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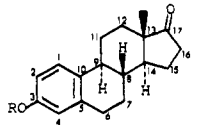
Transition-Metal-Catalyzed Alkyne Cyclizations. A Cobalt-Mediated Total Synthesis of *dl*-Estrone[1]

Raymond L. Funk[2] and K. Peter C. Vollhardt*[3]

Contribution from the Department of Chemistry, University of California, Berkeley, California 94720. *Received January 4, 1980*

Abstract: A cobalt-catalyzed total synthesis of racemic steroids (including estrone **1**) is described based on the cooligomerization of substituted 1,5-hexadiyne **3** with monoalkynes. An unsuccessful strategy for the synthesis of starting material **3** via chloroethyl derivative **18** was abandoned in favor of a convergent synthesis via 3-(2-iodoethyl)-1,5-hexadiyne (**19**) on one hand and enol ether **20** on the other. Compound **3** reacted with BTMSA in the presence of $CpCo(CO)_2$ to give racemic 2,3-bis(trimethylsilyl)estratrienone (**24a**) via benzocyclobutenes **23**. Similarly, **3** cyclized with trimethylsilyl(methoxy)ethyne to furnish in low yield (via benzocyclobutene intermediates) steroids **24c,d**, the former providing *dl*-estrone methyl ether on protodesilylation. Estrone could be obtained with poor regiochemical control from ketal **33** by bromination, followed by conversion of the bromine moiety to a hydroxyl group. However, selective protodesilylation of **24a** at low temperatures to 3-trimethylsilylestratrienone (**24g**) followed by oxidative cleavage of the phenyl–silicon bond with $Pb(OOCCF_3)_4$ gave **1**: five steps from 2-methylcyclopentenone (21.5%) and six steps from 1,5-hexadiyne (15.1%). A slight improvement of yields is realized via cyclization of the ethylene ketal **29** (23.1 and 16.2%, respectively).

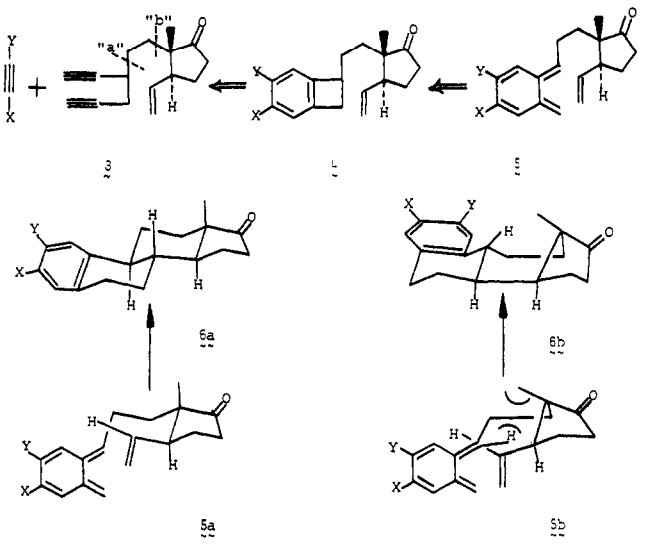
Estrone (**1**) constitutes a challenging synthetic target on which to measure the utility of novel methodology[4-6] and as a relay point en route to contraceptive drugs.[7,8] Of the many successful



1 R = H
2 R = Me

strategies the AD → ABCD[6] possibility has been exploited relatively infrequently. Rare examples are the Smith–Hughes synthesis employing a double condensation[6] and the Johnson–Bartlett approach utilizing a cationic olefin cyclization.[9] A retrosynthetic analysis of the estrone nucleus suggests another alternative in which the two central rings are constructed by an intramolecular Diels–Alder reaction of an intermediate *o*-xylylene **5** (Scheme I). Concurrent with and preceding our efforts in this field[10] several groups devised similar strategies to a variety of

Scheme I



steroids relying on the various ways available to construct precursors to *o*-xylylenes of type **5**.[11] Our approach to the steroid nucleus and ultimately **1** attempted to exploit a previously deveoped cobalt-catalyzed stereospecific one-step construction of tricyclic ring systems from acyclic precursors.[10,12]

Results and Discussion

Synthesis of Steroid Precursor Diyne 3. The highly stereoselective cobalt-catalyzed formation of trans-annelated polycycles,[12] particularly *trans*-1,2,3,4,4a,9,10,10a-octahydrophenanthrene, suggested the possibility of employing an intramolecular cycloaddition to an appropriate *o*-xylylene to construct what one might

(1) Taken in part from the Ph.D. Thesis of R. L. Funk, University of California, Berkeley, 1978.
(2) Regents' Intern Fellow, 1975–1978.
(3) Fellow of the Alfred P. Sloan Foundation, 1976–1980; Camille and Henry Dreyfus Teacher-Scholar, 1978–1983.
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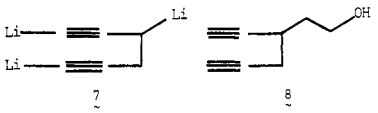
envisage as the ABC-ring portion of estrone. The requisite *o*-xylylene **5** was anticipated to choose one out of four (two exo, two endo) modes of cycloaddition. Based on model studies[12] at least one of the two exo transition states **5a** and **5b** appeared favored. Molecular models indicated that **5a** (addition of the vinyl group from the β face) should be preferred over **5b** (addition of the vinyl group from the α face). The reason for this preference may be found in steric considerations. Exo addition as in **5a** proceeds via a chair-like transition state to lead to the natural trans-anti-trans arrangement of isomer **6a**, whereas exo transition state **5b** adopts a boat-like conformation en route to the unnatural trans-syn-trans isomer **6b** containing a fused boat in a carbocyclic framework.

It was therefore hoped that intramolecular cycloaddition of *o*-xylylene **5** might occur with considerable stereoselectivity to provide the carbocyclic framework of the naturally occurring A-ring aromatic steroids. According to the retrosynthetic analysis in Scheme I the *o*-xylylene **5** was anticipated to arise from the benzocyclobutene **4**. The latter was thought to be accessible by cobalt-catalyzed cooligomerization of diyne **3** with an appropriate monoyne. If one were to use the previously employed[12] BTMSA (X, Y = $SiMe_3$) in this cyclization, then conversion of the resulting bistrimethylsilylated steroid **6** (X = Y = $SiMe_3$) to the target molecule estrone would require the development of a method capable of achieving regiospecific oxidative cleavage of the C-3 arylsilyl bond. Alternatively and more directly, a hindered alkoxyacetylene (X = OR; Y = $SiMe_3$) could be employed as the cyclization partner for **3**, the ultimate availability of estrone being contingent on regiospecificity in the trimerization step.

We envisaged the construction of diyne **3** by one of two possible routes. One could form bond "a" (Scheme I) in a strategic step by reacting the known 1,3,6-trilithio-1,5-hexadiyne (**7**)[12] with an



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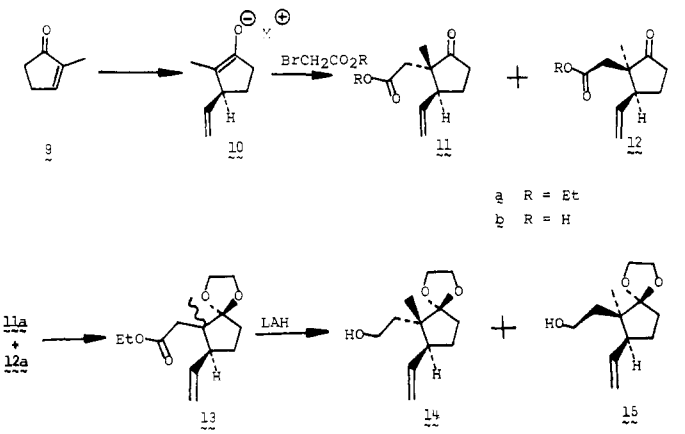
appropriate halide ultimately derivable via stereospecific functionalization of 2-methylcyclopentenone by vinylcuprate addition–enolate alkylation chemistry. Alternatively, bond "b" could arise by alkylation of a cyclopentanone enolate with a halide in turn readily available from known alcohol **8**.[12] Our initial investigation was directed to the bond "a" approach.

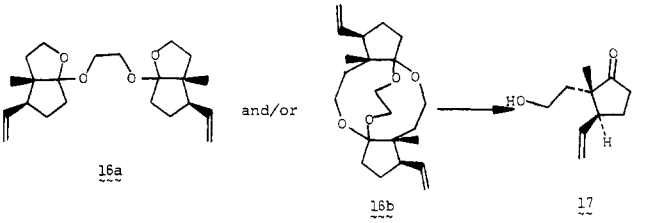
Treatment of 2-methylcyclopentenone (**9**)[13] with bromomagnesium divinylcuprate (formed from 2 equiv of vinylmagnesium bromide and 1 equiv of CuI)[14] allowed introduction of the vinyl group with concomitant generation of the enolate **10**.[15] The alkylation of this enolate, which must proceed both regio- and stereospecifically to generate what is to become the trans CD ring junction of the steroid nucleus, is a crucial step in the synthesis. Cyclopentanone enolate ions are known to undergo relatively rapid equilibration.[16a-c] On the other hand, Posner et al.[16c] had shown that the enolate anion generated from cyclopentenone with lithium divinylcuprate could be alkylated stereo- and regioselectively.

Addition of ethyl bromoacetate to the enolate **10** afforded a 3.1:1 mixture of isomers that were inseparable by TLC and gas chromatography (81%). The ^1H NMR spectrum showed only one methyl singlet and an integration indicated that a second methyl singlet may have been masked by the methyl triplet absorption due to the ethyl ester methyl protons. The ^{13}C NMR spectrum clearly revealed two isomers in 3.1:1 ratio. The assignment of the major isomer to structure **11a** is based on the expectation that the transition state involving trans attack is less hindered and on ^{13}C NMR arguments. Thus, the cyclopentanone methyl carbon absorption at δ 17.79 is shielded relative to the analogous absorption for **12a** at δ 22.81, in accordance with expectation based on steric interactions. Saponification of the mixture of isomers with methanolic KOH gave the substituted acetic acids **11b** and **12b**, which displayed two distinct methyl singlet absorptions in the ^1H NMR spectrum (3.1:1). The cyclopentanone methyl protons in the major isomer **11b** are shielded (δ 0.87) relative to the analogous protons in the minor isomer **11b** (δ 1.17). This difference in chemical shift has previously been observed in a similar compound[17] and is a result of the fact that the methyl protons in **11** are in the shielding cone of the vinyl group. It is interesting to note that the use of an inverse addition procedure[18] appears to improve stereoselection in reactions of **10**.

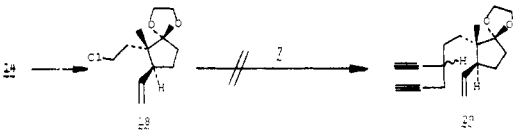
Conversion of the ester group of **11a** into a potential electrophilic function to be used in the formation of bond "a" (Scheme I) proceeded as follows. Ketalization of the mixture of stereosiomers **11a** and **12a** gave the ketal **13** (mixture of isomers) in excellent yield (95%). Reduction with $LiAlH_4$ afforded a readily separable (column chromatography) mixture of alcohols **14**:**15** (3.4:1) in good yield (**14**, 61%; **15**, 18%). As expected, the major isomer



14 displayed the more shielded methyl resonance in the ^1H NMR spectrum. The ketal alcohol **14** is relatively sensitive and on storage underwent rearrangement to a new compound. The latter was relatively nonpolar and nonhydroxylic (IR), and had a parent peak (*m/e* 362) in the mass spectrum which suggested the formation of a polyether dimer formed with concomitant loss of ethylene glycol. The polyethers **16a,b** are consistent with the spectral data as well as the finding that their treatment with aqueous acid gave the keto alcohol **17**.



