Monoclinic diffraction symmetry was confirmed by a fast, low-angle data collection. The systematic absences $0k0$ ($k = 2n + 1$) indicated the space groups $P2_1$ and $P2_1/m$, the former of which proved to be correct by successful structure solution and refinement. Intensity data were recorded with ω/θ scans (variable scan speed, maximum measuring time 30 s) up to a 2θ range of 50°. After correction for Lorentz and polarization effects, a unique data set of 1842 reflections (with intensities greater than twice the background) was used for all further calculations.

After several attempts of routine application of direct methods had failed (MULTAN 80), a suitable starting set (chosen by hand) of 12 reflections could be expanded by weighted tangent refinement to 174 phase sets, one of which showed in an E map 30 atoms in sensible positions. The remaining atoms were located on an difference map, including the atoms of the solvent methanol. Full-matrix least-squares refinement with isotropic temperature factors led to $R = 0.15$. A difference Fourier synthesis, in which all reflections with $\sin\theta/\lambda \leq 0.3$ were doubly weighted, allowed the location of all hydrogen atoms. The H atoms linked to the C atoms were refined in idealized positions (C–H 0.96 Å) riding on the parent carbon atoms. The refinement converged at $R = 0.114$ and $R_G = 0.111$ ($R_G = [\sum\Delta^2/\sum wF_o^2]^{1/2}$). At this stage, we decided to stop the refinement process, because further refinement with anisotropic temperature factors seemed not to improve the observed molecular geometry. An analysis of variance was very flat with respect to $\sin\theta$ and F_{max}/F. This demonstrated that unit weights in least-squares refinement have been most suitable in this case. A final difference map was featureless. The final atomic parameters are given in Table III.

All calculations were carried out on Univac 1100/80 and Telefunken TR440 computers by using the programs SHELX (G. M. Sheldrick), XANADU (J. Roberts and G. M. Sheldrick), and the plot program PLUTO (S. Motherwell).

Acknowledgment. Thanks are due to B. Hanisch for her diligent help with numerous fractionations and to the Fonds der Chemischen Industrie for financial support. The recording of the 400-MHz spectra by Dr. H. Günther and P. Schmidt, Gesamthochschule Siegen, West Germany, is gratefully acknowledged.

Registry No. 1, 79-69-6; 3, 79-68-5; 4, 81456-93-1; 5, 81456-94-2; 5a, 81456-95-3; 8a, 81456-96-4; 8b, 81456-97-5; 12, 81456-98-6.

Supplementary Material Available: Listing of the fractional atomic coordinates (Table III) (1 page). Ordering information is given on any current masthead page.

Synthesis and Photochemistry of Steroidal β,γ-Unsaturated Ketones: An Approach to Reversible Steroid–Diterpenoid Interconversions[1]

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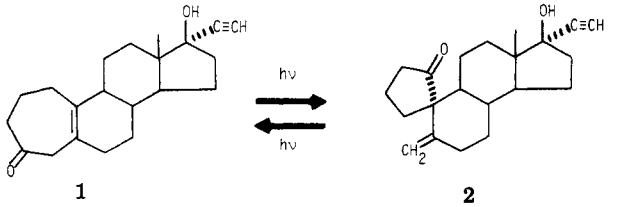
Received March 23, 1981

4,4-Dimethylandrost-8(14)-en-16-one (**3**) was synthesized in 14 steps from testosterone. Photolysis of **3** afforded the double-bond migration product 4,4-dimethyl-14β-androst-7-en-16-one (**8b**) together with a solvent-added product. Photolysis of the β,γ-unsaturated ketones **9**, **11**, and 4,4-dimethylandrost-8(14)-en-17-one (**16b**) afforded the [1,3] acyl shift products **10**, **12**, and 4,4-dimethyl-8α,17-cyclo-13,17-seco-5α-androst-13-en-17-one (**17**), respectively. Irradiation of **11** also afforded the photodecarbonylation products **13** and **14**, and **16b** gave the C-13 epimer **16a**. The α,α,α′,α′-tetramethyl β,γ-unsaturated ketone **15** was remarkably stable to photolysis.

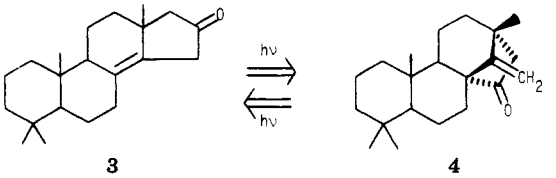
Due to the structural similarities between steroids and diterpenoids, there have been a number of studies involving the conversion of steroids into diterpenoids[2] and of diterpenoids into steroids.[3] We were interested in developing a reaction whereby steroids and diterpenoids could be interconverted reversibly. To this end the [1,3] acyl shift photoisomerization reaction of cyclic β,γ-unsaturated ketones appeared attractive.[4] Recently we have shown that the steroidal β,γ-unsaturated ketone **1** may be



1 **2**

photoisomerized to a photoequilibrium of **1** and **2**.[5] These isomers were easily separated and could be recycled to afford the desired isomer. Furthermore, this photoequilibrium was wavelength dependent, and by varying the wavelength of the exciting light the photoequilibrium may be shifted in the desired direction.[5]

Applying this photoisomerization reaction to the case in question suggests that the β,γ-unsaturated steroidal ketone **3** should afford the new β,γ-unsaturated di-



3 **4**

terpenoid[6] ketone **4**, via a [1,3] acyl shift. Furthermore, **4** should photoisomerize back to **3**. This latter reaction is important since several recent syntheses of tetracyclic diterpenoids[7] provide a convenient route for the synthesis of **4**. As an extension of this work, the photoepimerization of the C-18 methyl group in 17-keto steroids[8] should open

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0022-3263/82/1947-2536$01.25/0

