Comparison of the spectra in parts a, b, and c, especially the resonance of CO bound to heme iron, shows that they are essentially equivalent. The resonance due to CO bound to iron is at 206.7 ppm for the crystalline sample and 206.3 ppm for solution spectra.[14-18] This agreement is well within the experimental uncertainties, and one can conclude that the structure of the HbACO, especially in the bound CO region, is the *same in the solution and crystalline states of this sample*. This conclusion is in agreement with infrared results that give the same CO stretching frequency for crystalline and solution samples of HbAcO.[6]

Reproducibility of the solid-state ^{13}C NMR results described above is not always achieved. Part d of Figure 1 shows the spectrum of a crystalline HbACO sample with which the same care had not been exercised in transfers and in obtaining the ^{13}C CP/MAS spectrum (e.g., air driving the spinner instead of N_2, additional depletion of buffer). The visible spectrum taken from the ^{13}C CP/MAS experiment indicated that about 25% of the bound CO had been exchanged by O_2. For this sample, the resonance position of bound ^{13}CO is found to be at 212.3 ppm, approximately a 6-ppm shift from the values found for the other samples. There were other, smaller shifts in the ^{13}C resonance positions for this partially altered sample. The detailed reason for the significant difference between the CO resonance positions in the partially altered sample in comparison to the unaltered HbACO in the solution and crystalline states is not clear, but certainly reflects a significant difference in the local structural environment of the bound CO remaining in the partially altered crystals, which have experienced a significant depletion of buffer as well as partial O_2/CO exchange.

The magic-angle spinning ^{13}C NMR spectrum of a protein has recently been reported.[19] However, to our knowledge, this technique has not been applied to a crystalline protein or one in which the structure has been determined by X-ray diffraction. We believe that the technique holds great promise for comparing the crystalline and solution states, and such work is under way in these laboratories in the hemoglobin system and other systems.

Acknowledgment. We greatly acknowledge partial financial support by N.S.F. Grant CHE74-23980 (to G.E.M.) and NIH Grant HL-15980 (to W.S.C.) and the use of the Colorado State University Regional NMR Center, funded by National Science Foundation Grant CHE78-18581. We also acknowledge the technical assistance of Dr. V. J. Bartuska and D. W. Sindorf.

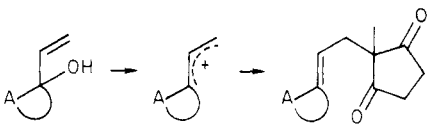
(15) Moon, R. B.; Richards, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 5093–5095.
(16) Oldfield, F.; Allerhand, H. *J. Biol. Chem.* **1975**, *250*, 6403–6407.
(17) Choc, M. G. Ph.D. Dissertation, Colorado State University, Ft. Collins, CO, 1979.
(18) Matwiyoff, N. A.; Needham, T. E. *Biochem. Biophys. Res. Commun.* **1972**, *49*, 1158–1164.
(19) Opella, S. J.; Frey, M. H.; Cross, T. A. *J. Am. Chem. Soc.* **1979**, *101*, 5856–5857.

G. E. Maciel,* M. P. Shatlock, R. A. Houtchens
W. S. Caughey*
Departments of Chemistry and Biochemistry
Colorado State University, Fort Collins, Colorado 80523
Received May 5, 1980

Silicon in Synthesis: An Exceptionally Short Synthesis of *dl*-11α-Hydroxyestrone Methyl Ether

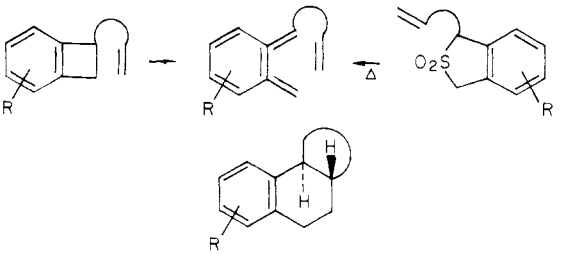
Sir:

