Cobalt-Mediated Total Synthesis of Steroids. The A → BCD Approach by Enediyne Cyclization

Ethan D. Sternberg and K. Peter C. Vollhardt*

Department of Chemistry, University of California, Berkeley, California 94720, and the Materials and Molecular Research Division, Lawrence Berkeley Laboratory, Berkeley, California 94720

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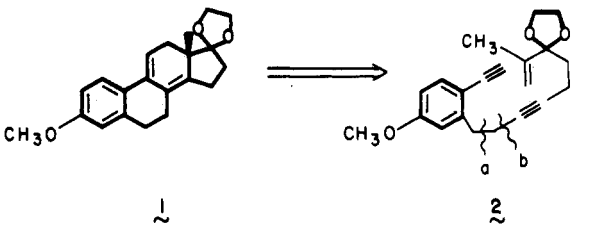
A novel cobalt-mediated steroid synthesis has been accomplished by the intramolecular [2 + 2 + 2] cycloaddition of enediyne **2** in which the B, C, D portion is fused onto the A ring in one step to give complex **38**. Oxidative demetalation furnishes an air-sensitive new steroid, pentaene **1**, which is readily converted to 3-methoxy-1,3,5(10),8,14-pentaen-17-one, the Torgov intermediate en route to estrone. Enediyne **2** was constructed by a sulfur template-controlled coupling of bromides **9** and **14**. Alternative routes were unsuccessful or suffered from poor yields. Using the same reaction five new complexed 7-oxa-B-homosteroids were synthesized, the stereochemistry of which may be tentatively rationalized by invoking control in a Diels–Alder cycloaddition step of the alkene unit to a metallacyclopentadiene formed by oxidative coupling of the two alkyne moieties.

We have noted that tricyclic diene complexes of (η^5-cyclopentadienyl)cobalt (CpCo) can be prepared in one step by the reaction of acyclic enediynes with $CpCo(CO)_2$.[1] Believing that the scope of new synthetic methods of this type should be tested on natural and/or unnatural molecules of reasonable complexity we embarked[2] on a novel approach to the steroid nucleus hoping to exploit the crucial retrosynthetic disconnection **1** → **2** (Scheme I). The varied physiological activity of the A ring aromatic steroids makes them an attractive target for synthesis. To our knowledge, if successful, the **2** → **1** conversion would constitute the first A → BCD[3] construction of the A ring aromatic system.[4] Moreover, steroid diene **1** is unknown and could provide a useful synthetic relay point en route to new hitherto inaccessible derivatives. It is, on the other hand, isomeric with the well-known 8,14-diene **40**, a key intermediate in the Torgov synthesis of estrone,[5] and, we felt, very likely rearrangeable to the latter by using catalytic acid, thus readily correlated with a known system.

Synthesis of Enediyne 2. We envisaged the construction of precursor **2** by one of two routes involving retrosynthetic cleavage at either "a" or "b". One could form bond "a" by either Wurtz coupling of the two corresponding bromides **9** and **14**, or by stepwise metallation of either starting material followed by alkylation with the other. Alternatively, bond "b" could be formed by alkylation of the iodoalkyne **21** with the phenethylcopper derivative **31** derived from bromide **29** (Scheme VII).[6]

Our initial investigations were directed toward the bond "a" approach, which required the preparation of benzyl bromide **9** (Scheme II) and propargyl bromide **14** (Scheme III).

Scheme I



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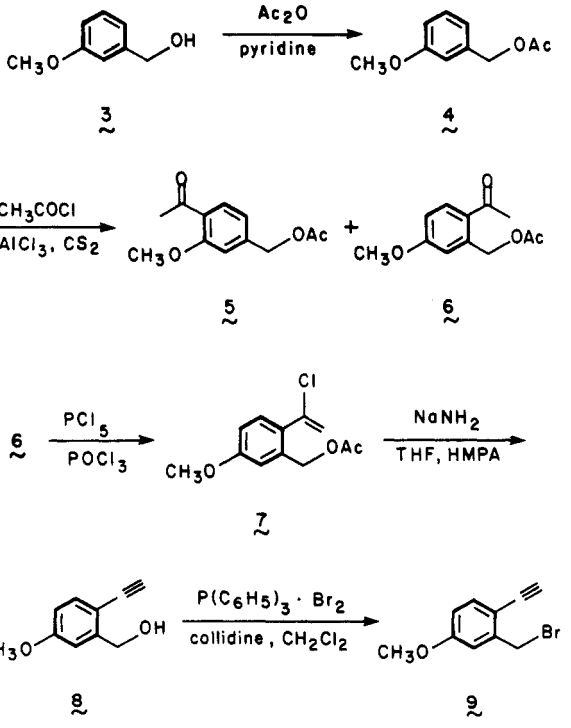
Scheme II



Commercial methoxybenzyl alcohol **3** was smoothly esterified in quantitative yield with acetic anhydride in pyridine (Scheme II). The acetate **4** was then acylated under Friedel–Crafts conditions (excess $AlCl_3$, acetyl chloride) in carbon disulfide. The necessity for the large excess (5 equiv) of $AlCl_3$ is probably due to its complexation to starting material and product. An ^1H NMR spectrum of the crude product of this reaction showed the presence of the two isomers **6** and **5** in a ratio of 3:1, from which **6** was crystallized selectively (68%).

The conversion of the acetophenone **6** to the vinyl chloride **7** was accomplished with 2 equiv of phosphorus

(1) Sternberg, E. D.; Vollhardt, K. P. C. *J. Org. Chem.*, the preceding paper in this issue.

(2) A preliminary report has appeared, albeit somewhat displaced: Sternberg, E. D.; Vollhardt, K. P. C. *J. Org. Chem.* **1982**, *47*, 3447. Note from editor: the paper was submitted for publication as a communication but was published in the "Articles" section in error; the editor expresses his regrets to the authors (see "Additions and Corrections", *J. Org. Chem.* **1983**, *48*, 5413).

(3) Akhrem, A. A.; Titov, Y. A. "Total Steroid Synthesis"; Plenum Press: New York, 1970. Blickenstaff, R. T.; Ghosh, A. C.; Wolf, G. C. "Total Synthesis of Steroids"; Academic Press: New York, 1974.

(4) However, other steroids have been made by this strategy using biomimetic alkene cyclizations. See, for example: Johnson, W. S.; Berner, D.; Dumas, D. J.; Nederlof, P. J. R.; Welch, J. *J. Am. Chem. Soc.* **1982**, *104*, 3508. Van Tamelen, E. E.; Hwu, J. R. *Ibid.* **1983**, *105*, 2490.

(5) Ananchenko, S. N.; Torgov, I. V. *Tetrahedron Lett.* **1963**, 1553. Zakharychev, A. V.; Ananchenko, S. N.; Torgov, I. V. *Steroids* **1964**, *4*, 31. Douglas, G. H.; Graves, J. M.; Hughes, G. A.; McLoughlin, B. J.; Siddall, J.; Smith, H. *J. Chem. Soc.* **1963**, 5073.

(6) Commercon, A.; Normant, J. F.; Villieras, J. *Tetrahedron* **1980**, *36*, 1215.

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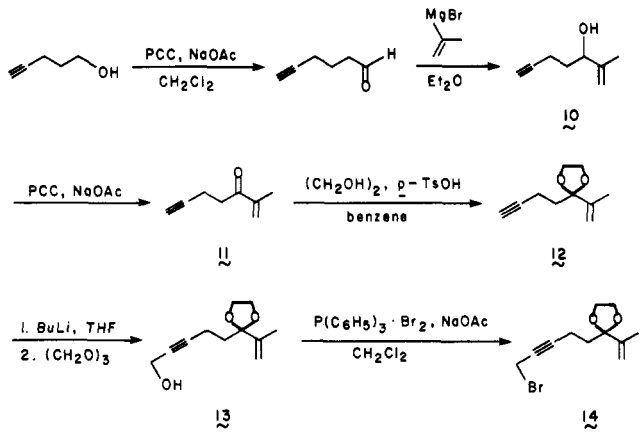
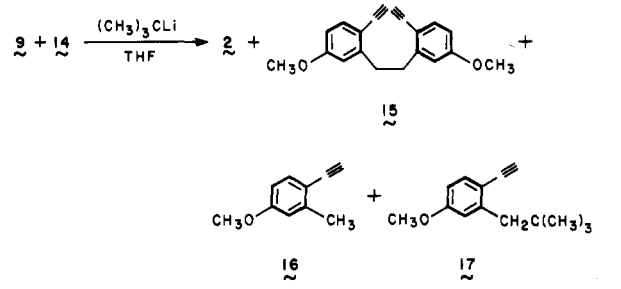
Scheme III



Scheme IV



pentachloride in phosphorus oxychloride at 45–50 °C for 2–3 h (95%).[7] The reaction was initially monitored by ^1H NMR and was found to proceed only in neat $POCl_3$ (not in $CHCl_3$ or CH_2Cl_2). The relatively severe reaction conditions for this conversion were probably necessary because of the vinylogous ester nature of the carbonyl group in **6**.

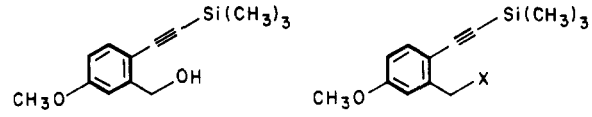
Both dehydrohalogenation and deacylation of the vinyl chloride **7** to the alkynol **8** occurred with excess $NaNH_2$ in THF/HMPA (95:5) in good yield (92%).[8] Conversion of **8** to benzyl bromide **9** also went smoothly and in good yield (94%) using triphenylphosphine dibromide in CH_2Cl_2 in the presence of added collidine.[9]

The synthesis of the propargyl bromide **14** proceeded as in Scheme III. Oxidation of 4-pentyn-1-ol with pyridine chlorochromate (PCC) in CH_2Cl_2 buffered by sodium acetate[10] gave 4-pentynal. To the crude aldehyde was added isopropenylmagnesium bromide. This treatment resulted in the formation of the alcohol **10** (85%, based on 4-pentyn-1-ol). Oxidation with PCC generated the α,β-unsaturated ketone **11** in good yield (86%). Ketalization (*p*-toluenesulfonic acid and ethylene glycol in boiling benzene) proved difficult to drive to completion. The final reaction mixture contained starting material (~20%) and the product **12** (52%). More severe reaction conditions led to decomposition of the product and starting material. Hydroxymethylation of **12** proceeded with *n*-butyllithium and formaldehyde to give the propargyl alcohol **13** (94%). Bromination as in the preparation of **9** furnished[11] compound **14** (54%).

We hoped that simple Wurtz reaction conditions (*tert*-butyllithium, THF, −78 °C) would suffice to effect the reductive coupling of **9** and **14** (Scheme IV).[12] However, this treatment resulted in the formation of only limited quantities of the desired enediyne **2** (~17%), in addition to other products, **15–17**.

The spectral characteristics of the desired **2** were in accord with its structure. A triplet in the ^1H NMR spectrum at δ 3.09 (J = 8.7 Hz, 2 H) was assigned to the benzyl hydrogens. In addition, there was a singlet for the methoxy group at δ 3.26, a singlet for the ketal group at δ 3.43, and a doublet of doublets at δ 1.71 (J = 1.6, 2.0 Hz) for the allylic methyl group.

The partial success of this reaction was encouraging enough to lead us to attempt variations of the coupling conditions in the hope of increasing the yield of **2**. However, changing the solvent to ether, utilization of sodium sand as the electron source, reverse addition of the bromides to *tert*-butyllithium in THF, use of *sec*-butyllithium as the electron source, cooling the reaction mixture to −100 °C in ether/pentane, and synthesis and attempted coupling of the trimethylsilylated benzylbromide **19** (in turn derived from **18**, see Experimental Section) with **14** led only to formation of greater amounts of the undesired components.



Presented with these discouraging results, we decided to explore a stepwise metalation procedure. Since metalation of a propargyl bromide is known to result in formation of allenes,[13] it was thought advantageous to metalate the benzyl bromide **19** under low-temperature conditions.