Table I. ^{13}C NMR Spectral Data of Steroids

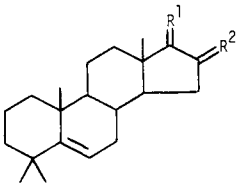
carbon	3	5a	5b	5d	5f	6	7a	7b	8a	8b	15	16b	17
1	38.9	38.7	38.5	38.6	38.8	39.7	39.0	38.4	39.6	39.9	39.0	38.9	42.4*
2	18.9	18.4	18.4	18.4	18.6	18.4	19.3	19.4	18.6	18.8	18.9	19.0	18.8
3	42.0	40.7	40.7	40.7	40.9	40.2	42.2	42.1	42.0	42.3	42.0	42.1	42.4*
4	38.2	35.6	37.0	37.0	37.0	37.4	38.2	38.1	35.6	35.2	38.5	38.3	38.0
5	54.6	150.6	150.5	150.8	150.6	151.1	54.9	54.9	51.5	50.9	54.6	55.0	56.5
6	22.1	117.1	117.1	117.0	117.7	117.7	22.4	22.3	22.9	23.6	22.3	22.8	19.0
7	30.8	31.0	30.3	32.0	32.4	117.1	36.6	36.6	118.9	124.2	30.7	29.7	42.7*
8	131.0	31.2	32.2	30.0	30.7	138.8	128.2	127.6	135.7	134.9	131.8	130.8	53.6
9	51.5	50.8	50.5	45.6	50.9	46.7	51.8	51.0	50.4	50.2	52.1	52.0	45.5
10	33.2	35.4	35.3	35.5	35.4	34.6	33.2	33.1	32.6	32.7	33.1	33.3	33.6
11	19.2	19.7	20.0	19.7	20.2	20.1	19.1	19.0	20.3	20.4	18.6	18.5	21.7
12	36.0	31.0	37.8	36.3	38.8	37.8	30.6	30.6	37.7	33.1	28.2	29.0	29.8
13	39.3	47.1	38.3	41.8	39.6	47.4	39.6	39.4	39.2	38.3	46.4	47.0	128.9
14	132.4	52.1	52.2	50.7	54.8	47.4	137.3	138.0	50.2	47.5	142.5	133.8	133.3
15	39.3	21.5	38.7	35.3	37.0	32.2	35.9	38.8	38.0	44.2	43.1	22.5	28.7
16	217.3	36.9	217.7	217.4	71.8	75.0	73.7	71.0	217.6	218.0	226.8	36.1	34.5
17	56.5	220.5	55.3	86.0	50.9	51.6	48.8	51.7	55.1	55.2	52.6	221.6	218.9
18	22.0	13.3	17.6	11.2	18.8	17.3	22.0	21.9	17.4	22.2	17.0	22.2	21.8
19	14.4	21.2	21.2	21.3	21.4	17.7	14.4	14.3	14.6	14.7	14.4	14.4	17.5
20	25.4	30.5	30.6	30.7	30.7	32.2	25.7	26.6	22.1	24.3	25.3	22.2	32.8
21	33.6	32.6	32.6	32.7	32.7	33.3	33.7	33.6	33.4	33.4	33.5	33.7	33.6
22						166.0	175.3				21.9*		
23						130.6	43.2				28.3*		
24						128.1	28.9				23.7*		
25						139.2	25.8				26.3*		
26						132.4	25.5						

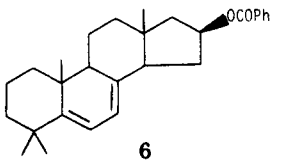
a route to the diterpenoids with the hibaene skeleton.

Results and Discussion

4,4-Dimethylandrost-8(14)-en-16-one (**3**) was synthesized starting from testosterone by using three transformations. First, ring A was dialkylated at C-4, followed by Wolff–Kishner reduction. Second, the keto group was transferred from C-17 to C-16, and finally the double bond was introduced at the C-8(14) position.

While the C-17 to C-16 ketone transposition seemed a relatively simple operation, a number of methods were tried[9] before the following sequence was found to afford the C-16 ketone **5b** in 55% overall yield. 4,4-Dimethyl-



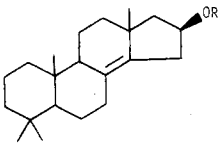


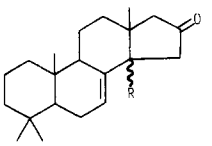
6

5a, $R^1 = O$; $R^2 = H_2$
b, $R^1 = H_2$; $R^2 = O$
c, $R^1 = O$; $R^2 = NOH$
d, $R^1 = \beta$-OH; $R^2 = O$
e, $R^1 = \beta$-OMs; $R^2 = O$
f, $R^1 = H_2$; $R^2 = \beta$-OH
g, $R^1 = H_2$; $R^2 = \beta$-OCOPh

androst-5-en-17-one (**5a**) was treated with base and isoamyl nitrite to yield the 16-oximido-17-ketone **5c**.[9a] Reduction of **5c** with zinc dust in aqueous acetic acid gave the 17β-hydroxy-16-ketone **5d** in 83% yield.[9e] Reductive elmination of the 17β-mesylate **5e** with chromous chloride[9f,g] gave the 16-ketone **5b** in 90% yield.

The final tranformation involved the isomerization of the olefin from C-5 to C-8(14). The C-16 ketone was first protected by reduction with sodium borohydride followed by esterification with benzoyl chloride to yield **5g**. Bromination of **5g** with 1,3-dibromo-5,5-dimethylhydantoin followed by dehydrobromination with trimethyl phosphite afforded 4,4-dimethylandrost-5,7-dien-16β-yl benzoate **6** in 78% yield.[10] Catalytic hydrogenation of **6** over platinum in acetic acid–ether afforded $\Delta^{8(14)}$ compound **7a**.[11]





7a, R = COC_6H_{11}
b, R = H

8a, R = α-H
b, R = β-H

Under these remarkably mild reducing conditions the aromatic ring was also reduced to the corresponding cyclohexane carboxylate **7a**. Saponification of **7a** afforded the alcohol **7b**, which was oxidized with chromic oxide-pyridine in methylene chloride[12] to yield 4,4-dimethylandrost-8(14)-en-16-one (**3**). The 14-step synthesis of **3** proceeded in a 10% overall yield starting from testosterone.

