suspension of 1[10] (2.1 mmol) in 50 mL of THF at −78 °C under nitrogen. After stirring at −78 °C for 12 h, the yellow solution is partitioned between brine and pentane. The aqueous layer is washed with pentane, and the pooled organic layers are concentrated after drying over Na_2SO_4. The oily residue was purified in the manner described in Table I. From 0.440 g of cyclohexanone, 0.395 g (58%) of pure **3**, 0.086 g (18%) of **4**, and 0.071 g (16%) of cyclohexanone were obtained.

The entries in Table I imply some limitations of this sequence. The reaction works well for aldehydes as illustrated by examples IV and V. The isolated yields of dihydroarene oxides from aldehydes are low owing to mechanical losses during purification. With certain cyclic ketones the selectivity is also good. Acyclic ketones have failed, as yet, to undergo epoxyannelation, providing only products analogous to **4**.[11] To further define the limitations of this process we have examined the substituent effects of the cyclohexanone enolate structure upon the course of this reaction. The methyl cyclohexanone enolate generated from cleavage of 1-(trimethylsilyloxy)-2-methylcyclohexene yields only products similar to 4. The kinetic enolate from 2-methylcyclohexanone affords some of the desired dihydroarene oxide accompanied by products such as 4 derived from both the kinetic enolate and from the isomeric, methyl-substituted enolate. Clearly enolate equilibration competes favorably with oxirane formation. Finally, as expected, 4-substituted cyclohexanones (methoxy or *tert*-butyl) behave as the parent ketone to provide epoxides in comparable isolated yields (see Table I, ref a, b, d). Thus, this sequence transforms aldehyde and nonhindered, cyclic ketone enolates into dihydroarene oxides in about 50% yield. Both structures of types **3** and **4** are novel products from vinyl[11] or butadienylsulfonium[2] salts.

Although we have examined this reaction in detail, we will defer most comments about the mechanism until a full paper. We observe products arising from ~90% 1,4 addition of enolates to 1. The product distribution depends upon temperature and solvent. For example, treatment of **2** as described above at 0 °C rather than −78 °C affords a **3** to **4** ratio of 1.5:1, while use of *tert*-butyl alcohol/*tert*-butoxide as the solvent/base at ambient temperature provides a **3** to **4** ratio of 1:4.

The dihydroarene oxides formed in this process are not available by the other common methods, including intramolecular Darzens condensations,[5] aromatic reduction followed by epoxidation,[1c] or cycloaddition–epoxidation.[1c] We believe this sequence will find application in several syntheses and are continuing our studies of **1**, **3**, and related species.

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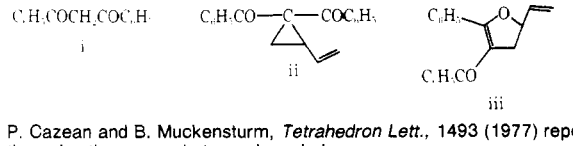
References and Notes

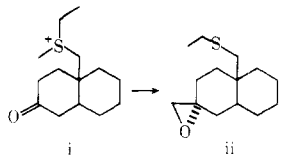
(1) (a) B. Ganem, *Tetrahedron*, **34**, 3353 (1978); (b) F. T. Sher and G. A. Berchtold, *J. Org. Chem.*, **42**, 2569 (1977); (c) D. M. Jerina, H. Yagi and J. W. Daly, *Heterocyles*, **1**, 267 (1973).

(2) H. Braun and G. Huber, *Tetrahedron Lett.*, 2121 (1976). Among the reactions noted by Braun is the conversion of i into ii and iii.



(3) P. Cazean and B. Muckensturm, *Tetrahedron Lett.*, 1493 (1977) reports the only other example to our knowledge.

(4) Several instances of the i to ii path have been reported: see R. S. Matthews and T. E. Meteyer, *Synth. Comm.*, **2**, 399 (1972); *Chem. Commun.*, 1576 (1971), and see ref 7.



(5) (a) D. R. White, *J. Chem. Soc., Chem. Commun.*, 95 (1975); J. M. McIntosh and H. Khalil, *J. Org. Chem.*, **42**, 2123 (1977); (b) S. Danishefsky and G. A. Koppel, *Chem. Commun.*, 367 (1971).

(6) J. K. Crandall, D. B. Banks, R. A. Colyer, R. J. Watkins, and J. P. Arrington, *J. Org. Chem.*, **33**, 423 (1968).