Rieke magnesium was prepared in THF ($MgCl_2$, KI, K)[14] and the bromide **19** added at 0 °C over a period of 30 min to unfortunately produce mainly dimer **15**. Similarly, treatment of the chloride **20** (made from **18**, see Experimental Section) with magnesium under analogous conditions,[15] followed by addition of $CuBr \cdot (CH_3)_2S$ and then propargyl bromide **14** to the reaction mixture failed to yield the desired product.

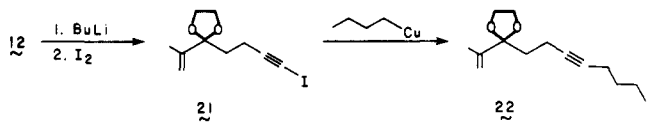
This was not a totally unexpected result. Alkylations with propargyl halides are known to be fraught with problems. Side reactions such as dehydrohalogenation to form cumulenes, and SN_2' additions to form alkylated allenes are known to be dominant.[16]

Disappointed by the above outcome we temporarily turned our attention away from bond "a" formation to the bond "b" approach (Scheme I). This route possessed certain synthetic advantages over the "a" route. It required the same number of synthetic steps to construct the aromatic portion of the molecule (Scheme VI) while reducing it for the production of the iodoalkyne **21** (Scheme V).

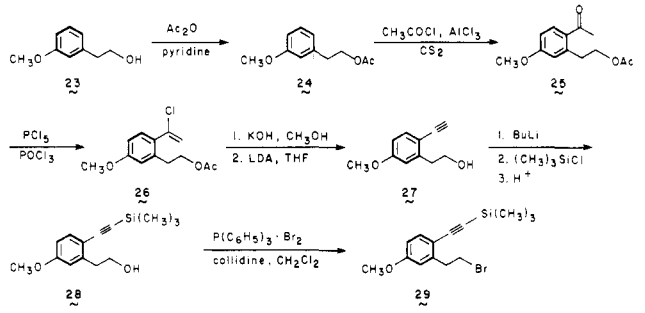
A model alkylation was run first involving alkyne **12** utilizing the new synthetic method developed by Normant[6]

(7) Newman, M. S.; Fraenkel, G.; Kirn, W. N. *J. Org. Chem.* **1963**, *28*, 1851.
(8) Jacobs, T. L. *Org. React. (N.Y.)* **1949**, *5*, 1. Villieras, J.; Perriot, P.; Normant, J. F. *Synthesis* **1975**, 458.
(9) Coe, D. G.; Landauer, S. R.; Rydon, H. N. *J. Chem. Soc.* **1954**, 2281.
(10) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(11) Black, D. K.; Landor, S. R.; Patel, A. N.; Whiter, P. F. *J. Chem. Soc. C* **1967**, 2260.
(12) Negishi, E. I. "Organometallics in Organic Synthesis"; Wiley: New York, 1980; pp 40, 41, 112.
(13) See, for example: Prevost, C.; Gaudemar, M.; Miginiac, L.; Bardone-Gaudemar, F.; Andrac, M. *Bull. Soc. Chim. Fr.* **1959**, 679. Andrac, M.; Gaudemar, F.; Gaudemar, M.; Gross, B.; Miginiac, L.; Prevost, C. *Ibid.* **1963**, 1385.
(14) Rieke, R. D.; Bales, S. E. *J. Am. Chem. Soc.* **1974**, *96*, 1775. Arnold, R. T.; Kulenovic, S. T. *Synth. Commun.* **1977**, *7*, 223.
(15) Theis, A. B.; Townsend, C. A. *Synth. Commun.* **1981**, *11*, 157.
(16) Wotiz, J. H. *J. Am. Chem. Soc.* **1955**, *73*, 693. Jacobs, T. L.; Meyers, R. A. *Ibid.* **1964**, *86*, 5244. Jacobs, T. L.; Prempree, P. *Ibid.* **1967**, *89*, 6177.

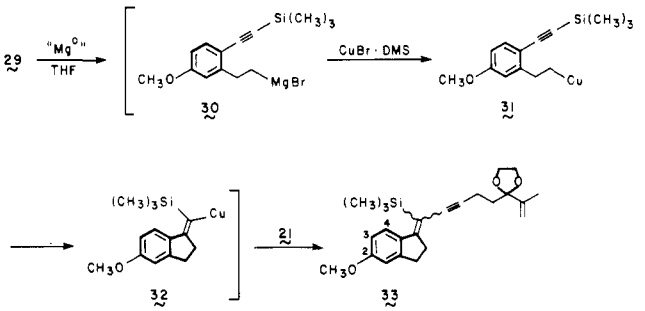
Scheme V



Scheme VI



Scheme VII

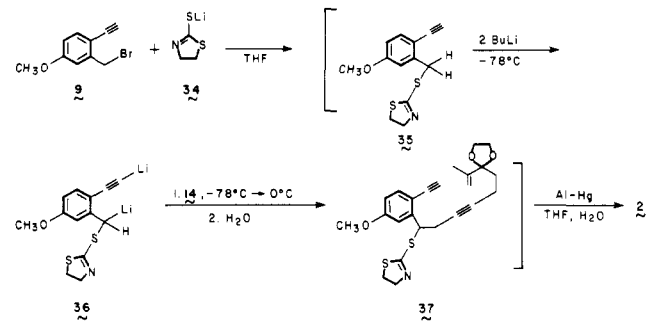


in which an alkylcopper reagent is coupled with an iodoalkyne. This reaction had been shown by us to be applicable in the ethynylation of a homopropargyl bromide in connection with a different project.[17] Since the bond "b" approach would have involved the reaction of an ethynyl anion (derived from **12**) with phenethyl bromide (Scheme VI) fraught with the danger of extensive elimination occurring instead of substitution, this alternative appeared particularly attractive.

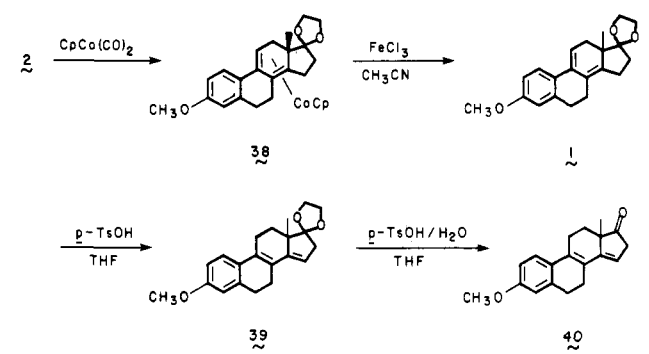
Butyllithium was added to CuBr·DMS complex in THF to form the *n*-butylcopper reagent. Synthesis of the iodoalkyne **21** proceeded by addition of *n*-butyllithium to alkyne **12** followed by addition of iodine (Scheme V). These two components were reacted in situ to give alkyne **22** in good yield (62%). This result was encouraging enough to justify the synthesis of the phenethylbromide **29** of route "b" (Scheme VI). Proceeding through the analogous series of steps used in the preparation of benzyl bromide **9**, namely acetylation of **23**, Friedel–Crafts acylation, chlorination, deacylation, silylation, and finally conversion to bromide, resulted in the formation of the desired product **29**. Comparison of the spectral evidence for **29** and its precursor with **9** and its precursors confirmed the substitution pattern of the aromatic ring.

Rieke magnesium was utilized to form the Grignard reagent **30** in situ from the phenethyl bromide **29** (Scheme VII). Transmetallation with $CuBr_2$·DMS at −40 °C was followed by addition of the iodoalkyne **21**. The product revealed a mass spectral parent ion corresponding to coupled product **2** (34%). However, the ^1H NMR spectrum of the product was quite different from that of **2**. A tentative assignment for the structure of this compound is either of the isomers **33**. The most characteristic single

Scheme VIII



Scheme IX



proton resonance at δ 8.65 (d, J = 8.5 Hz) could be assigned to the aromatic proton on C-4. Deshielding due to the steric bulk of the trimethylsilyl group or the anisotropy of the alkyne unit could be used to rationalize the chemical shift of this proton. Two proton multiplets at δ 2.98 (2 H) and 2.85 (2 H) were assigned to the protons of the fused cyclopentane ring. The remainder of the spectral data are also consistent with **33**.

The formation of **33** is explainable on the basis of literature precedent. Alkylcopper reagents are known to add intramolecularly to alkynes at elevated temperatures (e.g., 70–100 °C) in polar solvents.[18] Furthermore, vinylcopper reagents such as the proposed intermediate **32** (Scheme VII) couple with iodoalkynes at room temperature.[6,19]

Having weathered this failure we turned our attention to a sulfur template approach[20] to solving the coupling problem according to the original route "a" scheme (Scheme VIII). For this purpose the lithium thiolate **34** was treated with **9** at 0 °C for 1 h. Butyllithium (2 equiv) was then added to the resulting benzyl thiazoline **35** in order to generate the dianion necessary for the alkylation with propargyl bromide **14**. Desulfurization of crude **37** with aluminum amalgam finally gave enediyne **2** in good overall yield (65%). The spectral characteristics of this compound were identical with those of **2** made by the Wurtz-type coupling (Scheme IV).

Cyclization of 2 to the Steroid Nucleus. Exposure of **2** to excess $CpCo(CO)_2$ (Scheme IX) in boiling isooctane gave the red crystalline cobalt complex **38** in fairly good yield (65%). Since the completion of this work we have introduced a faster, more efficient cyclization procedure using light and heat, which has given us routinely 85–94% yields of similar structures.[21]

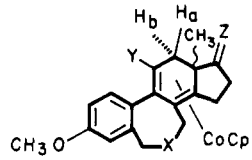
(17) Dower, W. V.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 685; *Angew. Chem. Suppl.* **1982**, 1545.

(18) Castro, C. E.; Havlin, R.; Honwad, V. K.; Malte, A.; Moje', S. *J. Am. Chem. Soc.* **1969**, *91*, 6464.

(19) Normant, J. F.; Cahiez, C.; Chuit, C.; Villieras, J. *J. Organomet. Chem.* **1974**, *77*, 269.

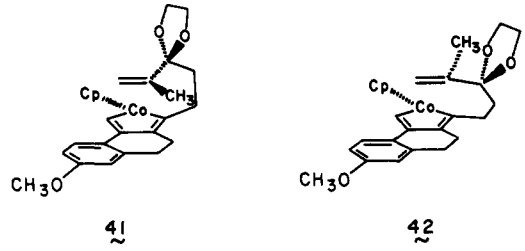
(20) Hirai, K.; Kishida, Y. *Tetrahedron Lett.* **1972**, 2117. See also: Hirai, K.; Iwano, Y.; Kishida, Y. *Ibid.* **1977**, 2677. Hirai, K.; Matsuda, H.; Kishida, Y. *Ibid.* **1971**, 4359. Mukaiyama, T. *Int. J. Sulfur Chem. B* **1972**, *7*, 180.