Photolysis of **3** in a wide range of solvents using a medium-pressure mercury lamp and a Pyrex filter afforded the isomer 4,4-dimethyl-14β-androst-7-en-16-one (**8b**) in 30% yield as the major product, together with a minor product. The ^1H NMR spectrum of **8b** showed the H-7 olefinic proton as a multiplet at δ 5.48 and the ^{13}C NMR showed C-7 as a doublet at δ 124.2 and C-8 as a singlet at δ 134.9 (see Table I). The mass spectrum of **8b** showed two fragments at *m/e* 176 and 124, characteristic of a retro Diels–Alder (rDA) fragmentation of a Δ^7 steroid.[13] So that

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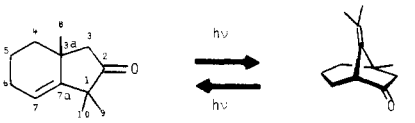
the stereochemistry at C-14, could be determined, the C-14α epimer, 4,4-dimethylandrost-7-en-16-one (*8a*), was synthesised from the 5,7-diene **6** by Raney nickel reduction[14] followed by hydrolysis and subsequent oxidation. The two C-14 epimers, **8a** and **b**, gave very similar IR, NMR, and mass spectra, but they were not identical. The calculated chemical shifts of the C-18 and C-19 methyl groups of the 14α derivative, **8a**, were δ 0.87 and 0.73, which were in close agreement with the observed values of δ 0.89 and 0.75, respectively.[15] These calculated values, however, were different from those of the photoproduct **8b**, in which the resonances were δ 1.12 and 0.88, respectively. Therefore, the photoproduct **8b** was assigned the 14β stereochemistry, i.e., the more stable cis-C,D ring junction. The 14β stereochemistry of **8b** was confirmed by circular dichroism since it gave a curve with $\Delta\epsilon$ of 2.00 at λ 299 nm, in agreement with that reported for other 16-oxo-14β steroids.[16]

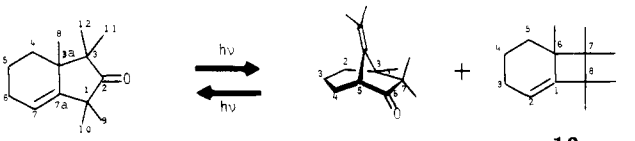
The double-bond migration obtained from photolysis of **3** probably results from intramolecular photosensitization. The excited n,π^* state of the ketone, rather than undergo α cleavage, transfers its energy to the $^3(\pi,\pi^*)$ state of the 8(14) double bond. Cis–trans isomerization of the excited olefin affords a very reactive, highly strained transoid intermediate.[17] In hydroxylic solvents protonation followed by subsequent olefin or ether formation occurs.[17] This mechanism is supported by the isolation of trace quantities of a second photoproduct whose molecular ion, in the mass spectrum, corresponds to that of the steroid plus a molecule of methanol. Photolysis of **3** in ethanol afforded a product that showed a similar shift in its mass spectrum. Photolysis of the 16β-hydroxy-$\Delta^{8(14)}$ steroid **7b** in methanol–xylene did not give a product with olefinic hydrogens, showing that intermolecular photosensitization did not afford the same rearrangement. While double-bond migration is a characteristic photochemical reaction of olefins,[17] this is the first reported case of a β,γ-unsaturated ketone being photoisomerized to that of a γ,δ-unsaturated ketone.

The lack of reactivity of **3** toward α cleavage could be attributed to either steric reasons that prevent the acyl radical migration or the lower triplet energy level of the olefin acting as a quencher for the excited ketone. The ultraviolet spectrum of **3**, λ_{max} 290 (ϵ 24), showed that the olefin caused almost no enhancement of the n-π^* transition of the C-17 ketone. This indicated that the olefin and carbonyl groups are close to being coplanar, and this is supported by Dreiding models. Thus, if α cleavage did occur in the photolysis of **3**, there would be very little orbital overlap of the C-15 radical with the olefin. Since α alkylation is known to increase the rate of α cleavage,[19] then dimethylation at C-15 should hopefully increase the rate of α cleavage and lead to a [1,3] acyl shift. We first synthesized the bicyclic analogue of the C,D ring system containing a gem dimethyl group between the carbonyl and olefin group, **9**, and studied its photochemistry.

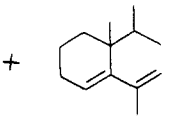


9 **10**

The trimethyl compound **9** was prepared by alkylation of 1,3a-dimethyl-4,5,6,7-tetrahydroindan-2-one[20] with potassium hydride and 1 mol of methyl iodide. When excess methyl iodide was used the pentamethyl derivative **11** was



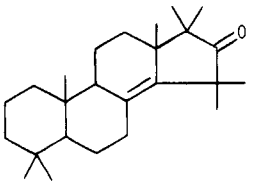
11 **12** **13**



14

obtained. Photolysis of the α,α-dimethyl-β,γ-unsaturated ketone **9** in pentane afforded the [1,3] acyl shift product **10** in a low yield. The photoisomerization was reversible since photolysis of **10** afforded **9**. Photolysis of the $\alpha,\alpha,\alpha',\alpha'$-tetramethyl-$\beta,\gamma$-unsaturated ketone **11** similarly gave the [1,3] acyl shift product **12** together with two more photoproducts, **13** and **14**, which came from photodecarbonylation of **11**. Thus in both examples of the α-alkylated bicyclic systems, photolysis afforded products resulting from α cleavage.

Attempts to alkylate **3** at only C-15 were unsuccessful; however, the 15,15,17,17-tetramethyl derivative **15** was



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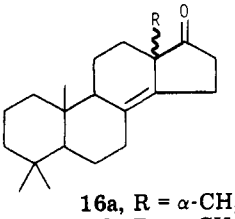

16a, R = α-CH_3
b, R = β-CH_3

obtained. Photolysis of **15** for more than 40 h in methanol or pentane resulted in very little reaction, whereas in acetone, polar products were formed very slowly. NMR spectra of the acetone products showed an absence of any olefinic protons or methyl groups, indicating no [1,3] acyl migration. The photostability of **15** was unexpected. At least normal ketone photochemistry[4] such as photodecarbonylation would be expected to occur by analogy with the model compound **11**. A Dreiding model of **15** shows the β,γ-unsaturated ketone to be nearly flat, indicating poor interaction between the carbonyl and olefinic groups.[18] This conclusion was supported by the ultraviolet spectrum of **15** [λ_{max} 300 (ϵ 40)], showing little enhancement. Furthermore, the rigidity of the steroid and the presence of large bulky groups seem to preclude photochemistry from this system, whereas **11** is far more flexible but with no enhanced ultraviolet absorption [λ_{max} 301 (ϵ 37)].

