mp 223–224 °C (lit.[2] mp 223–224 °C) (6% methanol–ethyl acetate), showed that **2a**, **3a**, and **4a** (one spot, R_f 0.42) were present, accompanied by minor quantities of the two more polar products **7a** and **8a** (one spot, R_f 0.22). Preparative TLC (on silica) separated (^{1}H NMR and mass spectral evidence) **2a**, **3a**, and **4a** from small amounts of **7a** and **8a**. **2a**, **3a**, and **4a** were then separated on silica–$AgNO_3$. The mixture of **7a** and **8a** could not be separated by preparative TLC. After acetylation the acetates **7b** and **8b** could be separated. Saponification of **7b** and **8b** regenerated **7a** and **8a** which were inseparable on TLC. When O_3-oxidation product was acetylated and crystallized from 95% ethanol, **7b** and **8b** remained in solution.

Composition of the Fieser "O_5-Oxidation Product". The O_5 product was isolated by following the described procedures.[2] TLC analysis (on silica) and development with 6% methanol–ethyl acetate showed the presence of **7a** and **8a** (one spot, R_f 0.22) and of small amounts of **2a**, **3a**, and **4a** (one spot, R_f 0.42). Preparative TLC on silica–$AgNO_3$ separated **2a**, **3a**, and **4a**, which were identical with those described above. **7a** and **8a** were separated as triacetates and were identical with those described above.

Acknowledgment. This research was supported by the Italian Research Council. We thank Professor G. Galli, Institute of Pharmacology and Pharmacognosy, University of Milan, for the mass spectra.

Registry No. 1, 57-87-4; **2a**, 71097-06-8; **2b**, 35691-23-7; **2b** maleic anhydride adduct, 71097-16-0; **3a**, 60497-23-6; **3b**, 33824-22-5; **4a**, 71097-07-9; **4b**, 71097-08-0; **5a**, 71097-09-1; **5b**, 71097-10-4; **6a**, 71097-11-5; **6b**, 71106-22-4; **7a**, 71097-12-6; **7b**, 71097-13-7; **8a**, 71097-14-8; **8b**, 71097-15-9; potassium permanganate, 7722-64-7; mercuric acetate, 1600-27-7; maleic anhydride, 108-31-6.

Short, Simple, Stereocontrolled, Steroid Synthesis: (±)-11-Oxoequilenin Methyl Ether and a New 9,11-Seco-13-ethyl Steroid

Gary H. Posner,* Marc J. Chapdelaine, and Carl M. Lentz

The Johns Hopkins University, Baltimore, Maryland 21218

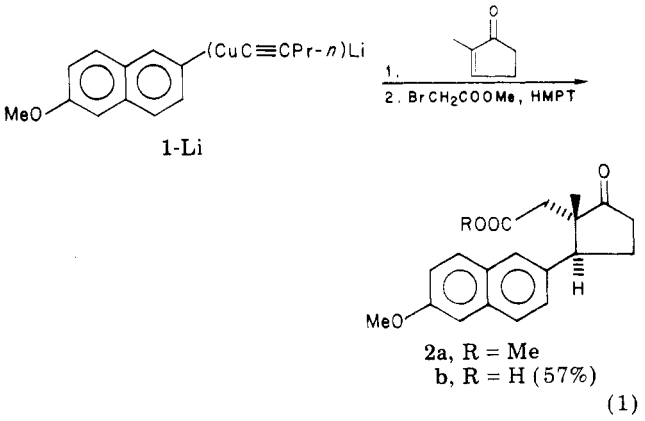
Received March 2, 1979

An improved procedure has been developed for efficient preparation of 9,11-seco steroid **2b** from 2-methyl-2-cyclopentenone in 85% yield and >99% stereochemical purity over three steps without chromatography. This high yield, almost double that previously reported by us, is achieved by using a magnesium instead of a lithium cuprate and ethyl iodoacetate instead of methyl bromoacetate. This procedure has been extended to stereocontrolled preparation of a new 9,11-seco-13-*ethyl* steroid (**5**) of potential contraceptive value directly from 2-ethyl-2-cyclopentenone. ^{1}H and ^{13}C NMR data confirm that the incipient C,D-ring stereochemistry of seco steroids **2** and **5** is that of the natural steroids (i.e., trans). A high-yield HF-promoted Friedel–Crafts intramolecular acylation completes an efficient (>50% overall yield) and stereocontrolled total synthesis of (±)-11-oxoequilenin methyl ether.

Two of the most challenging problems in devising new syntheses of steroids are control of stereochemistry[1] and efficiency in construction of the tetracyclic carbon skeleton. We have recently reported a new, convergent, steroid total synthesis based on organocopper β-addition and subsequent α-alkylation of a cyclopentenone in which control of relative stereochemistry is virtually complete and in which a usefully functionalized steroid is produced expeditiously in 31% yield over four steps from readily available starting materials.[2] We now report an improved procedure for stereocontrolled preparation of (±)-11-oxoequilenin methyl ether in >50% yield over four steps without chromatography. This improved procedure further permits stereocontrolled preparation of a new 9,11-seco-13-*ethyl* steroid of potential contraceptive value directly in a "one-pot" reaction from 2-ethyl-2-cyclopentenone.