Table I. Comparison of ^{1}H NMR Chemical Shifts of Steroidal Complexes



compd	X	Y	Z	stereochemistry	H_a	H_b	Y	CH_3
38		H	$(CH_2O)_2$	*exo*-methyl	1.14 (dd, J = 14.5, 4.7 Hz)	2.67 (dd, J = 14.5, 4.6 Hz)	3.52 (obscured)	0.96
46	O	H	$(CH_2O)_2$	*exo*-methyl	1.08 (dd, J = 15.0, 3.1 Hz)	2.53 (dd, J = 15.0, 3.4 Hz)	3.44 (obscured)	1.06
47	O	H	$(CH_2O)_2$	*endo*-methyl	0.56 (dd, J = 12.5, 1 Hz)	0.95 (dd, J = 12.5, 5.3 Hz)	3.39 (obscured)	1.64
48	O	Me_3Si	$(CH_2O)_2$	*exo*-methyl	0.84 (d, J = 14.6 Hz)	2.57 (d, J = 14.6 Hz)		0.83
49	O	H	O	*endo*-methyl	0.69 (dd, J = 13.5, 1.2 Hz)	1.03 (dd, J = 13.6, 5.5 Hz)	3.20 (dd, J = 5.6, 1.4 Hz)	1.33
50	O	H	O	*exo*-methyl				0.46

Chart I



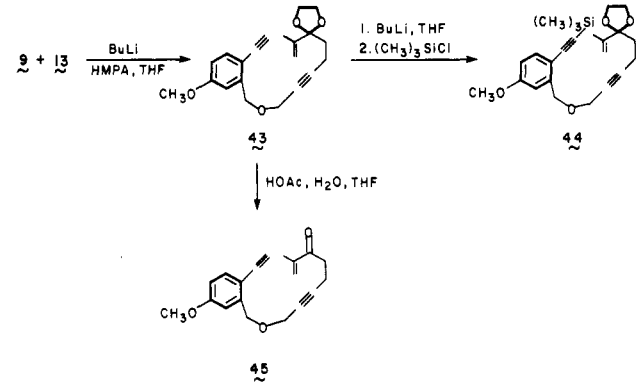
41 42

The spectral characteristics of **38** were in accordance with the assigned structure. Three singlets in the ^{1}H NMR spectrum at δ 4.58, 3.46, and 0.96 were assigned to the cyclopentadienyl, methoxy, and methyl groups, respectively. The chemical shift of the methyl group was significant in the assignment of its stereochemistry relative to the CpCo moiety. We had shown earlier that in complexes of this type, methyl groups endo to the cobalt nucleus are deshielded due to the anisotropy of the cobalt.[22] Since in our case the absorption of the methyl group was found within the normal range (δ 0.96), it was assigned the exo stereochemistry.

For comparison, Table I lists a number of significant chemical shifts for the series of complexed cyclohexadiene steroidal systems described in this paper. The assignments for **38** were made on the basis of a series of decoupling experiments. Most important was the irradiation at δ 1.14 (H-12 exo) which caused a doublet of doublets at δ 2.67 (J = 14.5, 4.6 Hz, H-12 endo) to change to a doublet (J = 4.6 Hz) and a sharpening in the three proton envelope at δ 3.52, thought to be caused by the narrowing of the signal for H-11. Irradiation at δ 3.52 effected the change of the two doublets of doublets at δ 1.14 and 2.67 to two doublets (J = 14.5 Hz).

The complete stereoselectivity observed in the formation of **38** (no other complexes were detectable even in crude product) is worthy of comment. If one supposes that product formation proceeds through a Diels–Alder type reaction in which the appended vinyl group functions as the dienophile, then the transition state arrangement **41** would account for the observed stereochemistry of the methyl group in **38** (Chart I). Steric interactions between the bulky ketal ring and the cobaltacyclopentadiene would seem to favor transition state **41** over **42**.

Scheme X



Oxidative demetalation[1] of **38** was accomplished with ferric chloride in acetonitrile at 0 °C to give the very air-sensitive free steroid **1** in 78% yield (Scheme IX). The origin of this unusual instability is probably associated with the cross-conjugated nature of the system. It is presumably in part this property which has precluded a previous preparation of such estrapentaenes. The ^{1}H NMR spectrum of this diene (taken under N_2) exhibited two singlets at δ 3.43 and 1.37. These resonances were assigned to the methoxy and 18-methyl group, respectively. The presence of a single vinyl proton resonance at δ 6.11 (dd, J = 6.8, 3.0 Hz) suggested that during the decomplexation the position of the conjugated diene was unchanged. Further evidence in favor of this assignment was obtained through an NOE experiment. Irradiation of the H-1 proton led to a 20% enhancement of the signal for the vinyl proton (H-11). Conversely, irradiation at the resonance frequency of the latter led to an 18% enhancement in the former. From this evidence it was concluded that the position of the diene unit could only be $\Delta^{9(11),8(18)}$.

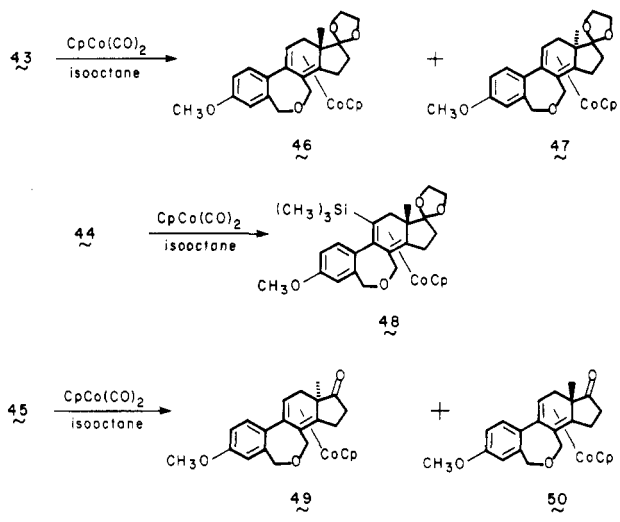
Smooth isomerization of **1** with concomitant hydrolysis of the ketal group was accomplished by treatment of the diene ketal with *p*-toluenesulfonic acid in wet THF (Scheme IX). The conversion of **1** to diene **39** proceeded at room temperature in a matter of a few hours. Deketalization required heating to reflux temperature for a period of 26 h to give the Torgov diene **40** (85%).

The synthetic steroid **40** was compared with an authentic, optically active sample from Wyeth Laboratories by a number of spectral and physical techniques. Thus, the two compounds were found to be indistinguishable by TLC, UV, ^{1}H NMR, and mass spectroscopy.

Extension to B Ring Homoxasteroids. The novelty of the successful cyclization of **2** suggested a brief exam-

(21) Clinet, J.-C.; Duñach, E.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1983**, *105*, 6710.
(22) Gadek, T. R.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 802.

Scheme XI



ination of its scope. The ready availability of the benzyl bromide **9** and alcohol **13** was exploited by coupling to the ether **43** (36%)[23] (Scheme X). The ^{1}H NMR spectrum exhibited the typical aromatic proton pattern found in these systems. It also showed a two proton singlet at δ 4.73 and a two proton triplet at δ 4.22 (J = 1.9 Hz) which was assigned to the methylene hydrogens next to the ether oxygen.

Compound **43** was silylated by sequential addition of butyllithium and trimethylsilyl chloride to give **44** (71%). On the other hand, hydrolysis of **43** with 10% aqueous HCl in THF resulted in the formation of the deketalized material **45** (63%).

Treatment of **43** with excess $CpCo(CO)_2$ in boiling isooctane effected intramolecular [2 + 2 + 2] cycloaddition to give a combined 60% yield of a mixture of two 7-oxa-B-homosteroid complexes **46** and **47** in a 2.6:1 ratio (Scheme XI) separated by column chromatography on activity III alumina. The major component **46** was crystalline and was assigned the indicated exo stereochemistry based on the chemical shift of the angular methyl group at δ 1.06 (Table I). In contrast, the relatively large downfield chemical shift of the endo methyl group in **47** was as expected for an endo configuration (Table I).

In contrast to **43**, the cyclization of silyl diene **44** proceeded to give only **48** (65%). The ^{1}H NMR peak of the methyl resonance was at δ 0.83, thus indicating its exo stereochemistry. The methylene protons next to the silyl group appear as two doublets with a geminal coupling constant of 14.6 Hz.

The final cyclization revealed an interesting perturbation in product stereochemistry. Thus, **45** was converted in 52% yield to two cobalt complexes in a 2:1 ratio (Scheme XI). The ^{1}H NMR spectrum of the crude reaction mixture exhibited two methyl proton singlets at δ 1.33 and 0.76. The more intense peak (δ 1.33) was assigned to complex **49** with endo stereochemistry, whereas the smaller peak was due to the exo methyl compound **50**. The major isomer was crystallized from petroleum ether. Besides the methyl singlet, the ^{1}H NMR spectrum of this compound showed two doublets of doublets at δ 0.69 (J = 13.5, 1.2 Hz, 1 H) and 1.03 (J = 13.6, 5.5 Hz, 1 H) which were assigned to the endo and exo methylene protons on C-13, respectively. The IR spectrum exhibited a ketone absorption at 1733 cm^{-1}. This high value, as compared to starting material (ν_{CO} = 1679 cm^{-1}) indicated the loss of the conjugation to the alkene upon cyclization.

The changes in observed stereochemistry within this series of cyclizations are again tentatively rationalizable within the framework of transition state models **41** and **42**. The bulk of the ketal function appears to lead to preferential formation of exo methyl products. On the other hand it is possible that the free carbonyl group in **45** now dictates the opposite stereochemistry by developing secondary orbital interactions of the type frequently discussed in classical Diels–Alder reactions. The answer to the mechanistic questions posed by these results will have to await the outcome of synthetic efforts aimed at the isolation of compounds of the type **41** and **42**.

Conclusion

This work establishes the feasibility of applying cobalt-mediated [2 + 2 + 2] cycloadditions in the total synthesis of natural products, as exemplified by the one-step assembly of the tetracyclic steroid nucleus starting from a monocyclic precursor. It also demonstrates the potential usefulness of the metals as a protecting group as in **38**, in which the complex is considerably less labile than the free ligand. Although presently mechanistically poorly understood, the reaction leads to stereospecific product formation in some cases, evidently controlled by the substitution pattern in the enediyne substrate. Such selectivity will become important in current efforts aimed at using optically active (catalytic?) metals in order to effect enantioselective cyclizations.

Experimental Section

For general data see ref 1.

3-Methoxybenzyl Acetate (4). To a stirred solution of 3-methoxybenzyl alcohol (18.5 g, 136 mmol) in pyridine (100 mL) at 0 °C was added acetic anhydride (15 g, 144 mmol). After 15 min the solution was allowed to warm to room temperature. After 12 h the reaction was worked up by simply vacuum transferring off the pyridine. The resulting slightly yellow oil of **4** (24.2 g, 99%) was pure by both gas liquid and thin-layer chromatography and was used as such: colorless oil; R_f 0.65, THF/petroleum ether (20:80) as eluent; ^{1}H NMR (60 MHz, CCl_4) δ 1.95 (s, 3 H), 3.71 (s, 3 H), 4.94 (s, 2 H), 6.69 (m, 2 H), 6.97 (d, J = 7.5, 1 H).

3-Methoxy-6-acetylbenzyl Acetate (6). To a stirred solution of 3-methoxybenzyl acetate (**4**) (5.0 g, 27.7 mmol) in CS_2 (250 mL) at 0 °C in a 1000-mL Erlenmeyer flask was added acetyl chloride (5.0 g, 63.7 mmol). To this solution were added 5 equiv (18.5 g, 138 mmol) of $AlCl_3$ over a period of 1 h. The resulting slightly yellow precipitate was assumed to be a complex of the product and $AlCl_3$. Therefore, the reaction was monitored by thin-layer chromatography (silica gel) to observe the disappearance of starting material. Stirring was continued for an additional 30 min at room temperature and the mixture was worked up as follows. The CS_2 was carefully decanted from the precipitate and to the residue was added CH_2Cl_2 (250 mL). The reaction flask was cooled to 0 °C, and pieces of ice were carefully added with swirling. After a brief induction period, large quantities of HCl evolved. After the solid had completely disappeared, H_2O (100 mL) was added. The organic layer was washed with 10% aqueous HCl (2 × 100 mL), aqueous $KHCO_3$ (2 × 100 mL), and H_2O (100 mL). To the resulting organic layer was added petroleum ether (100 mL) and Na_2SO_4 (anhydrous). The solvent was evaporated from this solution yielding a crude mixture of isomers **5** and **6** (6.10 g, 99%). Crystallization of the desired product was accomplished by adding first ethyl ether (50 mL) and then petroleum ether (125 mL). Light tan crystals formed at −78 °C overnight to give pure **6** (4.2 g, 68%): amorphous crystals; mp 69.5–71 °C (from ether–pentane); R_f 0.31, THF/petroleum ether (20:80) as eluent; IR (thin film) 2943, 1740, 1675, 1607, 1569, 1361, 1252, 1039 cm^{-1}; UV λ_{max} (MeOH) 272 nm; ^{1}H NMR (60 MHz, CCl_4) δ 2.21 (s, 3 H), 2.52 (s, 3 H), 3.86 (s, 3 H), 5.43 (s, 2 H), 6.94 (m, 2 H), 7.76 (d, J = 8.2, 1 H); MS, m/e 222 (39%), 207 (59), 162 (63), 149 (18), 135 (22), 119 (20), 77 (35). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.86; H, 6.30. Found: C, 65.19; H, 6.39.