Transformation of the hydroxy group of **14** was possible, however, if performed without delay. Treatment with *p*-toluenesulfonyl chloride in pyridine gave a tosylate which was directly converted to the chloride **18** by treatment with LiCl in HMPA[19] (65%).



(13) A. M. Gaddis and L. W. Butz, *J. Am. Chem. Soc.*, **69**, 1203 (1947); R. L. Funk and K. P. C. Vollhardt, *Synthesis*, 118 (1980).
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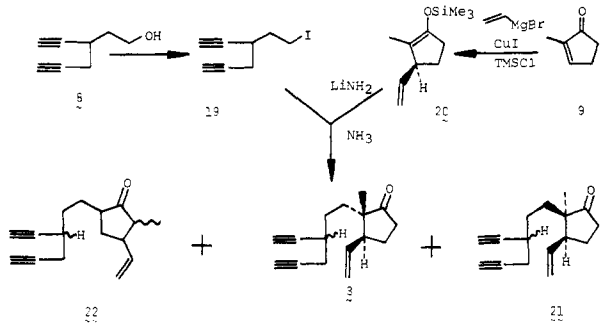
Unfortunately, addition of **18** to a solution of **7** in THF (−20 °C) led only to recovery of the chloride. Higher reaction temperatures (room temperature) and excess **7** were equally unsuccessful, as evidenced by the recovery of chloride **18**.

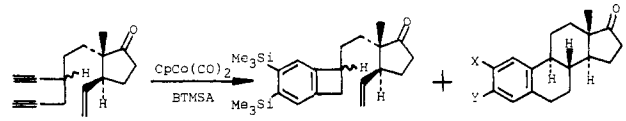
We therefore turned to the bond "b" approach designated in Scheme I. This route was initially disfavored because it required the alkylation of the regiospecific cyclopentanone enolate **10** with a relatively unreactive alkyl halide (**19**), a process where enolate equilibration was expected to compete with alkylation. However, Binkley and Heathcock[20] had demonstrated that lithium enolates generated from trimethylsilyl enol ethers with lithium amide undergo regiospecific alkylation in a mixture of liquid ammonia–tetrahydrofuran where proton transfer is an insignificant side reaction. The trimethylsilyl enol ether **20** was prepared in 89% yield by trapping the enolate **10** [generated by treating 2-methylcyclopentenone (**9**) with bromomagnesium divinylcuprate] with trimethylsilyl chloride. To prepare the required alkylating agent **19**, the diynol **8**[12] was quantitatively converted to the *p*-toluenesulfonate (TsCl, pyridine), which on exposure to NaI in acetone gave the iodide **19** in 96% yield. The enolate **10** was



generated regiospecifically from the enol ether **20** with $LiNH_2$ in NH_3–THF and then alkylated with the iodide **19** (3 equiv). Column chromatography gave recovered iodide (1.9 equiv), a small amount (4.6%) of regioisomerically alkylated cyclopentanone **22** (as a mixture of stereoisomers which showed a broad doublet at δ 1.00 in the NMR spectrum, characteristic of the expected splitting pattern for the methyl protons in **22**), and a 2:1 mixture (64%) of the diastereomeric cyclopentanones **3** and **21**. The assigned stereochemistry ultimately rests on conversion of **3** to estra-1,3,5(10)-trien-17-one. Instead of the anticipated four methyl singlet resonances in the ^1H NMR spectrum of this mixture only two methyl singlet absorptions are present at δ 1.03 and 0.85, indicating that the methyl singlet absorptions for each pair of diastereomers are isochronous. The methyl protons for **3** are shielded relative to the methyl protons for **21** owing to the anisotropy of the proximate vinyl group (vide supra). The ^{13}C NMR spectrum of the mixture **3** and **21** showed four distinct methyl-carbon resonances at δ 20.11, 19.97, 17.89, and 17.53. The two high-field absorptions are assigned to the methyl carbons of the diastereomers **3** which are sterically shielded by the cis vinyl group. Chromatography partially separated all four isomers. A pure sample of **3** exhibited only the upfield methyl singlet absorption in the ^1H NMR and the two upfield methyl carbon resonances in the ^{13}C NMR spectrum.

The decreased trans selectivity in the alkylation of enolate **10** with what we assumed to be a comparatively less reactive alkylating agent (**19** vs. ethyl bromoacetate; trans:cis ratio = 2:1 vs. 3.2:1) might have been due to solvent effects. Therefore, enolate **10** was generated with methyllithium and alkylated in THF–HMPA (5:1) to yield **3** and **21** in a 4:1 ratio but reduced yield (42%). The lower yield was due, in part, to competitive alkylation to the regioisomeric cyclopentanones **22** (10%).

Cobalt-Catalyzed Cyclization of Diyne 3 to 2,3-Bis(trimethylsilyl)estratrien-17-one (24a). The successful preparation of **3** suggested its application to steroid synthesis in analogy to our model studies.[12] Separation of the individual diastereomers was deemed unnecessary since it was anticipated that both diastereomers would cooligomerize with a suitable monoyne (BTMSA) to furnish two diastereomeric benzocyclobutenes **23**, each of which would open to the same *o*-xylylene intermediate (**5**, X = Y = $SiMe_3$) by conrotatory-outward opening of the four-membered ring. Cooligomerization of diyne **3** with BTMSA catalyzed by $CpCo(CO)_2$ gave the benzocyclobutene **23** (as an unseparated mixture of diastereomers) in 56% yield and a single estratrienone **24a** in 18% yield. The mixture **23** cyclized to **24a**



3 23

24a, X=Y=$SiMe_3$
24b, X=Y=H
24c, X=$SiMe_3$, Y=OMe
24d, X=OMe, Y=$SiMe_3$
24e, X=OMe, Y=H
24f, X=OH, Y=H
24g, X=H, Y=$SiMe_3$
24h, X=$SiMe_3$, Y=H

in 95% yield by heating in decane, resulting in a total isolated yield of 71%. Chemical structural proof for **24a** was obtained by nearly quantitative protodesilylation (97%) with CF_3CO_2H–CCl_4 to estra-1,3,5(10)-trien-17-one (**24b**). The synthetic estratrienone was identical (TLC R_f, IR, ^1H NMR, ^{13}C NMR,[21] *m/e*) with an authentic sample of *d*-estratrienone.[22] The stereospecificity of the transformation **3** → **24a** is remarkable and implies that only the chair-like exo transition state **5a** is operative as was predicted based on model systems and conformational analysis. Similar specificity has been observed in other steroid syntheses based on intramolecular Diels–Alder reactions of *o*-xylylenes.[11]

Introduction of the C-3 Oxygen Substituent. A Total Synthesis of *dl*-Estrone (1). Having achieved the stereoselective formation of the estratrienone carbocyclic framework, we turned our attention to the introduction of the physiologically important[23] C-3 oxygen substituent present in **1**. In a first approach, the direct cooligomerization of diyne **3** with an alkoxyacetylene seemed appealing if regioselective cyclization were to place the oxygen into the 3 position of the resulting steroid. The choice of such an alkyne was dictated by the necessity to provide large enough steric bulk to prevent autocyclization (but not the ability to cocyclize) and hence effect chemoselectivity, and the known propensity of alkoxyalkynes bearing β hydrogens to decompose to alkenes and ketenes.[24]

Trimethylsilyl(methoxy)acetylene[25] (prepared from sodium methoxyacetylide generated in situ[26] and trimethylsilyl chloride in 62% yield) appeared to meet these requirements. Since few transition metal catalyzed oligomerizations of alkoxyacetylenes had been reported,[27] a model study was undertaken. When neat trimethylsilyl(methoxy)acetylene was cocyclized with 1,5-hexadiyne, a quantitative conversion of $CpCo(CO)_2$ to a single complexed crystalline cyclobutadiene isomer **26** was observed (after

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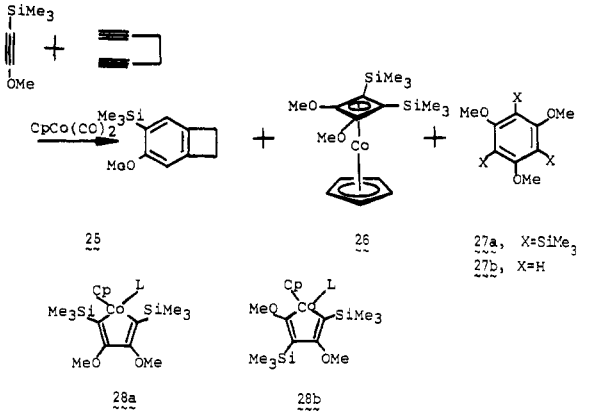
chromatography on alumina; partial decomposition is observed on silica) as well as the formation of a small amount of 1,3,5-trimethoxybenzene (**27b**).[28] The assignment of structure **26** rests

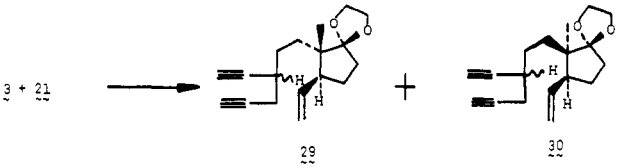


on spectral dat , particularly the characteristic fragmentation on electron impact[29] indicative of the substitution pattern. A plausible explanation for the regiospecific formation of **26** on the one hand and **27b** (apparently derived from **27a** by desilylation on chromatography) on the other is found on inspection of the two likely metallacycle intermediates **28a,b** to be expected from the reaction of $CpCo(CO)_2$ with the alkoxyalkyne.[30] The former, evidently too hindered to undergo further alkyne incorporation, exclusively rearranges to **26**, whereas the latter prefers regiospecific reaction with another molecule of alkyne to ultimately furnish only **27a**.

The failure to observe cooligomerized product **25** in this reaction was attributed to the excessive presence of alkoxyalkyne blocking coordination sites on cobalt and rapidly depleting the solution of active catalyst. Cooligomerization of only 1 equiv of trimethylsilyl(methoxy)acetylene with 1 equiv of 1,5-hexadiyne gave small amounts of the desired benzocyclobutene **25**; however, diyne oligomers were also formed. Employment of a ratio of monoyne:diyne = 4:1 in *n*-octane resulted in the formation of **25** in only moderate yield (15%), before all of the cobalt had been removed as **26**. A considerable amount of the diyne (50%) was recovered in this reaction. Although the above approach appeared synthetically unattractive en route to A-ring phenolic steroids, the trimethylsilyl(methoxy)acetylene nevertheless seemed a useful substrate with which to probe the question of regioselectivity in the cocyclization with **3**. Indeed a mechanistic analysis presented elsewhere[31] suggested the likelihood for predominant formation of the desired 3-oxygenated steroid nucleus in this process.