The isolation of estrone[1] in 1929 paved the way for many ingenious total syntheses, each in its own way reflecting, to some extent, the state of the art of synthesis at that time.[2] The early routes culminated in the Torgov method for connecting ring D



torgov method

to the A-ring system via a vinyl carbinol and 1,3-diketone.[3] Recently, the use of *o*-xylylenes has further simplified the synthesis of estrone. The methods for generating the *o*-xylylene (or *o*-quinodimethane) intermediate are usually based upon thermolysis of benzocyclobutenes,[4] or cheletropic extrusion of sulfur dioxide from a benzo[*c*]thiophene 2,2-dioxide.[5] A particularly innovative



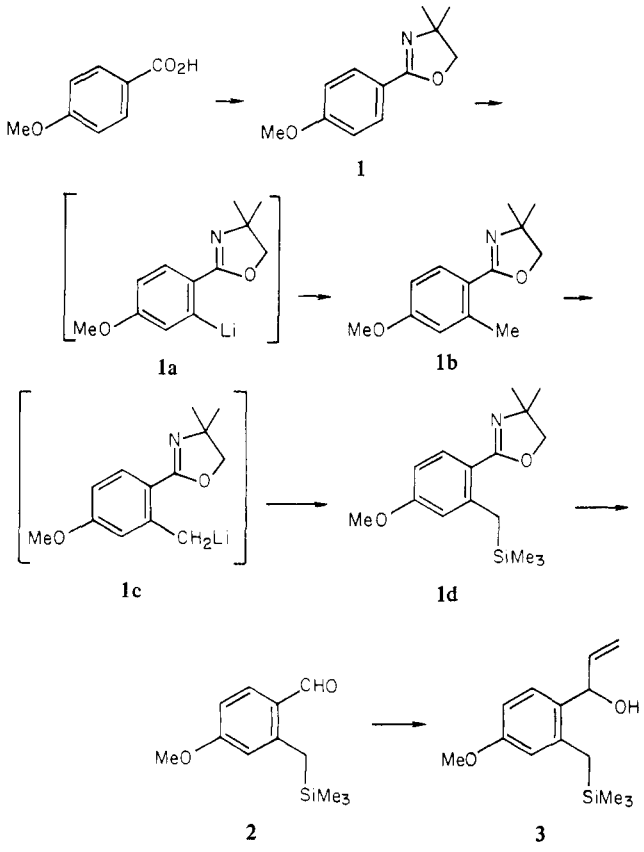
xylene method

way of constructing *o*-xylylenes by using a cobalt-mediated co-oligomerization of bis(trimethylsilyl)acetylene with a 1,5-hexadiyne has been used to synthesize estrone.[6]

Here we report a six-step synthesis of 11-oxygenated estrones that features in its key steps specific uses of organosilicon chemistry[7] and makes use of the Torgov and xylylene strategies mentioned above. The (*p*-methoxyphenyl)oxazoline **1**[8] was treated with *n*-butyllithium in ether at 0 °C to give **1a** which was quenched with methyl iodide, providing **1b** (96%)[9] [bp 107–110 °C (0.02 mm)]. When **1b** was further treated with *n*-butyllithium in ether at 0 °C, **1c** was formed, which on quenching with chlorotrimethylsilane gave **1d** [bp 127–129 °C (0.025 mm), 92%]. Unmasking **1d** was accomplished by treatment of **1d** in nitromethane with methyl iodide, removal of the nitromethane, and reaction with sodium borohydride in ethanol,[10] followed by workup with 90% aqueous acetic acid to give the aldehyde **2**, bp 96–103 °C (0.01 mm) (97%). The aldehyde **2** was converted into the vinyl carbinol **3** (95%) on treatment with vinylmagnesium bromide. The synthesis of **3** proceeds in three steps since isolation of **1b** is unnecessary, and the conversion of **1d** into **2** can be carried out

