Tetrahedron Vol. 37, No. 23, pp. 3921 to 3926, 1981
Printed in Great Britain.

0040-4020/81/233921-06$02.00/0
Pergamon Press Ltd.

TANDEM MICHAEL–MICHAEL-RING CLOSURE (MIMIRC) REACTIONS

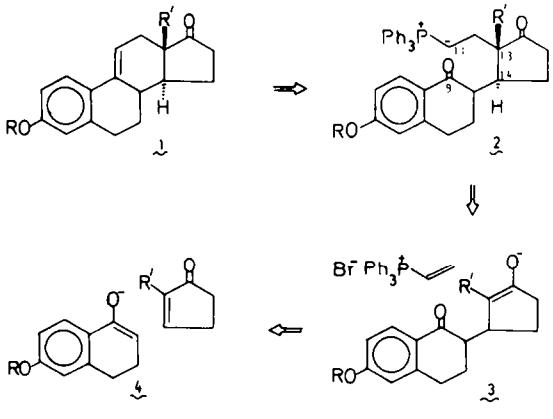
ONE-POT STEROID TOTAL SYNTHESIS—(±)-9,11-DEHYDROESTRONES

GARY H. POSNER,* JOHN P. MALLAMO and ALISON Y. BLACK
Department of Chemistry, The Johns Hopkins University, Baltimore, MD 21218, U.S.A.

(*Received USA 25 April* 1981)

Abstract—A new sequence of reactions involving tandem Michael–Michael-ring closure (MIMIRC) has been developed for efficient formation of three C–C bonds in one reaction vessel. The terminal ring closure reaction proceeds *via* either a 1,3- or a 1,6-cyclization, and this methodology also serves for construction of quaternary C centers. The usefulness of MIMIRC reactions is demonstrated by efficient assembly of cyclopropyl ketones and of *trans*-1-hydrindanones such as (±)-9,11-dehydroestrone **1b**. This one-pot approach represents the shortest known convergent total synthesis of a steroid, and subsequent straightforward transformations lead directly to natural (±)-estrone.

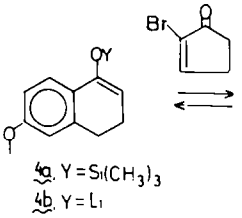
We have recently applied tandem Michael-ring closure (MIRC)[1] reactions to efficient construction of some decalin and hydroazulene sesquiterpenes.[2] Continuing our interest in developing new approaches to stereocontrolled total synthesis of steroids,[3] we reasoned retrosynthetically that an estrone derivative of general structure **1** might be prepared via intramolecular cyclization of a 9,11-secosteroid such as **2**.[4] Furthermore secosteroid **2**, having the desired relative *trans*-stereochemistry at C's 13 and 14, might be prepared via Michael reaction between a two-carbon electrophile and a cyclopentanone enolate nucleophile such as **3** which itself might also be produced using tetralone enolate **4** as a Michael donor (retrosynthetic scheme I). We report our success in preparing (±)-9,11-dehydroestrone methyl ether (**1**, R=R'=Me) using this highly convergent scheme in which tandem MIMIRC reactions are carried out conveniently in one reaction vessel and in which a *trans*-1-hydrindanone is formed stereo-specifically *via* annulation of a cyclohexene unit onto a 2-cyclopentenone. We report also a useful new procedure for preparing cyclopropyl ketones from vinyltriphenylphosphonium bromide (VTB) and ketone α-haloenolate ions generated in several different ways.



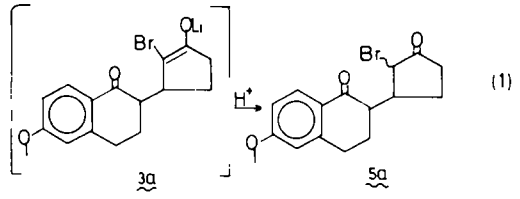
Retrosynthetic Scheme 1.

RESULTS AND DISCUSSION

Because the initial Michael reaction between tetralone enolate **4** and any cyclopentenone was expected to be reversible,[1b] 2-bromo-2-cyclopentenone was chosen so that the inductively withdrawing Br atom would stabilize enolate intermediate **3a** and thus would shift the equilibrium toward **3a**. To avoid any possible complication by free amine, tetralone enolate **4b** was prepared via methyllithium cleavage of tetralone enol silyl ether **4a** rather than by amide deprotonation of the parent tetralone; Michael addition of this tetralone enolate to 2-bromo-2-cyclopentenone in an aprotic medium[5] (i.e. THF), followed by aqueous work-up, gave Michael adduct **5a** which was isolated by preparative tlc in 60% yield.