Cooligomerization of **3** with the alkoxyalkyne and exposure of the resulting mixture (containing intermediate benzocyclobutene regio- and diastereomers) to refluxing decane gave, in addition to **26** and recovered **3** (52%), a 2:1 mixture of trimethylsilylmethoxyestratrienones **24c** (X = $SiMe_3$; Y = OMe) and **24d** (X = OMe; Y = $SiMe_3$) in 34% yield (based on recovered **3**) after column chromatography. The regiochemical assignment was made by analysis of the ^1H NMR spectrum of the aromatic region [δ 7.06 (br s, 0.68 H), 6.81 (br s, 0.32 H), 6.53 (br s, 0.32 H), 6.33 (br s, 0.68 H)] in a similar manner to that employed in the analysis of the spectra of substituted octahydrophenanthrenes.[12] Protons ortho to a methoxy substituent on an aromatic ring are shielded by 0.43 ppm (relative to benzene), whereas the meta protons are shielded only by 0.09 ppm.[32] Therefore, the furthest downfield aromatic proton of the two isomers should be the C-1-proton which is meta to the methoxy group and exposed to the sterically deshielding "bay region" effect as in the desired regioisomer **24c**. Conversely, the furthest upfield aromatic proton should be the C-4 proton that is ortho to the methoxy group as in **24c**. The NMR spectrum shows the predominance of these two signals; thus **24c** was assigned to be the major isomer. Nearly quantitative protodesilylation (CF_3CO_2H–CCL_4 (1:1); room temperature; 5 h) furnished 2-methoxyestratrienone **24e** (X = OMe; Y = H) and estrone methyl ether **2** in a 1:2 ratio, identified by spectral data (*m/e*, 180-MHz ^1H NMR, ^{13}C NMR, IR) and comparison with authentic material.[21,33] No other steroid isomers could be detected, again indicating the relatively preferred accessibility of exo transition state **5a** (X = OMe; Y = $SiMe_3$; Scheme I) in the intramolecular Diels–Alder reaction.

While the above method held promise, we turned our attention to bis(trimethylsilyl)estratrienone (**24a**), a potential estrone precursor if regioselective oxidative phenyl–silicon cleavage could be achieved. A promising reagent appeared to be lead tetrakistrifluoroacetate.[34] However, exposure of this reagent to a model compound, 6,7-bis(trimethylsilyl)tetralin,[30] led only to an intractable mixture. Since it appeared that *o*-bistrimethylsilylated arenes could not be selectively oxidized in the desired manner we turned to the possibility of using various two-step procedures, in which one trimethylsilyl group was to be replaced by an electrophile that could subsequently be converted to a hydroxy substituent. In a model study, 6,7-bis(trimethylsilyl)tetralin[30] was readily and selectively converted to 6-trimethylsilyl-7-acetoxytetralin in two steps (1. acetyl chloride–$AlCl_3$–CCl_4;[35] 2. CF_3CO_2H–Na_2HPO_4; 77% overall).[36] To apply this sequence to **24a** protection of the 17-keto group appeared desirable in order to prevent a potentially competitive Baeyer-Villiger oxidation.[37] Direct ketalization of **24a** was considered impractical owing to the presence of the acid-sensitive aryltrimethylsilyl groups; therefore, protection was introduced at an earlier stage in the synthesis. Ketalization of the crude 2:1 mixture of **3**:**21** gave a mixture of ketals in excellent yield (95%) separated by chromatography.



Cooligomerization of **29** with BTMSA proceeded smoothly to give the two diastereomeric benzocyclobutene isomers **31** (27.5%) and **32** (29.1%) (stereochemistry arbitrarily assigned), which were completely separable by column chromatography along with the desired steroid **33** (30%). The estratrienone ketal **33** could be selectively hydrolyzed without protodesilylation (catalytic CF_3CO_2H, CH_3CO_2H, H_2O) to the bis(trimethylsilyl)estratrienone **24a** (97%) or protodesilylated and hydrolyzed (CF_3CO_2H, H_2O) to the estratrienone **24b** (96%), confirming the structure of the cycloadduct. On heating in decane either isomer **31** or **32** was

(28) Identical with authentic material.

(29) (a) M. D. Rausch, I. Bernal, B. R. Davies, A. Siegel, F. A. Higbie, and G. F. Westover, *J. Coord. Chem.*, **3**, 149 (1973); (b) J. R. Fritch and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, **100**, 3643 (1978).

(30) For a mechanistic discussion, see K. P. C. Vollhardt, *Acc. Chem. Res.*, **10**, 1 (1977); R. L. Hillard III and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, **99**, 4058 (1977).

(31) K. P. C. Vollhardt, *Ann. N.Y. Acad. Sci.*, **333**, 241 (1980).

(32) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed., Pergamon Press, Oxford, 1969.

(33) (a) J. Fishman and M. Tomasz, *J. Org. Chem.*, **27**, 365 (1962); (b) J. Fishman and J. S. Liang, *Tetrahedron*, **24**, 2199 (1968); (c) W. Nagata, T. Terasawa, and K. Tori, *J. Am. Chem. Soc.*, **86**, 3746 (1964).

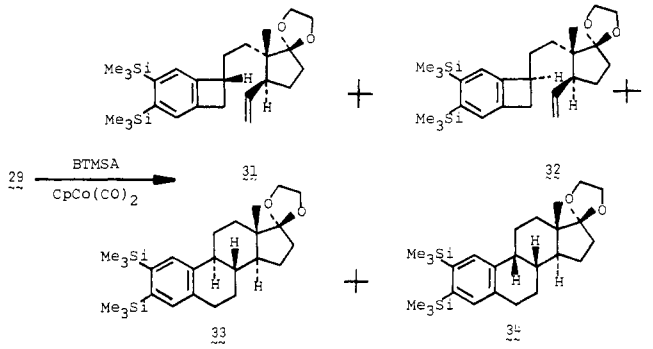
(34) (a) R. E. Partch, *J. Am. Chem. Soc.*, **89**, 3662 (1967); (b) J. R. Kalman, J. T. Pinhey, and S. Sternhell, *Tetrahedron Lett.*, 5369 (1972); (c) H. C. Bell, J. R. Kalman, J. T. Pinhey, and S. Sternhell, *ibid.*, 853 (1974); (d) D. Westphal and E. Zbiral, *Justus Liebigs Ann. Chem.*, 2038 (1975).

(35) Gratifyingly, upon chromatographic purification the diastereomers **29** could be readily and completely separated from the unwanted diastereomers **30**. Each pair of diastereomers showed only one methyl singlet absorption in the ^1H NMR spectrum with the methyl protons of the diastereomers **29** shielded relative to the methyl protons in **30**. Curiously, all of the carbon-13 resonances but one were isochronous for the diastereomers **29**, whereas all but five carbons for the diastereomers **30** were isochronous. Again, the methyl carbons of **29** (15.74 ppm) were sterically shielded relative to the methyl carbons of **30** (19.81, 19.47 ppm).

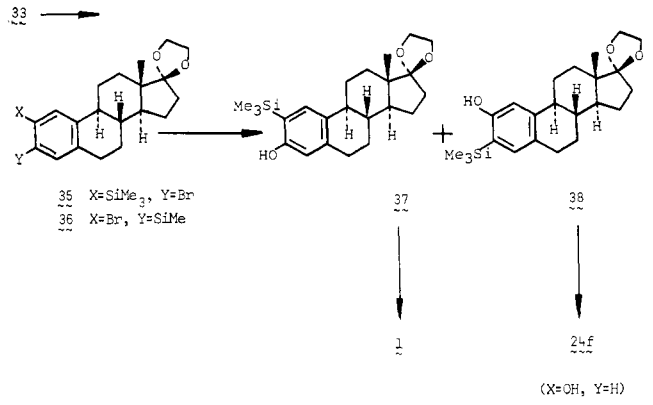
(36) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955).

(37) On the other hand, 2-acetylestra-1,3,5(10)-trien-17-one can be selectively oxidized to the 2-acetoxyestratrienone: T. Nambara, S. Honma, and S. Akiyama, *Chem. Pharm. Bull.*, **18**, 474 (1970).

transformed in high yield (90%) to crystalline **33**, providing an ultimate 81% overall yield.[38] From the mother liquors of crystallized **33** a less polar, stereoisomeric estratrienone ketal was isolated by preparative TLC in 3.6% yield, presumed to be **34**.[39]



When **33** was treated with acetyl chloride–$AlCl_3$, a complex mixture of products resulted, most of which formed by deketalization and protodesilylation. However, careful bromination (Br_2–pyridine (2:1), CCl_4, room temperature) monitored by NMR proceeded regioselectively to produce a 79:21 mixture of **36**:**35**. The aromatic region of the ^1H NMR spectrum displayed four singlets assigned on the basis of substituent effects on chemical shifts and the steric deshielding expected for the bay-region protons (H_1).[12] Chemical verification of the spectral assignment was obtained by converting the aryl bromides **35** and **36** to the corresponding phenols using the method of Hawthorne: transmetalation and treatment with trimethyl borate to form the aryl trimethoxyborate, followed by neutralization with acetic acid to give the aryldimethoxyborane, and finally oxidation with H_2O_2 to give the phenol.[40] Treatment of the mixture **35** and **36** successively with *n*-butyllithium, trimethyl borate, acetic acid, and H_2O_2 followed by chromatographic purification (preparative TLC) gave two easily separated trimethylsilylhydroxyestratrienone ketals **37** and **38** (68% overall combined yield). Treatment of the major



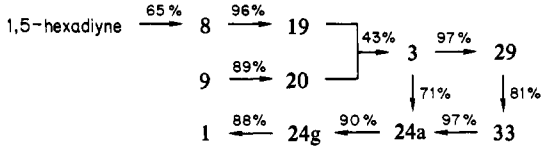
isomer **38** with H_3O^+ gave 2-hydroxyestratrienone **24f** (X = OH, Y = H). Similar treatment of the minor, isomeric ketal **37** afforded *dl*-estrone (**1**). The 2-hydroxy isomer **24f** showed the correct number of carbons in the ^{13}C NMR spectrum and had a ^1H NMR spectrum identical with a published one.[41] The increased reactivity at the C-2 position of **33** is difficult to explain, but is consistent with the finding that estra-1,3,5(10)trien-17-one (**24b**) reacts with acetyl chloride–$AlCl_3$ to preferentially give the 2-acetyl isomer.[37]

This behavior suggested that the trimethylsilyl group at C-2 might be selectively removed to leave the 3-silyl substituent as a substrate for direct oxidative cleavage reactions with lead tetrakistrifluoroacetate.[34b] Since protection of the 17-keto group appeared no longer necessary, the bis(trimethylsilyl)estratrienone **24a** was protodesilylated (CCl_4, CF_3CO_2H, room temperature) by monitoring the disappearance of the trimethylsilylmethyl proton resonance (δ 0.33) and the appearance of a new monosilylmethyl proton resonance to give a mixture of trimethylsilylestratrienones **24g,h** (3:1) in quantitative yield. The ^1H NMR (180 MHz) spectrum could not be used for the determination of the regioselectivity of this reaction. However, the ^{13}C NMR spectrum showed that indeed a regioselective protodesilylation had taken place. The aromatic carbon absorptions for the two isomers were assigned by taking into account relative peak heights and comparison of chemical shifts with calculated values derived from addition of the incremental chemical shift changes on the various positions by introduction of a trimethylsilyl group into benzene[42] (C-1, 11.3; ortho, 4.7; meta, −0.8; para, 0.2) to the chemical shift of the respective carbon in the model compound estra-1,3,5(10)-trien-17-one[21] (**24b**) (Table I).

