analysis. At the completion of the reaction, the solvent was removed in vacuo, and the residue was dissolved in methanol (20 mL) and stirred under a blanket of CO overnight. The mixture was concentrated, and the residue was purified by column chromatography (silica gel; 1:7 ethyl acetate/hexane) to afford cycloadduct **35**, 0.25 g (70%), as white solid: $[\alpha]^{25}_D = +245.4°$ ($c = 1$, $CHCl_3$); mp 175−176 °C (EtOAc/hexane); IR (NaCl, CH_2Cl_2) ν 3081, 3002, 2987, 1464, 1220, 1087 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.09 (s, 9H), 0.58 (s, 3H), 0.88 (s, 9H), 1.39−1.62 (m, 6H), 1.73 (m, 1H), 1.98 (m, 1H), 2.06 (m, 1H), 2.61 (m, 1H), 3.02−3.07 (m, 1H), 3.46 (t, $J = 7.0$ Hz, 1H), 3.58 (m, 1H), 3.73 (m, 1H), 3.95 (m, 1H), 5.11 (m, 1H), 5.57 (m, 2H), 6.03 (d, $J = 12.5$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.8, −4.4, −1.8, 1.0, 13.6, 18.0, 21.8, 25.8, 26.5, 28.2, 30.7, 34.6, 34.8, 43.0, 47.8, 66.8, 72.3, 81.5, 94.0, 120.5, 129.3, 129.9, 140.6, 144.8; MS *m*/*e* (rel int) 507 (100), 442 (57), 441 (46), 73 (69); HRMS calcd for $C_{27}H_{46}SO_3Si_2$ (M^+) 506.2706, found ($M^+ - 64$) 442.3090. Anal. Calcd for $C_{27}H_{46}SO_3Si_2$: C, 63.99; H, 9.16. Found: C, 63.12; H, 9.06.

1-[(*tert*-Butyldimethylsilyl)oxy]-3-trimethylsilyl-9*Hβ*-estra-1,3,5-(10),7-tetraene (36). A solution of the cycloadduct **35** (0.02 g, 0.039 mmol) in dry, degassed THF (5.0 mL) was cooled to −105 °C, and a solution of potassium *tert*-butoxide (1.0 M solution in THF, 0.04 mL, 0.043 mmol) was added dropwise using a syringe. The mixture was allowed to stir at −105 °C for a further 15 min with vigorous stirring. At this time, a solution of *N*-chlorosuccinimide (NCS) (10.0 mg, 0.075 mmol) in THF (2 mL) was added to the reaction via a cannula. The resultant mixture was allowed to stir for 1 h, while the temperature was allowed to warm to 25 °C. The mixture was cooled to −105 °C again, and a second equivalent of potassium *tert*-butoxide (1.0 M solution in THF, 0.04 mL, 0.04 mmol) was added. The resultant mixture was allowed to warm to room temperature over a period of 4 h. Water (2 mL) was added, and the mixture was extracted with pentane (3 × 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (100% hexane) to afford 10.4 mg (60%) of the rearranged product **36** as a white solid: $[\alpha]^{25}_D = +53.4°$ ($c = 2$, $CHCl_3$); mp 112−113 °C (CH_2Cl_2/pentane); IR (NaCl, CH_2Cl_2) ν 2955, 2929, 2857, 1471, 1249, 1099, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.08 (s, 3H), 0.27 (s, 9H), 0.82 (s, 3H), 0.92 (s, 9H), 1.49−1.80 (m, 5H), 1.92 (m, 1H), 2.01 (m, 1H), 2.32 (m, 1H), 2.44 (m, 1H), 3.22 (m, 2H), 3.35 (m, 1H), 3.86 (t, $J = 8.0$ Hz, 1H), 5.67 (m, 1H), 7.26−7.38 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.3, −1.0, 17.4, 18.1, 22.4, 23.3, 25.8, 31.4, 31.4, 33.7, 37.1, 43.0, 43.9, 83.0, 118.0, 123.4, 130.8, 132.2, 136.9, 137.1, 141.6, 146.2;

MS *m*/*e* (rel int) 147 (14), 75 (41), 73 (100); HRMS calcd for $C_{27}H_{44}OSi_2$ (M^+) 440.2903, found 440.2930.