4a, Y = $Si(CH_3)_3$
4b, Y = Li



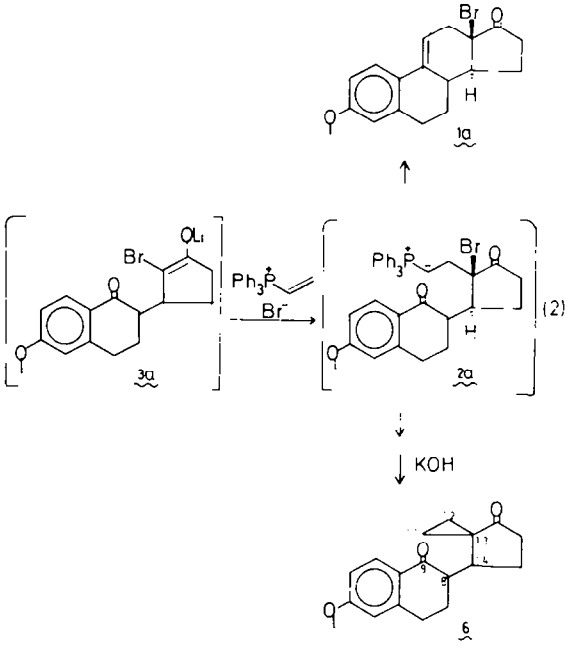
(1)

Bromocyclopentenone enolate **3a** reacted with VTB giving the presumed ylid intermediate **2a** which partitioned itself between unstable bromoestrone **1a** (*via* 1,6-cyclization, 2–5% yield, parent *m/e* 346, 348) and spirocyclopropyl ketone **6** (*via* 1,3-cyclization), isolated by column chromatography on gram scale in 57% yield. Formation of spirocyclopropyl cyclopentanone **6** in one-pot via consecutive Michael addition of tetralone enolate **4** to 2-bromo-2-cyclopentenone followed by Michael addition of this newly formed enolate ion to VTB followed, in turn, by an intramolecular ring closure (i.e. MIMIRC)

reaction involves extremely efficient formation of three C–C bonds in tandem fashion (C_8–C_{14}, C_{12}–C_{13}, C_{11}–C_{13}, steroid numbering).

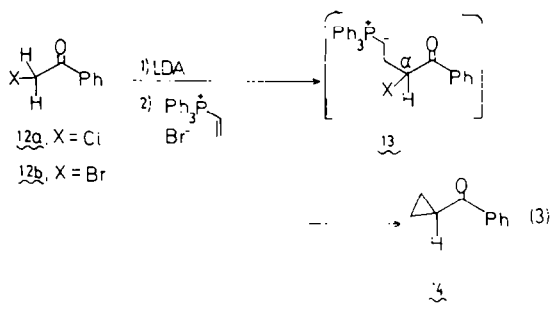
Although some 9,11-secosteroids possess contraceptive activity, 9,11-secosteroid **6** was found to be inactive in a rat antifertility assay and in an ovarian microsomal enzyme assay.[6]

Because cyclopropyl ketones are useful synthetic intermediates[7] and occasionally are found in nature,[8] we explored the generality of eqn (2) for formation of cyclopropyl ketones. Conversion of ketones into two-carbon homologous cyclopropyl ketones is usually achieved via reaction of the ketone



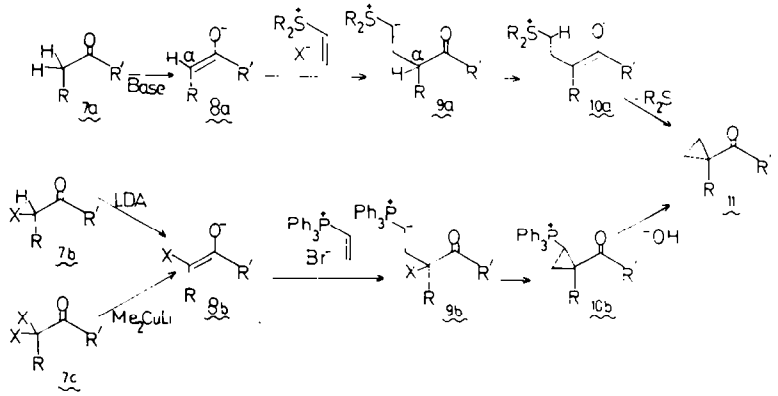
enolate ion with a vinyl*sulphonium* salt, followed by a 1,3-prototropic shift, and then intramolecular displacement of a neutral sufilde[9,10] (upper path, Scheme 2); in this process, the carbon atom α to the ketone carbonyl group acts twice as a *nucleophilic* center. Relatively few examples are known in which α-haloketones are converted into cyclopropyl ketones; such a process involves the α-carbon atom acting first as a *nucleophilic* and then as an *electrophilic* center (lower path, Scheme 2),[11] or *vice versa*.[12] We have found that ketone α-haloenolate ions, generated in several different ways, react with VTB and then with aqueous hydroxide to form cyclopropyl ketones in good yields and this process involves the ketone α-carbon atom acting first as a nucleophilic and then as an electrophilic center (lower path, Scheme 2).

α-Chloroacetophenone (**12a**) and α-bromoacetophenone (**12b**) reacted with lithium diisopropylamide and then with VTB presumably to form ylid intermediate **13**.[13] Even though this short-lived ylid could have undergone a 1,3-protopropic shift (i.e. an acidic α-hydrogen is available),[14] the predominant reaction pathway was rather a 1,3-displacement of halide to form cyclopropyl ketone **14** isolated in 60–70% yield after aqueous base treatment[15] and purification by preparative tlc.