(23) James, K.; Tatchell, A. R.; Ray, P. K. *J. Chem. Soc. C* **1967**, 2681.

3-Methoxy-6-(1-chlorovinyl)benzyl Acetate (7). To a stirred solution of $POCl_3$ (100 mL) and 3-methoxy-6-acetylbenzyl acetate (6) (7.19 g, 32.4 mmol) cooled to 0 °C was added PCl_5 (13.2 g, 63.3 mmol). The reaction flask was corked lightly and then warmed to 45–50 °C. The reaction was usually complete after ~2 h of stirring. On some occasions, an additional 0.5 equiv of PCl_5 had to be added and heating continued in order to drive the process to completion. The $POCl_3$ was vacuum transferred from the reaction mixture. The residue was combined with a solution of pyridine/CH_2Cl_2 (1:20, 100 mL) and transferred into a 500-mL Erlenmeyer flask containing aqueous $KHCO_3$ (supersaturated, 100 mL), CH_2Cl_2 (50 mL), and pyridine (2 mL), all cooled to 0 °C. The cooling bath was removed and the entire mixture was stirred overnight. To the organic layer was added petroleum ether (200 mL) and the solution washed sequentially with H_2O (5 × 150 mL), 5% aqueous HCl (2 × 100 mL), 5% aqueous $KHCO_3$ (100 mL), and H_2O (100 mL). The organic layer was dried over Na_2SO_4 (anhydrous) after the addition of a trace (0.1 mL) of pyridine to scavenge any residual HCl. The solvent was removed on the rotary evaporator leaving the desired product 7 (7.35 g, 95%), stored at −78 °C: tan oil; R_f 0.60, THF/petroleum ether (20:80) as eluent; ^1H NMR (60 MHz, CCl_4) δ 2.08 (s, 3 H), 3.81 (s, 3 H), 5.10 (s, 2 H), 6.35 (br s, 1 H), 6.60 (br s, 1 H), 6.79 (m, 2 H), 7.21 (d, J = 8.8, 1 H); MS, m/e 242 (7%), 240 (19), 198 (56), 163 (100), 145 (17), 133 (16), 103 (17), 91 (11), 77 (17); HRMS calcd for $C_{12}H_{13}O_3Cl$, 240.0554; found, 240.0560.

3-Methoxy-6-ethynylbenzyl Alcohol (8). To $NaNH_2$ (0.160 g, 4.1 mmol) in a dry 100-mL round-bottom flask equipped with a magnetic stir bar were added THF (10 mL) and HMPA (1 mL). The mixture was cooled with a dry ice/acetone bath. The vinyl chloride 7 (0.270 g, 1.125 mmol) was dissolved in THF (5 mL) and added to the above solution by cannula. The reaction mixture was allowed to warm to room temperature and then warmed to a bath temperature of 50 °C. Silica gel thin-layer chromatography indicated that the reaction was complete after 2 h of warming. The solution was poured into H_2O (10 mL) which had been placed in a 125-mL separatory funnel. To the mixture was added ethyl ether/petroleum ether (3:7, 35 mL). The resulting organic layer was washed with H_2O (5 × 25 mL) to remove residual HMPA and dried over Na_2SO_4 (anhydrous). Evaporation of the solvent left a slightly yellow oil which was dissolved in ether and filtered through 1.0 g of silica gel with ethyl ether as eluent to give 8 (0.168 g, 92%): white crystals; mp 71–72.5 °C (from MeOH/H_2O); IR (thin film) 3400, 3280, 2940, 2100, 1700, 1605, 1490, 1240, 1060 cm^{-1}; UV λ_{max} (MeOH) 261 nm; ^1H NMR (60 MHz, CCl_4) δ 2.54 (br s), 3.00 (s, 1 H), 3.63 (s, 3 H), 4.60 (s, 2 H), 6.64 (m, 2 H), 7.18 (d, J = 8.5, 1 H); MS, m/e 162 (100%), 147 (12), 133 (32), 119 (29), 105 (12), 91 (43), 77 (26). Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.17. Found: C, 73.78; H, 6.20.

3-Methoxy-6-ethynylbenzyl Bromide (9). Into a 10-mL pear-shaped flask were placed $P(C_6H_5)_3{\cdot}Br_2$ (1.04 g, 2.46 mmol), CH_2Cl_2 (5 mL), and collidine (0.2 mL). The flask was cooled to ice bath temperature, whereupon a solution of alcohol 8 (0.20 g, 1.23 mmol) in CH_2Cl_2 (3 mL) and collidine (0.1 ml) was added. The stirred mixture was allowed to warm to room temperature and stirred for 5 h. Workup with ice cold aqueous supersaturated $KHCO_3$ (15 mL), ethyl ether/petroleum ether (1:2, 30 mL), and collidine (0.1 mL), followed by drying over Na_2SO_4 (anhydrous), gave a tan solid which was extracted with ethyl ether/petroleum ether (1:4, 30 mL) and filtered through silica gel (10 g) using ethyl ether/petroleum ether (1:4) as eluent. This treatment gave 9 (0.260 g, 94%), recrystallized from MeOH/H_2O: tan needles; mp 65–67 °C; R_f 0.45, 10% THF/hexane (1:9) as eluent; IR (thin film) 3290, 2964, 2104, 1608, 1570, 1495, 1245, 1040 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.35 (s, 1 H), 3.79 (s, 3 H), 4.60 (s, 2 H), 6.75 (dd, J = 8.6, 3.3, 1 H), 6.89 (d, J = 3.3, 1 H), 7.35 (d, J = 8.6, 1 H); MS, m/e 226 (16%), 224 (16), 145 (100), 102 (50), 76 (12); HRMS calcd for $C_{10}H_9OBr$, 223.9836 (^{79}Br); found, 223.9837.

2-Methyl-1-hepten-6-yn-3-ol (10). 4-Pentyn-1-ol was oxidized by the method of Corey and Fuchs.[10] A 500-mL round-bottom flask was charged with dry CH_2Cl_2 (200 mL), pyridinium chlorochromate (16.2 g, 75 mmol), and sodium acetate (5.2 g). The pentynol (4.20 g, 50 mmol) in CH_2Cl_2 (20 mL) was added in one portion to this mixture with stirring. After 1.5 h, dry ether (200 mL) was added and the supernatant layer decanted off the resulting black oil. After trituration with ether (3 × 50 mL), the organic layers were combined and filtered through alumina (activity 3, 100 g). The solvent was carefully removed on the stream bath. This was followed by addition of ether (20 mL) and a second evaporation step. This procedure was repeated two more times to remove all traces of CH_2Cl_2. The product was transferred into a 500-mL round-bottom flask equipped with a stir bar and THF (100 mL). To this solution, cooled to −78 °C, was added isopropenylmagnesium bromide (200 mmol) in ether, prepared from isopropenyl bromide by standard techniques using $HgCl_2$ as catalyst. Standard aqueous NH_4Cl workup, followed by filtration through alumina (activity 5, 50 g) with ethyl ether (200 mL) as eluent, gave 10 (5.26 g, 85%): colorless oil; R_f 0.25, ethyl ether/petroleum ether (1:1) as eluent; IR (thin film) 3350, 3304, 2954, 2121, 1713, 1445, 1063, 903 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.41 (m, 2 H), 1.79 (br s, 3 H), 2.28 (m, 2 H), 3.42 (br s, 1 H), 4.85 (m, 3 H); MS, m/e 124 (2%), 109 (51), 95 (50), 91 (20), 81 (28), 79 (22), 71 (100), 55 (49); HRMS calcd for $C_8H_{12}O$, 124.0888; found, 124.0890.

2-Methyl-1-hepten-6-yn-3-one (11). Pyridinium chlorochromate (3.23 g, 15 mmol) was dissolved in CH_2Cl_2 (20 mL) along with sodium acetate (0.52 g). To the stirred solution was added in one portion the alcohol 10 (1.24 g, 10 mmol). After 1.5 h of stirring, dry diethyl ether (20 mL) was added. The resulting cloudy solution was decanted from the dark brown residue, the latter washed with ether, and the combined washings filtered through alumina (activity 3, 10 g) eluting with ethyl ether to give 11 (1.05 g, 86%): colorless oil; R_f 0.60, ethyl ether/petroleum ether (1:1) as eluent; IR (thin film) 3290, 2880, 2120, 1675, 1630, 1140, 948, 898 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.85 (br s, 3 H), 2.42 (m, 3 H), 2.85 (m, 2 H), 5.72 (br s, 1 H).

2-Methyl-1-hepten-6-yn-3-one Ethylene Ketal (12). The ketone 11 (1.00 g, 8.20 mmol) was dissolved in ethylene glycol (30 mL) in a 100-mL round-bottom flask. A Dean–Stark trap was attached after the addition of *p*-toluenesulfonic acid (0.02 g). The reaction mixture was heated for 7 h until no more water was collected. At this stage gas liquid chromatography showed that the reaction was only 70% complete. Bicarbonate workup gave an oil (1.2 g). This material was filtered through alumina (activity 3, 100 g) eluting with ethyl ether/hexane (1:9). Six 50-mL fractions were collected to yield 12 (0.71 g, 52%). Further elution yielded starting ketone 11 (0.22 g, 22%). The yield of ketal based on recovered starting material was 67%. Compound 12: colorless oil; R_f 0.42, ethyl ether/petroleum ether (1:10) as eluent; IR (thin film) 3303, 2968, 2123, 1448, 1194, 1038 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.75 (br s, 4 H), 2.20 (m, 4 H), 3.88 (br s, 4 H), 4.82 (m, 1 h), 5.08 (m, 1 H); MS (30 eV), m/e 125 (15%, M^+ − 41), 113 (20), 78 (100), 69 (6). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.24; H, 8.43. Found: C, 72.43; H, 8.29.

8-Hydroxy-2-methyl-1-octen-6-yn-3-one Ethylene Ketal (13). To alkyne 12 (2.40 g, 14.5 mmol) in THF (60 mL) cooled to dry ice/acetone bath temperature was added *n*-butyllithium in hexane (12.1 mL, 17.2 mmol). The solution was warmed to 0 °C and then transferred by cannula into paraformaldehyde (1.68 g, 18.7 mmol) in THF (30 mL). Aqueous workup, followed by filtration through alumina (activity 5, 20 g) with ethyl ether as eluent, gave 13 (2.66 g, 94%): colorless oil; R_f 0.31, ethyl ether/petroleum ether (1:1) as eluent; IR (thin film) 3350, 3045, 2954, 2153, 1448, 1193, 1035, 905 cm^{-1}; ^1H NMR (60 MHz, C_6D_6) δ 1.65 (s, 3 H), 1.87–2.80 (m, 4 H), 3.51 (s, 4 H), 4.17 (br s, 2H), 4.87 (br s, 1 H), 5.22 (br s, 1 H); MS (30 eV), m/e 155 (56%, M^+ − 41), 113 (100), 91 (14), 69 (59), 65 (14), 55 (22).

