A Convenient Route to the Dihydroxyacetone Substituent

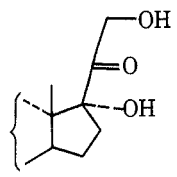
Jack E. Baldwin,* O. William Lever, Jr., and Nathan R. Tzodikov

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

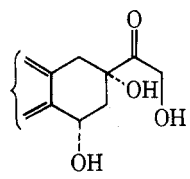
Received February 2, 1976

A method for the conversion of a ketone to the dihydroxyacetone substituent has been developed. This reaction of the ketone with methoxyvinyllithium (MVL) yields after oxidation with peracids the dihydroxyacetone derivative directly. Alternately the intermediate adduct, as its *p*-nitrobenzenesulfinyl ester, can be rearranged to the isomeric sulfone, oxidation of which may yield the hydroxy keto sulfone, thereby providing an alternative stereochemistry at the tertiary alcohol center. These reactions were exemplified by cyclohexanone and estrone-3-methyl ether.

The dihydroxyacetone unit is a structural feature common to the corticoid hormones, as **1**, and also the antitumor agent, adriamycin, as **2**. In an effort to develop a scheme for

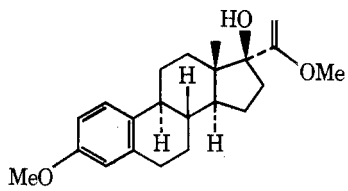


1

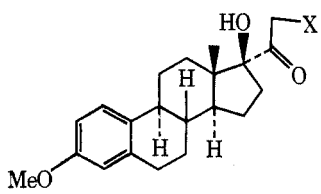


2

the introduction of this functionality we have examined transformations of the adducts from methoxyvinyllithium (MVL) with ketones.[1] Thus estrone methyl ether reacted with MVL to yield the 17α adduct **3** (83%), which was smoothly hydrolyzed (aqueous methanolic acetic acid, 76%) to the corresponding 17α-acetyl-17β-alcohol **4**. When the adduct **3** was oxidized with osmium tetroxide in pyridine or with *m*-chloroperbenzoic acid in wet ether it was transformed to the dihydroxy ketone derivative **5**, readily acetylated to the 21-acetate **6**. The stereochemical assignments are based on the



3

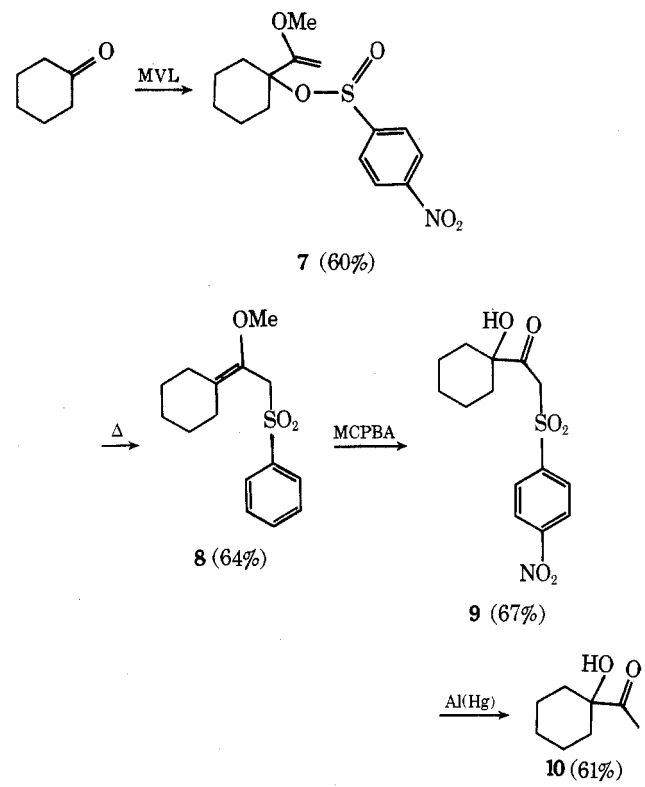


4, X = H
5, X = OH
6, X = OAc

known tendency for α-addition of organometallic reagents to the 17-ketone.[2] Thus the stereochemistry of the side chain is necessarily controlled by the stereochemistry of the initial adduct. In order to allow some control over this point we have developed the alternative process shown in Scheme I.