(7) J. Staroscik and R. B. Rickborn, *J. Org. Chem.*, **37**, 738 (1978).

(8) Prepared by the method of H. Varkony, S. Pass, and Y. Mazur, *J. Chem. Soc., Chem. Commun.*, 437 (1974).

(9) M. E. Garst and P. Arrhenius, work in progress.

(10) In our hands, the fluoborate salt is more stable than the corresponding bromide or chloride and appears to be somewhat more soluble in THF. Several modifications of butadienylsulfonium salt structure have failed to increase the amount of **3** formed.

(11) A different set of products has been observed with vinylsulfonium salts: K. Takai, H. Takahashi, Y. Ohshiro, and T. Agawa, *J. Chem. Soc., Chem. Commun.*, 675 (1977); K. Takai and T. Agawa, *J. Org. Chem.*, **42**, 3303 (1977).

Michael E. Garst

Department of Chemistry, D-006
University of California, San Diego
La Jolla, California 92093

Received September 22, 1978

Stereoselective Synthesis of 7-Thia-16-oxa-14β-estrones

Summary: An efficient and stereoselective synthesis of 3-methoxy-7-thia-16-oxa-14β-1,3,5(10),9(11)-estratetraen-17-one was achieved by an application of the Diels–Alder reaction between 7-methoxy-4-vinylthiaisochromene with citraconic anhydride, followed by reduction of the Diels–Alder adduct with $NaBH_4$.

Sir: Although much attention has been devoted to the synthesis of heterocyclic steroids[1] in view of their biological interests, there are few works on the synthesis of thia steroids.[2] An interest in a synthesis of thia estrogens led us to the preparation of 3-methoxy-7-thia-16-oxa-14β-1,3,5(10),-9(11)-estratetraen-17-one (**12**) in order to obtain physiological active steroidal derivatives. A short synthesis of 7-thia-16-oxa-14β-estrone analogues was realized by an application of the Diels–Alder reaction of 7-methoxy-4-vinylthiaisochromene. Herein we wish to report the results of our studies.

First, we explored the Vilsmeier reaction of 7-methoxythiaisochromene (**1**)[3] with dimethylformamide–phosphoryl chloride at 60 °C for 2 h to yield 4-formyl-7-methoxythiaisochromene (**2**),[4,5] mp 75–76 °C, in 90% yield. The Wittig reaction of **2** with methylenetriphenylphosphorane derived from methyltriphenylphosphonium bromide[6] by treatment with *n*-BuLi in THF at room temperature gave 7-methoxy-4-vinylthiaisochromene (**3**)[5] in 90% yield. The Diels–Alder reaction of this sulfur-substituted 1,3-diene was extended for formation of C and D rings of a steroidal system. Treatment of **3** with maleic anhydride in benzene at 60 °C for 5 h yielded the adduct (**4**), mp 202–205 °C (acetone), in 65% yield. Characteristic structural data for **4** are given below: ^1H NMR (acetone-d_6) δ 2.34–3.10 (4 H, m), 3.57 (1 H, d, J = 14 Hz), 3.76 (3 H, s), 3.91 (1 H, d, J = 14 Hz), 4.22 (1 H, d, J = 3 Hz), 6.36–6.56 (1 H, m), 6.72–6.88 (2 H, m), 7.43 (1 H, d, J = 8 Hz); mass spectrum 302 (M^+). Doublet signals at δ 4.22 ($J_{8,14}$ = 3