8-Bromo-2-methyl-1-octen-6-yn-3-one Ethylene Ketal (14). To a stirred solution cooled to 0 °C of $P(C_6H_5)_3{\cdot}Br_2$ (0.84 g, 2.0 mmol) and collidine (0.2 mL) in CH_2Cl_2 (5 mL) was added the alcohol 13 (0.196 g, 1.0 mmol) and collidine (0.1 mL) in CH_2Cl_2 (4 mL). The reaction mixture was stirred for 15 min at 0 °C and then worked up as in the preparation of 9 to give 14 (0.139 g, 54%): colorless oil; R_f 0.46, ethyl ether/hexane (1:9) as eluent; IR (thin film) 2967, 2238, 1732, 1263, 1074, 952 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 1.64 (dd, J = 1.2, 0.8, 3 H), 2.04 (t, J = 8.1, 2 H), 2.36 (m, 2 H), 3.41 (s, 4 H), 3.45 (d, J = 2.1, 2 H), 4.83 (br s, 1 H), 5.23 (br s, 1 H); MS (30 eV), m/e 219, 217 (1:1, 31%, M^+ − 41), 173 (11), 138 (4), 113 (100), 93 (12), 86 (25); HRMS calcd for $C_8H_{10}O_2Br$, 216.9863 (^{79}Br); found, 216.9858.

9-[3-(4-Ethynylanisyl)]-2-methyl-1-nonen-6-yn-3-one Ethylene Ketal (2), 1,2-Bis[3-(4-ethynylanisyl)]ethane (15),

4-Ethynyl-3-methylanisole (16), and 2,2-Dimethyl-3-[3-(4-ethynylanisyl)]propane (17). To a solution of propargyl bromide **14** (0.100 g, 0.386 mmol) and benzyl bromide **9** (0.87 g, 0.386 mmol) in THF (5 mL) cooled to −78 °C was added *tert*-butyllithium in pentane (0.64 mL, 7.4 mmol). The reaction mixture was allowed to warm to room temperature, and then exposed to aqueous workup. Thin-layer chromatography revealed four UV active compounds [R_f 0.19, 0.45, 0.58, 0.65, ethyl ether/hexane (1:9) as eluent], of which the fourth compound stained with I_2. HPLC separation on a reverse phase column (C-18, Ultrasphere) eluting with CH_2Cl_2/CH_3CN (5:95) gave four peaks of equal absorbance. The third compound to be eluted gave **2** (0.022 g, 17.6%). Separation of the components was also accomplished on a Chromatotron eluting with ethyl ether/petroleum ether (1:9 → 2:8).

Compound **2**: clear oil; R_f 0.19, ethyl ether/hexane (1:9) as eluent; IR (thin film) 3285, 2929, 2104, 1608, 1568, 1494, 1244, 1039 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.71 (dd, J = 2.0, 1.5, 3 H), 2.22 (br t, J = 8.7, 2 H), 2.55 (m, 4 H), 2.90 (s, 1 H), 3.09 (t, J = 8.7, 2 H), 3.26 (s, 3 H), 3.43 (br s, 4 H), 4.84 (q, J = 2.0, 1 H), 5.26 (q, J = 1.5, 1 H), 6.48 (dd, J = 8.8, 3.8, 1 H), 6.77 (d, J = 3.8, 1 H), 7.44 (d, J = 8.8, 1 H); MS (30 eV), m/e 324 (0.19%), 309 (2), 279 (4), 265 (8), 113 (100), 69 (59); HRMS calcd for $C_{21}H_{24}O_3$, 324.1727; found, 324.1722.

Compound **17**: colorless oil; R_f 0.75, ethyl ether/hexane (1:9) as eluent; ^{1}H NMR δ 1.05, (s, 9 H), 2.84 (s, 2 H), 2.91 (s, 1 H), 3.27 (s, 3 H), 6.52 (dd, J = 8.6, 2.3, 1 H), 6.78 (d, J = 2.3, 1 H), 7.53 (d, J = 8.6, 1 H).

Compound **16**: colorless oil; R_f 0.68, ethyl ether/hexane (1:9) as eluent; ^{1}H NMR δ 2.41 (s, 3 H), 3.01 (s, 1 H), 3.65 (s, 3 H), 6.54 (m, 2 H), 7.13 (d, J = 8.2, 1 H).

Compound **15**: colorless oil; R_f 0.55, ethyl ether/hexane (1:9) as eluent; ^{1}H NMR (200 MHz, C_6D_6) δ 2.95 (s, 2 H), 3.28 (s, 6 H), 3.42 (s, 4 H), 6.51 (dd, J = 8.5, 2.4, 2 H), 6.78 (d, J = 2.4, 2 H), 7.50 (d, J = 8.6, 2 H).

3-Methoxy-6-[(trimethylsilyl)ethynyl]benzyl Alcohol (18). To a solution of alcohol **8** (0.225 g, 1.39 mmol) in dry THF (10 mL) cooled to dry ice/acetone bath temperature was added *n*-butyllithium in hexane (2.09 mL, 2.92 mmol). The reaction mixture was warmed to 0 °C for 5 min and then cooled to dry ice/acetone bath temperature. Addition of trimethylsilyl chloride (0.35 g, 3.2 mmol) was followed by warming to room temperature. After stirring overnight, the mixture was worked up with bicarbonate to give a colorless oil of the presumed bissilylated product [R_f 0.81, ethyl ether/petroleum ether (1:9) as eluent].

To this oil in a 50-mL round-bottom flask was added MeOH (15 mL), the mixture cooled in an ice bath, and then 2% aqueous HCl (5 mL) added. After 15 min of stirring, the bissilyl compound had been completely consumed, as shown by TLC [R_f 0.91, MeOH/ethyl ether/petroleum ether (1:3:6) as eluent]. Aqueous workup gave **18** (0.245 g, 75%): colorless crystals; mp 82–84 °C (from ether–pentane); R_f 0.31, MeOH/ethyl ether/petroleum ether (1:3:6) as eluent; IR (thin film) 3400, 2959, 2152, 1608, 1569, 1494, 1252, 1036, 865 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 0.30 (s, 9 H), 3.36 (br s, 1 H), 3.82 (s, 3 H), 4.65 (br s, 2 H), 6.60 (dd, J = 8.4, 3.2, 1 H), 6.88 (d, J = 3.4, 1 H), 7.14 (d, J = 8.4, 1 H); MS, m/e 234 (100%), 219 (25), 205 (25), 189 (10), 159 (58), 145 (13), 128 (16), 102 (16), 91 (21); HRMS calcd for $C_{13}H_{18}O_2Si$, 234.1076; found, 234.1067.

3-Methoxy-6-[(trimethylsilyl)ethynyl]benzyl Bromide (19). To a solution of $P(C_6H_5)_3$ (0.135 g, 0.52 mmol) and CBr_4 (0.177 g, 0.53 mmol) in ethyl ether (5 mL) was added the alcohol **18** (0.050 g, 0.21 mmol). After 4 h of stirring and bicarbonate workup, the residue was chromatographed on a Chromatotron (1 mm silica gel plate) to give **19** (0.045 g, 72%): tan solid; mp 89–92 °C (from ether–pentane); R_f 0.65, ethyl ether/petroleum ether (15:85) as eluent; IR (thin film) 2961, 2154, 1607, 1566, 1495, 1251, 1041, 864, 763 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 0.28 (s, 9 H), 3.78 (s, 3 H), 4.52 (s, 2 H), 6.60 (dd, J = 8.6, 3.2, 1 H), 6.74 (d, J = 3.2, 1 H), 7.28 (d, J = 8.6, 1 H); MS, m/e 298 (65%), 296 (64), 283 (16), 217 (69), 206 (49), 189 (13), 159 (100), 128 (30), 115 (33); HRMS calcd for $C_{13}H_{17}OSiBr$, 298.0213; found, 298.0203.

3-Methoxy-6-[(trimethylsilyl)ethynyl]benzyl Chloride (20). To a solution of PCl_5 (0.84 g, 4.0 mmol) and pyridine (0.3 mL) in CH_2Cl_2 (10 mL) was added a solution of the alcohol **18** (0.46 g, 2 mmol) and pyridine (0.2 mL) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 2 h and then worked up as in the synthesis of **19**. The yellow residue after this treatment was filtered through silica gel (5 g) eluting with ethyl ether/petroleum ether (1:9) to give **20** (0.412 g, 81%): colorless crystals; mp 66–67 °C (from ether–pentane); R_f 0.60, ethyl ether/petroleum ether (15:85) as eluent; IR (thin film) 2975, 2140, 1600, 1360, 1240, 1180, 840 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 0.30 (s, 9 H), 3.78 (s, 3 H), 4.62 (s, 2 H), 6.60 (dd, J = 7.8, 3.0, 1 H), 6.83 (d, J = 3.2, 1 H), 7.32 (d, J = 7.8, 1 H); MS, m/e 254 (14%), 252 (38), 239 (8), 273 (20), 216 (16), 214 (22), 181 (40), 179 (16), 159 (54), 145 (32), 73 (100).

2-Methyl-1-undecen-6-yn-3-one Ethylene Ketal (22). To ketal **12** (0.10 g, 0.6 mmol) in THF (5 mL) at dry ice/acetone bath temperature was added *n*-butyllithium in hexane (0.46 mL, 0.66 mmol). The mixture was warmed to 0 °C over a period of 5 min and then cooled back to dry ice/acetone bath temperature. Iodine (0.167 g, 0.66 mmol) was dissolved in THF (3 mL) and then added via cannula to the cooled reaction flask. The iodine color quickly disappeared leaving a slightly yellow solution of (presumed) **21** after 30 min of stirring.

n-Butylcopper was prepared via the addition of *n*-butyllithium in hexane (0.45 mL, 0.63 mmol) to CuBr·DMS (0.128 g, 0.62 mmol) which had been dissolved in THF (3 mL) and cooled to dry ice/acetone bath temperature. The butylcopper solution was added via cannula to the cold solution of iodo compound **21**. After the reaction mixture had been stirred at dry ice/acetone bath temperature for 0.5 h, it was allowed to warm to 0 °C, quenched with 5% aqueous KCN (10 mL), and then extracted with petroleum ether. Filtration of the resulting slightly yellow oil through silica gel (1 g) eluting with ethyl ether/petroleum ether (1:3) gave **22** (0.083 g, 62%): colorless oil; R_f 0.37, ethyl ether/petroleum ether (3:7) as eluent; IR (thin film) 3105, 2960, 1665, 1458, 1200, 895 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 0.95 (t, J = 6, 3 H), 1.40 (m, 4 H), 1.64 (br s, 3 H), 2.05 (m, 6 H), 3.78 (br s, 4 H), 4.82 (m, 1 H), 5.01 (m, 1 H); MS (30 eV), m/e 222 (3%), 181 (74), 114 (63), 113 (94), 69 (89).

4-Ethynyl-3-(2-hydroxyethyl)anisole (27). Into a 250-mL Erlenmeyer flask was placed **24**[24] (1.10 g, 5.67 mmol), CS_2 (50 mL), a magnetic stirrer bar, and acetyl chloride (1.0 g, 12.7 mmol). After cooling this mixture to 0 °C, $AlCl_3$ (3.80 g, 28.5 mmol) was added over a period of 1 h until starting material had been consumed, as determined by silica gel thin-layer chromatography. Decanting of the CS_2 from the resulting tan solid residue was followed by addition of CH_2Cl_2 (50 mL). Hydrolysis of the residue was accomplished by careful addition of ice to the flask while maintaining stirring. The resulting organic layer was washed sequentially with 10% aqueous HCl (3 × 50 mL), 10% aqueous bicarbonate (50 mL), and H_2O (50 mL). After the addition of petroleum ether (50 mL) the organic layer was dried over Na_2SO_4 (anhydrous). Evaporation of solvent resulted in crude product (1.2 g, 90%) as a mixture of **25** and the *o*-methoxyacetophenone isomer (ratio 5:2). This mixture was used as such in the next step.

Crude **25** was dissolved in $POCl_3$ (10 mL) to which was added PCl_5 (1.90 g, 9.2 mmol). The reaction mixture was warmed to 40–45 °C for 2.5 h. Heating beyond this temperature rapidly decomposed all the material. The $POCl_3$ was then vacuum transferred off and a solution of ethyl ether/petroleum ether/pyridine (20:20:1, 40 mL) added. The mixture was carefully poured into a stirred, ice cooled solution of supersaturated aqueous $KHCO_3$ (50 mL) in a 250-mL Erlenmeyer flask. This was stirred overnight, and then subjected to aqueous workup. After evaporation of the solvent the residue was filtered through silica gel (10 g) eluting with ethyl ether/petroleum ether (1:1, 100 ml) to give only the vinyl chloride **26** (0.45 g, 34.7%) [R_f 0.55, THF/petroleum ether (1:2) as eluent].