Results and Discussion

The mixed aryl(alkynyl)copperlithium reagent 1-Li, prepared from the aryllithium and the alkynylcopper species, was allowed to react with 1 equiv of 2-methyl-2-cyclopentenone and then with methyl bromoacetate in hexamethylphosphoric triamide (HMPT) to give tricyclic keto ester **2a** which was isolated and, without purification, was saponified to form keto acid **2b**. One recrystallization gave pure 9,11-seco steroid **2b** in 57% yield (eq 1).[2]



2a, R = Me
b, R = H (57%)

(1)

Various attempts were made to improve the yield of this type of organocopper conjugate addition–α-alkylation process.[3] Variation of the Y group in aryl(Y)CuLi species[4] included Y = aryl, SPh,[5] and CN.[6] Despite the fact that

(1) (a) See, for example: Lansbury, P. T. *Acc. Chem. Res.* **1972**, *5*, 311. (b) For some very recent testimony to the difficulty in controlling especially the C,D-ring stereochemistry, see: Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 8341, ref 12. Johnson, W. S.; Huges, L. R.; Kloek, J. A.; Niem, T.; Ashok, S. *Ibid.*, **1979**, *101*, 1279.

(2) Posner, G. H.; Lentz, C. M. *Tetrahedron Lett.* **1978**, 3769.

(3) (a) Chapdelaine, M. J. Ph. D. Thesis, The Johns Hopkins University, 1979. (b) Cf.: Posner, G. H.; Lentz, C. M. *J. Am. Chem. Soc.* **1979**, *101*, 934 and references therein.

(4) For reviews, see: (a) Posner, G. H. *Org. React.*, **1972**, *19*, 1; **1975**, *22*, 253. (b) Normant, J. F. *J. Organomet. Chem. Libr.* **1976**, *1*, 219. (c) Normant, J. F. *Pure Appl. Chem.* **1978**, *50*, 709.

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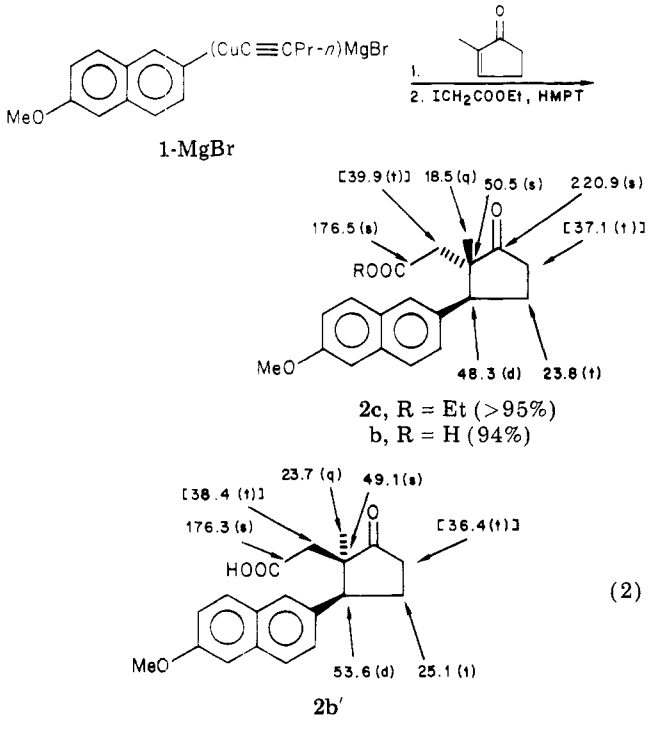
each of these species has been used successfully in other applications, none of them was better than aryl(*n*-pentynyl)copperlithium for the transformation of the type shown in eq 1. Likewise, although ketone enolate alkylation with sodium iodoacetate has been reported to be more effective than with iodoacetate *esters*,[7] sodium iodoacetate as electrophile in eq 1 failed completely. We therefore examined use of some *magnesio*cuprates.

Due to the work primarily of Normant[4b] and of Rivière,[6] organocopper*magnesium* reagents have been developed as very useful stoichiometric and catalytic organocopper reagents. *Magnesio*cuprates have different stabilities and reactivities from those of *lithio*cuprates and have been used successfully in various syntheses of complex organic compounds.[8] The mixed aryl(alkynyl)coppermagnesium reagent 1-MgBr, prepared from the readily available arylmagnesium bromide and alkynylcopper species, was permitted to react with 1 equiv of 2-methyl-2-cyclopentenone and then with ethyl iodoacetate in HMPT to give tricyclic keto ester **2c** in virtually quantitative yield (eq 2). Saponification of crude keto ester **2c** gave crude



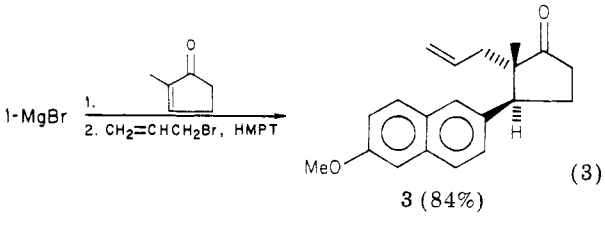
(2)

keto acid **2b** (94% yield) which was pure by high-pressure LC and which had IR and ^{1}H NMR spectroscopic properties *identical* with those of recrystallized keto acid **2b**. Furthermore, the ^{13}C NMR spectrum of *crude* keto acid **2b** showed no extraneous peaks, and it was clearly different from that of epiketo acid **2b′** (^{13}C absorptions below in ppm).