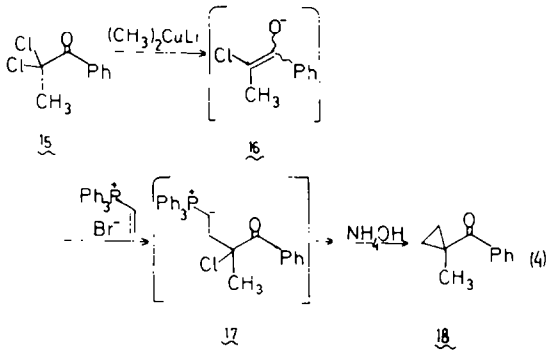


α,α-Dichloropropiophenone (**15**)[16] was converted into the corresponding α-chloroenolate (**16**) by treatment with dimethylcopperlithium;[17] reaction of enolate **16** with VTB and then with ammonium hydroxide gave cyclopropyl ketone **18** in 53% yield. It is noteworthy that intramolecular cyclization of presumed ylid intermediate **17** involves successful displacement of a chloride ion from a tertiary C atom (an "allowed" 3-*exo*-tet process according to Baldwin's rules)[18,19] to form a quaternary C center.[20] In contrast, we have found that lithium diisopropylamide deprotonation of α-chloropropiophenone and reaction with VTB did not produce cyclopropyl ketone **18**, and use of a vinyl*sulphonium* salt with the enolate ion formed by deprotonation of propiophenone gave no cyclopropyl ketone products.[9d] α,α-Dichlorocarboxylic esters underwent metal-halogen exchange,[21] but reaction of the corresponding α-haloester enolate ions with VTB failed to give useful amounts of cyclopropyl esters.

Thus cyclopropyl ketones can be prepared efficiently from VTB and ketone α-halo enolate ions which are generated by conjugate addition to α-bromocyclopentenone, by metalation of α-haloacetophenones, and by metal-halogen exchange of α,α-dichloropropiophenone.



Scheme 2.



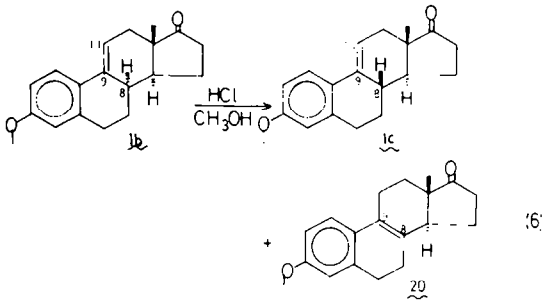
This one-pot carbocycle synthesis involves sequential formation of either three or two C–C bonds in a very efficient manner and, therefore, is a useful addition to modern synthetic methodology.

Returning to our original goal of steroid total synthesis, we found that tetralone enolate **4** reacted with 2-methyl-2-cyclopentenone to give regiospecifically generated enolate intermediate **3b**[22] and, after aqueous work-up, Michael adduct **19** in 55% yield after preparative tlc (eqn 5). Isolation of 1,5-diketone **19** in 55% yield is one of very few examples of successful Michael reactions performed in an aproptic medium.[5] Cyclopentanone enolate **3b** reacted with VTB in THF/DMF at 25° under dilute conditions to give as the only steroid product (±)-9,11-dehydro-8-epiestrone methyl ether (**1b**) in 8.4% yield (21.3% yield based on consumed tetralone) after preparative tlc (eqn 5). This tandem Michael–Michael-ring closure (MIMIRC) reaction involves consecutive formation of three C–C bonds (**1b**: C_8–C_{14}, C_{12}–C_{13}, C_9–C_{11}), and it represents the *shortest known steroid total synthesis* involving convergent connection in one-pot of a 10-carbon, a 6-carbon, and a 2-carbon unit leading directly to formation of a 19-nor steroid.

The major undesired products in eqn (5) appeared to be formed via polymerization of the ylid intermediate **2b** with VTB.[23]

Unsuccessful attempts to improve the intramolecular Wittig reaction and therefore the yield of estrone **1b** and to prepare closely related steroids included the following: (1) use of tetralone trimethylacetate **4**, R = Me_3CCO, instead of tetralone methyl ether **4**, R = Me, in the hope of making the C_9 CO group in ylid intermediate **2b** more electrophilic; (2) use of *iso-propenyl*triphenylphosphonium bromide (ITB) insteady of *vinyl*triphenylphosphonium bromide (VTB);[23] and (3) use of dimethyl vinylphosphonate, methyl acrylate, and α-chloroacrolein instead of VTB.

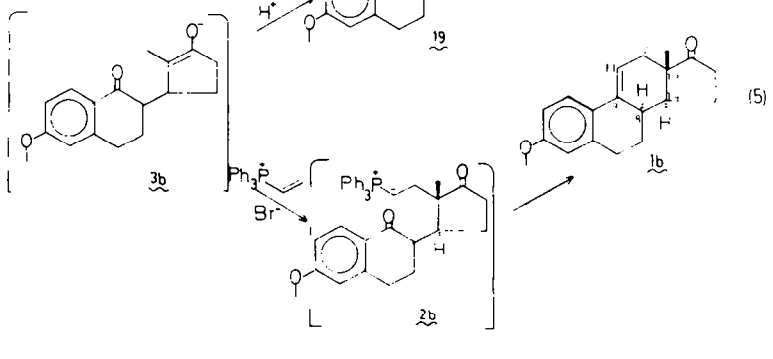
A single crystal x-ray analysis established that estrone **1b** did indeed have the natural relative configurations at C's 13 and 14 and the unnatural configuration at C 8. Several 8-epiestrones are known to possess significant contraceptive activity.[24] Knowing that acid-promoted isomerization of 9,11⇌8,9-dehydroestrones occurs easily,[25] we exposed 9,11-dehydro-8-epiestrone **1b** to refluxing methanolic hydrogen chloride and obtained a 3:1 mixture of 9,11-dehydroestrone **1c** of *natural relative configuration at all chiral centers* and 8,9-dehydroestrone **20** (eqn 6). Such a mixture of 9,11- and 8,9-dehydroestrones **1c** and **20** has previously been converted into estrone and into estradiol in high yield.[25] Therefore, one-pot MIMIRC formation of 9,11-dehydro-8-epiestrone **1b**, acid-promoted isomerization, and reduction constitute *one of the shortest stereocontrolled total syntheses of racemic estrone methyl ether of natural relative configuration.*