The initial adduct of MVL with the ketone, in this case cyclohexanone, was treated with *p*-nitrobenzenesulfinyl chloride to yield the sulfinate **7**, which on heating to 100 °C underwent a [2,3]-sigmatropic rearrangement[3] to the enol ether sulfone **8**. Such a rearrangement of an allylic sulfinate has precedence[4] but this appears to be the first example in which an enol ether has participated. The *p*-tolylsulfinate corresponding to **7** could be prepared but its thermolysis gave rise to a complicated series of products. Oxidation of **8** to **9** was

Scheme I



achieved (67%) with *m*-chloroperbenzoic acid in moist methylene chloride. Compounds of type **8** and **9** are certainly amenable to further transformation, e.g., alkylation α to the sulfonyl group. Removal of this sulfonyl function was readily achieved by reduction with aluminum amalgam in aqueous THF (61%) to the hydroxy ketone derivative **10**. Methods exist for the elaboration of such methyl ketones to the dihydroxyacetone substituent.[2a]

These two paths to the dihydroxyacetone substituent provide alternative sequences for the formation of the tertiary alcohol moiety of this substituent. It is reasonable to expect, therefore, that they may provide different stereochemistry at this center, since in the first case control is provided by the direction of addition of MVL and in the second case the stereochemistry emanates from the direction of epoxidation.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and have not been corrected. Microanalyses were performed by Midwest Microlabs, Inc. Indianapolis, Ind. Ir spectra were recorded on a Perkin-Elmer Model 700 spectrophotometer. NMR spectra were recorded on a Varian Associates T-60 spectrometer or a Hitachi Perkin-Elmer R-22B instrument. Silica gel for column chromatography was Davison Chemicals grade 950 (60–200 mesh) or Merck silica gel 60, no. 7734.

3-*O*-Methyl-17α-(α-methoxyvinyl)estra-3,17β-diol (3). To a

stirred solution of α-methoxyvinyllithium[1] (12 mmol) in THF–pentane at −60 °C under nitrogen was added estrone methyl ether (1.15 g, 4 mmol) dropwise in THF (20 ml). The reaction mixture was warmed to 0 °C over a period of 0.5 h, then quenched with aqueous ammonium chloride and extracted with ether. The organic layer was dried ($MgSO_4$) and most of the ether was removed under reduced pressure. Addition of hexane (50 ml) induced crystallization of the product in 74% yield (1.02 g), mp 144–146 °C (it should be noted that when the reaction was carried out with a twofold excess of MVL, crystalline **3** was obtained in 83% yield, mp 141–143 °C): ir (CCl_4) 3650, 1665, 1620 cm^{-1}; NMR (CCl_4) δ 0.90 (s, 3 H), 1.0–2.4 and 2.6–3.0 (m, 16 H), 3.54 (s, 3 H), 3.70 (s, 3 H), 4.02 and 4.15 (AB quartet, J_{AB} = 2.5 Hz, 2 H), 6.5–6.8 and 7.05–7.3 (aryl m, 3 H). Recrystallization from hexane–ether provided colorless plates, mp 147.5–149 °C.

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.20; H, 8.83. Found: C, 77.50; H, 8.55.

3-*O*-Methyl-17α-acetylestra-3,17β-diol (4). A solution of steroidal enol ether **3** (70 mg, 0.204 mmol) in methanolic acetic acid (1:1, 6 ml) containing a little water (0.5 ml) was stirred at 20 °C for 2 h, then taken up in ether (50 ml). The ethereal solution was washed with water, dried ($MgSO_4$), and concentrated to give a white solid (67 mg, 100%, mp 108–111 °C) which was recrystallized from hexane–methylene chloride to provide **4** 51 mg (76%), as colorless needles (mp 121–122 °C): ir ($CHCl_3$) 3600, 3450, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.00 (s, 3 H), 1.3–3.1 (series of multiplets with a three-proton singlet visible at δ 2.00, total integral 19 H), 3.77 (s, 3 H), 6.53–6.8 and 7.0–7.12 (aryl m, 3 H).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.7; H, 8.59. Found: C, 76.7; H, 8.65.

