Communications to the Editor

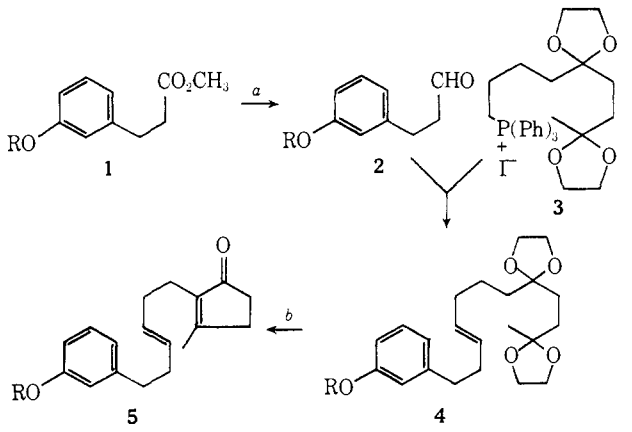
A Stereospecific Total Synthesis of Estrone *via* a Cationic Olefinic Cyclization[1]

Sir:

In connection with a program directed toward the synthetic development of cationic olefin cyclizations we decided to explore a new approach to estrone (**11**, R = H) *via* the cyclization **6** → **7**.[2,3] It was envisaged that this latter substance, on epoxidation (to give **10**) followed by pinacol-type rearrangement, could be converted into estrone. The present communication discloses the realization of these expectations.

The cyclopentenones **5** (R = CH_3 and H), from which the cyclopentenol derivatives **6** were prepared, were obtained in good yield by the convergent synthesis outlined in Scheme I. Thus, reduction of **1** (R = CH_3)[4]

Scheme I



R = CH_3

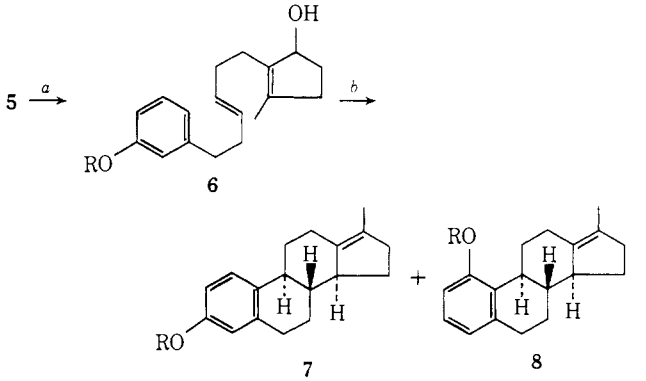
[a] $NaAlH_2(OCH_2CH_2OCH_3)_2$, THF, 3 hr, −75°. [b] 1:2 0.1 *N* HCl–EtOH, 5 hr, 50°, then 2 parts 0.1 *M* NaOH, 7 hr, reflux.

with Red-Al[5] followed by distillation[6] at 110° (0.01 mm) afforded a 95% yield of the aldehyde **2** (R = CH_3) (>95% pure by vpc analysis). A sample was purified *via* the bisulfite adduct and redistilled.[7] Wittig–Schlosser condensation of this aldehyde with the diketal phosphonium iodide **3** as previously described[8] afforded the diketal **4** (R = CH_3) in 65% yield after chromatography. Analysis by vpc of the cyclopentenone **5** (R = CH_3) (see below) showed that this reaction had proceeded with greater than 98% trans stereoselectivity. A sample of the diketal was distilled[6] at 200° (0.05 mm).[7] Hydrolysis of the diketal followed by cyclodehydration[2] gave after distillation[6] at 180° (0.02 mm) the cyclopentenone **5** (R = CH_3) in 91% yield.[7]

Employment of methyl 3-(*m*-methoxymethoxyphenyl)propionate[9] (**1**) (R = CH_3OCH_2) as starting material in this sequence gave **4** (R = CH_3OCH_2). Hydrolysis with methanolic sulfuric acid followed by cyclodehydration[2] afforded, upon distillation[6] at 220° (0.015 mm), the phenolic cyclopentenone **5** (R = H) in 83% yield, mp 88–91°, after recrystallization from diisopropyl ether.[7] The cyclopentenones **5** (R = CH_3 and H) were reduced in quantitative yield to the cyclopentenols **6** (R = CH_3 and H) which, due to their susceptibility to dehydration, were used for the cyclization step without purification. Rapid distillation[6] of **6** (R = CH_3) at 170° (0.05 mm) afforded an analytical specimen.[7]

Addition of stannic chloride to a solution of **6** (R = CH_3) in nitroethane at −75° resulted in the rapid formation of the tetracyclic compounds **7** and **8** (R = CH_3) in the ratio of 1.4:1 (determined by vpc analysis) (Scheme II). This ratio could be increased to 4.3:1 by conducting the cyclization in methylene chloride at −100° with inverse addition of the substrate to 3 mol equiv of stannic chloride. The isomers **7** and **8** (R = CH_3) were isolated in 59 and 12% yields, respectively, by chromatography on silica gel. Recrystallization from ethanol gave the racemic 3-methoxy isomer[10] **7** (R = CH_3): mp 80.5–

Scheme II



[a] For R = CH_3 or H, $NaAlH_2(OCH_2CH_2OCH_3)_2$, THF, 30 min, 0°. [b] For R = TMS, 3 equiv of $SnCl_4$, CH_2Cl_2, 30 min, −100°.