The MIMIRC sequence for formation of estrone **1b** represents a new and useful annulation process for fusing a six-membered carbocyclic ring onto a cyclopentenone system exclusively in a *trans*-fashion and for forming a quaternary C center[20] with complete stereocontrol.[3a] This *trans*-ring fusion stereochemistry complements the *cis*-ring fusion stereochemistry typical of Diels Alder 2 + 4 cycloaddition reactions. MIMIRC reactions of this sort, therefore, may indeed find many uses in synthesis of complex organic molecules.

EXPERIMENTAL

M.ps and b.ps are uncorrected. IR spectra were recorded with a Perkin–Elmer 599B or 457 Spectrometer. NMR spectra were recorded on Varian T-60, CFT-20 or Jeol MH-100 instruments at 60, 80 or 100 MHz as indicated. Mass spectra were recorded on a Hitachi Perkin–Elmer RMU-6 spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc.



Preparative GLC was done using a Varian Aerograph Model 90-P on a 10' × ¼" 10% carbowax C-20M-chromosorb W (40/60 mesh) column. Preparative TLC was done using Analtech pre-coated silicagel GF plates (20 × 20 cm, 1 mm or 1.5 mm thickness) using the solvents indicated.

The following materials were purchased from Aldrich Chemical Co. and were used as received: 6-methoxy-1-tetralone, 2-cyclopenten-1-one, vinyltriphenylphosphonium bromide (VTB), α-chloroacetophenone, α-bromoacetophenone and propiophenone.

Trimethylsilychloride (Aldrich) was distilled under N_2 and stored over 3 Å molecular sieves. Triethylamine and diisopropylamine (Aldrich) were distilled from calcium hydride and stored over KOH. Tetrahydrofuran (J. T. Baker) was distilled from sodium benzophenone ketyl and used immediately. Cuprous iodide (Fischer) was washed with anhydrous THF in a soxhlet extractor for 24 hr then dried *in vacuo* at 25°.[26] Alkyllithium reagents were purchased from Aldrich as solns in the solvent indicated and were titrated using anhyd diphenylacetic acid.[27] Solvents used for extractions were purchased as reagent grade and used as received.

2-Methyl-1-cyclopentenone was prepared on several gram scale according to Ref. 28.

Tetralone enol silyl ether **4a**

A dry 2-necked 100 ml flask fitted with a 25 ml pressure equalizing dropping funnel with N_2 inlet, serum cap and magnetic stirring bar, containing 25 ml anhyd THF was charged with diisopropylamine (4.70 ml, 33.5 mmol) then cooled to −78° (CO_2/acetone) and treated dropwise *via* syringe with n-BuLi in hexane (24 ml, 1.4 M, 33.6 mmol). Stirring was continued at −78° for 30 min, at which time 6-methoxy-1-tetralone (5.36 g, 30.5 mmol) in 25 ml anhyd THF was added dropwise via the addition funnel over 20 min. Stirring was continued at −78° for 90 min. The resulting enolate was treated, via syringe, with the supernatant from a centrifuged mixture of trimethylsilylchloride (11.6 ml, 91.4 mmol) and triethylamine (13.0 ml, 93.3 mmol) then warmed to 0° for 2 hr and finally stirred at room temp overnight. The cloudy soln was then poured into a separatory funnel containing 100 ml CH_2Cl_2, 50 g ice and 50 ml sat $NaHCO_3$ aq. This was quickly shaken and the organic phase poured on to anhyd K_2CO_3 for drying. Filtration and rotary evaporation (25 mm Hg) gave 7.05 g of crude silyl ether. Molecular distillation (90°, 0.05 mm Hg) gave 6.92 g (92%) of **4a** as a clear oil: NMR (CCl_4, 100 MHz no ref): δ7.30–6.45 (m, 3H), 4.85 (t, 1H), δ3.43 (s, 3H), 2.65–2.30 (t, 2H), 2.20–1.90 (m, 2H), 0.00 (s, 9H); IR (CCl_4): 1640 (m), 1602 (s) cm^{-1}; MS (70 eV): 248 *m/e* (M^+), 73, 75 *m/e* (base).