The ^{1}H NMR spectra of 9,11-seco steroids **2b** and **2b′** also clearly confirmed the stereochemical purity of *crude* 9,11-seco steroid **2b**. Having an authentic sample of pure epi-9,11-seco steroid **2b′**,[9] we were able to detect as little as 1% of **2b′** and therefore to ascertain that our *crude seco steroid* **2b** *was at least 99% stereochemically pure*!

In sharp contrast, Vollhardt has found much lower stereocontrol with a small vinyl group in place of the large naphthyl group in a reaction similar to eq 1 and 2.[10] Oppolzer has recently reported highly stereocontrolled preparation of 3-vinyl-2-(alkoxycarbonylmethyl)cyclopentanones and related species for steroid total synthesis.[11]

In a short communication in 1969, Horeau reported the preparation of γ,δ- olefinic ketone **3** via an elegant Claisen rearrangement of the corresponding allyl cyclopentenol ether.[12] The allyl group of allylcyclopentanone **3** was then oxidatively cleaved by potassium permanganate to form keto acid **2b**. For comparison, we have prepared allylcyclopentanone **3** in a completely stereocontrolled and efficient reaction as shown in eq 3. In our hands, potassium permanganate oxidation of allylcyclopentanone **3**, even using the new crown polyether modification,[13] resulted in very low yields of keto acid **2b**. Brain and co-workers[9a] also obtained very low (≈25%) yields in permanganate oxidative cleavage of allylcyclopentanone **3**. Repeating the Horeau–Claisen rearrangment, Brain and co-workers[9a] also obtained a small amount of the product epimeric with **3**, having the naphthyl and allyl groups cis.



(3)

Because of their significance, we mention the following variations of the reaction shown in eq 2. Use of *methyl* iodoacetate instead of *ethyl* iodoacetate in eq 2 gave poorer results possibly because iodide salts produced during the course of the enolate alkylation attacked the methyl ester and converted it into a carboxylate salt.[14] Ethyl *bromo*acetate instead of ethyl *iodo*acetate in eq 2 failed to produce any of 9,11-seco steroid **2c**; apparently the intermediate magnesio enolate formed in eq 2 is less reactive than the corresponding lithio enolate formed in eq 1. Replacing *n*-pentynylcopper by the less easily prepared and less easily stored 3,3-dimethylbutynylcopper[15,16] gave no change in the yield of 9,11-seco steroid **2c**. Inverse addition of the in situ-generated enolate to the electrophile in HMPT gave a moderate increase in yield, as has been noted previously by Semmelhack.[17] Use of 10% *n*-

(5) (a) Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788. (b) Posner, G. H.; Brunelle, D. J.; Sinoway, L. *Synthesis* **1974**, 662. (c) For a recent example, see: Piers, E.; Morton, H. E. *J. Chem. Soc., Chem. Commun.* **1978**, 1033.

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(10) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1977**, *99*, 5483; **1979**, *101*, 215. Personal communication from Professor Vollhardt.

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(12) Horeau, A.; Lorthioy, E.; Guetté, J. P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1969**, *269*, 558.

(13) Sam, D. J.; Simmons, H. E. *J. Am. Chem. Soc.* **1972**, *94*, 4024.

(14) Cf.: House, H. O.; Muller, H. C.; Pitt, C. G.; Wickham, P. P. *J. Org. Chem.* **1963**, *28*, 2407.

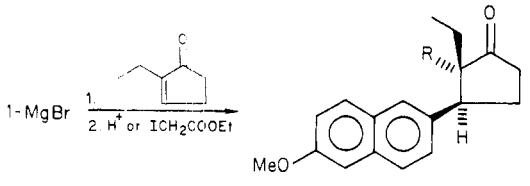
(15) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

(16) For recent examples using alkynyl cuprates, see: (a) Chen, S. M.; Schaub, R. E.; Grudzinskas, L. V. *J. Org. Chem.* **1978**, *43*, 3450. (b) Corey, E. J.; Floyd, D.; Lipschutz, B. H. *Ibid.* **1978**, *43*, 3418. (c) Trost, B. M.; Timko, J. M.; Stanton, J. L. *J. Chem. Soc., Chem. Commun.* **1978**, 436. (d) Newton, R. F., et al. *Ibid.* **1978**, 662. (e) Hart, T. W.; Metcalfe, D. A.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1979**, 156. (f) Ledlie, D. B.; Miller, G. *J. Org. Chem.* **1979**, *44*, 1006.

(17) Semmelhack, M. F.; Yamashita, A.; Tomesch, J. C.; Hirotsu, K. *J. Am. Chem. Soc.* **1978**, *100*, 5565. We thank Professor Semmelhack for sharing this inverse quench procedure with us before publication.

pentynylcopper as a *catalyst* for 6-methoxy-2-naphthylmagnesium bromide addition to 2-methyl-2-cyclopentenone[4b] gave a low-yield conjugate addition. Naphthyl(*n*-pentynyl)copperlithium adds to 2-methyl-2-cyclopentenone equally well in diethyl ether as in THF. Finally, the homocuprate dinaphthylcoppermagnesium bromide species, prepared from 2 equiv of 6-methoxy-2-naphthylmagnesium bromide and 1 equiv of copper(I) bromide–dimethyl sulfide complex,[19] gave no conjugate adducts whatsoever.