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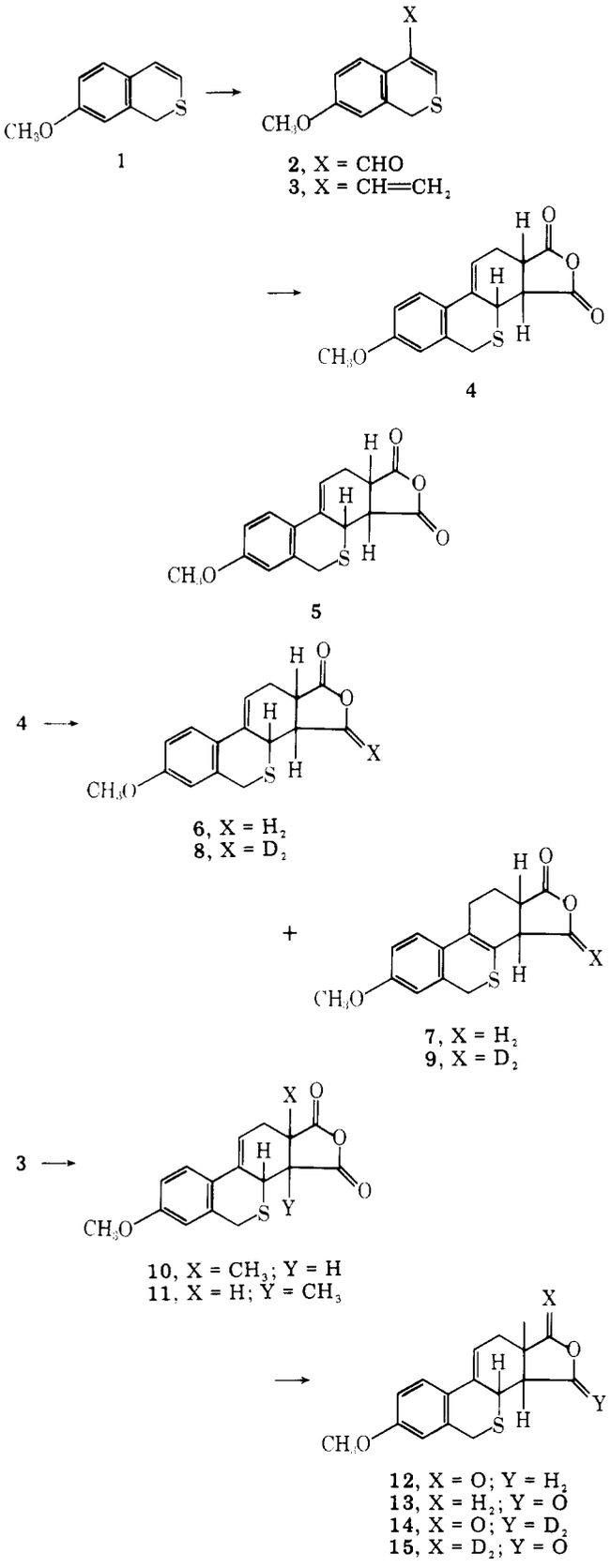
Scheme I