With our interest in the photochemistry of steroid β,γ-unsaturated ketones as a route for preparing novel steroid

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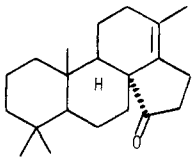
skeletons,[1,5] we investigated the photochemistry of 4,4-dimethylandrost-(14)-en-17-one (**16b**).[2]

Irradiation of **16b** [λ_{max} 292 (ϵ 55)] in benzene led to the rapid establishment of a photoequilibrium consisting of **16b**, the [1,3] acyl shift rearranged photoproduct 4,4-dimethyl-8α,17-cyclo-13,17-seco-5α-androst-13-en-17-one (**17**)



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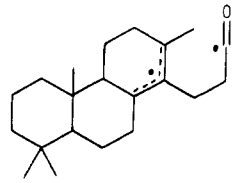

18

[λ_{max} 297.5 (ϵ 31)], and the C-13 epimer **16a** in the ratio of 78:14:6. The proton NMR spectrum of the $\beta\gamma$-unsaturated ketone **17** showed a broad singlet at δ 1.68 for the C-18 methyl. The ^{13}C NMR showed two singlets at δ 133.3 and 128.9 for the tetrasubstituted double-bond carbons and a singlet at δ 56.5 for the quaternary C-8 carbon, which is α to both the ketone and the double bond. Photolysis of **17** afforded the same photoequilibrium mixture. The structure of **16a** was established by spectral data, including molecular rotation[21] and circular dichroism.[14] The formation of **16a** and **17** from **16b** was the result of recombination of the diradical formed by α cleavage of the 17-keto steroid with either end of the allylic radical **18**. The photoepimerization of 17-keto steroids was first observed in 1939[22] and has been used for synthetic purposes.[21,23]

The carbon-13 chemical shifts of the various steroids reported in Table I were assigned by comparison with ^{13}C data for known steroids [24] and by adding or subtracting the "substituent" effect.[25]

Experimental Section

Melting points were taken with a Thomas-Hoover apparatus and are uncorrected. IR spectra were taken with a Perkin-Elmer 137 infrared spectrophotometer. UV spectra were recorded on a Cary recording spectrophotometer Model 14. Carbon-13 NMR spectra were recorded at 25.16 MHz on a Varian XL-100 spectrometer fitted with a Nicolet 1180 pulse system, and proton NMR spectra were recorded at 90 MHz on a Perkin-Elmer R-32 spectrometer. Chemical shifts are reported in δ units from the internal standard tetramethylsilane in chloroform-*d*. Circular dichroism spectra were measured on a Jasco J-41A spectropolarimeter using methanol as a solvent. Low-resolution mass spectra were taken with a Hitachi Perkin-Elmer RMU-6H. High-resolution mass spectra were taken with a Hitachi Perkin-Elmer RMH-2. TLC was carried out on silica gel GF plates, and column chromatography was performed by using activity III Woelm silica gel. Flash column chromatography was performed by using Merck silica gel (230–400 mesh). GLC analysis was carried out by using a Varian Aerograph 90-P for bicyclic and model compounds and Varian Aerograph Series 2100 for steroids. Elemental analyses were performed by Micro-Analysis Inc., Wilmington, DE, and by Galbraith Laboratories Inc., Knoxville, TN.

4,4-Dimethylandrost-5-en-17-one (5a). 17β-Hydroxy-4,4-dimethylandrost-5-ene[2] (10 g) was oxidized with Jones reagent to give **5a**[2] (9.5 g, 96%): mp 136–138 °C; IR (KBr) 1740 cm^{-1} (C=O); ^1H NMR δ 5.50 (m, 1, 6 H), 1.14 (s, 3, 21 H), 1.13 (s, 3, 19 H), 1.09 (s, 3, 20 H), 0.88 (s, 3, 18 H).

16-Oximido-4,4-dimethylandrost-5-en-17-one (5c). By use of the nitrosylation method of Huffman and Lott,[26] **5a** (10 g) afforded upon recrystallization from methanl **5c** (8.8 g, 80%): mp 229–231 °C; IR (KBr) 3200 (oxime OH), 1700 (C=), 1650 cm^{-1} (C=N).

Anal. Calcd for $C_{21}H_{31}O_2N$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.40; H, 9.25; N, 4.01.

17β-Hydroxy-4,4-dimethylandrost-5-en-16-one (5d). 16-Oximido-4,4-dimethylandrost-5-en-17-one (**5c**) (2 g) suspended in glacial acetic acid (50 mL) and water (3 mL) was treated at 50 °C with zinc dust (2.5 g) while stirring, then diluted with water (22 mL), and refluxing for 1 h. The zinc was filtered off, and the solution was diluted with water (10 mL) and allowed to stand overnight. The product, **5d**, was collected by filtration (1.6 g, 83%): mp 175–177 °C; IR (KBr) 3500 (OH), 1740 cm^{-1} (C=O); ^1H NMR δ 5.48 (m, 1, 6 H), 3.75 (s, 1, 17 H), 1.15 (s, 6, 19 H and 21 H) 1.10 (s, 3, 20 H), 0.75 (s, 3, 18 H).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.95; H, 9.91. Found: C, 79.53; H, 10.21.

4,4-Dimethyl-16-oxoandrost-5-en-17β-yl Mesylate (5e). To a solution of **5d** (9 g) in methylene chloride (250 mL) was added triethylamine (10 mL) followed by methane sulfonyl chloride (5 mL) in methylene chloride (25 mL) over a period of 10 min. The reaction mixture stirred for 40 min and then was extracted with ice water followed by 10% hydrochloric acid solution, saturated sodium bicarbonate, and brine. Drying of the methylene chloride solution ($MgSO_4$) followed by solvent removal gave **5e** (11 g, 98%): mp 162 °C (benzene–petroleum ether); IR (KBr) 1740 cm^{-1} (C=O); ^1H NMR δ 5.53 (m, 1, 6 H), 4.7 (s, 1, 17 H), 3.2 (s, 3, SO_2CH_3), 1.15 (s, 6, 19 H and 21 H), 1.10 (s, 3, 20 H), 0.9 (s, 3, 18 H); mass spectrum, *m/e* (rel intensity) 394 (M^+, 93), 379 (M – CH_3, 20), 378 (78), 307 (14), 83 (100).