3-*O*-Methyl-17α-(α-hydroxyacetyl)estra-3,17β-diol (5). To a solution of 3-*O*-methyl-17α-(α-methoxyvinyl)estra-3-17β-diol (539 mg, 1.58 mmol) in pyridine (10 ml) was added osmium tetroxide in pyridine (0.158 M, 10 ml, 1.58 mmol); a black color developed immediately and the reaction mixture was stirred at room temperature for 18 h. The osmate ester was reduced by shaking vigorously with an aqueous pyridine (10 ml H_2O/50 ml pyridine) solution of sodium bisulfite (4.0 g) for 3 h. The resulting solution was extracted with 5 × 50 ml of chloroform, and the chloroform was washed with 1 N HCl, saturated bicarbonate, and brine, dried (Na_2SO_4), and evaporated to leave a black tar.

The tar was chromatographed on silica gel; elution with benzene/ethyl acetate (9:1) gave estrone methyl ether. Ethyl acetate elution afforded 3-*O*-methyl-17α-(α-hydroxyacetyl)estra-3,17β-diol (**5**) as a white solid, 163 mg (30%), mp 139–145 °C.

The analytical sample was recrystallized from a boiling solution of 10% chloroform in hexane, and had mp 145–147 °C: ir ($CHCl_3$) 3575, 3455, 1710, 1610 cm^{-1}; 90-MHz NMR ($CDCl_3$) δ 7.1–6.45 (m, 3 H), 4.41 (br s, 2 H), 3.64 (s 3 H), 0.92 (s 3 H), 3.2–0.90 (complex m, 17 H); mass spectrum (70 eV) *m/e* 344 (M^+).

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.2; H, 8.19. Found: C, 73.1; H, 7.8.

To a cold (6 °C) solution of 95% *m*-chloroperbenzoic acid (106 mg, 585 μmol peracid) was added enol ether **3** (200 mg, 585 μmol) in *wet* ether (30 ml) at a rate such that the temperature remained below 6 °C, and was stirred at 0–6 °C for 1 h. The ethereal solution was washed with saturated bicarbonate and brine, dried (Na_2SO_4), and evaporated to leave 180 mg of **4** as a white solid (90% crude). The solid was recrystallized as above to give 130 mg (65%) of 3-*O*-methyl-17α(α-hydroxyacetyl)estra-3,17β-diol, mp 145–147 °C.

3-*O*-Methyl-17α-(α-acetoxyacetyl)estra-3,17β-diol (6). The steroidal keto diol **5** (176 mg, 570 μmol) in dry pyridine (3 ml) was stirred overnight under nitrogen with acetic anhydride (87 mg, 855 μmol). The excess acetic anhydride was hydrolyzed by stirring with water (4 drops) for 30 min and the acetate was precipitated upon addition of 1 N HCl (25 ml). The white solid was filtered and recrystallized from hexane/dichloromethane to afford **6** as colorless needles: mp 129–130 °C; 177 mg (83%); ir ($CHCl_3$) 3600–3200 br, 1745, 1721, 1605 cm^{-1}; NMR (90 MHz) ($CHCl_3$) δ 7.18–6.52 (m, 3 H), 5.22, 4.91 (AB q, *J* = 18 Hz), 3.77 (s, 3 H), 2.19 (s, 3 H), 0.99 (s, 3 H), 3.0–1.2 (complex multiplet, 16 H); uv (EtOH) λ_{max} 278 nm (ε 9300), 287 (8600).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.5; H, 7.82. Found: C, 69.8; H, 7.45.

1-(α-Methoxyvinyl)-1-cyclohexyl *p*-Nitrosulfinate (7). To a stirred solution of α-ketol, 1-hydroxy-1-(α-methoxyvinyl)cyclohexane[1] (1.0 g, 6.4 mmol) in dry tetrahydrofuran (15 ml) at 0 °C under dry nitrogen was added dropwise ethereal methyllithium (3.1 ml, 20 M, 6.2 mmol). After stirring for 5 min at 0 °C, the solution was cooled to −70 °C and *p*-nitrobenzenesulfinyl chloride[5] (1.25 g, 6.1 mmol) was added dropwise as a solution in tetrahydrofuran (10 ml). After stirring for 0.5 h at −70 °C and 0.5 h at 20 °C, the reaction mixture was taken up in ether (80 ml) and washed with aqueous sodium bicarbonate (three 100-ml portions), then brine (50 ml). After drying ($MgSO_4$) and concentration in vacuo, there was obtained a dark yellow oil (2.00 g) which was triturated thoroughly with ten portions (20 ml) of pentane. The residual gum (62 mg) was discarded and the combined extracts were concentrated and cooled to furnish the sulfinate **7**, 1.19 g (60%), as very pale yellow needles (mp 89–90 °C): NMR ($CDCl_3$) δ 1.4–2.4 (m, 10 H), 3.64 (s, 3 H), 4.36 and 4.56 (AB quartet, *J* = 3 Hz, 2 H), 7.83 and 8.3 (AB quartet, *J* = 8 Hz, 4 H); ir ($CHCl_3$) no hydroxyl present; the analytical sample was recrystallized from pentane as colorless needles, mp 89.5–90 °C.