Hz) attributable to C_8-H indicates a cis relationship between C_8-H and C_{14}-H. Therefore, of two possible structures, the product was assigned to the endo adduct (**4**) and a formation of an alternative exo adduct (**5**) was not observed. Conversion of 4 to 3-methoxy-7-thia-16-oxa-18-nor-14β-1,3,5(10),-9(11)-estratetraen-17-one (**6**; 24%) was well effected by reduction with $NaBH_4$[7] in THF at room temperature accompanied by formation of the $\Delta^{8,9}$ isomer (**7**; 10.4%); these were separated by preparative TLC.[8] In order to ascertain their structures, reduction of **4** was carried out with $NaBD_4$ to yield the corresponding C_{15}-deuterated product **8** and **9**.[8] Complex signals at δ 2.88–3.12 attributable to C_{14}-H in **6** was changed to a quartet by deuteration of C_{15}-H_2. Retention of cis relation between C_8-H and C_{14}-H in **6** was supported by the splitting pattern of signals at δ 4.00 (1 H, d, $J_{8,14}$ = ~2 Hz) due to C_8-H. Therefore, the position of the carbonyl group and the relative configuration at C_8, C_{13}, and C_{14} of the product are shown as in **6** (Scheme I). This sequence was applied to a synthesis of 3-methoxy-7-thia-16-oxa-14β-1,3,5(10),9(11)-estratetraene-15,17-dione (**10**) by the use of citraconic anhydride as a dienophile in the Diels–Alder reaction of **3**. The reaction proceeded with high regioselectivity to give **10**, mp 181–183 °C ($CHCl_3$–*n*-hexane), in 62.5% purified yield,[9] without formation of the 18-nor-14-methyl isomer (**11**). The structure of **10** was supported by the following spectral data: ^{1}HNMR ($CDCl_3$) δ 1.72 (3 H, s, 18-CH_3), 2.8–3.2 (3H, m, C_{14}-H and C_{12}-H_2), 3.44 (1 H, d, J = 16 Hz, C_6-H), 3.70 (1 H, d, $J_{8,14}$ = 2 Hz, C_8-H), 3.74 (1 H, d, J = 16 Hz, C_6-H), 3.78 (3 H, s, OCH_3), 6.36–6.52 (1 H, m, C_{11}-H), 6.62 (1 H, d, $J_{2,4}$ = 4 Hz, C_4-H), 6.76 (1 H, d d, $J_{1,2}$ = 8, $J_{2,4}$ = 4 Hz, C_2-H), 7.36 (1 H, d, $J_{1,2}$ = 8 Hz, C_1-H); IR ($CHCl_3$, cm^{-1}) 1840, 1760 (C=O); mass spectrum 316 (M^+). Since allyl coupling $J_{8,11}$ was not observed by the decoupling method, C_8-H was found to couple with only C_{14}-H with 2 Hz. This fact indicates that C_8-H and C_{14}-H takes cis relationship. Reduction of **10** with $NaBH_4$ afforded two products, which were separated by preparative TLC.[8] The first product was assigned as the expected 3-methoxy-7-thia-16-oxa-14β-1,3,5(10),9(11)-estratetraen-17-one (**12**; 36%) and the second one as the 15-oxo isomer (**13**; 17%). The same reaction with $NaBD_4$ gave the corresponding deuterated products **14** and **15**,[8] which were significantly important for assignment of their structures. Characteristic spectral assignment of **12** and **13** were given as follows: **12** ^{1}H NMR ($CDCl_3$) δ 1.46 (3 H, s, 18-CH_3), 2.30–2.76 (3 H, m, C_{12}-H_2 and C_{14}-H), 3.46 (1 H, d, $J_{8,14}$ = ~2 Hz, C_8-H), 3.74 (3 H, s, OCH_3), 3.80 (2 H, s, C_6-H_2), 3.94, 4.30 (2 H, each t, $J_{14,15}$ = $J_{15,15}$ = 8 Hz, C_{15}-H_2, disappeared in **14**), 6.02–6.18 (1 H, m, C_{11}-H), 6.58 (1 H, d, $J_{2,4}$ = 4 Hz, C_4-H), 6.72 (1 H, d d, $J_{1,2}$ = 8, $J_{2,4}$ = 4 Hz, C_2-H), 7.30 (1 H, d, $J_{1,2}$ = 8 Hz, C_1-H); **13** ^{1}H NMR ($CDCl_3$) δ 1.48 (3 H, d, 18-CH_3), 3.44, 3.72 (2 H, each d, J = 14 Hz, C_6-H_2), 3.72 (3 H, s, OCH_3), 3.82 (1 H, d, $J_{8,14}$ = ~2 Hz, C_8-H, overlapped with signals at δ 3.90, but observed in **15**), 3.90, 4.22 (2 H, each d, J = 10 Hz, C_{17}-H_2, disappeared in **15**), 6.24–6.40 (1 H, m, C_{11}-H), 6.62 (1 H, d, $J_{2,4}$ = 4 Hz, C_4-H), 6.74 (1 H, d d, $J_{1,2}$ = 8, $J_{2,4}$ = 4 Hz, C_2-H), 7.36 (1 H, d, $J_{1,2}$ = 8 Hz). It is apparent that both of **12** and **13** take cis relationship between C_8-H and C_{14}-H from the splitting pattern of signals due to C_8-H as shown above. Thus total synthesis of 3-methoxy-7-thia-16-oxa-14β-1,3,5(10),9(11)-estratetraen-17-one (**12**) was achieved in a few steps.

References and Notes

(1) (a) P. Morand and J. Lyall, *Chem. Rev.*, **68**, 85 (1968); (b) H. O. Huisman, *Bull. Soc. Chim. Fr.*, 13 (1968); (c) A. A. Akhrem and Y. A. Titov, "Total Steroid Synthesis", Plenum Press, New York, 1970; (d) H. O. Huisman, *Angew. Chem., Int. Ed. Engl.*, **10**, 450 (1971); (e) R. T. Blickenstaff, A. C. Ghosh, and G. C. Wolf, "Total Synthesis of Steroids", Academic Press, New York, 1974.

(2) (a) N. A. McGinnis and R. Robinson, *J. Chem. Soc.*, 404 (1941); (b) A. Fravolin, G. Grandolini, and A. Martani, *Gazz. Chim. Ital.*, **103**, 1073 (1973); (c) T. Terasawa and T. Okada, *J. Chem. Soc., Perkin Trans. 1*, 576 (1978); (d) T. Terasawa and T. Okada, *ibid.*, 1252 (1978); (e) T. Terasawa and T. Okada, *ibid.*, 1254 (1978).