Replacement of the natural 13-*methyl* group by a 13-*ethyl* group in some contraceptive steroids has been found to increase the steroid's effectiveness as an antifertility drug (i.e., separation of antifertility and estrogenic activity), and at least one 13-ethyl steroid (norgestrel) is currently used in a commercial oral contraceptive.[20] Because some 9,11-seco-13-*methyl* steroids also have been shown to possess antifertility as well as estrogenic properties,[21] it was of interest to prepare a 9,11-seco-13-*ethyl* steroid, a class of compounds which has not previously been prepared. Toward this end, we synthesized 2-ethyl-2-cyclopentenone[22] and treated it with naphthyl(alkynyl)-coppermagnesium species 1-MgBr. Quenching the reaction mixture with aqueous ammonium chloride gave 3-naphthyl-2-ethylcyclopentanone **4** in 53% yield. Variation



4, R = H (53%)
5, R = CH_2COOEt (31%)

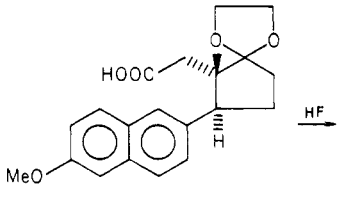
(4)

of time, temperature, or reagent concentration gave no increase in yield. Clearly, conjugate addition of a naphthyl group to a 2-cyclopentenone bearing a 2-*ethyl* group is much more difficult than to a 2-*methyl*-2-cyclopentenone, even though the reduction potentials[23] of 2-methyl- and 2-ethyl-2-cyclopentenone should be virtually the same. The naphthyl(alkynyl)copper*lithium* species **1**-Li failed to react at all with 2-ethyl-2-cyclopentenone. Quenching the intermediate enolate with ethyl iodoacetate gave the previously unknown 9,11-seco-13-ethyl steroid **5**, which was isolated in 31% yield by preparative TLC (eq 4).

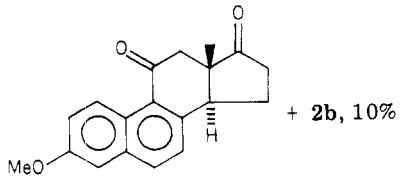
The stereochemical purity of 13-ethyl pro-C,D-ring trans steroid **5** was established by ^1H and ^{13}C NMR spectroscopy (see Experimental Section). The angular 13-ethyl group is substantially and characteristically shielded by its cis relationship to the naphthyl group: δ 0.6 (t, 3 H, J = 6.0 Hz) for the 13-CH_2CH_3 protons and δ 14.32 (13-CH_2CH_3) and 7.66 (13-CH_2CH_3) for the carbon atoms of the angular ethyl group. It is noteworthy that the CH_3 carbon atom of the angular 13-*ethyl* group in **5** absorbs at 14.32 ppm, whereas the CH_3 carbon atom of the angular 13-*methyl* group in **2b** absorbs at 18.15 ppm. The CH_3 of the 13-*ethyl* group in **5** is therefore heavily shielded by the aromatic naphthyl group *even though the ethyl group might have been expected to adopt a conformation in which its CH_3 group was distant from and therefore less shielded by the naphthyl group.* Biological testing of 13-ethyl seco steroid **5** is currently underway.

Although Friedel–Crafts cyclization of AB-aromatic 9,11-seco steroids has been used frequently in the past, there are serious problems with this intramolecular aromatic acylation. The most serious problem is the *low yields (≤35%) obtained in all previous attempts at forming trans-1-hydrindanones from trans-3-aryl-2-(carboxymethyl)cyclopentanones.*[24-26] Indeed, in 1970 Birch summarized his many efforts at steroid total synthesis by emphasizing that this disappointing Friedel–Crafts cyclization step was the most serious drawback to large-scale preparation of steroids via 9,11-seco steroids.[26]

We have found that HF-promoted cyclization of *keto* acid **2b** to form tetracyclic steroid **6** is indeed an unsatisfactory process (only 10% yield of **6**). However, HF-promoted cyclization of *ketal* acid **2d** produced chemically



2d



+ **2b**, 10%

6, 65%

(5)

and stereochemically pure (±)-11-oxoequilenin methyl ether in 65% yield (75% based on recovered seco steroid) after one recrystallization. ^1H NMR analysis showed a 13-methyl group absorption at δ 0.8 (singlet) for C,D-*trans* steroid **6** and no absorption whatsoever at δ 1.2 characteristic of C,D-*cis*-11-oxoisoequilenin methyl ether.[9a] The reasons for the ease of cyclization of *ketal* acid **2d** but the difficulty of cyclization of *keto* acid **2b** are obscure at this time.

The total yield of recrystallized equilenin **6** over four steps, without chromatography and based on readily available 2-methyl-2-cyclopentenone *or* on 6-methoxy-2-bromonaphthalene, was 52%. The stereochemical purity of equilenin **6** produced in this way was at least 99%. *This is one of the shortest, most efficient, and most highly stereocontrolled steroid syntheses ever reported!*

Experimental Section

High-pressure liquid chromatography was performed on a Waters Associates high-pressure liquid chromatograph, Model 6000 A, with a R401 differential refractometer. The column used was Corasil C-18, particle size 37–150 μm. Column conditions were 70:30 acetonitrile to water as the solvent and a flow rate of 0.8 mL/min. Infrared (IR) spectra were recorded on Perkin-Elmer 457A and 337 instruments using solvent-compensated solutions of chloroform (unless otherwise noted). Bands are expressed in reciprocal centimeters (cm^{-1}) by using polystyrene calibration and