Table I. Calculated and Observed ^{13}C NMR Chemical Shifts in **24g, h**

		C-1	C-2	C-3	C-4	C-5	C-10
3-Me_3Si	calcd	125.9	132.1	138.6	133.8	135.4	140.2
24g	obsd	124.7	130.8	137.5	134.2	135.7	140.4
2-Me_3Si	calcd	131.7	138.6	132.1	128.0	136.6	139.0
24h	obsd	130.2	137.5	130.8	128.6	137.3	138.9

Scheme II



The calculated values are in close agreement with the observed ones and an approximate ratio of 77:23 was obtained by measuring the peak height ratio of the C-4 carbon resonances of **24g**:**24h**. A more accurate ratio was determined by conversion to a mixture of **1** and **24f** in excellent yield (97%) on treatment with lead tetrakistrifluoroacetate. Integration of the C-1 proton resonance (δ 7.12) of *dl*-estrone (**1**) vs. the C-4 proton resonance (δ 6.94) of the 2-hydroxy isomer **24f** gave a 74:26 ratio of the two compounds. Pure *dl*-estrone (**1**) could be separated by fractional crystallization from acetone–ether and its structure ascertained by comparison with authentic material. Protodesilylation of **24a** at low temperature (−30 °C) followed by oxidative aryl–silicon cleavage gave racemic estrone (**1**) (80% yield) and the 2-hydroxy isomer **24f** with even higher regioselectivity (90:10).

Scheme II summarizes the overall efficiency of the processes connecting 1,5-hexadiyne and 2-methylcyclopentenone **9**, respectively, with **1**. This constitutes the shortest *dl*-estrone synthesis known to date from acyclic or monocyclic precursors [five steps from 2-methylcyclopenten-1-one (21.5% overall yield), six steps from 1,5-hexadiyne (15.1%)], and compares favorably with the recent Johnson–Bartlett[9] synthesis of *dl*-estrone [14 steps from *m*-hydroxycinnamic acid (6.9% overall yield)], the Hoffmann-La

(38) Interestingly, incomplete independent thermolysis of **31** and **32**, respectively, showed that neither one of the two isomers is converted into the other (by TLC), suggesting an appreciably lower barrier to intramolecular Diels–Alder reaction than to ring closure once the intermediate *o*-xylylene is generated. See also W. Oppolzer, *J. Am. Chem. Soc.*, **93**, 3834 (1971). The *o*-xylylene–benzocyclobutene ring closure requires substantial activation (E_a = 29.3 kcal mol^{-1}): W. R. Roth, M. Biermann, H. Dekker, R. Jochems, C. Musselman, and H. Hermann, *Chem. Ber.*, **111**, 3892 (1978).

(39) The stereochemistry of this isomer is tentatively assigned to be cis-anti-trans based on the finding that small amounts of cis isomers are formed in the cobalt-catalyzed formation of tricycles,[12] particularly 1,2,3,4,4a,9,10,10a-octahydrophenanthrene, precedence in the literature which demonstrates the strong sensitivity of the stereochemistry of intramolecular *o*-xylylene cycloadditions to changes in structural features,[11] and a stereochemical analysis indicating that the transition state leading to **34** should be the next preferred transition state after **5a**. The ^{13}C NMR spectrum displays the correct number of carbon resonances for a new stereoisomer, although they are not sufficiently characteristic to allow an unambiguous stereochemical assignment.

(40) M. F. Hawthorne, *J. Org. Chem.*, **22**, 1001 (1957).

(41) T. Nambara, M. Numazawa, and S. Akiyama, *Chem. Pharm. Bull.*, **19**, 153 (1971).

(42) J. Schraml, V. Chvalovsky, M. Mägi, and E. Lippmaa, *Collect. Czech. Chem. Commun.*, **40**, 897 (1975).

Roche approach[43] to (+)-estrone methyl ether [12 steps from 2-methylcyclopentane-1,3-dione (12% overall yield)], the recent Danishefsky–Cain[44] synthesis of optically pure (+)-estrone [11 steps from 2-methylcyclopentane-1,3-dione (13% overall yield), 14 steps from 2,6-lutidine (7.4%)], and the Torgov[4,45] synthesis of *dl*-estrone methyl ether [eight steps from 2-methoxynaphthalene (27% overall yield)]. It may, however, be noted that the synthetic sequence is not readily amenable to the synthesis of optically active steroids, the introduction of optical activity being dependent on an (as yet) difficult to accomplish asymmetric vinylcuprate addition to 2-methylcyclopentenone. Novel approaches need to be devised inducing asymmetry in the cobalt-mediated step, thus presenting an opportunity for asymmetric catalysis. This strategy is under active investigation.

Experimental Section

The apparatus, description of specific equipment, reagents, and standard procedures have been summarized previously.[12]

Ethyl (2α,3β)- (11a) and (2β,3β)-(2-Methyl-3-vinylcyclopentan-1-on-2-yl)acetate (12a). To magnesium (2.66 g, 109 mmol) and one crystal of I_2 in THF (100 mL) was added vinyl bromide (29.5 mL, 418 mmol) in THF (60 mL) at such a rate to maintain the reaction temperature at 45 °C. After all the magnesium had disappeared, the solution was heated at 45 °C under a stream of nitrogen to remove excess vinyl bromide. The mixture was then cooled to −5 °C, copper(I) iodide (10.44 g, 54.8 mmol) added, and the solution stirred until it was jet black. The mixture was quickly chilled to −70 °C and 2-methylcyclopentenone (**9**, 4.79 g, 49.9 mmol) in THF (45 mL) added dropwise. After the addition was complete (30 min) the solution was warmed to −30 °C, stirred for 45 min and cooled to −70 °C, and HMPA (50 mL) added, followed by ethyl bromoacetate (10 mL, 91 mmol). The solution was allowed to warm to room temperature over 90 min, then stirred for 30 min, quenched with methanol, diluted with ether, poured onto saturated NH_4Cl, and stirred for another 30 min. The aqueous layer was separated and extracted twice with ether. The combined ether extracts were washed with 5% aqueous $Na_2S_2O_3$, water, and brine and dried ($MgSO_4$). Evaporation of the ether left a yellow liquid which was distilled to give a colorless liquid (8.52 g, 81%), a single peak by gas chromatography (column temperature 185 °C, retention time 22 min) and a single spot by TLC (R_f 0.27, ether–petroleum ether (1:4) as eluent): bp 85–87 °C (0.5 mm); *m/e* (rel intensity) 210 (M^+, 6.41), 195 (8.31), 165 (18.13), 137 (17.30), 123 (100), 95 (18.94), 81 (28.55); IR (neat) 3100, 3000, 1740, 1645, 1470, 1210, and 1040 cm^{-1}; NMR (CCl_4) δ 5.80 (m, 1 H), 5.10 (m, 2 H), 4.05 (q, J = 7 Hz, 2 H), 3.23–1.53 (m, 7 H), 1.23 (t, J = 7 Hz, 3 H), 1.11 (s, 0.73 H), 0.82 (s, 2.27 H); ^{13}C NMR (C_6D_6) showed two isomers with resonances for the major isomer **11a** at δ 218.58, 170.98, 137.52, 116.63, 60.19, 49.31, 47.38, 40.07, 36.51, 24.75, 17.79, 14.05, and resonances for the minor isomer **12a** at δ 217.97, 170.97, 137.52, 116.63, 60.19, 51.42, 49.72, 38.90, 35.58, 24.75, 22.81, 14.05.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.26; H, 8.44.

(2α,3β)- (11b) and (2β,3β)-(2-Methyl-3-vinylcyclopentan-1-on-2-yl)acetic Acid (12b). The ethyl esters **11a** and **12a** (200 mg, 0.95 mmol) were dissolved in methanol (2 mL) and 3 M NaOH (2 mL) and stirred for 24 h. Acidic aqueous ethereal workup gave a thick oil (168 mg, 96%). An analytical sample of this oil was purified by distillation on a Kugelrohr apparatus (oven temperature 80 °C, 0.005 mm): IR (neat) 3500, 3000, 1740, 1660, 1410, 1200, and 920 cm^{-1}; NMR (CCl_4) δ 5.67 (m, 1 H), 5.06 (m, 2 H), 3.17–1.50 (m, 8 H), 1.17 (s, 0.73 H), 0.87 (s, 2.27 H).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 64.78; H, 7.75.

Ethyl (1,1-Ethylenedioxy-2-methyl-3-vinylcyclopent-2-yl)acetate (13). Ethylene glycol (890 mg, 14.3 mmol), triethyl orthoformate (630 mg, 4.2 mmol), *p*-toluenesulfonic acid (20 mg), and ethyl esters **11a** and **12a** (570 mg, 2.71 mmol) were stirred at room temperature for 24 h. The reaction mixture was worked up with saturated $NaHCO_3$ and ether and dried (K_2CO_3). Evaporation of the ether and filtration through silica gel (10 g, ether–petroleum ether (1:4) as eluent) left a colorless oil (653 mg, 95%): R_f 0.33 (ether–petroleum ether (1:4) as eluent); *m/e* (rel intensity) 254 (M^+, 0.42), 100 (18.83), 99 (100), 86 (26.25); IR (neat) 3100, 3000, 1730, 1645, 1465, 1150, and 1040 cm^{-1}; NMR (CCl_4) δ 5.77 (overlapping (5 lines) ddd, J = 17, 10, 9 Hz, 1 H), 5.00 (dd, J = 17, 2.5 Hz, 1 H), 4.98 (dd, J = 9, 2.5 Hz, 1 H), 4.03 (q, J = 7 Hz, 2 H), 3.87 (br s, 4 H), 2.70 (m, 1 H), 2.17 (br s, 2 H), 1.73 (m, 4 H), 1.23 (t, J = 7 Hz, 3 H), 1.13 (s, 0.75 H), 0.95 (s, 2.25 H).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.29; H, 8.62.

(2α,3β)- (14) and (2β,3β)-2-(1,1-Ethylenedioxy-2-methyl-3-vinylcyclopent-2-yl)ethanol (15). To $LiAlH_4$ (68 mg, 1.79 mmol) in ether (4 mL) was added the ethyl ester mixture **13** (455 mg, 1.79 mmol) in ether (5 mL) at such a rate as to maintain reflux. The solution was refluxed for another 1 h after the addition was complete. Water (70 μL), 10% NaOH (70 μL), and water (185 μL) were added sequentially and the solution was filtered. Aqueous workup left an oil which by TLC indicated two components. Chromatography on silica gel (40 g, ether–petroleum ether (1:1) as eluent) gave (A) the isomer **15** (67 mg, 18%) [R_f 0.42 (ether as eluent); *m/e* (rel intensity) 212 (M^+, 3.30), 197 (4.73), 184 (21.63), 169 (13.40), 157 (33.17), 151 (83.27), 143 (88.35), 135 (52.26), 99 (78.13), 81 (75.78), 41 (100); IR (neat) 3400, 2975, 2900, 1640, 1470, 1170, and 1075 cm^{-1}; NMR (CCl_4) δ 5.93 (m, 1 H), 5.00 (m, 2 H), 3.93 (br s, 4 H), 3.57 (m, 2 H), 2.67–1.10 (m, 8 H), 0.97 (s, 3 H)]; (B) the major isomer **14** (231 mg, 61%) [R_f 0.38; *m/e* (rel intensity) 212 (M^+, 2.55), 197 (3.88), 184 (19.90), 169 (12.33), 157 (27.12), 151 (82.45), 143 (68.78), 135 (53.81), 99 (65.18), 81 (62.60), 55 (100); IR (neat) 3400, 2975, 2900, 1640, 1470, 1160, and 1080 cm^{-1}; NMR (CCl_4) δ 5.73 (overlapping (5 lines) ddd, J = 18, 10, 9 Hz, 1 H), 5.01 (dd, J = 9, 2.5 Hz, 1 H), 5.00 (dd, J = 18, 2.5 Hz, 1 H), 3.93 (m, 4 H), 3.53 (br t, J = 7 Hz, 2 H), 2.67–1.10 (m, 8 H), 0.92 (s, 3 H)].