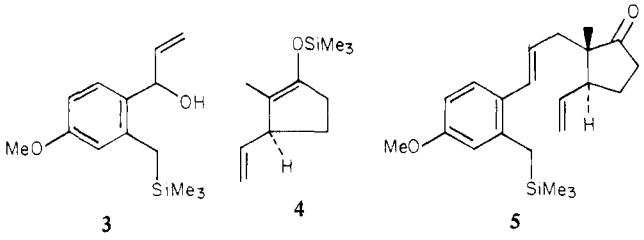
(1) Butenandt, A. *Naturwissenschaften* **1929**, *17*, 879. Doisy, E. A.; Veler, C. D.; Thaley, S. A. *Am. J. Physiol.* **1929**, *90*, 329.
(2) For a comprehensive account of the synthesis of estrone up to the Velluz synthesis, see: Taub, D. In "The Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley-Interscience: New York, 1973. For more recent syntheses, see: Bartlett, P. A.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 7501. Danishefsky, S.; Cain, P. *Ibid.* **1976**, *98*, 4975. For recent methods developed for the synthesis of 11-keto steroids, see: Stork, G.; Logusch, E. W. *Ibid.* **1980**, *102*, 1218, 1220.
(3) Ananchenko, S. N.; Torgov, I. V. *Tetrahedron Lett.* **1963**, 1553.
(4) For a review of *o*-quinodimethanes in synthesis, see: Oppolzer, W. *Synthesis* **1978**, 793. For steroid syntheses, see: Oppolzer, W.; Bättig, K.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 1945; *Ibid.* **1977**, *60*, 2964. Kametani, T.; Nemoto, H.; Ishikawa, H.; Shiroyama, K.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 3378. Kametani, T.; Nemoto, H.; Ishikawa, H.; Shiroyama, K.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 3378. Kametani, T.; Nemoto, H.; Ishikawa, H.; Shiroyama, K.; Matsumoto, H.; Fukumoto, K. *Ibid.* **1977**, *99*, 3461.
(5) Oppolzer, W.; Roberts, D. A.; Bird, T. G. C. *Helv. Chim. Acta* **1979**, *62*, 2017. Nicolaou, K. C.; Barnette, W. E.; Ma, P. *J. Org. Chem.* **1980**, *45*, 1463.
(6) Funk, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1979**, *101*, 215; *Ibid.* **1977**, *99*, 5483.
(7) For part 8 in this series, see: Cooke, F.; Moerck, R.; Schwindeman, J.; Magnus, P. *J. Org. Chem.* **1980**, *45*, 1046.
(8) Meyers, A. I.; Mihelich, E. D. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 270. Meyers, A. I.; Lutomski, K. *J. Org. Chem.* **1979**, *44*, 4463.
(9) Gschwend, H. W.; Rodriquez, H. R. *Org. React. (N.Y.)* **1980**, *26*, 1. Gschwend, H. W.; Hamden, A. *J. Org. Chem.* **1975**, *40*, 2008.
(10) Nordin, I. C. *J. Heterocycl. Chem.* **1966**, *3*, 53. Leed, A. R.; Boettger, S. D.; Ganem, B. *J. Org. Chem.* **1980**, *45*, 1098.

0002-7863/80/1502-6885$01.00/0



in one pot; the overall yield of **3** from **1** with purification of **1b**, **1d**, and **2** by bulb-to-bulb distillation is 81%. The conversion of **1a** into **1d** can be carried out directly by using ICH_2SiMe_3 or $CF_3SO_2OCH_2SiMe_3$[11] to introduce the $-CH_2SiMe_3$ group, but the yields of **1d** are very low.

2-Methylcyclopentenone was converted into the trimethylsilyl enol ether **4** by using the described procedure.[6] When a 1:1 mixture of **3** and **4** in dichloromethane at −78 °C was treated with