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(19) House, H. O.; Chu, C.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.
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(26) Birch, A. J.; Subba Rao, G. S. R. *Aust. J. Chem.* **1970**, *23*, 547; *Tetrahedron Lett.* **1967**, 2763.

are designated as strong (s), medium (m), weak (w), shoulder (sh), or broad (b). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded by using a Varian A-60, Varian T-60, or JEOL MH-100 instrument; carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were obtained on a Varian CFT-20 instrument. Spectra were taken as chloroform-*d* solutions (unless otherwise noted) with tetramethylsilane as internal standard. Peak positions are located as downfield shifts in parts per million (δ) from Me_4Si. Resonances are characterized as multiplet (m), quartet (q), triplet (t), doublet (d), singlet (s), or broad (b). Mass spectra (MS) were measured on a Hitachi RMU-6 instrument at a 70- or 15-eV beam intensity. The liquid or solid sampler was heated just to a temperature sufficient to volatilize the sample. Elemental analyses were performed by Chemalytics, Inc. (Tempe, AZ), or by MicroTech Laboratories, Inc. (Skokie, IL).

Melting points (mp) were determined with a Mel-Temp apparatus and are uncorrected. All materials were the best commercially available reagent grades or were prepared from such. Purity was tested before use (mp, VPC, or NMR). Halogenated solvents were used as received (Baker Reagent Grade). All other solvents were reagent grade and were dried before use by distillation from calcium hydride, sodium benzophenone ketyl, sodium, magnesium, or potassium hydroxide as appropriate and on to molecular sieves under an atmosphere of nitrogen. The apparatus described by Johnson and Schneider[34] was used to maintain a nitrogen or argon atmosphere in the reaction flask. Solutions were dried with anhydrous sodium sulfate unless otherwise noted.

Alkyllithium reagents were purchased from Aldrich or Ventron as 1.0–2.0 M solutions. The concentration of organolithium reagents was determined by the standard double-titration procedure[27] or by titration of a diphenylacetic acid solution.[28]

Grignard reagents were generated by using magnesium metal that was freshly pulverized and washed in boiling tetrahydrofuran three times under a nitrogen atmosphere. The concentrations of Grignard reagents were determined by titration with benzyl alcohol in toluene using 1,10-phenanthroline or 2,2′-biquinoline as indicator.[29]

Cuprous iodide and cuprous bromide were continuously extracted with THF in a Soxhlet extractor for 1 week and dried under reduced pressure at 30 °C for 12 h. The copper(I) salts thus purified were stored under argon for periods up to 6 months and used in aliquots to generate organocuprates. *n*-Pentynylcopper was prepared by using the procedure of Stephens and Castro.[30] All organocuprate reactions were done under an inert atmosphere with all due precautions to exclude moisture and oxygen. 6-Hydroxy-2-bromonaphthalene was purchased from the Aldrich Chemical Co.

Preparation of (6-Methoxy-2-naphthyl)(1-pentynyl)-copperlithium (1-Li). The required 6-methoxy-2-naphthyllithium, prepared as described by Newman from 6-methoxy-2-naphthyl bromide (mp 106–107 °C),[25] was added via syringe to a cold (−5 to 0 °C) slurry of *n*-pentynylcopper (314 mg, 2.46 mmol) in 10 mL of dry diethyl ether under an inert atmosphere and the mixture stirred for 30 min at −5 to 0 °C.

Preparation of Methyl *trans*-2-(6-Methoxy-2-naphthyl)-1-methyl-5-oxocyclopentane-*r*-1-acetate (2a). To 1.5 mmol of (6-methoxy-2-naphthyl)(1-pentynyl)copperlithium, prepared as described above, at 0 °C in diethyl ether was added via syringe in 20 mL of diethyl ether 140.0 mg (1.50 mmol) of 2-methyl-2-cyclopentenone[31] with stirring at 0 °C for 4 h. After this time the resulting dark green mixture was added via syringe to a 0 °C solution of 5.0 mL of HMPT and 10.0 mmol (0.89 mL) of methyl bromoacetate. The addition was accompanied by the immediate formation of a bright yellow solid. The mixture was allowed to warm to ambient temperature and stirred for 18 h. The crude mixture was poured into 50 mL of aqueous saturated ammonium chloride and diluted with diethyl ether. The crude product was purified by preparative TLC (silica gel, $CHCl_3$, two developments, R_f 0.35) to afford 218 mg (49%) of the β-addition–α-alkylation product **2a**, having spectral data matching those in the literature.[9a]

Preparation of *trans*-2-(6Methoxy-2-naphthyl)-1-methyl-5-oxocyclopentane-*r*-1-acetic Acid (2b). To methyl *trans*-2-(6-methoxy-2-naphthyl)-1-methyl-5-oxocyclopentane-*r*-1-acetate (120 mg, 0.36 mmol) in 5.0 mL of absolute methanol was added 674 mg (12.0 mmol) of potassium hydroxide with stirring for 12 h at reflux. The product was isolated by the addition of 10 mL of diethyl ether, the two-phase system was cooled to 0 °C, and concentrated HCl was added dropwise until the aqueous phase was acidic as indicated by pH paper. The solvent was removed in vacuo and the resulting solid recrystallized from benzene/cyclohexane to afford 104 mg (92%) of the keto acid **2b**: mp 153–154 °C (lit.[9a] mp 153.4–154.5 °C); ^{1}H NMR ($CDCl_3$) δ 9.8 (m, 1 H, COO**H**); 7.65 (t, 2 H), 7.38–7.05 (m, 4 H), 3.90 (s, 3 H, OCH_3), 0.68 (s, 3 H, C_{13}–CH_3); IR (KBr) 1755 (s), 1730 cm^{-1} (s). Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C 73.22; H, 6.58.