Exact mass. Calcd for $C_{12}H_{20}O_3$: 212.1412. Found: 212.1413.

Rearrangement of Alcohol 14 to 16. Hydrolysis of 16 to 17. A neat sample of alcohol **14** underwent a rearrangement to an oily solid after 1 week at room temperature. This new compound was filtered through silica and assigned structure(s) **16a,b** on the basis of the following data: R_f 0.70 (ether as eluent); *m/e* (rel intensity) 362 (M^+, 0.49), 197 (12.77), 196 (69.53), 184 (11.49), 150 (46.30), 99 (70.88), 93 (72.90), 43 (100); IR (neat) 2995, 1640, 1450, 1375, 1310, and 930 cm^{-1}; NMR (CCl_4) δ 5.67 (m, 2 H), 5.00 (m, 4 H), 3.83 (m, 4 H), 3.60 (br s, 4 H), 2.6–1.5 (m, 14 H), 0.95 (s, 3 H), 0.91 (s, 3 H).

The rearranged compound **16** (161 mg, 0.44 mmol) was dissolved in THF (3 mL, saturated with water) containing 3 M HCl (three drops). The mixture was stirred for 18 h and then partitioned between ether and saturated $NaHCO_3$. Aqueous workup gave a colorless oil (124 mg; 84%): R_f 0.38 (ether as eluent); *m/e* (rel intensity) 168 (M^+, 0.58), 153 (5.08), 151 (3.50), 135 (10.25), 124 (100), 109 (21.82), 95 (21.94), 81 (32.68); IR (neat) 3450, 3000, 1740, 1650, 1460, 1090, and 920 cm^{-1}; NMR (CCl_4) δ 5.67 (m, 1 H), 5.06 (m, 2 H), 3.93 (br t, 0.66 H), 3.60 (br t, 1.33 H), 3.0–1.3 (m, 7 H), 0.95 (s, 1 H), 0.87 (s, 2 H).

Exact mass. Calcd for $C_{10}H_{16}O_2$: 168.1150. Found: 168.1149.

(2α,3β)-2-(2-Chloroethyl)-2-methyl-3-vinylcyclopentan-1-one Ethylenedioxy Ketal (18). To the alcohol **14** (360 mg, 1.70 mmol) in pyridine (7 mL, 0 °C) was added *p*-toluenesulfonyl chloride (518 mg, 2.71 mmol) with stirring. The solution was kept in the refrigerator at 0 °C overnight, lactic acid (75 μL) added, and the mixture placed in the refrigerator for another 5 h. Aqueous workup (with added ether) (including washing the combined ether extracts with a saturated copper sulfate solution) left a thick oil (573 mg, 88%). The oil and LiCl (398 mg, 9.4 mmol) were dissolved in HMPA (6 mL) and heated at 90 °C for 22 h. Aqueous workup with added petroleum ether left a yellow oil which was chromatographed on silica gel (50 g, ether–petroleum ether (1:9) as eluent) to give a colorless oil (256 mg, 65% from alcohol **14**): R_f 0.36 (ether–petroleum ether (1:9) as eluent); *m/e* (rel intensity) 232 (M^+ + 2, 0.58), 230 (M^+, 1.18), 215 (1.14), 195 (7.30), 161 (19.87), 151 (12.14), 139 (33.94), 113 (18.92), 100 (65.85), 99 (100), 86 (90.59); IR (neat) 2995, 1640, 1400, 1100, and 930 cm^{-1}; NMR (CCl_4) δ 5.73 (overlapping (5 lines) ddd, J = 17.5, 9, 9 Hz, 1 H), 5.02 (dd, J = 17.5, 2.5 Hz, 1 H), 5.00 (dd, J = 9, 2.5 Hz, 1 H), 3.90 (m, 4 H), 3.48 (t, J = 8.5 Hz, 2 H), 2.83–1.17 (m, 7 H), 0.90 (s, 3 H).

3-(2-Iodoethyl)-1,5-hexadiyne (19). The ethynylhexynol **8** (6.34 g, 51.9 mmol) was dissolved in pyridine (104 mL) and cooled to 0 °C. *p*-Toluenesulfonyl chloride was added (18.8 g, 98.6 mmol) and the reaction mixture was kept at 0 °C in a refrigerator. After 13 h lactic acid (7.8 mL) was added and the solution was placed in the refrigerator for another 5 h. The mixture was then poured onto ice-cold ether (260 mL) and ice-cold 3 M HCl (450 mL). The aqueous layer was extracted with another portion of cold ether (300 mL) and the combined ether extracts were washed with cold 3 M HCl until acidic, 5% $NaHCO_3$ until pH 8, and brine and dried (Na_2SO_4). Evaporation of the ether left the crude tosylate (14.24 g, 99%) as a colorless oil. The crude tosylate was dissolved in dry acetone (200 mL), sodium iodide (37.4 g, 250 mmol) was added, and the solution was stirred at 45 °C for 30 h. The sodium tosylate was filtered away and the solution worked up with water and petroleum ether. Evaporation of the petroleum ether followed by dis-

(43) N. Cohen, B. L. Banner, W. F. Eichel, D. R. Parrish, G. Saucy, J.-M. Cassal, W. Meier, and A. Fürst, *J. Org. Chem.*, **40**, 681 (1975).
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tillation gave a colorless liquid (11.53 g, 96% from **8**): bp 92 °C (6 mm); *m/e* (rel intensity) 232 (M^+, 0.29), 204 (28.12), 105 (21.67), 103 (38.36), 79 (74.30), 77 (100); IR (neat) 3310, 2950, 2145, 1430, 1210, 1175, and 640 cm^{-1}; NMR (CCl_4) δ 3.28 (dt, J = 6, 1.5 Hz, 2 H), 2.67 (m, 1 H), 2.43 (d, J = 2.5 Hz, 1 H), 2.33 (t, J = 2.5 Hz, 1 H), 2.26–1.9 (m, 4 H), 2.02 (dd, J = 6, 2.5 Hz, 2 H).

Anal. Calcd for C_8H_9I: C, 41.41; H, 3.91. Found: C, 41.42; H, 4.00.

3-Vinyl-2-methyl-1-trimethylsilyloxy-1-cyclopentene (20). The initial stages of this reaction were performed as in the preparation of **11a** and **12a** with magnesium (6.07 g, 250 mmol), vinyl bromide (70.5 mL, 1 mol), and copper(I) iodide (25.70 g, 135 mmol). 2-Methylcyclopentenone (**9**, 10.56 g, 110 mmol) in THF (40 mL) was added dropwise and the solution stirred at −40 °C for 45 min. After subsequent cooling to −60 °C trimethylsilyl chloride (34 mL, 365 mmol), HMPA (70 mL), and triethylamine (50 mL) were added sequentially. The reaction mixture was allowed to warm to room temperature over a period of 2 h. Standard aqueous petroleum ether workup, followed by distillation, gave a colorless liquid (19.19 g, 89%): bp 64–66 °C (3.1 mm); *m/e* (rel intensity) 196 (M^+, 21.93), 181 (35.75), 79 (12.23), 75 (50.95), 73 (100), 45 (29.38); IR (neat) 2990, 1690, 1640, 1250, 1210, 1090, 990, and 840 cm^{-1}; NMR (CCl_4) δ 5.70 (overlapping (5 lines) ddd, J = 17.5, 10, 9 Hz, 1 H), 5.00 (dd, J = 17.5, 2.5 Hz, 1 H), 4.93 (dd, J = 9, 2.5 Hz, 1 H), 3.00 (m, 1 H), 2.5–1.4 (m, 4 H), 1.47 (br s, 3 H), 0.22 (s, 9 H).

Anal. Calcd for $C_{11}H_{20}OSi$: C, 67.28; H, 10.26. Found: C, 67.04; H, 10.18.

[2β(*R),3β]- and [2β(*S**),3β]- (3) and [2α(*R**),3β]- and [2α-(*S**),3β]-2-(3-Ethynyl-5-hexynyl)-2-methyl-3-vinylcyclopentanone (21). Alkylation in NH_3–THF.** To lithium amide [prepared from lithium (247 mg, 35.7 mmol)] in liquid ammonia (200 mL) was added THF (65 mL), followed by the dropwise addition of the enol ether **20** (6.68 g, 34 mmol) in THF (65 mL). The solution was allowed to stir at reflux for 30 min and cooled to −45 °C, and the iodide **19** (23.2 g, 100 mmol) was added in THF (60 mL) in one portion. The mixture was allowed to stir at −45 to −35 °C for 9 h. NH_4Cl was cautiously added and the ammonia allowed to evaporate. Water–ether workup gave an oil which was chromatographed on silica gel (675 g, ether–petroleum ether (7:93) as eluent) to give the following compounds: the iodide **19** (14.79 g), R_f 0.58 (ether–petroleum ether (1:4) as eluent), the regioisomerically alkylated cyclopentanone **22** (358 mg, 4.6%) as a colorless oil [R_f 0.42; *m/e* (rel intensity) 228 (M^+, 1.43), 189 (6.15), 131 (11.11), 124 (45.79), 91 (54.34), 77 (34.72), 67 (97.85), 28 (100); IR (neat) 3340, 3120, 3000, 2150, 1740, 1650, 1460, 1170, and 920 cm^{-1}; NMR (CCl_4) δ 5.73 (m, 1 H), 5.00 (m, 2 H), 2.9–1.1 (m, 14 H), 1.00 (br d, J = 7 Hz, 3 H)], and a mixture of the stereoisomers **3** and **21** in a 2:1 ratio (4976 mg, 64%) [R_f 0.38 for diastereomers **21**, 0.37 for diastereomers **3**; *m/e* (rel intensity) 228 (M^+, 122), 213 (0.79), 129 (11.53), 124 (100), 117 (15.30), 109 (15.93), 105 (22.59), 91 (40.03), 79 (35.91), 55 (39.23); IR (neat) 3330, 3000, 2150, 1740, 1640, 1460, 1300, and 920 cm^{-1}; NMR (CCl_4) δ 5.90 (m, 1 H), 5.14 (dd, J = 10, 2.5 Hz, 1 H), 5.13 (dd, J = 16, 2.5 Hz, 1 H), 2.8–1.2 (m, 14 H), 1.03 (s, 0.96 H), 0.85 (s, 2.04 H); ^{13}C NMR (C_6D_6) δ 219.88, 219.16, 218.94, 137.87, 137.76, 137.41, 116.20, 85.69, 81.37, 70.64, 52.41, 51.18, 51.08, 50.94, 48.22, 47.64, 36.71, 36.57, 35.51, 33.42, 31.62, 29.24, 29.10, 28.61, 28.41, 28.22, 28.09, 24.71, 24.53, 24.43, 24.05, 20.11, 19.97, 17.89, 17.53]. Repeated chromatography (three times) of the 2:1 mixture of stereoisomers **3** and **21** gave the diastereomers **3** uncontaminated with diastereomers **21**: NMR (CCl_4) identical with the NMR of the 2:1 mixture except that the resonance at δ 1.03 is absent; ^{13}C NMR (C_6D_6) δ 219.88, 137.87, 137.58, 116.20, 85.69, 81.37, 70.64, 52.41, 50.94, 48.22, 47.64, 36.71, 36.57, 33.42, 31.62, 28.61, 28.41, 24.71, 24.53, 24.43, 17.89, 17.53.

Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.11; H, 8.66.

Alkylation in THF–HMPA. Methyllithium (1 mL of a 1.6 M solution in hexane, 1.6 mmol) was added to a flame-dried flask and the hexane was evaporated under a stream of nitrogen. THF (0.5 mL) was added immediately followed by the enol ether **20** (294 mg, 1.5 mmol) in THF (0.5 mL) and the solution was stirred for 30 min. The reaction mixture was cooled to 0 °C, HMPA (25 μL) and the iodide **19** (696 mg, 3 mmol) were added in THF (0.5 mL), and the mixture was allowed to warm to room temperature. After 12 h of stirring at room temperature, the mixture was worked up with water and ether. Chromatography on silica (100 g, ether–petroleum ether (5:95) as eluent) gave recovered iodide **19** (390 mg), the regioisomerically alkylated cyclopentanone **22** (33 mg, 10%), and a 4:1 ratio of the stereoisomers **3** and **21** (143 mg, 42%). The 4:1 ratio was determined by integrating the respective methyl proton absorptions in the NMR spectrum.

***dl*-2,3-Bis(trimethylsilyl)estra-1,3,5(10)-trien-17-one (24a).** The cyclopentanone **3** (146 mg, 0.64 mmol) and $CpCo(CO)_2$ (10 μL, 0.08 mmol) in BTMSA (10 mL) were added to $CpCo(CO)_2$ (10 μL, 0.08 mmol) in refluxing BTMSA (25 mL) over a period of 35 h and then the mixture was refluxed for an additional 6 h. The solvent was vacuum transferred leaving a reddish brown residue which was chromatographed on silica gel (75 g, ether–petroleum ether (8:92) as eluent) to give two compounds: (A) the benzocyclobutene diastereomers **23** as an oil (142 mg, 56%) [R_f 0.53 (ether–petroleum ether (1:4) as eluent); *m/e* (rel intensity) 398 (M^+, 5.91), 383 (4.05), 294 (13.28), 259 (7.70), 187 (19.64), 149 (14.36), 73 (100); IR (neat) 3110, 2995, 1640, 1250, 1180, 1090, 840, and 760 cm^{-1}; NMR (CCl_4) δ 7.33 (br s, 2 H), 5.83 (m, 1 H), 5.06 (m, 2 H), 3.60–2.43 (m, 3 H), 2.43–1.10 (m, 9 H), 0.88 (s, 3 H), 0.37 (s, 18 H)] and (B) the bis(trimethylsilyl)estratrienone **24a** (46 mg, 18%) as colorless crystals [mp 155–157 °C (recrystallized from petroleum ether); R_f 0.39; *m/e* (rel intensity) 398 (M^+, 27.47), 384 (22.97), 383 (73.37), 368 (16.45), 367 (45.75), 147 (11.77), 131 (12.82), 97 (17.25), 81 (17.58), 73 (100); IR ($CHCl_3$) 2995, 1745, 1440, 1370, 1250, 940, 840, and 755 cm^{-1}; NMR (CCl_4) δ 7.52 (br s, 1 H), 7.27 (br s, 1 H), 3.0–1.0 (m, 15 H), 0.90 (s, 3 H), 0.37 (s, 18 H)].

Anal. Calcd for $C_{24}H_{38}OSi_2$: C, 72.29; H, 9.60. Found: C, 72.47; H, 9.47.

The benzocyclobutenes **23** (142 mg) were dissolved in degassed decane (35 mL) and refluxed for 20 h. The solvent was vacuum transferred and the residue was filtered through silica and crystallized from petroleum ether to give more estratrienone **24a** (135 mg, 95% conversion; 181 mg total, 71%).

***dl*-Estra-1,3,5(10)-trien-17-one (24b).** The bis(trimethylsilyl)estratrienone **24a** (55.1 mg, 0.138 mmol) was dissolved in CCl_4 (1 mL) and CF_3CO_2H (1 mL) and stirred for 20 h. Standard ethereal aqueous workup gave a colorless solid (34 mg, 97%) identical with an authentic sample[22] of *d*-estra-1,3,5(10)-trien-17-one: mp 107–109 °C (recrystallized from petroleum ether, lit.[46] for *d*-estratrienone 138–141 °C); *m/e* (rel intensity) 254 (M^+, 100), 210 (33.72), 198 (29.83), 197 (37.04), 156 (27.58), 143 (33.04), 128 (42.42), 115 (32.42), 97 (19.23), 91 (25.06), 43 (47.36); IR ($CHCl_3$) 2955, 1740, 1495, 1455, 1260, 1050, and 740 cm^{-1}; NMR (CCl_4) δ 7.04 (m, 4 H), 3.1–1.1 (m, 15 H), 0.89 (s, 3 H); ^{13}C NMR (C_6D_6) δ 217.66, 140.00, 136.44, 129.17, 127.39, 127.02, 50.24, 47.61, 44.51, 38.14, 35.48, 32.05, 29.55, 26.59, 25.81, 22.35, 13.58.

Anal. Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 84.77; H, 8.63.

Trimethylsilyl(methoxy)acetylene. Sodamide in liquid ammonia (1000 mL) was prepared from sodium (72.9 g, 3.17 mol). Chloroacetaldehyde dimethyl acetal (114 mL, 1.0 mol) was added slowly over a period of 30 min and the solution was then stirred for another 60 min. The ammonia was allowed to evaporate over a period of 24 h and then ether (1100 mL) was added. The solution was cooled to 5 °C and trimethylsilyl chloride was added (285 mL, 2.25 mol). The mixture was refluxed for 15 h and methanol (50 mL) added, followed by water (1 L). Ethereal aqueous workup gave an oil which was distilled to give a colorless liquid (78.4 g, 61%): bp 123–124 °C (760 mm, lit.[25] 124 °C); IR (neat) 2995, 2200, 1250, 920, and 845 cm^{-1}; NMR (CCl_4) δ 3.86 (s, 3 H), 0.10 (s, 9 H).

4-Methoxy-5-trimethylsilylbenzocyclobutene (25). 1,5-Hexadiyne (265 mg, 3.39 mmol) and trimethylsilyl(methoxy)acetylene (1739 mg, 13.6 mmol) in octane were cocylized in the presence of $CpCo(CO)_2$ (60 μL, 0.24 mmol) over a period of 30 h.[12] Chromatography on neutral alumina (50 g, activity grade III) gave the following compounds: (1) cyclobutadiene complex **26** (180 mg, 99% based on $CpCo(CO)_2$) as yellow crystals [mp 83.5–85 °C (recrystallized from petroleum ether); *m/e* (rel intensity) 380 (M^+, 89.87), 294 (79.36), 252 (30.72), 209 (15.38), 207 (21.29), 181 (14.63), 155 (18.88), 124 (19.09), 89 (41.04), 73 (100); IR (CCl_4) 3000, 1610, 1460, 1330, 1250, 1050, and 840 cm^{-1}; NMR (CCl_4) δ 4.73 (s, 5 H), 3.30 (s, 6 H), 0.21 (s, 18 H)]; (2) the benzocyclobutene **25** (120 mg, 17%) as a colorless oil [*m/e* (rel intensity) 206 (M^+, 51.27), 191 (51.42), 161 (100), 159 (19.62), 117 (34.84), 75 (13.46), 73 (10.38); IR (neat) 3000, 1590, 1460, 1380, 1240, 1105, 950, and 840 cm^{-1}; NMR (CCl_4) δ 7.21 (br s, 1 H), 6.42 (br s, 1 H), 3.70 (s, 3 H), 3.04 (s, 4 H), 0.25 (s, 9 H)].

Anal. Calcd for $C_{12}H_{18}OSi$: C, 69.84; H, 8.79. Found: C, 69.66; H, 8.73.

***dl*-2-Methoxy-3-trimethylsilyl- (24d) and *dl*-3-Methoxy-2-trimethylsilylestra-1,3,5(10)-trien-17-one (24c).** To refluxing, degassed octane (10 mL) containing $CpCo(CO)_2$ (8 μL) were added cyclopentanone **3** (515 mg, 2.26 mmol), trimethylsilyl(methoxy)acetylene (1445 mg, 11.3 mmol), and $CpCo(CO)_2$ (50 μL) in degassed octane (10 mL) at a rate of 0.19 mL/h for 20 h, then at a rate of 0.27 mL/h for the next 21 h. The mixture was refluxed for 6 h after addition was complete and the solvent was vacuum transferred leaving a brown residue. Chromatography on neutral alumina (100 g, activity grade III, ether–petroleum ether (12:88) as eluent) gave cyclobutadiene complex **26** (84 mg, 50% based on $CpCo(CO)_2$), unchanged cyclopentanone **3** (270 mg), and a

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mixture of two regioisomeric benzocyclobutenes (130 mg, 34% based on recovered **3**): NMR (CCl_4) δ 6.83 (br s, 1 H), 6.43 (br s, 1 H), 5.80 (m, 1 H), 5.13 (m, 1 H), 4.87 (m, 1 H), 3.73 (br s, 3 H), 3.20 (m, 3 H), 2.8–1.1 (m, 9 H), 0.83 (s, 3 H), 0.23 (s, 9 H). This mixture was dissolved in degassed decane (20 mL) and refluxed for 12 h to give a 2:1 mixture of **24c,d** (120 mg, 92%): *m/e* (rel intensity) 356 (M^+, 11), 311 (10), 121 (29), 117 (100), 73 (23); IR (neat) 3000, 1740, 1620, 1410, 1268, and 860 cm^{-1}; NMR (CCl_4) δ 7.06 (br s, 0.67 H), 6.81 (br s, 0.33 H), 6.53 (br s, 0.33 H), 6.33 (br s, 0.67 H), 3.73 (br s, 3 H), 3.0–1.1 (m, 15 H), 0.86 (s, 3 H), 0.23 (s, 9 H).

Exact mass. Calcd for $C_{22}H_{32}O_2Si$: 356.2171. Found: 356.2178.

2-Methoxy- (24e) and 3-Methoxyestra-1,3,5(10)-trien-17-one (2). The mixture of **24c,d** (45 mg, 0.126 mmol) was protodesilylated with CF_3CO_2H–CCl_4 (1:1, 2 mL) to give a thick oil (35 mg, 98%) as a 2:1 mixture of **2** and **24e**: *m/e* (rel intensity) 284 (M^+, 8.97), 143 (6.09), 129 (10.92); IR (neat) 2970, 1740, 1605, 1500, and 1225 cm^{-1}; NMR (180 MHz, $CDCl_3$) δ 7.20 (d, J = 7 Hz, 0.67 H), 7.02 (d, J = 7 Hz, 0.33 H), 6.84 (d, J = 2 Hz, 0.33 H), 6.72 (dd, J = 7, 2 Hz, 1 H), 6.64 (d, J = 2 Hz, 0.67 H), 3.78 (s, 3 H), 2.90 (m, 3 H), 2.7–1.2 (m, 12 H), 0.89 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 157.55, 137.60, 131.98, 129.79,* 126.31, 113.85, 111.54, 111.25,* 55.20, 50.40, 48.00, 44.59,* 43.97, 38.37, 38.00,* 35.87, 31.58, 29.67, 26.63,* 26.56, 25.93, 25.65,* 21.59, 13.85. The unstarred peaks are identical with a reported ^{13}C NMR spectrum of **2**.[21] The starred values may be assigned to the C-4, -1, -9, -9, -7, and -11 carbons of **24e**.