81°;[7] $\lambda_{max}^{CHCl_3}$ 6.20, 6.36 (w), 6.68, 6.9 μ; λ_{max}^{MeOH} 277 (log ε 3.43), 286 mμ (3.39). The nmr spectrum ($CDCl_3$) showed singlets at δ 1.63 and 3.74 ppm for the 17-methyl and methoxyl groups, respectively, as well as a pattern in the aromatic region similar to that of estradiol.[11] The 1-methoxy isomer, which is presumed to have the configuration shown in formula **8** (R =

(1) This represents part of a general study of nonenzymic biogenetic-like olefinic cyclizations. For the previous paper of this series, see D. R. Morton and W. S. Johnson, *J. Amer. Chem. Soc.*, **95**, 4419 (1973).

(2) *Cf.* S. J. Daum, R. L. Clarke, S. Archer, and W. S. Johnson, *Proc. Nat. Acad. Sci. U. S.*, **62**, 333 (1969).

(3) *Cf.* D. J. Goldsmith and C. F. Phillips, *J. Amer. Chem. Soc.*, **91**, 5862 (1969).

(4) A. Cohen, *J. Chem. Soc.*, 429 (1935).

(5) Aldrich Chemical Co.; 70% $NaAlH_2(OCH_2CH_2OCH_3)_2$ in benzene; *Eastman Org. Chem. Bull.*, **42** (3), 1 (1970).

(6) Evaporative bulb-to-bulb distillation using a Büchi kugelrohrofen.

(7) The nmr and ir spectra, as well as the combustion analysis, of this specimen were consistent with the assigned structure.

(8) W. S. Johnson, M. B. Gravestock, and B. E. McCarry, *J. Amer. Chem. Soc.*, **93**, 4332 (1971).

(9) Methyl *m*-hydroxycinnamate (T. Posner, *J. Prakt. Chem.*, **82**, 425 (1910)) was hydrogenated over platinum oxide to give the phenolic ester **1** (R = H)[7] followed by treatment with sodium hydride and chloromethyl methyl ether to give **1** (R = CH_3OCH_2).[7]

(10) This substance is known in its natural enantiomeric form: A. Cohen, J. W. Cook, and C. L. Hewett, *J. Chem. Soc.*, 445 (1935); W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961); G. Stork, H. N. Khastgir, and A. J. Solo, *J. Amer. Chem. Soc.*, **80**, 6457 (1958).

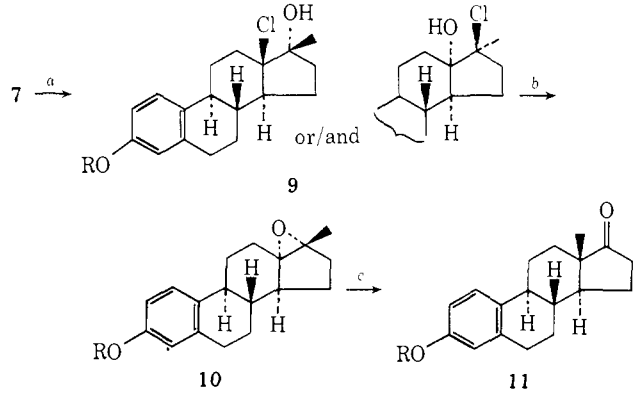
(11) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, p 98.

CH_3), after recrystallization from ethanol, melted at 110–112°:[7] $\lambda_{max}^{CHCl_3}$ 6.24 (w), 6.32, 6.85, 6.95 μ; λ_{max}^{MeOH} 272 (log ϵ 3.34), 279 mμ (3.33). The nmr ($CDCl_3$) showed absorption at δ 3.76 ppm for the methoxyl group and an aromatic proton pattern consistent with the presence of three vicinal protons.[11]

The monotrimethylsilyl (TMS) derivative **6** (R = TMS), prepared by selective silylation of **6** (R = H) at 0° with bis(trimethylsilyl)trifluoroacetamide, gave, under the preferred cyclization conditions (see above), a very satisfactory para–ortho ratio of about 20:1, in essentially quantitative yield. The crude product was hydrolyzed with methanol and benzoylated (C_6H_5COCl, C_5H_5N) to yield **7** (R = C_6H_5CO), mp 114–116°, after recrystallization from methanol.[7]

Direct peracid epoxidation of the methoxy olefin **7** (R = CH_3) led to a 5:1 mixture of β and α epoxides[12] as judged by vpc analysis; however, stereoselective formation of the desired α epoxide could be accomplished *via* the chlorohydrin **9**. The benzoate chlorohydrin **9** (R = C_6H_5CO), after preparative tlc (40% yield, not optimized, based on **5** (R = H)) and recrystallization from acetone, melted at 183–189°.[7] The 17-methyl nmr signal occurred at δ 1.50 ppm; however, no decision could be made between the two possible α-hydroxy β-chloro isomers. The phenolic epoxide **10** (R = H), after chromatography and recrystallization from methanol, melted at 196–202°.[7]

Scheme III



[a] *p*-$TsNCl_2$, 1:9 H_2O–$CH_3OCH_2CH_2OCH_3$, 10 min, 0°. [b] $(CH_3)_4NOH$, aqueous acetone, 2 hr, 25°. [c] $BF_3 \cdot Et_2O$, benzene, 1 min, 25°.