Crude **26** (0.085 g, 0.33 mmol) was then subjected to saponification in 20% aqueous methanol (2 mL) containing added KOH (0.100 g). After 10 min of stirring, the reaction was shown to be complete by thin-layer chromatography. Aqueous workup yielded a clear oil which was filtered through silica gel (1 g) to give the free alcohol (0.065 g, 93%) [R_f 0.15, ethyl ether/petroleum ether (1:1) as eluent].

(24) Audier, H. E.; Bouchoux, G.; Fetizon, M. *Bull. Soc. Chim. Fr.* **1971**, 858. Weibel, P. A.; Hesse, M. *Helv. Chim. Acta* **1973**, *56*, 2460.

To the crude alcohol (0.065 g, 0.3 mmol) in THF (2 mL) was added lithium diisopropylamide (1.2 mmol) in THF (3 mL). The reaction mixture was allowed to stir at room temperature for 1 h until conversion to the alkyne **27** was indicated to be complete by thin-layer chromatography. Aqueous workup and filtration of the resulting oil through silica gel (1 g) eluting with ethyl ether gave **27** (0.048 g, 91%): white needles (from ether–pentane); mp 55–57 °C; R_f 0.11, ethyl ether/petroleum ether (1:1) as eluent; IR (thin film) 3280, 2957, 2101, 1605, 1567, 1495, 1167, 1040, 817 cm^{-1}; UV λ_{max} (MeOH) 253 nm; ^1H NMR (250 MHz, $CDCl_3$) δ 1.60 (br s, 1 H) (resonance disappears on addition of D_2O), 3.03 (t, J = 6.7, 2 H), 3.18 (s, 1 H), 3.79 (s, 3 H), 3.90 (t, J = 6.7, 2 H), 6.73 (dd, J = 8.4, 2.6, 1 H), 6.78 (dd, J = 8.4, 2.6, 1 H), 7.42 (d, J = 8.6, 1 H); MS, m/e 176 (99%), 161 (23), 145 (82), 131 (55), 115 (74), 102 (100), 77 (50); HRMS calcd for $C_{11}H_{12}O_2$, 176.0837; found, 176.0838.

Compound **24**:[24] crude oil; R_f 0.35, ethyl ether/petroleum ether (1:3) as eluent; IR (thin film) 2960, 1741, 1605, 1495, 1157, 701 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 2.00 (s, 3 H), 2.87 (t, J = 8.5, 2 H), 3.72 (s, 3 H), 4.25 (t, J = 8.5, 2 H), 6.75 (m, 3 H), 7.15 (m, 1 H); MS, m/e 194 (20%), 135 (41), 134 (81), 121 (45), 91 (53), 43 (100); HRMS calcd for $C_{11}H_{14}O_3$, 194.0941; found, 194.0937.

25: crude oil; R_f 0.37, ethyl ether/petroleum ether (9:1) as eluent; IR (thin film) 2960, 1735, 1676, 1602, 1580, 1422, 1138 cm^{-1}.

26: crude oil; R_f 0.65, ethyl ether/petroleum ether (9:1) as eluent; ^1H NMR (60 MHz, $CDCl_3$) δ 2.02 (s, 3 H), 3.05 (t, J = 8.2, 2 H), 3.78 (s, 3 H), 4.28 (t, J = 8.2, 2 H), 5.29 (s, 1 H), 5.66 (s, 1 H), 6.82 (m, 2 H), 7.15 (d, J = 8.4, 1 H).

Hydrolysis product from **26**: crude oil; R_f 0.10, ethyl ether/petroleum ether (9:1) as eluent; ^1H NMR (60 MHz, $CDCl_3$) δ 1.70 (br s, 1 H), 3.01 (br t, J = 8.1, 2 H), 3.79 (s, 3 H), 3.83 (br t, J = 8.0), 5.28 (s, 1 H), 5.55 (s, 1 H), 6.72 (m, 2 H), 7.15 (d, J = 8.5, 1 H).

4-[(Trimethylsilyl)ethynyl]-3-(2-hydroxyethyl)anisole (28). To the alcohol **27** (0.40 g, 2.27 mmol) in dry THF (30 mL) at −78 °C was added *n*-butyllithium in hexane (1.6 ml, 4.6 mmol). The solution was warmed to 0 °C for 5 min and then cooled back to −78 °C. To this mixture was added trimethylsilyl chloride (0.55 g, 5.10 mmol), and the solution was warmed to room temperature and then stirred overnight. Aqueous workup gave a colorless oil which was dissolved in MeOH (20 mL) and cooled to 0 °C. To this solution was added 2% aqueous HCl (10 mL), and the mixture was stirred for 1 h and then exposed to bicarbonate workup to give crude alcohol **28** (0.50 g, 89%): colorless oil; R_f 0.17, ethyl ether/petroleum ether (9:1) as eluent; IR (thin film) 3380, 2955, 2150, 1605, 1568, 1495, 1250, 760 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 0.28 (s, 9 H), 1.40 (br s, 1 H), 3.41 (m, 4 H), 3.76 (s, 3 H), 6.62 (m, 2 H), 7.31 (d, J = 9.5, 1 H); MS, m/e 248 (63%), 218 (22), 215 (66), 159 (17), 149 (16), 75 (100), 73 (82); HRMS calcd for $C_{14}H_{20}O_2Si$, 248.1233; found, 248.1226.

4-[(Trimethylsilyl)ethynyl]-3-(2-bromoethyl)anisole (29). To triphenylphosphine dibromide (0.86 g, 2.02 mmol) in CH_2Cl_2 (5 mL) was added collidine (0.15 mL), the solution cooled to 0 °C, and a solution of alcohol **28** (0.248 g, 1.0 mmol) in CH_2Cl_2 (4 mL) containing collidine (0.1 mL) added. The reaction mixture was warmed to room temperature and then stirred for 5 h. Bicarbonate workup yielded a tan crystalline mass which was triturated with ethyl ether/petroleum ether (1:9), and the resulting extracts were filtered through silica gel (10 g) eluting with ethyl ether/petroleum ether (1:9) to furnish **29** (0.25 g, 80%): tan oil; R_f 0.67, ethyl ether/petroleum ether (5:95) as eluent; IR (thin film) 2958, 2150, 1603, 1565, 1493, 1250, 1038, 760 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.27 (s, 9 H), 3.33 (t, J = 7.5, 2 H), 3.57 (t, J = 7.8, 2 H), 3.82 (s, 3 H), 6.65 (m, 2 H), 7.35 (d, J = 8.7, 1 H); MS, m/e 312 (55%), 310 (55), 282 (11), 215 (97), 205 (66), 173 (31), 67 (100); HRMS calcd for $C_{14}H_{19}OSiBr$, 310.0389 (^{79}Br); found, 310.0387.

Ketal 33. A small scale preparation of "Rieke" magnesium was carried out as follows.[14] Dry magnesium chloride was prepared by placing oven-dried magnesium (0.250 g, 10.3 mmol) into a dry single neck, 14/20 50-mL round-bottom flask equipped with an overhead condenser and a magnetic stir bar. THF (30 mL) and 1,2-dichloroethane (0.43 mL, 5.05 mmol) were added and the mixture heated to reflux for 2 h. In a separate single neck 14/20 50-mL round-bottom flask fitted with a condenser and a stir bar was placed potassium (0.058 g, 1.48 mmol) and THF (10 mL), and subsequently THF (5 mL) added containing I_2 (0.063 g, 0.25 mmol). Heating to reflux for 1 h was followed by addition of 30 mL (0.5 mmol) of the above $MgCl_2$ solution. The mixture was subsequently heated to reflux and stirred for 2 h.

The condenser was removed and replaced with a rubber septum. To this flask, cooled to 0 °C, was added via syringe pump the phenethyl bromide **29** (0.130 g, 0.418 mmol) in THF (1 mL) over a period of 0.5 h. The reaction mixture was then cooled in a dry ice/acetone bath, and solid CuBr·DMS (0.086 g, 0.42 mmol) added.

To the alkyne **12** (0.076 g, 0.459 mmol) in a separate flask were added sequentially butyllithium in hexane (0.35 mL, 0.498 mmol) and I_2 (0.112 g, 0.441 mmol) in THF (3 mL), all cooled to dry ice/acetone bath temperature. After 1 h of stirring the solution containing the iodoalkyne **21** was added to the solution of alkylcopper **31**, which had been cooled to dry ice/acetone bath temperature. The solution was allowed to slowly warm to room temperature (~1 h) and then stirred for 1 h. The mixture was quenched with 5% aqueous KCN (10 mL). The resulting yellow oil was purified on a Chromatotron using a 2-mm silica gel plate eluting with a gradient from petroleum ether to ethyl ether/petroleum ether (1:3) to give **33** (0.056 g, 31%): colorless oil; R_f 0.65, ethyl ether/petroleum ether (1:3) as eluent; IR (thin film) 2950, 2148, 1610, 1485, 1250, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.28 (s, 9 H), 1.78 (br s, 3 H), 2.16 (t, J = 6.1, 2 H), 2.56 (t, J = 6.1, 2 H), 2.85 (m, 2 H), 2.98 (m, 2 H), 3.86 (s, 3 H), 3.94 (m, 4 H), 4.98 (br s, 1 H), 5.21 (br s, 1 H), 6.80 (m, 2 H), 8.65 (d, J = 8.5, 1 H); MS (30 eV), m/e 396 (64%), 381 (34), 355 (11), 323 (38), 309 (30), 295 (54), 237 (75), 197 (22), 113 (98), 73 (100).

9-[3-(4-Ethynylanisyl)]-2-methyl-1-nonen-6-yn-3-one Ethylene Ketal (2). To a stirred solution of lithiothiazoline **34** (0.45 mmol) dissolved in THF (5 mL) in a dry 100-mL round-bottom flask cooled in a dry ice/acetone bath was added the benzyl bromide **9** (0.104 g, 0.462 mmol) in THF (4 mL). The reaction mixture was warmed to 0 °C and maintained at this temperature in an ice bath for 1 h before being cooled back to −78 °C. This process was followed by addition of *n*-butyllithium in hexane (0.65 mL, 0.8 mmol). The mixture was stirred at this bath temperature for 15 min and then warmed over a period of 20 min to a bath temperature of −25 °C. This temperature was maintained for 15 min until dianion formation was assumed to be complete. The temperature of the bath was once again brought down to −78 °C. To the mixture was added via cannula a solution of propargyl bromide **14** (0.100 g, 0.461 mmol) in THF (4 mL). The mixture was warmed slowly to 0 °C over a period of ~20 min, and the reaction temperature was maintained at 0 °C while the alkylation was going to completion. Silica gel thin-layer chromatography showed the coupled thiazoline [R_f 0.34, ethyl ether/petroleum ether (1:1) as eluent], together with a trace of lower R_f material (R_f 0.1).

Desulfurization was accomplished by the addition of THF (4 mL) and H_2O (1 mL), made slightly basic by stirring over $KHCO_3$, and Al(Hg), prepared as follows. Small strips of aluminum foil (0.010–0.015 g) were sequentially dipped into ethyl ether, 2% aqueous $HgCl_2$ (for 30 s), and H_2O and added to the reaction flask. A total of 0.100 g of amalgamated aluminum was added in this way. This treatment was repeated after 3 h. The greyish solution was then stirred overnight, and then filtered through silica gel (10 g) with ethyl ether as solvent to remove the mercury and aluminum salts. Chromatography on a Chromatotron using a 2-mm silica gel plate eluting with ethyl ether/petroleum ether (1:9) yielded **2** (0.084 g, 65%).