Anal. Calcd for $C_{22}H_{34}O_4S$: C, 66.97; H, 8.68; S, 8.12. Found: C, 67.88; H, 8.52; S, 7.97.

4,4-Dimethylandrost-5-en-16-one (5b). Chromic chloride (12 g) in water (15 mL) and 12 N hydrochloric acid (25 mL) was mixed with excess granulated zinc under nitrogen. To the resulting blue chromous chloride solution was added a solution of **5e** (3.7 g) in acetone (150 mL) over a period of 15 min. The reaction mixture was refluxed for 3 h under nitrogen, then 12 N HCl (~8 mL) was added, and the reflux continued overnight under nitrogen. The product was extracted with ether, and the ether layer was washed with distilled water, dried ($MgSO_4$), and evaporated to leave the crude product, which upon recrystallization from methanol gave pure **5b** (2.53 g, 90%): mp 123–124 °C; IR (KBr) 1750 cm^{-1} (C=O); ^1H NMR δ 5.5 (m, 1, 6 H), 1.15 (s, 6, 19 H and 21 H), 1.1 (s, 3, 20 H), 0.91 (s, 3, 18 H); mass spectrum *m/e* (rel intensity) 300 (M^+, 100), 285 (M – CH_3, 100), 257 (5), 215 (22), 203 (9), 189 (11), 135 (25), 124 (22), 82 (79).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 83.59 H, 11.03.

4,4-Dimethylandrost-5-en-16β-ol (5f) and 4,4-Dimethylandrost-5-en-16β-yl Benzoate (5g). To a solution of **5b** (1 g) in ethanol (100 mL) was added sodium borohydride (0.6 g) dissolved in a few milliliters of water. The reaction mixture was stirred for 1 h at room temperature. The ethanol was evaporated in vacuo, and the product was suspended in water and extracted with ether. The ether was dried ($MgSO_4$) and evaporated to produce a quantitative yield of **5f**. Analysis sample was recrystallized from methanol (or hexane); mp 155–156 °C; IR (KBr) 3500 cm^{-1} (16-OH); ^1H NMR δ 5.45 (m, 1, 6 H); 4.4 (m, 1, 16 H), 1.12 (s, 6, 19 H and 21 H), 1.08 (s, 3, 20 H), 0.93 (s, 3, 18 H); mass spectrum, *m/e* (rel intensity) 302 (M^+, 100), 287 (M – CH_3, 60), 269 (M – CH_3, H_2O, 43), 220 (11), 217 (14), 199 (11), 178 (17), 175 (14), 173 (20), metastable peak at 252.1 (287 → 269).

The benzoate **5g** was obtained by reacting **5f** with benzoyl chloride in pyridine in 95% yield: mp 115–117 °C; ^1H NMR δ 8.05 (m, 2, ortho H), 7.45 (m, 3, Ar H), 5.46 (m, 2, 6 H and 16 H), 1.14 (s, 6, 19 H and 21 H), 1.09 (s, 3, 20 H), 1.01 (s, 3, 18 H).

Anal. Calcd for $C_{28}H_{38}O_2$: C, 82.71; H, 9.42. Found: C, 82.24; H, 9.12.

4,4-Dimethylandrost-5,7-dien-16β-yl Benzoate (6). A solution of **5g** (0.6 g) in petroleum ether (bp 63 °C, 20 mL) was

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treated with 1,3-dibromo-5,5-dimethylhydantoin (0.4 g). The mixture was refluxed for 15 min and cooled slowly to room temperature. The solution was filtered off from the dimethylhydantoin and the solvent evaporated to leave an oil (0.65 g). The oil was dissolved in xylene (10 mL) and added to a boiling solution of trimethyl phosphite (0.7 mL) in xylene (10 mL), and the mixture was refluxed for 1.5 h. The solvent was evaporated on the rotovap at 80 °C, and the residual oil was treated with acetone–methanol (2:1) to give a solid. The contents were heated on a steam bath until all the solid dissolved and was left to stand overnight to give pure crystals of **6** (0.47 g, 78%): mp 142–143 °C; IR (KBr) 1700 cm^{-1} (ester carbonyl); ^1H NMR δ 8.05 (m, 2, ortho H), 7.45 (m, 3, Ar H), 5.87 (d, part of an AB pattern, 1, 6 H), 5.6 (m, 2, 7 H and 16 H), 1.19 (s, 3, 21 H), 1.15 (s, 3, 20 H), 1.00 (s, 3, 19 H), 0.94 (s, 3, 18 H); mass spectrum, m/e (rel intensity) 404 (M^+, 49) 318 (15), 282 (M – $PhCO_2$, 30), 267 (79), 197 (100), 105 (55); UV (ethanol) λ_{max} 275 (ϵ 11 875), 283 nm (ϵ 11 666).

Anal. Calcd for $C_{28}H_{36}O_2$: C, 83.12; H, 8.97. Found: C, 83.09; H, 8.96.

4,4-Dimethylandrost-8(14)-en-16β-yl Cyclohexanecarboxylate (7a). A solution of **6** (0.35 g) in acetic acid–ether (1:1) (20 mL) was hydrogenated at atmospheric pressure over platinum oxide (100 mg). The hydrogen uptake was more than the stoichiometric amount when the reaction stopped. The solution was filtered through celite and then poured into water, and the product was extracted with ether. The ether extract was washed with sodium bicarbonate solution and water, then dried ($MgSO_4$), and evaporated to give an oily glassy residue (0.37 g). The oil solidified upon treatment with methanol to afford **7a** (0.25 g, 70%): mp 87 °C; IR (KBr) 1725 cm^{-1} (ester carbonyl); ^1H NMR δ 5.15 (m, 1, 16 H), 1.12 (s, 3, 18 H), 0.89 (s, 3, 21 H), 0.85 (s, 3, 20 H), 0.75 (s, 3, 19 H); mass spectrum m/e (rel intensity) (no M^+ peak), 285 (M – $C_7H_{11}O_2$, 98), 270 (M – CH_3, $C_7H_{11}O_2$, 7), 163 (53), 151 (24), 150 (100), 149 (21), 108 (29).