The crude phenolic epoxide **10** (R = H), upon treatment with boron trifluoride,[13] followed by chromatography, afforded *dl*-estrone **11** (R = H) (Scheme III), mp 243–252°, in 22% overall yield (eight steps) from **5** (R = H). Recrystallization from acetone gave material, mp 251–255°, which was identical with authentic *dl*-estrone by mixture melting point, vpc, and ir (KBr).

In the course of studying the cyclization of derivatives of **6** we observed that the para–ortho ratio (**7**/**8**) was strikingly dependent upon modification of the leaving (allylic) group of the substrate **6**. This result suggested that the cyclization might be a concerted process; hence the matter has been studied in some detail.[14]

(12) *Cf.* J. Bascoul, C. Reliaud, A. Guinot, and A. Crastes de Paulet, *Bull. Soc. Chim. Fr.*, 4074 (1968); S. K. Pradhan and V. M. Girijavallabhan, *Steroids*, **13**, 11 (1969).

(13) *Cf.* J. Bascoul and A. Crastes de Paulet, *Bull. Soc. Chim. Fr.*, 189 (1969).

(14) P. A. Bartlett, J. I. Brauman, W. S. Johnson, and R. A. Volkmann, *J. Amer. Chem. Soc.*, **95**, 7502 (1973).

For more than 25 years, the synthesis of estrone has held the special interest of chemists,[15] partly because it not only is an important intermediate in the production of 19-nor steroids[16] but it is one of few steroids produced commercially by total synthesis. Although in its present unrefined state[17] our synthesis is not as practical as the Torgov–Smith route,[16] it represents a fundamentally new approach based on a highly efficient, stereospecific olefinic cyclization, and it has versatile potential for development.

Acknowledgments. We are indebted to the National Institutes of Health and the National Science Foundation for support of this research.

(15) For a partial review and bibliography see N. Anand, J. Bindra, and S. Ranganathan, "Art in Organic Synthesis," Holden-Day, San Francisco, Calif., 1970, pp 177–181.

(16) See R. Pappo in "The Chemistry and Biochemistry of Steroids," Vol. 3, No. 1, N. Kharasch, Ed., Intra-Science Research Foundation, Santa Monica, Calif., 1969, pp 123–130.

(17) Pertaining to one of various possible improvements, mechanistic studies[14] suggest the possibility that the resolved form of substrate **6** may cyclize with retention of optical activity, a matter which is currently under investigation.

(18) National Science Foundation Predoctoral Fellow, 1969–1972.

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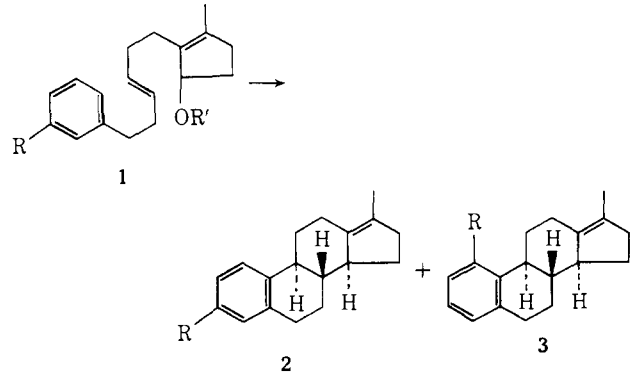
Concerning the Mechanism of a Nonenzymic Biogenetic-Like Olefinic Cyclization

Sir:

The question of the mechanism of nonenzymic polyolefinic cyclizations, involving the formation of more than one ring, has been open to debate, and up until now there has been no direct evidence on this point. On the one hand, the intermediacy of partially cyclized cations has been shown to be consistent with the observed stereospecificity of such cyclizations.[1] The present communication, on the other hand, presents evidence which supports a process involving concerted formation of two rings in the cyclization of compounds **1** → **2** and **3**.



The major synthetic transformation in a total synthesis of estrone,[2] namely the Lewis acid catalyzed cyclizations of allylic alcohols **1**, to the corresponding

(1) See *inter alia* W. S. Johnson, *Trans. N. Y. Acad. Sci.*, **29**, 1001 (1967); K. E. Harding, R. C. Ligon, T.-C. Wu, and L. Rodé, *J. Amer. Chem. Soc.*, **94**, 6245 (1972); K. E. Harding, *J. Biorg. Chem.*, **2** (3), 248 (1973).

(2) P. A. Bartlett and W. S. Johnson, *J. Amer. Chem. Soc.*, **95**, 7501 (1973).