In one run **37** was isolated as a sensitive yellow oil; R_f 0.34, ethyl ether/petroleum ether (1:1); ^1H NMR (200 MHz, $CDCl_3$) δ 1.63 (dd, J = 1.3, 1.0, 3 H), 1.78 (m, 2 H), 2.09 (m, 2 H), 2.89 (m, 2 H), 3.22 (s, 1 H), 3.27 (t, J = 7.9, 2 H), 3.74 (s, 3 H), 3.78 (m, 4 H), 4.13 (t, J = 7.6, 2 H), 4.82 (dq, J = 1.9, 1.4, 1 H), 5.01 (dq, J = 2.0, 1.1, 1 H), 5.35 (t, J = 6.6, 1 H), 6.72 (dd, J = 8.6, 2.7, 1 H), 6.99 (d, J = 2.6, 1 H), 7.35 (d, J = 8.5, 1 H); MS (30 eV), m/e 441 (4%), 398 (22), 322 (13), 262 (65), 165 (56), 113 (100), 99 (52), 69 (100).

(8,9,11,14-η^4-3-Methoxy-13a-*exo*-estra-1,3,5,8(14),9(11)-pentaen-17-one ethylene ketal)(η^5-cyclopentadienyl)cobalt (38). To a degassed solution of **2** (0.037 g, 0.114 mmol) in degassed isooctane (5 mL) in a dry 10-mL pear-shaped flask equipped with a stir bar was added $CpCo(CO)_2$ (0.045 mL, 0.36 mmol). This excess is recommended in small scale preparations. On a larger

scale (0.5 g) typically only 10% excess cobalt has to be used.[21] After 46 h of heating at reflux, all starting material had been consumed, as determined by silica gel thin-layer chromatography. The solvent and excess $CpCo(CO)_2$ were removed, first in an N_2 stream and then by exposure to high vacuum for 0.5 h. The reddish-brown residue was dissolved in ethyl ether/petroleum ether (5:95) and chromatographed on alumina (activity 3, 5 g). Elution with ethyl ether/petroleum ether (5:95) yielded a fraction containing some residual $CpCo(CO)_2$. Elution with ethyl ether/petroleum ether (20:80) gave an orange fraction containing complex **38** (0.035 g, 68.5%): orange crystals; mp 108–110 °C (from petroleum ether); R_f 0.65, ethyl ether/hexane (1:1) as eluent; IR (thin film) 2931, 1608, 1575, 1502, 1257, 1076, 808 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 0.96 (s, 3 H), 1.14 (dd, J = 14.5, 4.7, 1 H), 1.50 (ddd, J = 17.0, 7.4, 7.4, 1 H), 1.75 (ddd, J = 17.0, 8.5, 8.5, 1 H), 2.19 (dd, J = 8.6, 8.6, 2 H), 2.35 (m, 3 H), 2.67 (dd, J = 14.5, 4.7, 1 H), 2.90 (ddd, J = 16.0, 5.3, 2.0, 1 H), 3.46 (s, 3 H), 3.52 (m, 3 H), 3.74 (t, J = 7.5, 2 H), 4.58 (s, 5 H), 6.74 (dd, J = 8.5, 3.6, 1 H), 6.93 (d, J = 3.6, 1 H), 7.28 (d, J = 8.5, 1 H); irradiation (200 MHz, C_6D_6) at δ 1.11 (H-12 exo) caused a simplification at δ 2.67 (H-12 endo) to a broad doublet, J = 4.8, and at δ 3.55; irradiation at δ 1.50 (H-7) caused a simplification at δ 2.19 (H-6, CH_2) to a broad doublet, J = 9.5, and at δ 1.75; irradiation at δ 1.75 (H-7) caused a simplification at δ 2.19 to a broad doublet, J = 8.8, and at δ 1.50; irradiation at δ 2.20 (H-6, CH_2) caused a simplification at δ 1.75 to a broad doublet, J = 17.4, and at δ 1.50 to a broad doublet, J = 17.0; irradiation at δ 2.35 (H-15,16, CH_2) caused a simplification at δ 2.90; irradiation at δ 2.67 (H-12 endo) caused a simplification at δ 1.14 to a broad doublet, J = 5.0, and at δ 3.55; irradiation at δ 2.90 (H-15,16, CH_2) caused a simplification at δ 2.35; irradiation at δ 3.55 (H-11 vinyl, OCH_2) caused a simplification at δ 3.74 (OCH_2) to a broad singlet, at δ 2.67 to a doublet, J = 17, and at δ 1.14 to a doublet, J = 17; irradiation at δ 3.74 (H OCH_2) caused a simplification at δ 3.55; MS (30 eV), m/e 448 (100%), 324 (10), 310 (70), 304 (51), 263 (40), 124 (53); HRMS calcd for $C_{26}H_{29}O_3Co$, 448.1448; found, 448.1447.

3-Methoxyestra-1,3,5,8(14),9(11)-pentaen-17-one Ethylene Ketal (1). A solution of $FeCl_3 \cdot 2H_2O$ (0.017 g, 0.086 mmol) in CH_3CN (3 mL) was cooled in a dry ice/acetone bath at ~40 °C, and complex **38** (0.035 g, 0.078 mmol) in CH_3CN (2 mL) added via cannula to the stirred mixture. The temperature was maintained at −35 °C for 5 min and then at ice bath temperature for an additional 20 min. Aqueous workup, followed by filtration through silica gel (1 g) eluting with ethyl ether and chromatography using a 2-mm silica gel plate on a Chromatotron eluting with ethyl ether/petroleum ether (1:9), yielded initially a colorless fraction, followed by some starting material. Evaporation of the solvent in an N_2 stream followed by high vacuum resulted in the isolation of starting material (0.014 g, 40%) and the steroid (0.012 g, 47%, 78% based on recovered starting material) as an oil. This material proved to be extremely air sensitive; therefore, extensive manipulation in air should be avoided.

Compound 1: colorless oil; R_f 0.32, benzene as eluent; R_f 0.65, chloroform as eluent; R_f 0.54, ethyl ether/hexane (1:1) as eluent, stains slowly with iodine; IR (thin film) 2968, 1608, 1573, 1497, 1250, 1047, 953, 816 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 1.37 (s, 3 H), 2.08 (dd, J = 17.0, 6.8, 1 H), 2.35 (m, 6 H), 2.60 (t, J = 6.4, 2 H), 3.14 (br d, J = 17.0, 1 H), 3.43 (s, 3 H), 3.56 (m, 4 H), 6.11 (dd, J = 6.8, 3.0, 1 H), 6.70 (d, J = 2.5, 1 H), 6.84 (dd, J = 8.6, 2.5, 1 H), 7.60 (d, J = 8.6, 1 H); irradiation at δ 6.11 caused an 18% NOE enhancement of the resonance at δ 7.60, whereas irradiation at δ 7.60 caused a 17% enhancement at δ 6.11; MS (30 eV), m/e 324 (71%), 309 (97), 263 (100), 238 (51), 223 (97), 208 (32), 149 (34).

3-Methoxyestra-1,3,5,8,14-pentaen-17-one (40). To a solution of the steroid 1 (0.0061 g, 0.0188 mmol) in degassed THF-d_8 (0.5 mL) in an NMR tube was added H_2O (0.005 mL, 0.28 mmol) and a trace of *p*-toluenesulfonic acid. The tube was sealed under high vacuum. After a period of 1 h at room temperature an ^1H NMR spectrum was taken which showed 20% isomerization to the isomer **39**, complete after 6 h. Hydrolysis of the ketal functionality required heating the NMR tube in boiling THF for 23 h. At that point the ^1H NMR spectrum revealed 96% of the diene **40** contaminated with a small amount (4%) of the ketal **39**. Preparative silica gel chromatography on a 250 micron plate (10 cm × 10 cm) eluting with ethyl ether/petroleum ether (1:9) yielded the Torgov diene **40** (0.0044 g, 85%) which was recrystallized from $MeOH/H_2O$: white crystals; mp 101–105 °C; R_f 0.34, benzene as eluent; R_f 0.65, chloroform as eluent; R_f 0.54, ethyl ether/hexane (1:1) as eluent (stains intensely with I_2); UV λ_{max} (MeOH) 282 nm; ^1H NMR (250 MHz, $CDCl_3$) δ 1.13 (s, 3 H, 18-Me), 1.61 (m, 1 H), 2.08 (dt, J = 11, 2.5, 1 H, H-12), 2.35 (m, 1 H), 2.64 (m, 3 H), 2.80 (t, J = 7.5, 2 H, H-6α,β), 2.94 (dd, J = 17.2, 1.6, 1 H, H-16), 3.34 (br d, J = 17, 1 H, H-16), 3.82 (s, 3 H, OMe), 5.88 (t, J = 1.6, 1 H, H-15), 6.95 (m, 2 H, H-2 and H-4), 7.23 (d, J = 8, 1 H, H-1); MS (30 eV), m/e 280 (38%), 252 (52), 237 (16), 223 (9), 175 (9), 165 (14), 149 (28), 112 (11), 95 (30), 57 (100).

10-[3-(4-Ethynylanisyl)]-9-oxa-1-decen-6-yn-3-one Ethylene Ketal (43). To a solution of propargyl alcohol **13** (0.096 g, 0.49 mmol) in THF (10 mL) and HMPA (1 mL) cooled to dry ice/acetone bath temperature was added *n*-butyllithium in hexane (0.38 mL, 0.539 mmol). The reaction mixture was allowed to warm to 0 °C and was then cooled back to dry ice/acetone bath temperature. To this solution was added via cannula the benzyl bromide **9** (0.110 g, 0.49 mmol) dissolved in THF (3 mL). The reaction mixture was allowed to warm to room temperature and then heated to 45–50 °C for 2 h. Aqueous workup furnished a crude colorless oil (0.120 g). Chromatography on a Chromatotron using a 2-mm silica gel plate eluting with ethyl ether/petroleum ether (1:9) yielded starting bromide (0.050 g, 45%) and **43** (0.060 g, 36%): colorless oil; R_f 0.34, ethyl ether/petroleum ether (3:7) as eluent; IR (thin film) 3283, 2947, 2103, 1608, 1569, 1494, 1048, 951 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.73 (br s, 3 H), 2.00 (dd, J = 7.7, 1.9, 2 H), 2.30 (m, 2 H), 3.22 (s, 1 H), 3.82 (s, 3 H), 3.85 (m, 4 H), 4.22 (t, J = 1.9, 2 H), 4.73 (s, 2 H), 4.91 (br d, J = 1.5, 1 H), 5.12 (br d, J = 1.2, 1 H), 6.77 (dd, J = 8.5, 2.6, 1 H), 7.02 (d, J = 2.6, 1 H), 7.41 (d, J = 8.5, 1 H); MS, m/e 340 (0.20%), 335 (0.48), 299 (3), 279 (3), 253 (3), 113 (100), 69 (53); HRMS calcd for $C_{21}H_{24}O_4$, 340.1674; found, 340.1667.

10-[3-(4-((Trimethylsilyl)ethynyl)anisyl)]-2-methyl-9-oxa-1-decen-6-yn-3-one Ethylene Ketal (44). To **43** (0.040 g, 0.118 mmol) dissolved in THF (5 mL) cooled to dry ice/acetone bath temperature was added *n*-butyllithium in hexane (0.085 mL, 0.134 mmol). The reaction mixture was allowed to warm to 0 °C, and trimethylsilyl chloride (0.018 g, 0.166 mmol) added. After 12 h at room temperature aqueous workup and separation using a Chromatotron on a 2-mm silica gel plate eluting with ethyl ether/petroleum ether (1:10) yielded starting material **43** (0.015 g, 37.5%) and product **44** (0.022 g, 45%): colorless oil; R_f 0.45, THF/hexane (1:9) as eluent; IR (thin film) 2961, 2153, 1608, 1569, 1494, 1252, 763 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.40 (s, 9 H), 1.71 (br s, 3 H), 1.98 (t, J = 7.8, 2 H), 2.25 (dd, J = 7.7, 2.0, 2 H), 3.80 (s, 3 H), 3.84 (m, 4 H), 4.20 (d, J = 1.8, 2 H), 4.70 (br s, 2 H), 4.89 (br s, 1 H), 5.10 (br s, 1 H), 6.73 (dd, J = 8.5, 2.6, 1 H), 7.00 (d, J = 2.5, 1 H), 7.35 (d, J = 8.5, 1 H); MS, m/e 412 (2%), 371 (11), 367 (294), 339 (4), 113 (84), 73 (100); HRMS calcd for $C_{24}H_{32}O_4Si$, 412.2070; found, 412.2062.