Preparation of 6-Methoxy-2-naphthylmagnesium Bromide.[32] To a dry, argon-purged, three-necked round-bottom flask was added 0.48 g (20 mmol) of magnesium turnings in 1 mL of dry THF. Via addition funnel was slowly added 2.37 g (10 mmol) of 6-methoxy-2-naphthyl bromide in 9 mL of THF. At the end of the addition the mixture was refluxed for 1 h. When stored at −5 °C under argon, the Grignard reagent concentration (usually 0.7–0.8 M) remained constant for periods up to 6 weeks.

Generation of (6-Methoxy-2-naphthyl)(1-pentynyl)coppermagnesium Bromide (1-MgBr). In a dry, argon-purged, round-bottom flask with a gas inlet and serum stopper was placed 0.065 g (0.5 mmol) of *n*-pentynylcopper. To this was added 0.61 mL (0.5 mmol, 0.82 M in THF) of 6-methoxy-2-naphthylmagnesium bromide via syringe. The mixture was stirred rapidly for 1 h at room temperature during which time the solution became dark green and homogeneous.

Preparation of 9,11-Seco Steroid 2c. To the (6-methoxy-2-naphthyl)(1-pentynyl)coppermaganesium bromide (0.5 mmol) generated in the fashion described above was added 0.05 mL (0.5 mmol) of 2-methyl-2-cyclopentenone. During the course of stirring for 3 h the solution turned black but remained homogeneous. In a separate, dry, argon-purged, two-necked round-bottom flask fitted with a gas inlet and serum stopper was added 10 mL of dry hexamethylphosphoramide and 0.66 mL (5.0 mmol) of ethyl iodoacetate. The enolate solution was diluted with 2.5 mL of dry THF and transferred via syringe to the room temperature HMPT solution, and stirring was continued for 16 h. The dark green-black solution became faint yellow over this period. The reaction mixture was then diluted with 10 mL of diethyl ether and saturated, aqueous ammonium chloride, and the phases were separated. High-pressure LC analysis indicated no unalkylated material: IR ($CHCl_3$) 3040 (w), 2945 (s), 1745 (s), 1730 (s), 1640 (s), 1600 (s), 1400 (s), 1380 (m), 1260 (s) 1150 (s), 1010 (m), 880 (m), 850 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 7.4(b, 6 H), 4.18 (q, 2 H, J = 7 Hz, OCH_2CH_3), 3.85 (s, 3 H, OCH_3), 2.45 (b, 7 H), 1.32 (t, 3 H, J = 7 Hz, OCH_2CH_3), 0.62 (s, 3 H, C_{13}–CH_3); MS (70 eV) m/e (rel intensity) 340 (M^+, 5), 295 (M^+ − 45, 3), 45 (base).

Preparation of Keto Acid 2b via Saponification of Keto Ester 2c. Crude ethyl *trans*-2-(6-methoxy-2-naphthyl)-1-methyl-5-oxocyclopentane-*r*-1-acetate (**2c**), prepared as described above, was dissolved in 10 mL of methanol. To this solution was added 2.8 g (5.0 mmol) of potassium hydroxide, and the mixture was refluxed for 12 h. After the mixture was cooled, 20 mL of water and of diethyl ether were added, the phases were separated, and the ether phase was extracted three more times with an equal volume of water. The combined aqueous extracts were added to 30 mL of diethyl ether and chilled to 0 °C. To the cooled heterogeneous mixture was slowly added concentrated hydrochloric acid until pH 2 was reached (the organic phase became cloudy during this procedure). The phases were separated, and the aqueous phase was extracted twice with diethyl ether. After

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the removal of the solvent there was obtained 0.148 g (95%) of *trans*-2-(6-methoxy-2-naphthyl)-1-methyl-5-oxocyclopentane-*r*-1-acetic acid (**2b**), having the same physical and spectral properties as those of an authentic sample of keto acid **2b**.

Preparation of 2-Allylcyclopentanone 3. The addition of 0.5 mmol of (6-methoxy-2-naphthyl)(1-pentynyl)coppermagnesium bromide to 0.5 mmol of 2-methyl-2-cyclopentenone was carried out as described above. High-pressure LC analysis indicated that 90% of *trans*-2-allyl-*r*-3-(6-methoxy-2-naphthyl)-2-methylcyclopentanone (**3**) was present. Preparative thin-layer chromatography using chloroform resulted in isolation of **3** in 84% yield: IR ($CHCl_3$) 3030 (w), 2920 (m), 1740 (s), 1660 (m), 1610 (s), 1470 (m), 1450 (m), 1270 (s), 850 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 7.5 (b, 6 H), 5.75 (m, 1 H, =C**H**—), 5.2 (m, 2 H, =C**H**$_2$), 3.9 (s, 3 H, OC**H**$_3$), 3.6 (m, 2 H, =CHC**H**$_2$), 2.4 (b, 5 H), 0.7 (s, 3 H, C_{13}–C**H**$_3$); MS (70 eV) *m/e* (rel intensity) 279 (M − 15, 35), 41 (base). These data match those in the literature.[9a,12]