Michael adduct **5a**

A dry 2-necked 50 ml flask with N_2 inlet, magnetic stirring bar and serum cap, was charged with **4c** (155 mg, 0.63 mmol) in 10 ml anyhyd THF. The flask was cooled to 0° and treated dropwise *via* syringe with MeLi (547 μl, 0.65 mmol) in Et_2O. This was stirred at room temp for 60 min. The flask was then cooled to −50° ($CO_2 + CaCl_2 + H_2O$) and treated dropwise with 2-bromo-2-cyclopenten-1-one (102 mg, 0.63 mmol)[29] in 1 ml THF via syringe. Stirring was continued at −50° for 60 min, then quenching was achieved by the addition of solid NH_4Cl, pouring into a separatory funnel containing 25 g ice/25 ml water and extracting with Et_2O. The Et_2O layer was washed once with 25 ml H_2O and dried over Na_2SO_4. Filtration and rotary evaporation (25 mm Hg) gave 173 mg crude product which was diluted with $CHCl_3$ for preparative tlc (3% EtOAc/benzene, $R_f = 0.20$). Desorption with Et_2O, filtration and rotary evaporation gave 127 mg (61%) of pure **5a**, m.p. 129–130.5° which was recrystallized from Et_2O/hexane to give 119 mg (57%) of **5a** m.p. 130.5–131°: NMR ($CDCl_3$): δ8.05 (d, 1H, J = 8.5 Hz), 7.00–6.65 (m, 2H), 5.15–4.90 and 4.4–4.41 (2m, 1H), 3.85 (s, 3H), 3.2–1.6 (bm, 11H); IR ($CHCl_3$): 1748 (s), 1670 (s), 1599 (vs), 1258 (s), 1245 (s) cm^{-1}; Exact Mass: Calc for $C_{16}H_{17}O_3$ Br: 336.034; Found: 336.036. Found: C, 57.17; H, 5.30: Br, 24.14. Calc for $C_{16}H_{17}O_3$ Br: C, 56.98; H, 5.13; Br, 23.73.

Spirocyclopropyl cyclopentanone **6**

A dry 3-necked 250 ml flask fitted with N_2 inlet, magnetic stirring bar, 25 ml addition funnel and serum cap was charged with **4a** (1.26 g, 5.1 mmol) in 50 ml anhyd THF and then cooled to 0°. To this was added dropwise via syringe MeLi (3.33 ml, 1.6 M, 5.33 mmol); the cold bath was removed, and stirring was continued at room temp for 90 min then cooled to −50°. A soln of 2-bromo-2-cyclopenten-1-one (823 mg, 5.1 mmol) in 20 ml anhy THF was added dropwise via the addition funnel over 10 min and the funnel was rinsed clean with an additional 5 ml THF. Stirring was continued at −50° for 60 min after which time a soln of VTB (2.00 g, 5.41 mmol) in 20 ml DMF was added via the same addition funnel over a 10 min period. The cold bath was not replenished with solid CO_2 to effect slow warming to room temp overnight. The mixture was then treated with 100 ml 10% KOH aq and the THF was removed by rotary evaporation. The alkaline soln was brought to pH 7 with dil HCl and extracted 4 times with 100 ml portions Et_2O. The combined Et_2O layers were washed 3 times with 100 ml portions H_2O and dried over $MgSO_4$. Filtration and rotary evaporation gave the crude product (3.05 g). This product was then purified by column chromatography (SiO_2, 150 g, 15% EtOAc/benzene) to give as the major fraction 6 (822 mg, 57%) m.p. 91–93°. The analytical sample was recrystallized from Et_2O/hexane, m.p. 94.0–94.5°. NMR ($CDCl_3$): δ8.01 (d, 1H, J = 8.5 Hz), 7.10–6.70 (m, 2H), 3.85 (s, 3H), 3.35–2.92 (m, 3H), 2.6–1.6 (m, 7H, (1.40–0.85 (m, 4H); IR ($CHCl_3$): 1720 (s), 1670 (s), 1601 (vs) cm^{-1}. Found C, 75.96; H, 7.16; Calc for $C_{18}H_{20}O_3$: C, 76.02, H, 7.09%. *Mass spec* (70 eV): 284 *m/e* (M^+).

Cyclopropyl phenyl ketone (**14**)

(a) From α-bromoacetophenone. To 10–15 ml of anhyd THF in a serum-stoppered round-bottomed flask containing a magnetic stirring bar under N_2 was added 267 mg (2.75 mmol) of anhyd diisopropylamine. The flask was cooled to −78°, and 1.8 ml of 1.6 M (2.89 mmol) n-BuLi was added *via* syringe. After stirring for 0.5 hr at −78°, 500 mg (2.50 mmol) of α-bromacetophenone in 10 ml THF was added dropwise via syringe. After stirring for 1 hr at −78°, 1.385 g (3.75 mmol) of VTB in 7 ml of anhyd DMF was added dropwise via syringe with vigorous stirring. The Dry-ice—acetone bath was not replenished with Dry-Ice; the temp was allowed to reach 25° slowly (1–2 hr), and stirring was continued at 25° for 24 hr. Rotary evaporation of the THF was followed by addition of pentane. The pentane phase was washed first with KOH aq then with 15% HCl, and then three times with water. Drying the pentane phase and preparative tlc gave 257 mg (70%) of pure **14** as an oil which was identical in all respects to an authentic sample (Aldrich).

From α-chloroacetophenone. In a similar fashion, 510 mg (3.30 mmol) of α-chloroacetophenone gave 294 mg (61%) of pure **14**.