Exact mass. Calcd for $C_{19}H_{24}O_2$: 284.1776. Found: 284.1772.

[2α(*R),3β]- and [2α(*S**),3β]-2-(3-Ethynyl-5-hexynyl)-2-methyl-3-vinylcyclopentanone Ethylenedioxy Ketal (29).** The 2:1 mixture of cyclopentanone diastereomers **3** and **21** (995 mg, 4.36 mmol) and ethylene glycol (1083 mg, 17.4 mmol) were exposed to a catalytic amount of *p*-toluenesulfonic acid in toluene (8 mL) under standard conditions. Ether–water workup, followed by chromatography on silica (100 g, ether–petroleum ether (4:96) as eluent), gave three major fractions: (A) unchanged cyclopentanones **3** and **21** (290 mg), R_f 0.37–0.38 (ether–petroleum ether (1:4) as eluent); (B) the undesired cyclopentanone ketal **30** as a mixture of diastereomers (262 mg, 31% based on recovered **3** and **21**) [R_f 0.45; *m/e* (rel intensity) 272 (M^+, 0.38), 257 (0.48), 233 (4.0), 124 (73), 55 (100); IR (neat) 3340, 3000, 2320, 1465, and 1175 cm^{-1}; NMR (CCl_4) δ 5.80 (overlapping (5 lines) ddd, J = 17.5, 10, 9 Hz, 1 H), 4.93 (m, 1 H), 4.73 (m, 1 H), 3.80 (br s, 4 H), 2.30 (br s, 4 H), 2.0–1.13 (m, 10 H), 0.93 (s, 3 H); ^{13}C NMR (C_6D_6) δ 140.97, 140.70, 119.86, 114.77, 114.53, 86.33, 81.86, 70.54, 70.46, 65.01, 64.13, 52.54, 52.40, 48.65, 48.51, 33.06, 32.25, 29.48, 29.04, 25.53, 24.81, 19.81, 19.47]; (C) the desired cyclopentanone ketal **29** as a mixture of diastereomers (545 mg, 64% based on recovered **3** and **21**) [R_f 0.41; *m/e* (rel intensity) 272 (M^+, 1.08), 257 (1.38), 233 (11.21), 124 (22.5), 99 (93.4), 55 (100); IR (neat) 3340, 3000, 2155, 1650, and 1170 cm^{-1}; NMR (CCl_4) δ 5.80 (overlapping (5 lines) ddd, J = 17.5, 9, 10 Hz, 1 H), 5.00 (m, 1 H), 4.77 (m, 1 H), 3.81 (br s, 4 H), 2.33 (br s, 4 H), 2.0–1.7 (m, 10 H), 0.87 (s, 3 H); ^{13}C NMR (C_6D_6) δ 139.83, 119.82, 115.65, 86.37, 81.90, 70.44, 64.44, 63.95, 51.03, 48.02, 33.08, 32.54, 32.23, 32.10, 28.65, 25.30, 24.73, 15.74].

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.13; H, 8.64.

***dl*-2,3-Bis(trimethylsilyl)estra-1,3,5(10)-trien-17-one Ethylenedioxy Ketal (33).** The diastereomeric mixture of cyclopentanone ketals **29** (425 mg, 1.56 mmol) was cocyclized with BTMSA as described in the preparation of **24a**. Chromatography on silica gel (140 g, ether–petroleum ether (4:96) as eluent, one 35-mL fraction every 25 min) gave three compounds: (A) one of the diastereomeric benzocyclobutenes (arbitrarily assigned) **31**, as a colorless oil (190 mg, 27.5%) [R_f 0.63 (ether–petroleum ether (1:4) as eluent); *m/e* (rel intensity) 442 (M^+, 11.66), 245 (7.46), 100 (47.3), 99 (100), 73 (88.2); IR (neat) 2995, 1640, 1250, and 830 cm^{-1}; NMR (CCl_4) δ 7.22 (br s, 2 H), 5.69 (overlapping (5 lines) ddd, J = 18, 10, 9 Hz, 1 H), 5.00 (m, 1 H), 4.91 (m, 1 H), 3.73 (br s, 4 H), 3.27 (m, 2 H), 2.63 (m, 2 H), 2.0–1.0 (m, 8 H), 0.84 (s, 3 H), 0.33 (s, 18 H). Exact mass. Calcd for $C_{26}H_{42}O_2Si_2$: 442.2722. Found: 442.2725]; (B) the other diastereomeric benzocyclobutene **32** as a colorless oil (201 mg, 29.1%) [R_f 0.59; *m/e* (rel intensity) 442 (8.18), 243 (5.78), 147 (13.08), 99 (100), 73 (82.53); IR (neat) 2995, 1640, 1250, and 830 cm^{-1}; NMR (CCl_4) δ 7.22 (br s, 2 H), 5.70 (overlapping (5 lines) ddd, = J = 18, 10, 9 Hz, 1 H), 5.01 (m, 1 H), 4.83 (m, 1 H), 3.77 (br s, 4 H), 3.27 (m, 2 H), 2.62 (m, 2 H), 2.0–1.0 (m, 8 H), 0.86 (s, 3 H), 0.33 (s, 18 H). Exact mass. Calcd for $C_{26}H_{42}O_2Si_2$: 442.2722. Found: 442.2712]; (C) the bis(trimethylsilyl)estratrienone ketal **33** as a white solid, crystallized from ether–methanol (210 mg, 30%) [mp 109.5–111 °C; R_f 0.53; *m/e* (rel intensity) 442 (M^+, 12.90), 427 (8.18), 294 (31.18), 147 (12.24), 100 (21.97), 99 (96.34), 73 (100); IR (KBr) 2990, 1250, 1110, 1050, and 830 cm^{-1}; NMR (CCl_4) δ 7.40 (br s, 1 H), 7.13 (br s, 1 H), 3.80 (br s, 4 H), 3–1.1 (m, 15 H), 0.83 (s, 3 H), 0.33 (s, 18 H); ^{13}C NMR ($CDCl_3$) δ 142.39, 139.62, 136.46, 136.17, 132.57, 119.38, 65.20, 64.52, 49.51, 46.17, 44.22, 38.93, 34.21, 30.83, 29.46, 26.98, 25.64, 22.37, 14.31, 2.48].

Anal. Calcd for $C_{26}H_{42}O_2Si_2$: C, 70.527; H, 9.56. Found: C, 70.36; H, 9.46.

The benzocyclobutene isomers **31** and **32** (190, 201 mg) were separately dissolved in degassed decane (30 mL) and heated to 180 °C (oil-bath temperature) for 20 h. A TLC monitor of the reaction showed no interconversion of the benzocyclobutenes. The decane was removed from each sample by vacuum transfer. NMR analysis as well as TLC indicated that each isomer transformed to **33** as well as a trace of another isomer. The two mixtures were combined and crystallized to give **33** (350 mg, 560 mg total, 81%). The mother liquor contained the isomer **34** and was purified by preparative thin layer chromatography (ether–petroleum ether (2.5–97.5) as eluent, 4-h continuous elution) to give an oil (25 mg, 3.6%): R_f 0.59 (ether–petroleum ether (1:4) as eluent); *m/e* (rel intensity) 442 (M^+, 45.38), 341 (25.79), 131 (16.25), 99 (91.85), 73 (100); IR (neat) 3990, 1460, 1250, 1140, and 840 cm^{-1}; NMR (CCl_4) δ 7.48 (br s, 1 H), 7.15 (br s, 1 H), 3.71 (br s, 4 H), 3.0–1.1 (m, 15 H), 0.92 (s, 3 H), 0.33 (s, 18 H); ^{13}C NMR ($CDCl_3$) δ 142.43, 142.36, 137.69, 137.02, 136.67, 133.52, 119.68, 64.92, 64.53, 46.28, 41.65, 37.59, 34.67, 33.93, 27.10, 25.60, 25.22, 24.29, 22.72, 13.99, 2.04.

Exact mass. Calcd for $C_{26}H_{42}O_2Si_2$: 442.2722. Found: 442.2716.

***dl*-2,3-Bis(trimethylsilyl)estra-1,3,5(10)-trien-17-one (24a) from Ketal 33.** To the bis(trimethylsilyl)estratrienone ketal **33** (103 mg, 0.23 mmol) in aqueous THF (1 mL) were added acetic acid (13 mg, 0.22 mmol) and trifluoroacetic acid (2 μL, 0.026 mmol). After the mixture was stirred for 5 days standard aqueous workup gave a white solid (90 mg, 97%) which exhibited spectra identical with those of the previously reported sample of **24a**.

***dl*-3-Bromo-2-trimethylsilyl- (35) and 2-Bromo-3-trimethylsilylestra-1,3,5(10)-trien-17-one Ethylenedioxy Ketal (35).** The bis(trimethylsilyl)estratrienone ketal **33** (57 mg, 0.128 mmol) in an NMR tube was dissolved in CCl_4 (0.3 mL). Pyridine (141 μL of a 0.91 M solution in CCl_4, 0.128 mmol) was added followed by bromine (289 μL of a 0.89 M solution in CCl_4, 0.256 mmol) and the reaction mixture was quickly placed in the NMR probe. The reaction was monitored in the NMR instrument by following the disappearance of the starting material's silylmethyl proton absorption (δ 0.33) and the appearance of the product's silylmethyl proton absorption (δ 0.36) as well as the appearance of a proton absorption due to trimethylsilyl bromide (δ 0.59). After 75 min the reaction was complete (δ 0.36 and 0.59 absorptions of equal intensity, complete disappearance of δ 0.33 absorption). The reaction mixture was poured onto a saturated sodium thiosulfate solution, the aqueous layer was extracted with ether, and the combined ether extracts were washed with thiosulfate, water, and brine and dried ($MgSO_4$). Evaporation gave a colorless oil (60 mg) which was chromatographed on a preparative thin layer plate (ether–petroleum ether (1:9) as eluent) to give an inseparable 4:1 mixture of monobromides **35** and **36** (50 mg, 87%): R_f 0.49 (ether–petroleum ether (1:4) as eluent); *m/e* (rel intensity) 450 (M^+, 6.26), 448 (M^+, 6.36), 391 (10.82), 307 (32.46), 100 (42.54), 99 (100), 73 (61.67); IR (neat) 2990, 1305, 1255, 1050, and 840 cm^{-1}; NMR (CCl_4) δ 7.27 (br s, 0.79 H), 7.17 (br s, 0.21 H), 7.05 (br s, 0.21 H), 6.90 (br s, 0.79 H), 3.79 (br s, 4 H), 3.0–1.1 (m, 15 H), 0.83 (s, 3 H), 0.36 (s, 9 H).

Exact mass. Calcd for $C_{23}H_{33}{}^{79}BrO_2Si$: 448.1433. $C_{23}H_{33}Br^{81}O_2Si$: 450.1414. Found: 448.1430; 450.1415.