Anal. Calcd for $C_{15}H_{19}NO_5S$: C, 55.37; H, 5.89. Found: C, 55.22; H, 6.06.

1-(2-Cyclohexylidene-2-methoxy)ethyl *p*-Nitrophenyl Sulfone (8). Thermal Rearrangement of 1-(α-Methoxyvinyl)-1-cyclohexyl *p*-Nitrosulfinate (7). The sulfinate **7** was observed to undergo rapid thermal reorganization at 130 °C. For example, in 60 s 40% sulfone was present, and after 90 s, 78%. However, in runs where rearrangement was complete (120–180 s), other products had been formed in small, but variable, amounts.[6] The reaction was more sluggish at 100 °C, i.e., 25% conversion in 7.5 min, but it was observed that the rearrangement could be carried to completion by heating for 30–70 min at 100 °C without significant decomposition. All glassware was washed with concentrated ammonium hydroxide and dried at 130 °C before use.

Pyrolysis at 130 °C. The sulfinate (231 mg) was heated under nitrogen at 130 ±1 °C for 130 s, and then the flask was immediately cooled in ice–water. Thorough treatment with carbon tetrachloride (8 ml) brought all but a small amount of dark solid into solution. Filtration and concentration provided a dark yellow solid (220 mg) which was triturated with pentane (1 ml), ether (0.5 ml), then pentane (1 ml) to furnish pale yellow crystals of the sulfone **8**, 129 mg (56%), with mp 118–120 °C. In another experiment, treatment of the melt with 1 ml of 1:1 pentane–ether gave a 41% yield of crystals with mp 121–123 °C.

Pyrolysis at 100 °C. A sample (0.500 g) of the sulfinate was heated at 100 ± 1 °C under nitrogen for 70 min. Thorough extraction with carbon tetrachloride (13 ml) followed by filtration and concentration provided yellow crystals (0.480 g, 96%) which upon trituration with ether (1 ml) provided pale yellow crystals, 0.32 g (64%), of the sulfone **8**, mp 121–123 °C: NMR ($CDCl_3$) δ 1.46 (bm, 8 H), 1.88 (m, 2 H), 2.18 (m, 2 H), 3.32 (s, 3 H), 4.05 (s, 2 H), 8.02 and 8.32 (AB quartet, *J* = 9 Hz, 4 H).

The analytical sample was recrystallized from pentane–ether, mp 121.5–123 °C.

Anal. Calcd for $C_{15}H_{19}NO_5S$: C, 55.37; H, 5.89. Found: C, 55.14; H, 6.14.

1-[α-(p-Nitrobenzenesulfonyl)]acetylcyclohexanol (9). To a stirred solution of the sulfonyl enol ether **8** (0.390 g, 1.20 mmol) in methylene chloride (15 ml) at 0 °C was added dropwise a solution of *m*-chloroperbenzoic acid (85%, 0.245 g, 1.20 mmol) in methylene chloride (10 ml). After 0.5 h at 0 °C and 0.5 h at 20 °C, the solution was washed twice with aqueous sodium bicarbonate (20 ml), then water (20 ml). After drying ($MgSO_4$) and evaporation of solvent there remained a yellow solid (0.390 g) which was recrystallized from benzene to provide the product **9** as faintly yellow crystals: 0.219 g (67%), mp 155–157 °C; ir ($CHCl_3$) 3540, 1710, 1540, 1360, 1330, 1170 cm^{-1}; NMR ($CDCl_3$) δ 1.61 (bs, 10 H), 2.88 (s, 1 H, exchangeable with D_2O), 4.59 (s, 2 H), 8.05 and 8.44 (AB quartet, *J* = 9 Hz, 4 H). The analytical sample was prepared by recrystallization from benzene, mp 162–163°.