1-*Methylcyclopropyl phenyl ketone* (**18**)

To a −20° soln of dimethylcopperlithium, prepared from 243 mg (1.28 mmol) of THF-washed cuprous iodide and 2.13 ml of 1.2 M (2.55 mmol) MeLi in Et_2O, was added dropwise via syringe 200 mg (0.98 mmol) of α,α-dichloropropiophenone[16] in 0.5 ml of Et_2O. After stirring for 0.5 hr at −10°, the vessel was cooled to −20° and 471 mg (1.28 mmol) of VTB in 2 ml of DMF was added dropwise via syringe with vigorous stirring. An additional 2–3 ml of Et_2O was added to facilitate stirring. The mixture was allowed to reach 25° slowly and then was stirred at 25° for 24 hr. Addition of 16% NH_4OH and stirring for 1 hr was followed by pentane extraction. The pentane phase was washed three times with 16% NH_4OH, once with 15% HCl and three times with water. Drying and preparative glpc gave 85 mg (53%) of **18** as an oil: NMR ($CDCl_3$) δ0.80 and 1.15 (cyclopropyl, 4H), 1.45 (s, 3H), 7.6 (m, 3H), 7.8 (m, 2H); IR ($CHCl_3$): 1670 cm^{-1}. These spectroscopic properties are identical with lit values.[30]

Michael adduct **19**

A dry 2-necked 100 ml round-bottomed flask fitted with N_2 inlet, magnetic stirring bar and serum cap was charged with **4a** (250 mg, 1.00 mmol) and 10 ml anhyd THF then cooled to 0°. The chilled soln was treated dropwise *via* syringe with MeLi in Et_2O (710 μl, 1.5 M, 1.06 mmol). The cold bath was removed and stirring was continued at room temp. After 60 min the reaction

was cooled to −30° ($CaCl_2 + CO_2 + H_2O$) and a soln of 2-methyl-2-cyclopentenone (100 mg, 1.14 mmol) in 2 ml anhyd THF was added dropwise via syringe. After 30 min at −30° the cold bath was removed. After warming to 0°, the reaction was treated with 10 ml sat NaH_2PO_4 aq and 5 ml distilled water. The 2 phase system was rotary evaporated (25 mm Hg) to remove the THF then poured into a separatory funnel and extracted with 100 ml ether. The organic phase was dried over Na_2SO_4; filtration and rotary evaporation gave the crude product (*ca* 360 mg). Preparative tlc (8% EtOAc/benzene, $R_f = 0.30$) gave the pure Michael adduct **6a**, 154 mg (56%): NMR ($CDCl_3$, 100 MHz): δ8.15 (d, 1H); 7.1–6.8 (m, 2H), 3.93 (s, 3H), 3.2–1.6 (m, 11H), 1.05 (d, J = 6 Hz, 3H); IR ($CHCl_3$): 1735 (s), 1675 (s), 1600 (s) cm^{-1}; Exact Mass: $C_{17}H_{20}O_3$ Calc: 272.1412, Found: 272.1406.

(±)-9,11-*Dehydro-8-epiestrone* **1b**

A dry 3-necked 250 ml flask fitted with N_2 inlet, magnetic stirring bar, 50 ml pressure equalizing dropping funnel and serum cap was charged with **4a** (137 mg, 0.55 mmol) and 10 ml anhyd THF. The flask was cooled to 0° and treated, via syringe, with MeLi (483 μl, 1.2 M, 0.58 mmol) in Et_2O and stirred at room temp for 60 min. The flask was then cooled to −30° and treated dropwise (via syringe) with 2-methyl-2-cyclopentenone (65 mg, 0.67 mmol) in 1 ml THF. After 30 min the reaction was diluted with 150 ml anhyd THF and 10 ml anhyd DMF, then warmed to room temp. The resulting orange-yellow soln was treated dropwise with a solution of VTB (426 mg, 1.15 mmol) in 50 ml anhyd DMF over a period of 4–6 hr. Stirring was continued at room temp overnight. Transfer to a 1-necked round-bottomed flask and rotary evaporation to remove the THF was followed by removal of DMF under vacuum (0.1 mm Hg) at 30° to give a crude viscous oil which was diluted with $CHCl_3$ for preparative tlc (8% EtOAc/benzene, $R_f = 0.40$). Desorption of this band with EtOAc (100 ml) gave, after concentration, 13.2 mg of **1b** (8.4%), m.p. 141–146°, which was recrystallized from EtOAc/EtOH (12.6 mg, 8.0%, m.p. 149.5–150°: NMR ($CDCl_3$, 80 MHz): δ7.54–6.60 (m, 3H), 6.01 (m, 1H), 3.79 (s, 3H), 2.99–1.56 (m, 12H), 0.96 (s, 3H); IR ($CHCl_3$: 1735, 1603 cm^{-1}; MS (70 eV): 282 *m/e* (M^+, base); UV (EtOH): λ_{max} 264 nm (ε = 17,900). Found: C, 80.69; H, 7.83. Calc for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85.

Exact Mass: $C_{19}H_{22}O_2$, calc: MW = 282.1620 Found: 282.1615.

This reaction was also performed on 2.9 mmol scale to give 62 mg of **1b** (7.8%) and 482 mg of recovered 6-methoxy-1-tetralone. Therefore the yield of **1b** based on reacted tetralone is 21.3%. Similar results were obtained using a motor-driven syringe to deliver the VTB to enolate **3b** slowly and continuously over a 10 hr period.