Preparation of 3-Naphthyl-2-ethylcyclopentanone 4. As described above, 0.024 mL (0.2 mmol) of 2-ethyl-2-cyclopentenone[22] was added to (6-methoxy-2-naphthyl)(1-pentynyl)coppermagnesium bromide and the reaction allowed to proceed for 3 h at 25 °C. After workup as usual, high-pressure LC analysis indicated that 2-(6-methoxy-2-naphthyl)-1-ethyl-5-oxocyclopentane (**4**) had been formed in 53% yield. Preparative thin-layer chromatography using chloroform led to the isolation of two major fractions: 2-methoxynaphthalene and compound **4** (52% yield): IR ($CHCl_3$) 3010 (w), 2930 (s), 1725 (s), 1605 (s), 1585 (w), 1455 (w), 1370 (w), 1210 (m), 890 (m), 850 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 7.6 (b, 6 H), 3.96 (s, 3 H, OC**H**$_3$), 2.3 (b, 4 H), 1.6 (m, 2 H, CH_3C**H**$_2$), 1.24 (b, 2 H), 0.8 (t, 3 H, J = 8 Hz, CH_2C**H**$_3$); MS (70 eV) *m/e* 268 (M^+) base; exact mass *m/e* 268.147 (calcd for $C_{18}H_{20}O_2$ *m/e* 268.146).

Preparation of 9,11-Seco-13-ethyl Steroid 5. The addition of 0.2 mmol of 2-ethyl-2-cyclopentenone to 0.2 mmol of (6-methoxy-2-naphthyl)(1-pentynyl)coppermagnesium bromide was carried out as described above. In a separate, dry, argon-purged, two-necked round-bottom flask fitted with a gas inlet and serum stopper was placed 4 mL of dry HMPT and 0.22 mL (2.0 mmol) of ethyl iodoacetate. The enolate solution was diluted with 1 mL of dry THF and transferred via syringe to the ethyl iodoacetate solution, and stirring was continued for 16 h. The dark-green black solution became a faint yellow over this period. The reaction mixture was then diluted with 5 mL of diethyl ether and an equal volume of saturated, aqueous ammonium chloride. After the mixture was dried, the solvent was removed in vacuo and excess alkylating reagent was removed at high vacuum. Preparative thin-layer chromatography using chloroform as eluent gave three major components: 2-methoxynaphthalene, 2-(6-methoxy-2-naphthyl)-1-ethyl-5-oxocyclopentane (**4**) and ethyl *trans*-2-(6-methoxy-2-naphthyl)-1-ethyl-5-oxocyclopentane-*r*-1-acetate (**5**) in 31% yield: IR ($CHCl_3$) 3040 (w), 2925 (m), 1730 (s), 1630 (m), 1600 (s), 1460 (m), 1370 (m), 1260 (s), 1150 (s), 1010 (m), 880 (m), 850 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 7.5 (b, 6 H), 4.24 (q, 2 H, J = 7.5 Hz, OC**H**$_2$CH$_3$), 3.9 (s, 3 H, OC**H**$_3$), 2.5 (b, 4 H), 1.6 (m), 1.32 (t, 3 H, J = 7.5 Hz, OCH$_2$C**H**$_3$), 0.88 (m), 0.6 (t, 3 H, J = 6.0 Hz, C**H**$_3$CH$_2$); MS (70 eV) *m/e* (rel intensity) 354 (M^+, 3), 309 (M^+ − 45, 4), 43 (base); exact mass *m/e* 354.184 (calcd for $C_{22}H_{26}O_4$ *m/e* 354.183); ^{13}C NMR ($CDCl_3$) δ 218.7 (s), 171.9 (s), 157.7 (d), 134.0 (s), 133.7 (s), 129.3 (d), 127.7 (d), 127.1 (d), 126.7 (d), 126.5 (s), 119.1 (d), 105.6 (d), 60.6 (t), 55.2 (q), 53.2 (s), 48.5 (d), 37.0 (t), 23.8 (t) 23.3 (q), 14.3 (q), 7.6 (t).

Preparation of Methyl *trans*-(6-Methoxy-2-naphthyl)-1-methyl-5-oxocyclopentane-*r*-1-acetate Ethylene Ketal. Methyl *trans*-2-(6-methoxy-2-naphthyl)-1-methyl-5-oxocyclopentane-*r*-1-acetate (**2a**; 0.270 g, 0.81 mmol) in 15 mL of anhydrous benzene was treated with 8.7 mmol (0.54 g) of ethylene glycol and 0.56 g (0.29 mmol) of *p*-toluenesulfonic acid monohydrate. The resulting mixture was refluxed 12 h with continuous removal of water via a Dean-Stark trap. Normal workup followed by preparative TLC (silica gel, 10% ethyl acetate/benzene, R_f 0.35) gave 0.258 g (86%) of a colorless highly viscous oil: ^1H NMR ($CDCl_3$) δ 7.31 (b, 6 H), 3.90 (s, 4 H, OC**H**$_2$C**H**$_2$O), 3.8 (s, 3 H, ArOC**H**$_3$), 3.6 (s, 3 H, CO_2C**H**$_3$), 2.25–1.78 (b, 7 H), 0.9 (s, C_{13}–C**H**$_3$); IR (CCl_4) 1732 (s), 1605 (m), 1170 (s), 900 cm^{-1} (m); MS (70 eV) *m/e* (rel intensity) 370 (M^+, 50), 297 (base).