***dl*-3-Hydroxy-2-trimethylsilyl- (37) and 2-Hydroxy-3-trimethylsilylestra-1,3,5(10)-trien-17-one Ethylenedioxy Ketal (38).** To the mixture of aryl bromides **35** and **36** (37.5 mg, 0.083 mmol) in THF (1 mL) at −78 °C was added butyllithium (50.6 μL of a 2.14 M solution in hexane, 0.108 mmol). The yellow solution was stirred for 10 min, trimethyl borate (119 μL of a 0.975 M solution in THF, 0.117 mmol) added, and the mixture placed in an ice bath and stirred for 45 min. Acetic acid was then added (127 μL of a 1.09 M solution in THF, 0.133 mmol) immediately followed by H_2O_2 (221 μL of a 1.88 M solution in THF, 0.416 mmol) and the mixture was allowed to stir at room temperature for 45 min. The mixture was diluted with ether and then washed with water and brine and dried ($MgSO_4$) to give an oily solid (34 mg) after evaporation. TLC indicated three components. Chromatography on a preparative thin layer plate (4-h continuous elution, ether–petroleum ether (1:4) as eluent) gave (A) 2-trimethylsilyl- and 3-trimethylsilylestra-1,3,5(10)-trien-17-one ethylenedioxy ketals (2 mg) [R_f 0.51 (ether–petroleum ether (1:4) as eluent); *m/e* (rel intensity) 370 (M^+, 5.34), 234 (10.11), 99 (85.05), 73 (30.82)]; (B) 3-hydroxy-2-trimethylsilylestratrienone ketal **37** (4 mg, 12.4%) [R_f 0.29, mp 235–239 °C (crystallized from ether–petroleum ether); *m/e* (rel intensity) 386 (M^+, 10.08), 371 (2.37), 107 (100), 99 (73.38), 91 (14.82), 79 (72.09), 73 (31.30); IR (KBr) 3400, 2990, 1600, 1595, 1100, 1040, and 840 cm^{-1}; NMR (180 MHz, $CDCl_3$) δ 7.27 (s, 1 H), 6.40 (s, 1 H), 4.61 (s, 1 H),

3.90 (br s, 4 H), 2.77 (m, 3 H), 2.4–1.2 (m, 12 H), 0.86 (s, 3 H), 0.27 (s, 9 H). Exact mass. Calcd for $C_{23}H_{34}O_3Si$: 386.2277. Found: 386.2274]; (C) 2-hydroxy-3-trimethylsilylestratrienone ketal **38** (18 mg, 56%) [R_f 0.21; mp 210–212 °C (crystallized from ether–petroleum ether); *m/e* (rel intensity) 386 (M^+, 12.80), 371 (2.76), 113 (12.73), 100 (17.59), 99 (83.08), 73 (71.78); NMR (180 MHz, $CDCl_3$) δ 7.04 (s, 1 H), 6.62 (s, 1 H), 4.67 (s, 1 H), 3.91 (br s, 4 H), 2.78 (m, 3 H), 2.4–1.2 (m, 12 H), 0.86 (s, 3 H), 0.27 (s, 9 H). Exact mass. Calcd for $C_{23}H_{34}O_3Si$: 386.2277. Found: 386.2278].

***dl*-2-Hydroxyestra-1,3,5(10)-trien-17-one (24f).** The hydroxytrimethylsilylestratrienone ketal **38** (17 mg, 0.044 mmol) was protodesilylated in CF_3CO_2H (0.5 mL) and water (3 h). Aqueous ethereal workup gave a white solid (12 mg, 100%) which was crystallized from acetone–ether: R_f 0.53 (ether as eluent); mp 216–220 °C; *m/e* (rel intensity) 270 (M^+, 85.26), 213 (16.93), 172 (12.63), 145 (17.14), 43 (100); IR (KBr) 3490, 2990, 1740, 1300, and 1210 cm^{-1}; NMR (180 MHz, $CDCl_3$) δ 6.94 (d, J = 8.5 Hz, 1 H), 6.75 (d, J = 2.3 Hz, 1 H), 6.60 (dd, J = 8.5, 2.3 Hz, 1 H), 2.82 (m, 3 H), 2.65–1.10 (m, 12 H), 0.89 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 153.82, 141.05, 129.94, 128.24, 112.95, 112.124, 50.52, 47.98, 44.49, 38.03, 35.87, 31.57, 29.40, 26.64, 25.66, 21.59, 13.84.

Exact mass. Calcd for $C_{18}H_{22}O_2$: 270.1620. Found: 270.1616.

***dl*-Estrone (1) from 37.** The hydroxytrimethylsilylestratrienone ketal **37** (4 mg, 0.01 mmol) was treated in the same manner as the regioisomer **38** to give estrone (**1**) as a white solid (2.6 mg, 93%). The synthetic **1** had an identical R_f of 0.53 (ether as eluent) when compared with authentic estrone, as well as spectral properties: mp 251–254 °C (crystallized from acetone–ether); *m/e* (rel intensity) 270 (M^+, 62.02), 254 (4.94), 185 (19.69), 130 (32.13), 83 (42.45), 73 (29.56), 44 (100); IR ($CHCl_3$) 3440, 2960, 1740, 1370, 1300, and 1060 cm^{-1}; NMR (180 MHz, $CDCl_3$) δ 7.12 (d, J = 8.7 Hz, 1 H), 6.62 (dd, J = 8.7, 2.5 Hz, 1 H), 6.56 (d, J = 2.5 Hz, 1 H), 4.65 (br s, 1 H), 2.85 (m, 3 H), 2.6–1.1 (m, 12 H), 0.89 (s, 3 H).

Exact mass. Calcd for $C_{18}H_{22}O_2$: 270.1620. Found: 270.1624.

***dl*-3-Trimethylsilyl- (24g) and -2-Trimethylsilylestra-1,3,5(10)-trien-17-one (24h). Room Temperature Protodesilylation.** The bis(trimethylsilyl)estratrienone **24a** (90 mg, 0.27 mmol) was dissolved in CCl_4 (0.75 mL) and placed in an NMR tube. CF_3CO_2H (50 μL, 0.65 mmol) was added and the sample was rapidly placed in the NMR probe. The reaction was monitored by observing the disappearance of the starting material's silylmethyl proton absorption (δ 0.33) and the appearance of the products' silylmethyl proton absorption (δ 0.24) as well as the appearance of an absorption presumably due to $CF_3CO_2SiMe_3$ (δ 0.40). The reaction was complete after 10 min (δ 0.24 and 0.40 absorptions of equal intensity, complete disappearance of δ 0.33 absorption) and the mixture was quickly partitioned between saturated $NaHCO_3$ and ether. The ether layer was washed with $NaHCO_3$ and brine and dried ($MgSO_4$). Evaporation of the solvent gave a colorless oil (74 mg, 100%), homogenous by TLC: R_f 0.28 (ether–petroleum ether (1:4) as eluent); *m/e* (rel intenssity) 326 (M^+, 5.35), 311 (21.37), 254 (1.03), 99 (1.46), 73 (9.22), 28 (100); IR (neat) 2990, 1740, 1460, 1250, and 830 cm^{-1}; NMR (CCl_4) δ 7.10 (m, 3 H), 3.0–1.1 (m, 15 H), 0.88 (s, 3 H), 0.24 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 140.42, 138.89, 137.49, 137.31, 135.67, 134.25, 130.80, 130.20, 128.60, 124.75, 50.55, 48.00, 44.54, 38.08, 35.86, 31.60, 29.40, 26.55, 25.55, 21.58, 13.84, –1.07.

Exact mass. Calcd for $C_{21}H_{30}OSi$: 326.2066. Found: 326.2060.

Low-Temperature Protodesilylation. The bis(trimethylsilyl)estratrienone **24a** (33 mg, 0.083 mmol) was dissolved in $CDCl_3$ (0.7 mL) and CCl_4 (0.1 mL), placed in an NMR tube, and cooled to –60 °C. CF_3CO_2H (210 μL of a 3 M solution in CCl_4, 0.636 mmol) was added slowly and the sample was placed in the NMR (180 MHz) probe which had been previously cooled to –60 °C. The reaction was monitored in the same manner as was the room temperature experiment. No significant reaction took place at –60 °C after 1 h, so the probe was warmed to –50 °C. The reaction could be oserved to take place now, but was extremely slow. The probe was warmed to –30 °C, where the reaction had a half-life of ca. 5.5 h. After 14 h at –30 °C the reaction was 80% complete and the mixture was warmed to –20 °C for 3 h followed by 2 h at –10 °C. Reaction was complete and the mixture was worked up as before. Evaporation gave a colorless oil (27 mg, 100%). This compound exhibited identical spectra when compared with the room temperature protodesilylation product except for a different ratio of the aromatic carbon resonances in the ^{13}C NMR (see text).

***dl*-Estrone (1) from 24g. Oxidation of Room Temperature Protodesilylation Product.** The 3:1 mixture of trimethylsilylestratrienones **24g**:**24h** (69.0 mg, 0.212 mmol) was cooled to –30 °C and $Pb(OAc)_4$ (95.8 mg, 0.216 mmol) added in precooled (–30 °C) CF_3CO_2H (0.8 mL). The reaction mixture was allowed to warm from –30 to –5 °C over a period of 30 min. The mixture was then poured onto $NaHCO_3$ and the aqueous layer extracted with ether. The ether extract was treated with NaOH (3 mL of 3 M solution) and neutralized with 3 M HCl and the aqueous layer extracted with another portion of ether. The combined ether extracts were washed with $NaHCO_3$ and brine and dried ($MgSO_4$). Evaporation of the ether gave a white solid (55.5 mg, 97%) which showed only one component by TLC (R_f 0.53, ether as eluent). NMR (180 MHz, $CDCl_3$) examination of the crude material showed a 74:26 ratio of the 3-hydroxy- (**1**) and 2-hydroxyestratrienone (**24f**) isomers, respectively: δ 7.12 (d, J = 8.7 Hz, 0.74 H), 6.94 (d, J = 8.5 Hz, 0.26 H). Two recrystallizations (acetone–ether) gave a mother liquor (19 mg, 2:1 ratio of **24f**:**1**) and pure estrone (**1**, 35 mg, 62%): mp 251–254 °C (lit.[9] 251–254 °C); *m/e*, IR, and NMR identical with those of estrone obtained via acid treatment of **37**; ^{13}C NMR ($CDCl_3$) δ 153.49, 138.00, 132.01, 126.50, 115.26, 112.80, 50.39, 48.04, 38.33, 35.89, 31.55, 29.47, 26.49, 25.92, 21.58, 13.86.

Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.89; H, 8.05.

Oxidation of Low-Temperature Protodesilylation Product. The 9:1 mixture of trimethylsilylestratrienones **24g**:**24h** (23.1 mg, 0.071 mmol) was treated in the same manner with $Pb(OAc)_4$ (32 mg, 0.072 mmol). After evaporation of solvent, a white solid was obtained (18.1 mg, 95%). NMR examination (180 MHz, $CDCl_3$) revealed a 9:1 ratio of **1**:**24f**: δ 7.12 (d, J = 8.7 Hz, 0.89 H), 6.94 (d, J = 8.5 Hz, 0.11 H). Crystallization from acetone–ether gave pure estrone (**1**, 15.2 mg, 88%, 80% from **24a**).

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