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).

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(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.

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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.

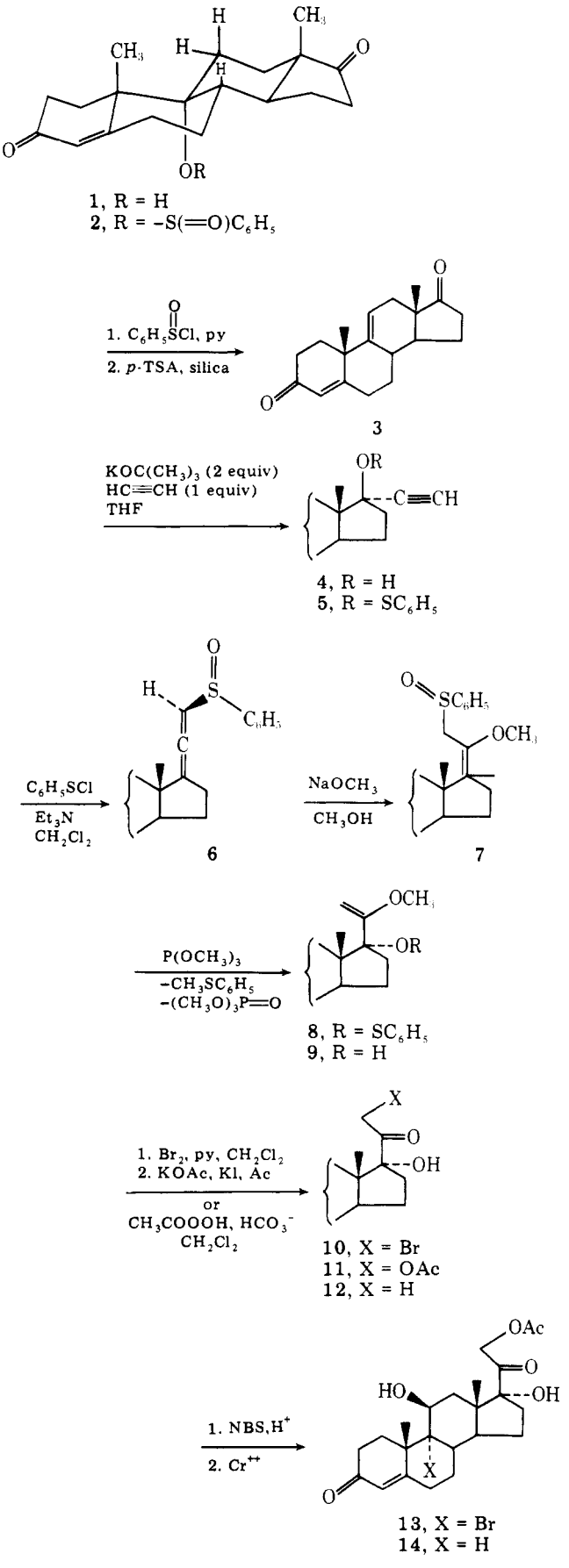
Sir: Cortico steroids are produced commercially by chemical degradation of deoxycholic acid, diosgenin, and stigmasterol.[1] The possibility of a much cheaper and readily available raw material arose with the finding that the side chain saturated sterols can be biodegraded to androst-4-ene-3,17-dione,[2] 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.