Anal. Calcd for $C_{28}H_{44}O_2$: C, 81.49; H, 10.74. Found: C, 81.31; H, 10.73.

4,4-Dimethylandrost-8(14)-en-16β-ol (7b). Saponification of **7a** (0.5 g) using sodium hydroxide in aqueous ethanol and recrystallization from methanol–water afforded **7b**: mp 115–117 °C; IR (KBr) 3400 cm^{-1} (OH); ^1H NMR δ 4.34 (m, 1, 16 H), 1.19 (s, 3, 18 H) 0.89 (s, 3, 21 H), 0.87 (s, 3, 20 H), 0.78 (s, 3, 19 H); mass spectrum m/e (rel intensity) 302 (M^+, 62), 287 (33), 269 (5), 178 (45), 151 (22), 147 (71), 137 (100), metastable peak at 272.7 (302 → 287).

Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.22. Found: C, 83.14; H, 11.31.

4,4-Dimethylandrost-8(14)-en-16-one (3). Oxidation of **7b** (0.5 g) using chromium trioxide (1.2 g, 12 mmol) and pyridine (1.9 g, 24 mmol) in methylene chloride (30 mL)[12] afforded the crude ketone **3** (0.4 g, 80%). Purification by column chromatography gave pure **3**: mp 94–95 °C; IR (KBr) 1750 cm^{-1} (C=O); UV (MeOH) λ_{max} 290 (ϵ 24) ^1H NMR δ 2.95 (d, 1), 2.17 (d, 1), 1.1 (s, 3, 18 H), 0.9 (s, 3, 21 H), 0.87 (s, 3, 20 H), 0.80 (s, 3, 19 H); mass spectrum m/e (rel intensity) 300 (M^+, 46), 285 (M – CH_3, 13), 215 (5), 189 (6), 176 (35), 163 (26), 137 (100), 124 (20), 123 (18), 109 (18).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 84.17; H, 10.52.

Photolysis of 4,4-Dimethylandrost-8(14)-en-16-one (3). 4,4-Dimethylandrost-8(14)-en-16-one (**3**) (160 mg) was irradiated in methanol (125 mL) by using a 450-W Hanovia lamp through a Pyrex filter for 20 h. The solvent was evaporated to leave a gum (162 mg), which was chromatographed on silica gel (10 g). Elution with 5% ether in hexane afforded a minor product as an oily material (10 mg, 6%): the IR ($CHCl_3$) showed a broad band at 1725 cm^{-1} for a carbonyl; ^1H NMR δ 3.59 (s, 3), 0.89 (s, 3), 0.87 (s, 6), 0.82 (s, 3); mass spectrum, m/e (rel. intensity) 334 (M^+, 13), 319 (6), 300 (8), 260 (100), 245 (23), 174 (19), 134 (54). Further elution afforded the starting ketone **3** (65 mg, 40%) and finally the major product 4,4-dimethyl-14β-androst-7-en-16-one (**8b**) (42 mg, 25%): mp 129 °C; IR (KBr) 1735 (16 C=O); ^1H NMR δ 5.48 (m, 1, 7 H), 2.1 (s, 2, 17 H), 1.11 (s, 3, 18 H), 0.95 (s, 3, 21 H), 0.90 (s, 3, 20 H), 0.89 (s, 3, 19 H); mass spectrum m/e (rel intensity) 300 (M^+, 30), 285 (M – CH_3, 24), 215 (11), 189 (14), 176 (rDA, 46), 124 (rDA, 84), 108 (100). CD $[\theta]_{299}$ +6600 deg cm^2 $dmol^{-1}$; $\Delta\epsilon$ +2.00.

Anal. Calcd for $C_{21}H_{34}O$: C, 83.94; H, 10.73. Found: C, 83.78; H, 10.78.

Photolysis of **3** in ethanol afforded a similar minor product with mass spectrum m/e 346 (M^+).

Photolysis of 7b. Irradiation of **7b** in methanol–xylene afforded a mixture of products, the ^1H NMR of which showed no olefinic hydrogens.

4,4-Dimethylandrost-7-en-16-one (8a). A solution of **6** (0.6 g) in ethanol (~300 mL) was hydrogenated over Raney nickel (2 g) under pressure (56 psi ≃ 3.8 atm) for 20 h. The catalyst was filtered through celite and the solvent evaporated to leave an oily residue (0.58 g). Recrystallization from methanol–water afforded 4,4-dimethylandrost-7-ene-16β-yl benzoate (0.52 g, 86%): mp 93–95 °C. IR (KBr) 1710 (benzoate carbonyl); ^1H NMR δ 5.51 (m, 1, 16 H), 5.27 (m, 1, 7 H), 0.90 (s, 3, 18 H), 0.87 (s, 6, 20 H and 21 H), 0.85 (s, 3, 19 H).

Anal. Calcd for $C_{28}H_{38}O_2$: C, 82.71; H, 9.42. Found: C, 82.71; H, 9.67.

Saponification of the 16-benzoate with NaOH in aqueous ethanol afforded the 16-alcohol, which was recrystallized from acetone–water; mp 162–163 °C; IR (KBr) 3400 cm^{-1} (OH); ^1H NMR δ 5.27 (m, 1, 7 H), 4.48 (m, 1, 16 H), 0.95 (s, 3, 18 H), 0.90 (s, 6, 20 H and 21 H), 0.84 (s, 3, 19 H).

Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.22. Found: C, 83.09; H, 11.32.

4,4-Dimethylandrost-7-en-16-ol (0.17 g) was oxidized by using the procedure of Ratcliffe and Rodehorst.[12] The product was recrystallized from methanol–water to give pure **8a** (0.14 g, 82%): mp 104–105 °C; IR (KBr) 1740 cm^{-1} (C=O); ^1H NMR δ 5.27 (m, 1, 7 H), 2.2 (s, 2, 17 H), 0.95 (s, 3, 21 H), 0.92 (s, 3, 20 H), 0.90 (s, 3, 18 H), 0.75 (s, 3, 19 H); mass spectrum, m/e (rel intensity) 300 (M^+, 6) 285 (3), [176 (14), 124 (17), rDA], 119 (17), 117 (17), 115 (11), 109 (34), 105 (31), 91 (45), 55 (58), 41 (100); CD $[\theta]_{299}$ −19 655 deg cm^2 $dmol^{-1}$; $\Delta\epsilon$ = −5.96.