Isomerization of 8-epiestrone **1b** *into* (±)-9,11-*dehydroestrone methyl ether* (**1c**)

8-Epiestrone **1b** (5.2 mg, 18.4 μmol, ^1H NMR, C_{18}–CH_3, δ0.96) was refluxed in 3 ml of 5:1 MeOH/10 N HCl for 6 hr. The MeOH was removed with gentle heating under a stream of N_2. The remaining aqueous suspension was cooled, diluted with 5 ml NaH_2PO_4 buffer (pH = 4) and extracted 3 times with 5 ml Et_2O. The combined Et_2O extracts were dried over $MgSO_4$. Filtration and rotary evaporation gave 5.1 mg (98%) of a white solid m.p. 139–146°. NMR analysis of this sample ($CDCl_3$, 80 MHz) indicated the presence of a 3:1 mixture of **1c** (C_{18}–CH_3, δ0.93)[31] and **20** (C_{18}–CH_3, δ0.89).[32] These characteristically different positions of the angular C_{18}–Me groups in the ^1H NMR spectra of **1b**, **1c** and **20** allow very easy and clear distinction among the three.

Acknowledgements—We thank the National Science Foundation (CHE 79-15161), the Donors of the Petroleum Research Fund, administered by the American Chemical Society, and the G.D. Searle Co. for generous financial support. We also thank Martin Hulce and Leah Frye for experimental assistance with parts of this project, and Drs. D. J. Duchamp, G. Bundy, and J. A. Campbell of the Upjohn Company for performing the *x*-ray analysis of estrone **1b** and for providing us with a sample of 9,11-dehydroestrone. Drs. J. Ackrell and J. A. Edwards of Syntex Research kindly provided a sample of 9,11-dehydro-estrone methyl ether (**1c**). We also thank Prof. C. H. Robinson (Johns Hopkins) for a helpful discussion.

REFERENCES

[1a]The term *MIRC reaction* was first coined by R. D. Little and J. R. Dawson, *Tetrahedron Letters*, 2609 (1980); [b]for a review of the Michael reaction, see E. D. Bergmann, D. Ginsburg and R. Pappo, *Org. Reactions* **10**, 179 (1975) which includes as Michael acceptors alkenes activated by groups other than carbonyl (e.g. phosphonium groups).

[2a]G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz and D. J. Brunelle, *J. Am. Chem. Soc.* **97**, 107 (1975); [b]A. Alexakis, M. J. Chapdelaine, G. H. Posner and A. W. Runquist, *Tetrahedron Letters* 4205 (1978).

[3a]G. H. Posner, M. J. Chapdelaine and C. M. Lentz, *J. Org. Chem.* **44**, 3661 (1979); [b]G. H. Posner, J. P. Mallamo and K. Miura, *J. Am. Chem. Soc.* **103**, 2886 (1981).

[4]Intramolecular Wittig reactions have been used extensively in preparation of natural products (e.g. of penicillin and analogs) and of many structurally interesting compounds: [a]for a review, see K. B. Becker, *Tetrahedron* **36**, 1717 (1980); [b]for Michael initiated intramolecular Wittig reactions see W. Flitsch and E. R. Gesing, *Chem. Ber.* **113**, 614 (1980) and J. M. Muchowski and P. H. Nelson, *Tetrahedron Letters* 4585 (1980) and I. Kawamoti, S. Muramatsu and Y. Yura, *Ibid.* 4223 (1974).

[5a]G. A. Kraus and J. U. Pezzanite, *J. Org. Chem.* **44**, 2480 (1979); [b]J. Boyer, R. J. P. Corniu, R. Perz and C. Réyé, *J. Chem. Soc. Chem. Commun.* 122 (1981).

[6]This biological screening was kindly performed by Dr. L. J. Chinn and his associates at the G. D. Searle research and development laboratories in Chicago, Illinois.

[7a]M. Demuth and P. R. Raghavan, *Helv. Chim. Acta* **62**, 239 (1979); [b]P. Bennet, J. A. Donnelly and M. J. Fox, *J. Chem. Soc.* Perkin I, 2990 (1979); [c]C. N. Rentzea, *Angew. Chem. Int. Ed. Engl* **19**, 199 (1980); [d]W. S. Murphy and S. Wattanasin, *Tetrahedron Letters* 1887 (1980).

[8]Isoilludins: A. Ichihara and T. Matsumoto, *Bull. Chem. Soc. Japan* **47**, 1030 (1974).

[9a]J. Gosselck, H. Ahlbrecht, F. Dost, H. Shenk and G. Schmidt, *Tetrahedron Letters* 995 (1968); [b]C. R. Johnson and J. P. Lockard, *Ibid.* 4589 (1971); [c]C. R. Johnson and P. E. Rogers, *J. Org. Chem.* **38**, 1793 (1973); [d]K. Takaki and T. Agawa, *Ibid.* **42**, 3303 (1977); [e]K. Takaki and K. Negoro, *J. Chem. Soc.* Perkin I, 1490 (1979) and refs therein.

[10]Cyclopropane formation via intramolecular 1,3-displacement of halide and oxyanion leaving groups has also been reported: [a]U. Schmidt, *Angew. Chem. Int. Ed. Engl.* **4**, 238 (1965); [b]M. S. Newman, V. DeVries and R. Darlak, *J. Org. Chem.* **31**, 2171 (1966); [c]H. Takei, Y. Fukuda, K. Sugaya, T. Taguchi and T. Kawara, *Chem. Letters* 1307 (1380). Vinyl selenides have also recently been used successfully: M. Shimizu and I. Kuwajima, *J. Org. Chem.* **45**, 2921 (1980).

[11a]J. Causse-Zoller and R. Fraisse-Jullien, *Bull. Soc. Chim. Fr* 430 (1966); [b]R. Becker, G. Berz, M. Rösner, U. Rosentreter and E. Winterfeldt, *Chem. Ber.* **112**, 1879 (1979).