10-[3-(4-Ethynylanisyl)]-2-methyl-9-oxa-1-decen-6-yn-3-one (45). To ketal **43** (0.020 g, 0.059 mmol) in 10% aqueous THF was added 5% aqueous HCl (0.1 mL). After 2 h of heating at 50 °C the reaction mixture was poured into 5% $KHCO_3$ (10 mL) and ethyl ether/petroleum ether (1:2, 20 mL) for an aqueous workup. Separation of the resulting oil on a Chromatotron eluting with ethyl ether/petroleum ether (1:9) yielded the ketone **45** (0.011 g, 63%): colorless oil; R_f 0.33, THF/hexane (1:9) as eluent; R_f 0.29, ethyl ether/petroleum ether (3:7) as eluent; IR (thin film) 3283, 2926, 2104, 1679, 1609, 1570, 1494, 1165 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.87 (br s, 3 H), 2.55 (dd, J = 7.8, 2.2, 2 H), 2.95 (t, J = 7.7, 2 H), 3.22 (s, 1 H), 3.83 (s, 3 H), 4.21 (t, J = 2.1, 2 H), 4.72 (s, 2 H), 5.80 (dd, J = 0.9, 0.6, 1 H), 5.98 (s, 1 H), 6.77 (dd, J = 8.5, 2.5, 1 H), 7.02 (d, J = 2.6, 1 H), 7.41 (d, J = 8.5, 1 H); MS, m/e 296 (2%), 239 (15), 227 (37), 145 (61), 131 (31), 115 (51); HRMS calcd for $C_{19}H_{20}O_3$, 296.1412; found, 296.1399.

(8,9,11,14-η^4-B-(6a-Oxa)-homo-13-*exo*-3-methoxyestra-1,3,5,8(14),9(11)-pentaen-17-one ethylene ketal)(η^5-cyclopentadienyl)cobalt (46) and (8,9,11,14-η^4-B-(6a-Oxa)-homo-13-*endo*-3-methoxyestra-1,3,5,8(14),9(11)-pentaen-17-one ethylene ketal)(η^5-cyclopentadienyl)cobalt (47). To **43** (0.0041 g, 0.012 mmol) in degassed isooctane (7 mL) was added $CpCo(CO)_2$ (0.015 mL, 0.12 mmol). The reaction mixture was heated to reflux for 3.5 h until starting material had been consumed. The solvent was then removed by evaporation under a stream of N_2. The

resulting reddish-brown residue was dissolved in ethyl ether/petroleum ether (1:9, 2 mL) and chromatographed on alumina (activity 3, 5 g) using ethyl ether/petroleum ether (1:9) as eluent. Two distinct orange bands were observed. The faster moving, more intense band yielded a fraction containing the exo compound **46** (0.0023 g, 42%), while the slower band contained the endo complex **47** (0.0009 g, 16%).

Complex **46**: red crystals; mp 210–212 °C; R_f 0.47, ethyl ether/methanol/hexane (3:1:6) as eluent; IR (thin film) 2967, 1609, 1574, 1502, 1244, 1063, 808 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 1.06 (s, 3 H), 1.08 (dd, J = 15.0, 3.1, 1 H), 1.40 (m, 1 H), 1.83 (ddd, J = 15.6, 10.8, 6.3, 1 H), 2.10 (m, 2 H), 2.53 (dd, J = 15.0, 3.4, 1 H), 3.40 (s, 3 H), 3.44 (m, 3 H), 3.69 (t, J = 6.1, 2 H), 4.51 (s, 5 H), 4.57 (d, J = 11.7, 1 H), 4.80 (d, J = 11.7, 1 H), 4.98 (d, J = 11.9, 1 H), 5.02 (d, J = 11.6, 1 H), 6.84 (d, J = 2.7, 1 H), 6.89 (dd, J = 8.4, 2.7, 1 H), 7.15 (d, J = 8.4, 1 H); MS (30 eV), m/e 464 (100%), 339 (11), 322 (23), 294 (88), 225 (13), 124 (73); HRMS calcd for $C_{26}H_{29}O_4Co$, 464.1400; found, 464.1392.

Complex **47**: orange oil; R_f 0.37, ethyl ether/methanol/hexane (3:1:6) as eluent; IR (thin film) 2966, 1609, 1570, 1502, 1261, 1046, 813 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 0.56 (dd, J = 12.5, 1, 1 H), 0.95 (dd, J = 12.5, 5.3, 1 H), 1.39 (m, 2 H), 1.64 (s, 3 H), 1.89 (ddd, J = 12.2, 4.9, 4.9, 1 H), 2.16 (m, 2 H), 3.39 (m, 4 H), 3.40 (s, 3 H), 4.41 (d, J = 13.8, 1 H), 4.44 (s, 5 H), 4.45 (d, J = 13.5, 1 H), 4.80 (d, J = 11.6, 1 H), 5.16 (d, J = 11.6, 1 H), 6.84 (d, J = 2.9, 1 H), 6.92 (dd, J = 8.6, 2.6, 1 H), 7.27 (d, J = 8.6, 1 H); MS (30 eV), m/e 464 (100%), 339 (12), 322 (25), 294 (96), 223 (22), 124 (71); HRMS calcd for $C_{26}H_{29}O_4Co$, 464.1400; found, 464.1392.

(8,9,11,14-η^4-B-(6a-Oxa)-homo-11-(trimethylsilyl)-13-*exo*-3-methoxyestra-1,3,5,8(14),9(11)-pentaen-17-one ethylene ketal)(η^5-cyclopentadienyl)cobalt (48). To **44** (0.008 g, 0.0194 mmol) in degassed isooctane (5 mL) was added $CpCo(CO)_2$ (0.020 mL, 0.16 mmol). The reaction mixture was then heated for 21 h until starting material had disappeared. After evaporation of the solvent the resulting brown-red residue was dissolved in ethyl ether/petroleum ether (1:9). Chromatography with this solvent system on alumina (activity 2.5) provided a single red-orange fraction leaving a red-orange powder (0.063 g, 61%) which was recrystallized from MeOH/H_2O: red crystals; mp 172–175 °C; R_f 0.32, THF/hexane (1:9) as eluent; IR (thin film) 2961, 1609, 1573, 1497, 1312, 1249, 809, 682 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 0.28 (s, 9 H), 0.83 (s, 3 H), 0.84 (d, J = 14.6, 1 H), 1.43 (m, 2 H), 2.11 (m, 2 H), 2.57 (d, J = 14.6, 1 H), 3.38 (s, 3 H), 3.49 (t, J = 6.4, 2 H), 3.73 (t, J = 6.4, 2 H), 4.29 (d, J = 12.8, 1 H), 4.38 (d, J = 12.8, 1 H), 4.82 (d, J = 11.5, 1 H), 4.84 (s, 5 H), 6.08 (d, J = 11.5, 1 H), 6.85 (dd, J = 8.5, 2.7, 1 H), 6.97 (d, J = 2.7, 1 H), 7.53 (d, J = 8.5, 1 H); MS (30 eV), m/e 536 (48%), 463 (17), 325 (35), 339 (14), 325 (35), 124 (42), 73 (100); HRMS calcd for $C_{29}H_{37}O_4SiCo$, 536.1818; found, 536.1805.

(8,9,11,14-η^4-B-(6a-Oxa)-homo-13-*endo*-3-methoxyestra-1,3,5,8(14),9(11)-pentaen-17-one)(η^5-cyclopentadienyl)cobalt (49). To **45** (0.007 g, 0.024 mmol) in degassed isooctane (5 mL) was added $CpCo(CO)_2$ (0.014 mL, 0.112 mmol). The reaction mixture was heated to reflux for 24 h until all starting material had been consumed. Column chromatography on alumina (activity 3, 5 g) eluting with ethyl ether/petroleum ether (1:9) yielded an orange fraction. ^1H NMR spectroscopy of the crude material (0.0034 g, 34%) showed it to be a mixture of endo and exo isomers in a ratio of 2.5:1 (Cp endo at δ 4.36, Cp exo at δ 4.21; Me endo δ 1.33, Me exo δ 0.76). Crystallization of the major isomer from petroleum ether at −70 °C gave compound **49**: yellow crystals; mp 139–142 °C; R_f 0.10, THF/hexane (1:9) as eluent; IR (thin film) 2960, 1733, 1610, 1572, 1503, 1248, 1047 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 0.69 (dd, J = 13.5, 1.2, 1 H), 1.03 (dd, J = 13.6, 5.5, 1 H), 1.33 (s, 3 H), 1.88 (m, 2 H), 2.21 (m, 2 H), 3.20 (dd, J = 5.6, 1.4, 1 H), 3.38 (s, 3 H), 4.31 (d, J = 12.6, 1 H), 4.36 (s, 5 H), 5.43 (d, J = 12.6, 1 H), 4.62 (s, 2 H), 6.72 (d, J = 2.6, 1 H), 6.86 (dd, J = 8.5, 2.5, 1 H), 7.13 (d, J = 8.6, 1 H); MS (30 eV), m/e 420 (13%), 392 (3), 364 (3), 339 (4), 296 (5), 69 (15), 44 (100); HRMS calcd for $C_{24}H_{25}O_3Co$, 420.1128; found, 420.1118.

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Photochemistry of Alkyl Halides. 11. Competing Reaction via Carbene and Carbocationic Intermediates[1]

Paul J. Kropp,* Joy A. Sawyer, and John J. Snyder

Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina 27514

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Isotopic analysis of the unsaturated products **6** and **15** resulting from irradiation of the labeled iodides **1-*1,1-d*$_2$**, **1-*2,2-d*$_2$**, and **13-*1-d*** has revealed that they are formed substantially, but not exclusively, via α elimination. The unsaturated products thus arise via competing pathways involving carbene intermediates as well as the previously recognized radical and carbocationic intermediates. Irradiation of iodide **22** in methanol-*d* afforded ether **23** with partial incorporation of deuterium, but the accompanying ether **24** was formed with no detectable incorporation. Thus, ether **23** is formed via competing pathways involving the carbene **28** and the carbocation **25**, whereas ether **24** is formed exclusively via the carbocationic pathway. A mechanism involving formation of the carbene intermediates via either α-hydrogen atom or α-proton transfer within the previously proposed intervening radical and ion pairs is suggested. One iodide studied, **17-2-*d***, exhibited no detectable α elimination.

Previous studies in these laboratories have shown that irradiation of alkyl iodides in solution is a powerful and convenient method for the generation of carbocations, via a process thought to involve light-induced homolytic cleavage of the carbon–iodine bond followed by electron transfer within the initially formed caged radical pair (Scheme I).[2,3] In bridgehead systems structurally incapable of readily undergoing elimination, the resulting carbocationic intermediate undergoes efficient nucleophilic trapping. However, iodides more capable of undergoing

(1) Part 10: Kropp, P. J.; McNeely, S. A.; Davis, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 6907.

(2) Kropp, P. J.; Poindexter, G. S; Pienta, N. J.; Hamilton, D. C. *J. Am. Chem. Soc.* **1976**, *98*, 8135–8144. Kropp, P. J.; Davidson, R. I.; Worsham, P. R. *J. Am. Chem. Soc.* **1982**, *104*, 3972–3980.

(3) The solution-phase photobehavior of alkyl halides was previously explained only in terms of radical intermediates. See: Sammes, P. G. In "Chemistry of the Carbon–Halogen Bond"; Patai, S., Ed.; Wiley: New York, 1973; Chapter 11.

0022-3263/84/1949-1583$01.50/0