Anal. Calcd for $C_{21}H_{34}O$: C, 83.94; H, 10.73. Found: C, 83.88; H, 10.75.

1,1,3a-Trimethyl-3a,4,5,6-tetrahydroindan-2-one (9). 1,3a-Dimethyl-4,5,6,7-tetrahydroindan-2-one[19] (1 g) was added to a suspension of potassium hydride (1.5 equiv) in dimethoxyethane (20 mL) and the mixture refluxed under nitrogen for 3 h. After cooling to room temperature, methyl iodide (1 g) was added and the mixture stirred for an additional hour at room temperature. Excess potassium hydride was destroyed by slow addition of water and the product extracted with ether. Chromatography on silica gel afforded **9** (0.2 g, 18%): IR (film), 1745 cm^{-1} (C=O); ^1H NMR δ 5.52 (t, 1, 7 H), 2.23 (s, 2, 3 H), 1.18 (s, 6, two methyls on C-1), 1.16 (s, 3, methyl on C-3a).

Photolysis of 1,1,3a-Trimethyl-3a,4,5,6-tetrahydroindan-2-one (9). A solution of **9** (100 mg) in pentane (25 mL) was irradiated with a 450-W Hanovia medium-pressure mercury lamp through a Pyrex filter for 5 h under nitrogen. Evaporation of the solvent and chromatography of the product mixture afforded 8-isopropylidene-1-methylbicyclo[3.2.1]octan-6-one (**10**) (7 mg, 7%): ^1H NMR δ 3.12 (t, 1, 5 H), 2.19 (s, 2, 7 H), 1.82 (s, 3, isopropylidene) and 1.64 (s, 3, isopropylidene), 1.42 (s, 3, methyl on C-1); high-resolution mass spectrum calculated for $C_{12}H_{18}O$ 178.13576, found 178.1358.

Photolysis of 2 mg of **10** in pentane for 3 h was shown by GC analysis to give **9** together with two other products.

1,1,3,3,3a-Pentamethyl-3a,4,5,6-tetrahydroindan-2-one (11). To a suspension of potassium hydride (1.5 g) in dimethoxyethane (60 mL), was added 1,3a-dimethyl-4,5,6,7-tetrahydroindan-2-one[19] (1.8 g). The mixture was refluxed for 3 h under nitrogen and then cooled to room temperature. Methyl iodide (5 g) was added and the mixture stirred for 2 h at room temperature. The reaction was worked up as before and the product mixture chromatographed on silica gel with hexane and then 10% ether–hexane to give **11** (1.2 g, 60%): IR (film), 1740 cm^{-1} (C=O); ^1H NMR δ 5.6 (t, 1, 7 H), 1.16, 1.15, 1.07, 0.99, 0.93 (s, 3 each, five methyls); mass spectrum, m/e (rel intensity), 206 (M^+, 80), 191 (M – CH_3, 100), 178 (M – CO, 6), 163 (M – CH_3, CO, 55), 135 (56), 107 (38); high-resolution mass spectrum calculated for $C_{14}H_{22}O$ 206.1671, found 206.1680.

Photolysis of 1,1,3,3,3a-Pentamethyl-3a,4,5,6-tetrahydroindan-2-one (11). A solution of **11** (2 g) in pentane (120 mL) was irradiated with a 450-W Hanovia lamp through a Pyrex filter

under nitrogen for 15 h. The solvent was evaporated, and the product mixture was chromatographed on silica gel with 5% ether–hexane as an intial eluent. The first fraction afforded a mixture of **13** and **14** that was separated on GC. The first product was **13** (0.41 g, 21%): IR (film) 2940 (C–H), 1670, 810 cm^{-1} (C=CH); ^1H NMR δ 5.31 (t, 1, 2 H), 2.6–1.4 (m, 6, 3 H, 4 H, and 5 H), 1.3, 1.25, 1.00, 0.95, 0.90 (s, 3 each, five methyls); mass spectrum, *m/e* (rel intensity) 178 (M^+, 28) 163 (M – CH_3, 7), 135 (100), 121 (7), 119 (7), 107 (35), 96 (35), 93 (38), 91 (15), 81 (34), 79 (22); high-resolution mass spectrum calculated for $C_{13}H_{22}$ 178.1724, found 178.1735. The second product was 1-isopropenyl-6-isopropyl-6-methylcyclohexene (**14**) (0.17 g, 9%): ^1H NMR δ 5.57 (t, 1, 2 H), 4.73 (m, 2, isopropenyl olefinic protons), 1.88 (s, 3, isopropenyl methyl), 1.2 (s, 3, 6-methyl), 0.85, 0.78 (d, 3 each, isopropyl methyls); UV (MeOH) λ_{max} 228 nm (ϵ 8080); mass spectrum, *m/e* (relative intensity), 178 (M^+, 15), 165 (7), 135 (100), 119 (28), 107 (47), 105 (11), 93 (49), 91 (31); high-resolution mass spectrum calculated for $C_{13}H_{22}$ 178.1724, found 178.1725.

Further elution afforded starting material **11** (1 g, 50%) and finally **12** (0.12 g, 6%): ^1H NMR δ 3:1 (t, 1, 5 H), 1.81, 1.64 (s, 3 each, olefinic methyls), 1.2 (s, 3, methyl on C-1), 0.98, 0.89 (s, 3 each, methyls on C-7); mass spectrum, *m/e* (relative intensity) 206 (M^+, 92), 191 (M– CH_3, 100), 178 (M – CO, 26), 163 (M– CH_3, CO, 62), 150 (31), 121 (77), 107 (72), 93 (88), 91 (98); high-resolution mass spectrum calculated for $C_{14}H_{22}O$ 206.1671, found 206.1694.

Irradiation of **12** for about 5 h and analysis of the product mixture by GC showed the formation of **11** together with other photolysis products.