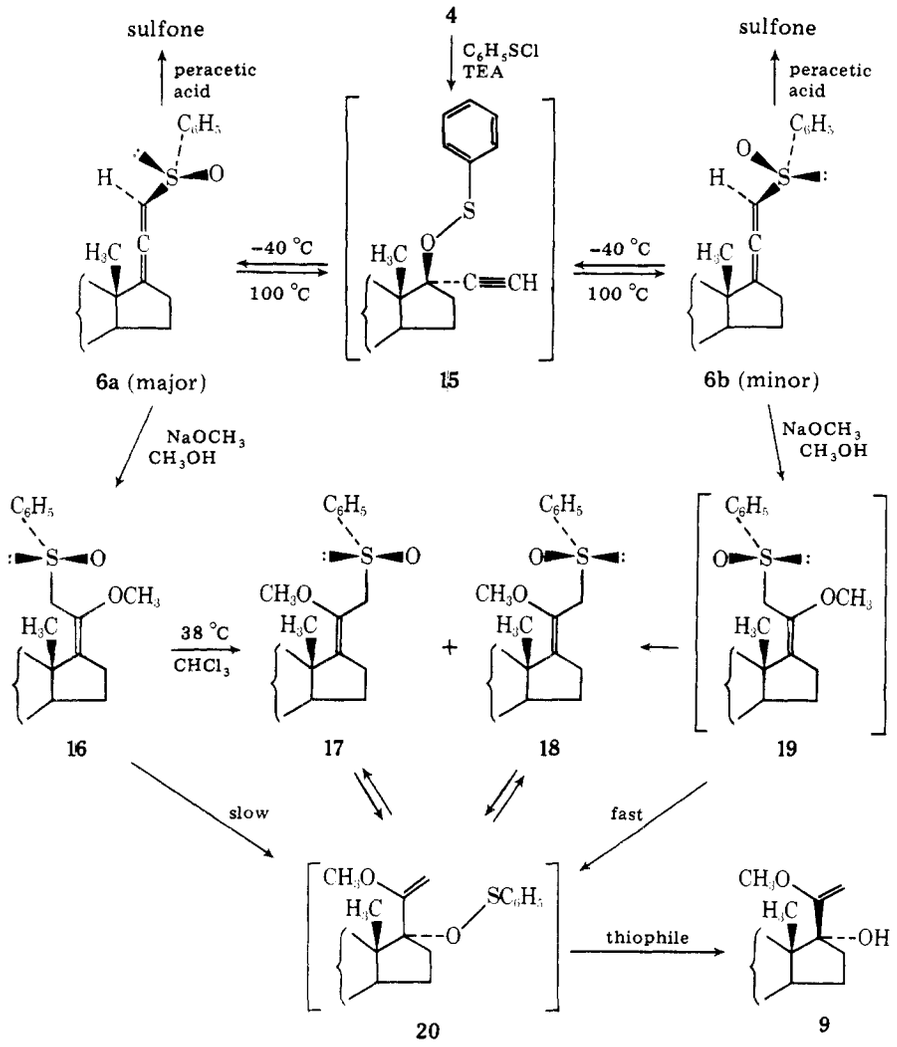
The two carbons of the dihydroxyacetone side chain were introduced exclusively at C-17 by reaction of **3** with dipotassium acetylide[9] in THF (**3** was added to a THF slurry of acetylide, obtained by reacting 2 equiv of $KOC(CH_3)_3$ and 1 equiv of acetylene at 25 °C; 90% yield of **4**, mp 246–250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

Scheme I



0022-3263/79/1944-1582$01.00/0

Scheme II



Selective acetylene addition at C-17 was accomplished without separate protection of the Δ^4-3-ketone because under these conditions the Δ^4-3-ketone was rapidly and completely blocked as its stable enolate, as shown by enolate trapping experiments.[11] The 17-ketone, however, was sufficiently ketonic at equilibrium to allow addition of acetylide at C-17 to proceed to completion.

The $\Delta^{9(11)}$-ethisterone **4** has the opposite configuration at C-17 to that required for the cortico steroids. Inversion of the stereochemistry at C-17 and elaboration of the two-carbon side chain was accomplished by taking advantage of some unique features of the [2,3] sigmatropic rearrangement of unsaturated sulfenates and sulfoxides.[12]

Reaction of **4** with phenyl sulfenyl chloride[13] (CH_2Cl_2, Et_3N, −70 °C) produced the 17-sulfenate ester **5**. Warming ester **5** above −40 °C resulted in a [2,3] sigmatropic rearrangement[14] to the allene sulfoxide **6**, isolated in 94% yield.[15] Treatment of **6** with sodium methoxide in methanol at 25 °C resulted in conjugate addition of methoxide to the α,β-unsaturated sulfoxide, giving a mixture of enol ether sulfoxides **7**. This reaction served both to functionalize the C-20 position and to allow the sulfoxide access to the α face of the molecule for a final sulfoxide–sulfenate rearrangement. Thus, exposure of **7** to refluxing methanol, where an equilibrium exists between **7** and sulfenate **8**, and reaction with the reactive thiophile trimethyl phosphite, provided 17α-hydroxy-20-methyl enol ether **9** (mp 181.5–182.5 °C) isolated pure in 72% yield from allene **6**. The steric bulk of the C-18 angular methyl group forced this rearrangement to occur predominantly on the α face of the molecule.[16]

Conversion of **9** into the dihydroxyacetone side chain was accomplished in two ways. Reaction with peracetic acid (CH_2Cl_2, $NaHCO_3$) gave directly, without separate acetylation,[17] the cortico steroid 21-acetate **11**. Yields were higher, however, when **9** was brominated to **10** (Br_2, CH_2Cl_2, pyridine, 0 °C, and acidification), followed by displacement of the 21-bromide with acetate (KOAc, KI, HOAc, acetone reflux). In this way **11** was obtained in 93% yield.

Transformation of **11** into the antiinflammatory agent hydrocortisone acetate (**14**) followed a known procedure[18] with bromohydrin **13** prepared by reaction with HOBr, and the 9α-bromide reductively removed with chromous ion. The overall yield to **14** from **11** was greater than 90%.