Attempted Migration of the $\Delta^{7,8}$ Double Bond in 36 to the $\Delta^{9,11}$ Position with Potassium 3-Aminopropylamide (KAPA). A dry, 25 mL tube was charged with 25% potassium hydride in oil (0.57 g, 3.55 mmol). The oil was removed by washing with dry pentane (3 × 8 mL). After removal of the residual pentane, 3-aminopropylamine (3.50 mL) was injected in a stream of argon; formation of KAPA was complete in 1 h. Concurrently, a 10 mL flask suitable for vigorous stirring was charged with compound **36** (0.03 g, 0.061 mmol) in dry THF (1 mL). With vigorous stirring a small amount of KAPA stock solution was injected (3 drops). The resultant mixture was allowed to stir at room temperature for 15 h. At this time, the reaction mixture was quenched by addition of water. The resultant mixture was extracted with pentane (3 × 10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (100% hexane) to afford the 0.02 g (71%) of compounds **37** and **38** as an inseparable mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.98 (s, 3H), 0.30 (s, 9H), 0.76 (s, 3H), 0.94 (s, 9H), 1.74−2.81 (m, 12H), 3.78 (t, J = 7 Hz, 1H), 5.44 (m, 0.60H), 7.23−7.40 (m, 3H).

1β-Hydroxy-3-trimethylsilylestra-1,3,5(10)-triene (39). A mixture of **37** and **38** (27 mg, 0.061 mmol) was dissolved in acetonitrile (2 mL), and a 48% solution of HF (2 drops) was added at room temperature. The mixture was allowed to stir at room temperature while the progress of the reaction was monitored by TLC. At the completion of the reaction, the solvent was removed in vacuo, and the residue was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ and water and dried (Na_2SO_4). The solvent was removed in vacuo, and the residue was purified by column chromatography (silica gel; 1:10 ethyl acetate/hexane) to afford 17 mg (85%) of alcohols as an inseparable mixture.This mixture of crude alcohols (10 mg, 0.03 mmol) was dissolved in anhydrous benzene (1 mL) and treated with a mixture of trifluoroacetic acid (46 μL, 0.60 mmol) and triethylsilane (48 μL, 0.30 mmol). The reaction mixture was allowed to stir at room temperature for 15 h. The mixture was then added to a saturated solution of $NaHCO_3$ (5 mL) at 0 °C, and the resultant mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo, and the residue was purified by column chromatography (silica gel; 1:10 ethyl acetate/hexane) to afford compound **39**, 4.52 mg (45%), as a colorless oil: $[\alpha]^{25}_D$ = +68.0° (c = 1, $CHCl_3$); IR (neat) 3054, 2857, 1654, 1222, 870 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.24 (s, 9H), 0.81 (s, 3H), 1.12−3.90 (m, 16H), 3.85 (t, J = 7.5 Hz, 1H), 7.12 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.1, 11.8, 24.1, 27.7, 28.7, 30.8, 38.1, 40.7, 44.5, 45.5, 48.5, 48.7, 51.4, 82.6, 124.8, 130.8, 134.3, 135.8, 137.6, 14.04; MS *m*/*e* (rel int) 328 (45), 255 (67), 73 (100); HRMS calcd for $C_{21}H_{32}OSi$ (M^+) 328.2222, found 328.2220.

Preparation of Estra-1,3,5(10)-triene-3,17β-diol (8). To a solution of alcohol **39** (6.0 mg, 0.018 mmol) in trifluoroacetic acid (1 mL) was added lead tetrakistrifluoroacetate (17 mg, 0.03 mmol) at room temperature. Within 5 min, the solid oxidant turned black and became gummy. The stirring was continued for 30 min, and the mixture was treated with an equal volume of aqueous NaOH solution with stirring and after neutralization was made basic again with $NaHCO_3$. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The organic solutions were combined, dried over Na_2SO_4, and concentrated, and the residue was purified (silica gel; 1:10 ethyl acetate/hexane) to afford β-estradiol, 3.98 mg (80%), as a white solid, the ^{1}H NMR and ^{13}C NMR of which were identical with those of an authentic sample: mp 175−176 °C (lit.[28] mp 178−179 °C); $[\alpha]^{25}_D$ +78.8° (c = 1, dioxane) [lit.[28] $[\alpha]^{25}_D$ +80.4° (c = 1, dioxane)].

Acknowledgment. The authors thank the National Institutes of Health (GM-30771) for their generous support of this research. They also thank Dr. Bruce A. Pearlman of Pharmacia & Upjohn for a very generous supply of indandione **13**.

JA991016W