Anal. Calcd for $C_{14}H_{17}NO_6S$: C, 51.4; H, 5.24. Found: C, 51.7; H, 5.44.

The crude sulfone obtained from pyrolysis of the sulfinate could be epoxidized without purification, e.g., the pyrolysate from 136 mg of sulfinate was epoxidized as described above to afford a waxy solid (103 mg) which upon trituration with ether (1 ml) provided the hydroxy keto sulfone (mp 155–157 °C), 58 mg (43% based on sulfinate).

Reduction of 1-(α-*p*-Nitrobenzenesulfonyl)acetylcyclohexanol (9) with Aluminum Amalgam. 1-Acetylcyclohexanol (10). Aluminum foil (430 mg) was cut into strips (ca. 1 × 5 cm) and immersed for 15 s in 2% aqueous mercuric chloride, then rinsed with absolute ethanol followed by anhydrous ether, and cut into 1-cm squares directly into a flask containing the hydroxy keto sulfone **9** (510 mg, 1.56 mmol) in 10% aqueous tetrahydrofuran (30 ml). The stirred mixture was gently refluxed in a 65 °C bath for 70 min, at which time it was cooled and filtered through sintered glass. The solids were washed with ether, and then combined filtrate and washings were concentrated to a volume of several milliliters at 1 atm (15-cm Vigreux column). Ether (10 ml) was added, the water layer separated, and the dried ($MgSO_4$) ether layer concentrated at 1 atm (Vigreux). Methylene chloride (10 ml) was added and the solution concentrated under reduced pressure to leave a pale yellow oil (233 mg) which was extracted thoroughly with two portions of warm distilled pentane (10

ml). Removal of solvent then furnished 1-acetylcyclohexanol (10), 136 mg (61%), as a colorless liquid: ir (film) 3600–3150, 1710 cm^{-1}; NMR ($CDCl_3$) δ 1.3–2.0 (m, 10 H), 2.27 (s, 3 H), 3.65 (br s, 1 H, exchanges with D_2O).

Acknowledgments. We wish to thank the National Science Foundation, the National Institutes of Health, and Merck Sharp and Dohme for their generous support and Dr. V. Kane for estrone methyl ether.

Registry No.—**3**, 58873-40-8; **4**, 34965-67-8; **5**, 58917-11-6; **6**, 58917-12-7; **7**, 58873-41-9; **8**, 58873-42-0; **9**, 58873-43-1; **10**, 1123-27-9; 2-methoxyvinyllithium, 42722-80-5; estrone methyl ether, 1624-62-0; 1-hydroxy-1-(α-methoxyvinyl)cyclohexane, 54123-63-6; *p*-nitrobenzenesulfinyl chloride, 13088-17-0; *m*-chloroperbenzoic acid, 937-14-4.

References and Notes

(1) J. E. Baldwin, G. A. Höfle, and O. W. Lever, Jr., *J. Am. Chem. Soc.*, **96**, 7125 (1974).
(2) (a) L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, N.Y., 1959; (b) J. Von Euw and T. Reichstein, *Helv. Chim. Acta*, **23**, 1114 (1940).
(3) J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *Chem. Commun.*, 537 (1968).
(4) (a) S. Braverman and H. Michoulam, *Isr. J. Chem.*, **4**, 17 (1966); (b) S. Braverman and Y. Stabinsky, *Chem. Commun.*, 270 (1967); (c) C. J. M. Stirling, *ibid.*, 131 (1967); (d) G. Smith and C. J. M. Stirling, *J. Chem. Soc. C*, 1530 (1971); (e) A. C. Cope et al., *J. Am. Chem. Soc.*, **72**, 59 (1950).
(5) F. Muth in Houben-Weyl, "Methoden der Organischen Chemie", Vol. 9, Georg Thieme Verlag, Stuttgart, 1955, pp 309, 340.
(6) At 130 °C, the sample began to darken rapidly after heating in the melt ca. 90 s and rearrangement was still incomplete. At 100 °C, the melt did not become darkened even upon heating for over 1 h.