This synthesis of cortico steroids has the additional flexibility of being able to produce 17α-hydroxyprogesterones, starting material for a variety of commercially important antifertility agents. Thus, simple acidic hydrolysis of **9** gave **12** quantitatively.

Scheme II illustrates some of the stereochemical aspects of the above sulfoxide–sulfenate rearrangement.[19] Allene sulfoxide **6** is composed of a 60:40 mixture of isomers which were separated by acetone crystallization.[20] Each isomer was oxidized (peracetic acid, $CHCl_3$) to an identical sulfone (mp 172–178 °C), showing that these compounds differ only with respect to chirality at sulfur. Furthermore, each isomer was equilibrated to a 1:1 mixture of both allenes by heating in

Me_2SO-d_6 for 2 h at 100 °C.[21] The chiral center at sulfur, therefore, is being racemized thermally by [2,3] sigmatropic rearrangement through the symmetrical sulfenate ester **15** leading to a thermodynamic ratio of allenes. The unequal amounts of the two allenes in the original mixture must be a kinetic effect arising from the energetically most favorable transition state for collapse of sulfenate ester **15** to allene **6** being one where the phenyl group is at the greatest distance from the bulky angular C-18 methyl group and the C ring. This reasoning predicts that the predominant diastereomer arising from the least hindered transition state is the allene structure **6a.**

Conjugate addition of sodium methoxide to the two diastereomeric allene sulfoxides **6a** and **6b** results in surprisingly different stereochemistry in the products. On reaction of the major allene **6a** with sodium methoxide in methanol at 25 °C, a single enol ether **16**[22] was isolated which had an unusually high-field C-18 resonance in ^1H NMR at δ 0.46.[23] Under identical conditions, the minor allene **6b** was transformed into two different but isomeric enol ether sulfoxides[24] having C-18 resonances at δ 0.78 and 0.83 in the NMR. An important clue to the stereochemistry of these isomeric enol ethers resulted from heating the single isomer **16** at 38 °C in $CDCl_3$. We observed clean first order ($t^{1/2} \simeq 2$ h) disappearance of **16** and formation of the same two enol ethers obtained on methoxide treatment of the minor allene **6b.** It is clear that these latter two enol ethers have the most stable side chain arrangement and can therefore be assigned structures **17** and **18,** having the trans-olefin geometry and differing in configuration at sulfur. The single diastereomer **16** from the major allene must have the less stable cis-olefin geometry and the same sulfur chirality as in the original allene.

These results are interpretable mechanistically if one assumes that methoxide attack on the allenes occurs only from the least hindered side, the side opposite to C ring and the C-18 methyl group. Such attack on the major allene **6a** provides the observed cis enol ether **16,** a configurationally stable compound at 25 °C which is reluctant to undergo [2,3] sigmatropic rearrangement. This stability derives from congestion in the transition state for rearrangement, for when the sulfoxide oxygen becomes attached to C-17 from the α face, it demands that the phenyl group come in close proximity to the bulky C ring and the C-18 methyl group. Similar least hindered attack of methoxide on the minor allene **6b,** however, produces the cis enol ether **19** whose sulfur chirality allows facile [2,3] sigmatropic rearrangement to occur with the phenyl group away from the bulk of the steroid molecule. Therefore, cis enol ether **19** is unstable at room temperature, and rearranges spontaneously via sulfenate **20** to the more stable trans isomers **17** and **18.**[25]

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(20) Major allene sulfoxide **6a:** mp 163 °C; $[\alpha]^{25}_D$ +93.5° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.92 (C-18), 1.48 (C-19), 7.36 (t, 1, J = 4 Hz). Minor allene sulfoxide **6b:** mp 144–155 °C; $[\alpha]^{25}_D$ +288° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) same as major allene except C-18 methyl δ 0.97.
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(22) Cis enol ether **16:** mp 116–162 °C; $[\alpha]^{25}_D$ +180° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.46 (C-18), 1.27 (C-19), 3.51 (OCH_3); UV (CH_3OH) 239 nm (ϵ 20 600).
(23) The C-18 methyl group of **16** would be expected to be upfield relative to the C-18 group in **17** and **18** because of its proximity to sulfur, which bears three groups having shielding capabilities.[19]
(24) A 1:1 mixture of the two trans enol ether sulfoxides **17** and **18:** mp 154–155 °C; $[\alpha]^{25}_D$ +30° (*c* 1.0, $CHCl_3$); UV (CH_3OH) 237 nm (ϵ 23 000); ^1H NMR ($CDCl_3$) δ 0.78 and 0.83 (C-18), 1.31 (C-19), 3.47 and 3.53 (OCH_3).
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