(3) G. Canalini, I. Degani, R. Fochi, and G. Spunta, *Ann. Chim. (Rome)*, **61**, 504 (1971).

(4) The reaction sequence was found to be an effective method for preparation of β-sulfenyl-α,β-unsaturated aldehyde; for instance, 2-(methylthio)cyclohexenealdehyde from 2-(methylthio)cyclohexene.

(5) All new compounds gave satisfactory microanalyses and spectroscopic data. Melting points are uncorrected. Infrared spectra were taken on a 215 Hitachi grating spectrometer, NMR spectra on a JNM-PS-100 spectrometer in the

solvent specified. Mass spectra were obtained on a Hitachi RMU-7L spectrometer. **2:** ^{1}H NMR ($CDCl_3$) δ 3.67 (5 H, s, OCH_3 and C_1-H_2), 6.27–6.88 (3 H, m), 7.97 (1 H, d, J = 8 Hz), 9.35 (1 H, s); mass spectrum 206 (M^+). **3:** ^{1}H NMR ($CDCl_3$) δ 3.68 (2 H, s), 3.80 (3 H, s), 5.17 (1 H, d d, J = 11 and 2 Hz), 5.42 (1 H, d d, J = 18 and 2 Hz), 6.33–7.53 (5 H, m). **7:** ^{1}H NMR ($CDCl_3$) δ 3.67 (1 H, d, J = 14 Hz), 3.80 (3 H, s), 3.91 (1 H, d, J = 14 Hz), 4.08 (1 H, d d, J = 8 and 3 Hz, disappeared in **9**), 4.38 (1 H, d d, J = 8 and 6 Hz, disappeared in **9**), 6.66 (1 H, d, J = 3 Hz), 6.76 (1 H, d d, J = 8 and 3 Hz), 7.20 (1 H, d, J = 8 Hz).

(6) G. Wittig and U. Schoelkopf, *Org. Synth.*, **40**, 66 (1960).
(7) (a) D. M. Bailey and R. E. Johnson, *J. Org. Chem.*, **35**, 3574 (1970); (b) S. Takano and K. Ogasawara, *Synthesis*, 42 (1974).
(8) Isolation and determination of yields required preparative TLC on silica gel (PF_{254}). Development was repeated three times using $CHCl_3$ as eluent.
(9) The product was purified by column chromatography on silica gel using benzene as eluent.

Shinzo Kano, Kohtaro Tanaka
Satoshi Hibino, Shiroshi Shibuya*
Tokyo College of Pharmacy, 1432-1 Horinouchi
Hachioji, Tokyo 192-03, Japan
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New Synthesis of Cortico Steroids from 17-Keto Steroids: Application and Stereochemical Study of the Unsaturated Sulfoxide–Sulfenate Rearrangement

Summary: An efficient synthesis of hydrocortisone acetate from a biodegradation product of β-sitosterol is described which makes use of the sulfenate–sulfoxide rearrangement to define the stereochemistry at C-17.