[12a]P. Bravo, G. Gaudiano, C. Ticozzi and A. Umani-Ronchi, *Tetrahedron Letters* 4481 (1968); [b]P. Bennett and J. A. Donnelly, *Chem. Ind.* 783 (1969); [c]P. Bravo, G. Fromza, G. Gaudiano, C. Ticozzi and M. G. Zubiani, *Tetrahedron* **27**, 3563 (1971).

[13]See E. E. Schweizer, A. T. Wehman and D. M. Nycz, *J. Org. Chem.* **38**, 1583 (1973).

[14]The acidities of the α-H in intermediate **13** and of the protons adjacent to a phosphonium P atom appear to be approximately of the same magnitude: [a]H. O. House, *Modern Synthetic Reactions* (2nd Edn) p. 684; Benjamin Menlo Park, Calif. (1972); [b]H. O. House, W. F. Fischer Jr., M. Gall, T. E. McLaughlin and N. P. Peet, *J. Org. Chem.* **36**, 3429 (1971).

[15a]Very little of neutral product **14** was formed *before* exposing the reaction mixture to hydroxide ions; [b]cyclopropyl-phosphonium salts are known to give neutral cyclopropanes in good yield upon treatment with aqueous hydroxide; F. Hammerschmidt and E. Zbiral, *Liebigs Ann.* 1026 (1977).

[16]Prepared according to N. DeKimpe, L. De Buyck, R. Verhé, F. Wychuyse and N. Schamp, *Synth. Commun.* **9**, 575 (1979).
[17]For use of dimethylcopperlithium in converting various α-heteroatom substituted ketones into the corresponding enolate species, see: [a]G. H. Posner and J. J. Sterling, *J. Am. Chem. Soc.* **95**, 3076 (1973); [b]J. R. Bull and Tuinman, *Tetrahedron Letters* 4349 (1973); [c]J. Villieras, J. R. Disnar and J. F. Normant, *J. Organomet. Chem.* **81**, 295 (1974); [d]E. W. Logusch, *ibid* 3365 (1979); [e]P. T. Lansbury, R. W. Erwin and D. A. Jeffrey, *J. Am. Chem. Soc.* **102**, 1602 (1980); [f]J.-P. Deprés and A. E. Greene, *J. Org. Chem.* **45**, 2037 (1980); [g]G. H. Posner, *An Introduction to Synthesis Using Organocopper Reagents*. Wiley, New York (1980).
[18]J. E. Baldwin, *J. Chem. Soc. Chem. Commun.* 734 (1976).
[19]Use of a vinylsulphonium salt in a very similar system failed to give a cyclopropane: see Ref. 9*d*.
[20]For a review of construction methodology for quaternary C centers, see S. F. Martin, *Tetrahedron* **36**, 419 (1980).
[21]H. Normant, *J. Organomet. Chem.* **100**, 189 (1975).
[22]Regiospecific generation of a monoenolate ion from an unsymmetrical diketone is a very difficult and useful reaction that has attracted some recent attention: [a]P. A. Grieco, S. Ferrino and T. Oguri, *J. Org. Chem.* **44**, 2593 (1979); [b]W. G. Dauben and D. M. Walker, *Ibid.* **46**, 1103 (1981).
[23]For another such example, see R. M. Cory, D. M. T. Chan, Y. M. A. Naguib, M. H. Rastall and R. M. Renneboog, *J. Org. Chem.* **45**, 1852 (1980).
[24a]U. Eder, *J. Steroid Biochem.* **11**, 55 (1979); [b]M. Kakushima, L. Allain, R. A. Dickinson, P. S. White and Z. Valenta, *Can. J. Chem.* **57**, 3354 (1979); [c]Y. Nishino, F. Neumann, K. Prezewowski and R. Wiechert, *Steroids*, **28**, 325 (1976); [d]C. Rufer, E. Schroder and H. Gibian, *Liebigs Ann.* **752**, 1 (1971); [e]L. Velluz, G. Nominé and R. Bucourt, *C. R. Acad.* **253**, 811 *Sci., Paris* (1963).
[25a]G. H. Doublas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall and H. Smith, *J. Chem. Soc.* 5072 (1963); [b]G. Quinkert, W.-D. Weber, U. Schwartz, G. Dürner, *Angew. Chem. Int. Ed. Engl.* **19**, 1027 (1980).
[26]G. H. Posner, C. E. Whitten and J. J. Sterling, *J. Am. Chem. Soc.* **95**, 7788 (1973).
[27]W. G. Kofron and L. M. Baclawski, *J. Org. Chem.* **41**, 1879 (1976).
[28]P. G. Gassman and J. M. Pascone, *J. Am. Chem. Soc.* **95**, 7801 (1973).
[29]S. J. Branca and A. B. Smith III, *J. Am. Chem. Soc.* **100**, 7767 (1978).
[30]C. L. Baumgardner and K. G. McDaniel, *Ibid.* **91**, 6821 (1969).
[31]An *authentic* sample of 9,11-dehydroestrone **1c** showed a ^{1}H NMR singlet for the angular C_{18}–Me group at δ0.93 (see also Ref. 25*b*).
[32]C. Rufer, E. Schröder and H. Gibian, *Liebigs Ann.* **705**, 211 (1967), report a ^{1}H NMR singlet for the angular C_{18}–Me group of 8,9-dehydroestrone **20** at δ0.89.