4,4,15,15,17,17-Hexamethylandrost-8(14)-en-16-one (15). To a suspension of potassium hydride (26% in oil, ~0.3 g) in dimethoxyethane (25 mL) was added **3** (200 mg) and the mixture was refluxed under nitrogen for 3 h. The mixture was cooled to room temperature and then methyl iodide (4 mL) was added and the mixture was stirred at room temperature under nitrogen overnight. The excess potassium hydride was destroyed by slow addition of water and the product was extracted with ether. The ether dried ($MgSO_4$) and was evaporated to leave an oil which was flash chromatographed over silica, using hexane and then 10% ether–hexane, to afford **15**. Recrystallization from ether–methanol gave the pure material (165 mg, 70%): mp 147–149 °C; IR (KBr) 1740 cm^{-1} (C=O); UV (MeOH) λ_{max} 300 (ϵ 40); ^1H NMR (recorded on a Bruker WH-360/180 NMR spectrometer) δ 1.35 (s, 3), 1.25 (s, 3), 0.93 (s, 6), 0.91 (s, 3), 0.89 (s, 3), 0.86 (s, 3), 0.83 (s, 3); mass spectrum, *m/e* (rel intensity) 356 (M^+, 50), 341 (M – CH_3, 28), 232 (20), 217 (14), 216 (13), 204 (10), 202 (11), 191 (18), 137 (100), metastable peak at 326.6 (356 → 341).

Anal. Calcd for $C_{25}H_{40}O$: C, 84.27; H, 11.23. Found: C, 84.09; H, 10.97.

Photolysis of 4,4,15,15,17,17-Hexamethylandrost-8(14)-en-16-one (15). Photolysis of **15** in pentane, methanol, and acetone for 40 h proceeded with the slow disappearance of starting material but no new products could be identified.

Photolysis of 4,4-Dimethylandrost-8(14)-en-17-one (16b). A solution of **16b**[2] (100 mg) [λ_{max} 292 (ϵ 55) (MeOH)] in anhydrous benzene (100 mL) was stirred with a stream of nitrogen and was irradiated with a 450-W Hanovia lamp through a Pyrex filter. The course of the reaction was followed by removing small aliquots at various intervals and examining them by GC. After 15 min, a photostationary state consisting of approximately 14% of **17**, 6% of **16a** and 78% of **16b** was attained. A total of 500 mg of this mixture from combined runs was chromatographed on preparative scale thin-layer silica plates. Elution with 10% ether–hexane afforded 60 mg of pure **17** (14%), which was recrystallized from ether–methanol; mp 150–151 °C; IR (KBr) 1740 (C=O), 1665 cm^{-1} (C=C); UV (MeOH) λ_{max} 297.5 (ϵ 31); ^1H NMR δ 2.56 (m, 4, 15 H and 16 H), 1.68 (br s, 3, 18 H), 0.93 (s, 3, 21 H), 0.88 (s, 3, 20 H), 0.80 (s, 3, 19 H); mass spectrum, *m/e* (rel intensity) 300 (M^+, 53), 285 (M – CH_3, 9), 272 (M – CO, 12), 257 (11), 243 (12), 187 (11), 176 (20), 150 (37), 137 (100).

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.74. Found: C, 84.3; H, 10.69.

The second product was extracted with ethyl acetate and yielded 18 mg of **16a** (6%); mp 120–121 °C; IR (KBr) 1745 cm^{-1}; ^1H NMR δ 1.23 (s, 3, 18 H), 0.88 (s, 6, 20 H and 21 H), 0.81 (s, 3, 19 H); mass spectrum, *m/e* (rel intensity) 300 (M^+, 91), 285 (34), 272 (8), 257 (8), 243 (5), 190 (16), 176 (47), 150 (45), 137 (100); high-resolution mass spectrum calculated for $C_{21}H_{32}O$ 300.2453, found 300.2442; $[\alpha]_D$ –108.6° ($CHCl_3$); CD ($CHCl_3$) $[\theta]_{306}$ –3806 deg cm^2 $dmol^{-1}$; $\Delta\epsilon$ –1.15.

The third material isolated ws unreacted **16b** (390 mg, 78%).

Irradiation of **17** foı 15 min also gave a mixture of **16b**, **17**, and **16a**, in which **16b** was the major product.

Acknowledgment. We thank Dr. A. Magnani of Smithkline for a generous sample of testosterone, the National Institutes of Health for financial support (Grant No. HD-09146), and the National Science Foundation (Grant No. CHE-76-05757) for partial support.

Registry No. **3**, 81535-11-7; **5a**, 6560-99-2; **5b**, 81535-12-8; **5c**, 81535-13-9; **5d**, 81535-14-0; **5e**, 81535-15-1; **5f**, 81535-16-2; **5g**, 81535-17-3; **6**, 81535-18-4; **7a**, 81535-19-5; **7b**, 81535-20-8; **8a**, 81535-21-9; **8b**, 81600-19-3; **9**, 81535-22-0; **10**, 81535-23-1; **11**, 81535-24-2; **12**, 81535-25-3; **13**, 81535-26-4; **14**, 81535-27-5; **15**, 81553-84-6; **16a**, 81600-20-6; **16b**, 66500-27-4; **17**, 81535-28-6; 17β-hydroxy-4,4-dimethylandrost-5-ene, 6560-97-0; 4,4-dimethylandrost-7-en-16β-yl benzoate, 81535-29-7; 4,4-dimethylandrost-7-en-16-ol, 81535-30-0; 1,3a-dimethyl-4,5,6,7-tetrahydroindan-2-one, 60415-97-6.

Total Synthesis of Frustulosin and Aurocitrin

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Received October 15, 1981

The regioselective total syntheses of the novel fungal antibiotics frustulosin (**1**) and aurocitrin (**2**) were accomplished from 3,6-dihydroxy-2-iodobenzaldehyde (**10**) which was prepared by a regiodirected metalation of 2,5-dimethylbenzyl vinyl ether to establish the 1,2,3,4-tetrasubstitution pattern of these compounds. The unsaturated side chains of these hydroquinone antibiotics were attached by using the iodo aldehyde functionalities. The structures of these antibiotics are confirmed by synthesis.

Frustulosin (**1**)[1,2] and aurocitrin (**2**)[3] are two hydroquinone antibiotics recently isolated by Nair and coworkers from fungal sources. Frustulosin and related compounds were obtained from *Stereum frustulosum*; aurocitrin was obtained from *Hypocrea citrina*. These

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0022-3263/82/1947-2541$01.25/0