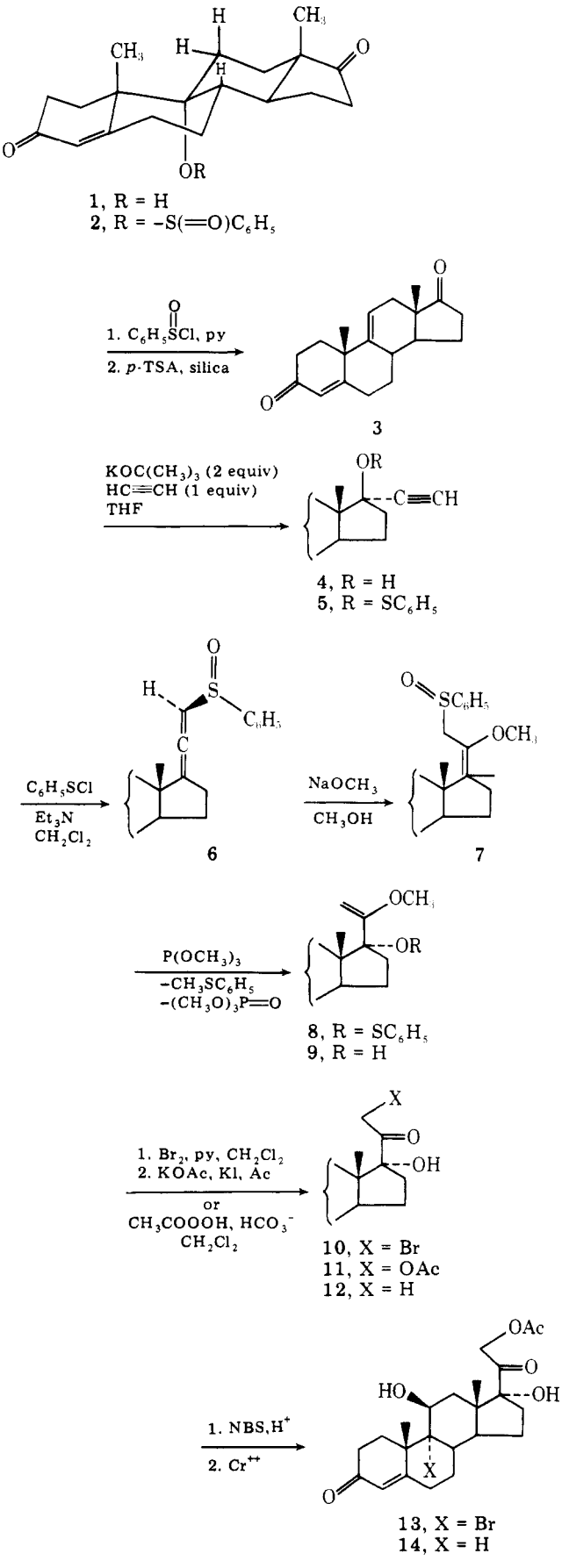
Sir: Cortico steroids are produced commercially by chemical degradation of deoxycholic acid, diosgenin, and stigmasterol.[1] The possibility of a much cheaper and readily available raw material arose with the finding that the side chain saturated sterols can be biodegraded to androst-4-ene-3,17-dione,[2] but even more important for cortico steroid production was the discovery that the abundant soya bean derived sterols, sitosterol and campesterol, can be degraded by a mutant of *Micobacterium fortuitum* to 9α-hydroxyandrost-4-ene-3,17-dione (**1**).[3] Compound **1** is an ideal starting material for a cortico steroid synthesis because the A ring is fully functionalized, the C ring is functionalized as the 9α-hydroxy group, and the 17-ketone provides a handle to elaborate the side chain.

We report here an efficient synthesis of the cortico steroid hydrocortisone acetate (**14**), a synthesis which features the unsaturated sulfoxide–sulfenate rearrangement to stereoselectively introduce the dihydroxyacetone side chain at the C-17 position of **1**.[4] The dihydroxyacetone side chain is not only common to a wide variety of cortico steroid antiinflammatory drugs, but is also a structural component in adriamycin, a potent antitumor agent.

Elimination of the 9α-hydroxy group from **1** by the usual methods of thionyl chloride–pyridine and bromine–SO_2–pyridine gave mixtures of the $\Delta^{9(11)}$ and $\Delta^{8(9)}$ isomers, presumably because trans-diaxial elimination can occur from either side. Preparation of the very hindered 9α-acetate or 9α-tosylate required harsh conditions and gave low yields. The 9α-benzenesulfinate **2** (mp 111–113 °C),[5] however, could be prepared quantitatively under mild conditions[6] (benzenesulfinyl chloride,[7] pyridine, 20 °C, 45 min). Paralleling sulfoxide eliminations,[8] this group could be removed by pyrolysis (GLC at 220 °C or refluxing xylene), but the elimination was most efficient (90%) under specially designed acidic conditions (silica gel, p-toluenesulfonic acid, $CHCl_3$ reflux for 3 h). Both conditions selectively produced androst-4,9(11)-diene-3,17-dione (**3**) with the near exclusion of the $\Delta^{8(9)}$ isomer.

The two carbons of the dihydroxyacetone side chain were introduced exclusively at C-17 by reaction of **3** with dipotassium acetylide[9] in THF (**3** was added to a THF slurry of acetylide, obtained by reacting 2 equiv of $KOC(CH_3)_3$ and 1 equiv of acetylene at 25 °C; 90% yield of **4**, mp 246–250 °C).[10]

Scheme I



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