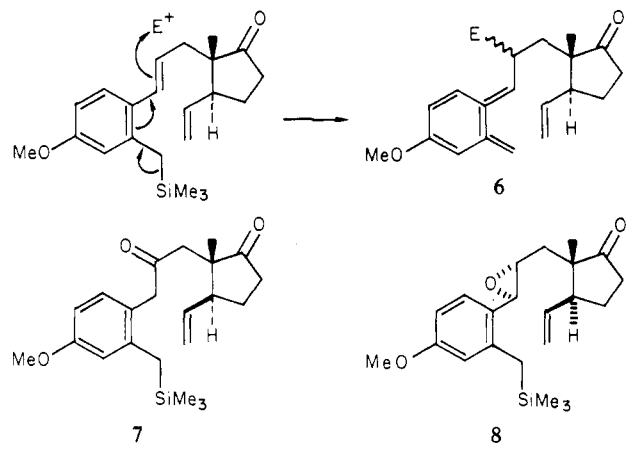


zinc bromide (catalyst) and warmed to −20 °C, a clean transformation took place to give **5** (88%) as a mixture of diastereomers, with the desired trans-D ring predominating (ca. 4:1) by NMR. The structure of **5** was readily confirmed by NMR, IR, and mass spectroscopy; in particular, the λ_{max} 265-nm value demonstrated the presense of the *p*-methoxystyrene chromophore.

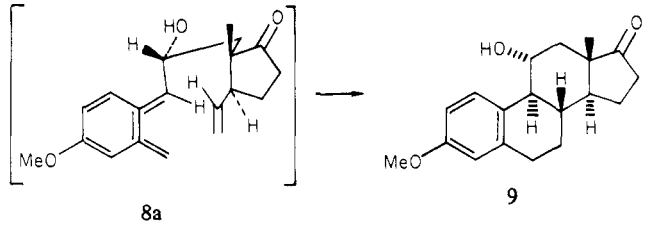
It should be noted that the benzylsilane **5** is stable to the electrophilic conditions used to prepare it, although it is readily polymerized by chromatography over silica gel and exposure to proton acids.

The conversion of **5** into ring A aromatic steroids may be triggered by the addition of an appropriate electrophile to the electron-rich 9,11-double bond, followed by cleavage of the Si–C bond to generate the quinodimethane **6**. In the event, treatment of **5** with *m*-chloroperbenzoic acid in dichloromethane (1 h at 0 °C), buffered with sodium bicarbonate to prevent formation of the 11-oxo *BC*-secosteroid **7**, gave a single epoxide **8** (60%).

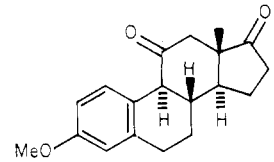
When the epoxide **8** was treated with cesium fluoride (2 equiv/20 h) in diglyme at room temperature (27 °C), a clean



transformation took place to give 11α-hydroxyestrone methyl ether **9** (70%).[12] These extremely mild conditions (cf. ref 4)[13] should



be compared with the usual thermal (ca. 200 °C) methods for generating *o*-xylylene intermediates for steroid synthesis. Oxidation of **9** with pyridinium chlorochromate gave 11-oxoestrone methyl ether **10** (70%).



This synthesis of *dl*-11α-hydroxyestrone methyl ether **9** (overall yield 30%)[14] illustrates two useful aspects of organosilicon chemistry as applied to steroid synthesis: the trapping of the allyl cation (from **3**) by the nucleophilic trimethylsilyl enol ether **4** is completely regiospecific and proceeds under exceptionally mild conditions. The mild, neutral conditions for generating *o*-xylylenes (**8** → **8a**) are compatible with a wide range of functionalities and lend themselves, in particular, to the introduction of an oxygen functionality at C-11.

We are, at present, investigating other applications of these methods and suitable precursors for the synthesis of chiral steroids.

Acknowledgment. The National Institutes of Health is gratefully thanked for their support of our program (GM25231-01). Dr. Richard Laub is thanked for advice concerning chromatographic systems and characterization of 11-hydroxy steroids.

(11) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452.

(12) Compared with an authentic sample prepared from 11α-hydroxyestrone, kindly supplied by Dr. John Babcock (Upjohn).

(13) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 863. These authors described a Sommelet rearrangement route to benzylsilanes and their cleavage to *o*-xylylenes.

(14) The yields of **8** and **9** are not optimized. All new compounds were characterized by IR, NMR, mass spectroscopy, and/or microanalysis.

Stevan Djuric, Tarun Sarkar, Philip Magnus*

Evans Chemistry Laboratory, The Ohio State University Columbus, Ohio 43210

Received July 10, 1980