Preparation of *trans*-2-(-6-Methoxy-2-naphthyl)-1-methyl-5-oxocyclopentane-*r*-1-acetic Acid Ethylene Ketal (2d). In a round-bottom flask was placed 0.046 g (0.12 mmol) of methyl *trans*-(6-methoxy-2-naphthyl)-1-methyl-5-oxocyclopentane-*r*-1-acetate ethylene ketal in 10 mL of absolute methanol containing 0.12 g (1.8 mmol) of potassium hydroxide. The resulting solution was refluxed 6 h when the formation of a white precipitate was observed. After this time 10 mL of saturated, aqueous sodium bicarbonate was added, and the resulting solution was cooled in an ice bath and diluted with 30 mL of diethyl ether. To the stirred two-phase system was added concentrated HCl dropwise until neutrality was reached as indicated by pH paper. Evaporation of the organic phase in vacuo gave a white solid which was recrystallized from benzene/cyclohexane to afford 40 mg (94%) of a crystalline solid: mp 176–178 °C; ^1H NMR ($CDCl_3$) δ 7.35 (b, 6 H), 4.0 (s, 4 H, OC**H**$_2$C**H**$_2$O), 3.82 (s, 3 H, ArOC**H**$_3$), 2.52–1.95 (b, 6 H), 0.9 (s, 3 H, C_{13}–C**H**$_3$); IR ($CHCl_3$) 3520 (b), 3140 (w), 2945 (s), 1725 (s), 1600 (m), 1265 (m), 1150 (s), 855 cm^{-1} (m).

Preparation of (±)-11-Oxoequilenin Methyl Ether (6). Into a dry two-necked 25-mL previously dried round-bottom flask was placed 130 mg (0.36 mmol) of the neat ketal acid **2d** under an argon atmosphere. The dry reaction vessel under argon was cooled to −78 °C, and approximately 5 mL of anhydrous HF was condensed into the flask. The reaction was allowed to warm to room temperature and let stand under argon for 14 h with periodic swirling. After evaporation of the residual HF by a stream of argon, 10 mL of aqueous saturated sodium bicarbonate and 10 mL of diethyl ether was added. The ether phase was separated and the aqueous phase was extracted with diethyl ether. The combined ether extracts were dried and evaporated in vacuo to afford 98.4 mg of a white solid. This solid was recrystallized from benzene/petroleum ether to afford 80 mg (65%) of 11-oxoequilenin methyl ether: mp 220.5–222.0 °C (lit.[12] 222–224 °C); ^1H NMR ($CDCl_3$) δ 8.02 (d, J = 9 Hz, 1 H), 7.60 (d, J = 7 Hz, 1 H), 3.80 (s, 3 H, ArOC**H**$_3$), 0.83 (s, 3 H, C_{13}–C**H**$_3$); (CD_3COCD_3) δ 8.02 (d, J = 9 Hz, 1 H), 7.2–7.4 (4 H), 3.9 (s, 3 H, ArOC**H**$_3$), 0.85 (s, 3 H, C_{13}–C**H**$_3$); IR ($CHCl_3$) 2940 (s), 2840 (s), 1730 (s), 1670 (m), 1600 cm^{-1} (m); UV λ_{max} (95% EtOH) 242 nm (24500), 316 (4500); mass spectrum, *m/e* 294 (M^+). These NMR, IR, and UV data correspond to those reported for steroid **6**.[12,33]

The aqueous phase was acidified with concentrated HCl and extracted twice with diethyl ether. The ether extracts were combined and dried. The solvent was removed in vacuo to afford 12 mg (10%) of *trans*-2-(6-methoxy-2-naphthyl)-1-methyl-5-oxocyclopentane-*r*-1-acetic acid (**2b**).

Acknowledgment. Financial support from the National Science Foundation (Grant No. GP 43419X) for part of this work and from G. D. Searle is gratefully acknowledged. We thank Dr. David Barrett (John Hopkins University) for help with one critical NMR measurement and Dr. Charles Sweeley (Michigan State) for providing us with high-resolution mass spectral data. A sample of *epi*-9,11-seco steroid **2b′** was kindly provided by Dr. E. G. Brain, Beecham Research Labs (England). G. D. Searle is also acknowledged for the biological screening of 13-ethyl seco steroid **5**.

Registry No. 1-Li, 70345-32-3; 1-MgBr, 71341-68-9; **2a**, 22913-71-9; **2b**, 22913-72-0; **2c**, 71341-06-5; **2d**, 70139-59-2; **3**, 22913-70-8; **4**, 71341-07-6; **5**, 71341-08-7; **6**, 16373-41-4; 6-methoxy-2-naphthyllithium, 32725-08-9; 6-methoxy-2-naphthyl bromide, 5111-65-9; pentynylcopper, 19093-51-7; 2-methyl-2-cyclopentenone, 1120-73-6; 2-ethyl-2-cyclopentenone, 2931-10-4; 2-methoxynaphthalene, 93-04-9; methyl *trans*-(6-methoxy-2-naphthyl)-1-methyl-5-oxocyclopentane-*r*-1-acetate ethylene ketal, 70139-58-1.