Macrocycles. Synthesis and Thermal Decomposition of 3-Benzosuberone Diperoxide

B. Lee,* P. R. Story, and J. R. Sanderson

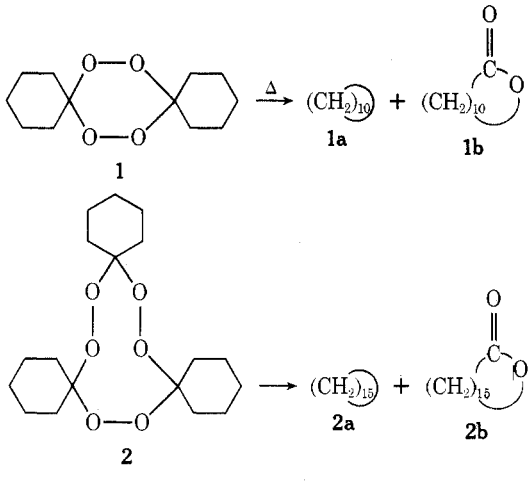
Story Chemical Corporation, Muskegon, Michigan 49445 and Chemistry Department, University of Georgia, Athens, Georgia 30601

Received December 4, 1975

The synthesis and pyrolysis of 3-benzosuberone diperoxide (**4**) gave a fair yield of the macrocyclic hydrocarbon (**5**) and the lactone (**6**). The hydrocarbon (**5**) was converted to 1,6,11,16-tetraketocyclocosane (**9**) using conventional synthetic procedures.

It has been previously reported that cyclic ketone peroxides such as dicyclohexylidene diperoxide (**1**) and tricyclohexylidene triperoxide (**2**) are precursors to macrocyclic hydrocarbons (**1a, 2a**) and macrocyclic lactones (**1b, 2b**).[1] The reactions are illustrated in Scheme I.

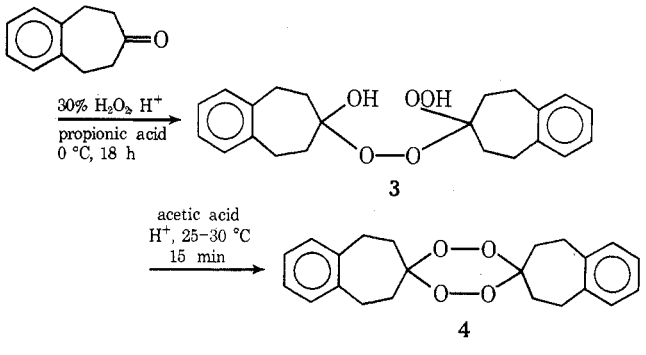
Scheme I



The thermal decomposition of these peroxides was found to give higher, more reproducible yields of the macrocyclic products than photolysis and these results were reported.[2] Improvements have also been reported on synthesis of the precursor triperoxide,[3] diperoxides,[4] and mixed triperoxides.[5]

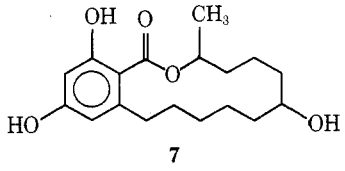
As an extension of the earlier work reported by Story and co-workers,[1] we have undertaken a study of the thermal decomposition of a variety of cyclic ketone peroxides for the purpose of macrocyclic synthesis. In this note, we wish to report our results on the synthesis and thermal decomposition of 3-benzosuberone diperoxide (**4**). The synthesis of this peroxide is outlined in Scheme II.

Scheme II



4 was decomposed in refluxing hydrocarbon solvent to yield the macrocyclic products shown in Scheme III. The products (**5** and **6**) were isolated by a combination of vacuum distillation and column chromatography.

This work greatly extends the utility of the macrocyclic synthesis[1] because it suggests a new approach to the synthesis of molecules similar to animal growth regulators.[6-10] For example, zeranol (**7**) has been used to improve the growth in livestock.[8,9]



5 was converted by the known procedures shown in Scheme IV to 1,6,11,16-tetraketocyclododocosane (**9**). **9** was tested and found to be unsuccessful as a selective ion reagent.[11]

In conclusion, the synthesis of **5, 6,** and **9** would be difficult to accomplish by conventional syntheses alone. Indeed, the procedures outlined in this paper may be used to synthesize a variety of novel large-ring compounds.