Cleavage of Unsaturated α-Ketols to ω-Oxo-α,β-unsaturated Acids

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Sodium periodate is a better reagent than sodium bismuthate, manganese dioxide, or lead tetraacetate for the cleavage of unsaturated α-ketols and affords ω-oxo-α,β-unsaturated acids in good yield. The combination of this cleavage reaction and a rhodium(I)-mediated decarbonylation of ω-oxo-α,β-unsaturated esters derived from polycyclic systems provided an enantioselective synthesis of cyclic systems bearing contiguous quaternary centers where one of the centers possessed *gem*-dimethyl groups.

Among the various reagents for the cleavage of diols and α-ketols are sodium periodate,[1] sodium bismuthate,[2] manganese dioxide,[3] lead tetraacetate,[4] chromium(VI) reagents,[5] alkaline hydrogen peroxide,[6] ceric ammonium nitrate,[7] and calcium hypochlorite.[8] In connection with several synthetic projects, we required an enantioselective synthesis of a monocyclic α,β-unsaturated ester **3** bearing two contiguous quaternary centers, one of which possessed *gem*-methyl groups.[9] Since bicyclic enones **1** (n = 1 or 2) are available in high enantiomeric excess, we investigated the oxidation of **1** to an unsaturated α-ketol **2**, the cleavage of the unsaturated α-ketol **2** to an aldehyde, and a rhodium-(I)-catalyzed decarbonylation to afford **3** as shown in Figure 1.[10] It was not clear, on the basis of literature precedent for related cleavages of *saturated* α-ketols,[1-8] which reagent would be preferable in unsaturated cases. We report that the cleavage of unsaturated α-ketols to furnish ω-oxo-α,β-unsaturated acids is best achieved using sodium periodate in aqueous THF. Other common oxidizing agents showed an interesting pattern of reactivity with respect to saturated and unsaturated α-ketols.

The scope of this cleavage process was investigated using a selection of saturated and unsaturated α-ketols **6** shown in Table I. The saturated α-ketols **6** were prepared according to literature procedures. The unsaturated α-ketols **6** were synthesized from the corresponding α,β-unsaturated ketones **4** in a two-step process using a manganese(III) acetate[11] or lead tetraacetate[12] oxidation of **4** to an α'-acetoxy-α,β-unsaturated ketones **5** followed by a saponification of **5** (Figure 2). As shown in Table I, the cleavage of the α-ketols **6** was best accomplished with sodium periodate. In order to facilitate the isolation of the carboxylic acid **7** that emerged from the oxidation, the

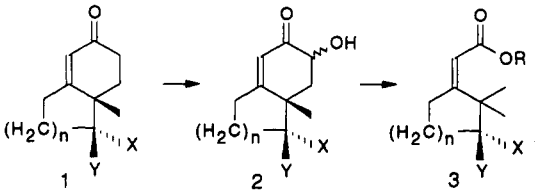
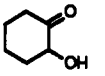
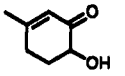
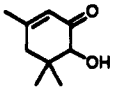
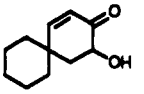
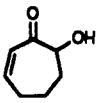
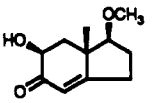
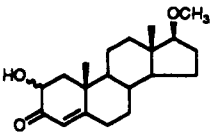


Figure 1.

Table I. Cleavage Reactions of Saturated and Unsaturated α-Ketols 6

	α-ketol 6	$NaIO_4$, % yield	$NaBiO_3$, % yield	$Pb(OAc)_4$, % yield
a		81	72	70
b		84	0	0
c		70	20	60
d		75	0	0
e		70	0	30
f		60	0	5-10
g		85	44	0

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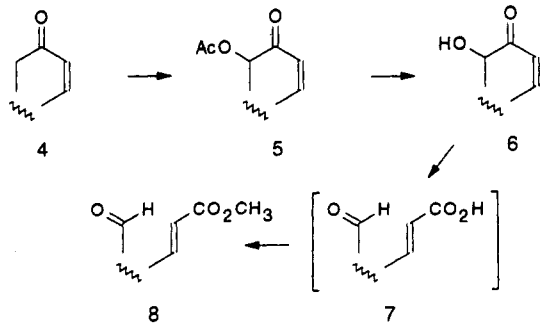

Figure 2.

crude product was typically treated with diazomethane in order to secure the ω-oxo-α,β-unsaturated methyl esters **8**. Other reagents such as sodium bismuthate effected the cleavage of saturated but not unsaturated ketols, and lead tetraacetate, a reagent recommended for such cleavage reactions, was successful in some cases but provided inferior yields to those achieved with sodium periodate.

To test the feasibility of the decarbonylation step in the proposed syntheses, the cleavage and decarbonylation of several model α-ketols **6f** and **6g** was investigated in some detail. As shown in Figure 3, the cleavage of the unsaturated α-ketol **6f** with $NaIO_4$ in aqueous THF led, following diazomethane treatment, to the α,β-unsaturated ester **8f**, and the decarbonylation of **8f** led uneventfully to the α,β-unsaturated ester **9**. It was of interest, however, that the oxidation of **6f** with $NaIO_4$ in an aqueous solution led unexpectedly to the lactone **10**. Presumably, in the absence of THF that may have served as a trap for hydrogen iodide, the iodination of the intermediate aldehyde and cyclization to the lactone **10** occurred.

In the case of **6g**, the cleavage reaction led to the intermediate hemiacetal **7g** that was converted to the methyl ester **8g** in 61% overall yield (Figure 4). Unexpectedly, the decarbonylation of **8g** provided not only the anticipated α,β-unsaturated ester **11** but also the unexpected β-keto ester **12** resulting from an acylrhodium addition to the proximal α,β-unsaturated ester. Although the addition of rhodium–carbonyl bonds to ω-olefins has been well studied,[13] it was surprising that the deactivated α,β-unsaturated ester in **8g** would participate in this process. The failure to observe a similar outcome in the case of **8f** may reflect the higher relative strain in a bicyclo[3.3.0]octane than in a bicyclo[4.3.0]nonane system. The outcome in these model studies suggested that the approach delineated in Figure 1 will prove satisfactory for the construction of contiguous quaternary centers in five-membered rings (n = 1) but may suffer poor yields in six-membered ring cases (n = 2). Further studies designed to make use of these findings will be reported in due course.

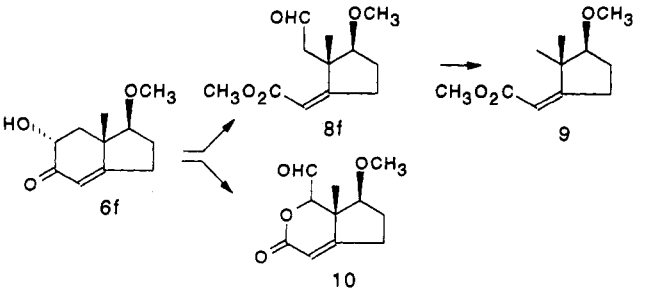

Figure 3.

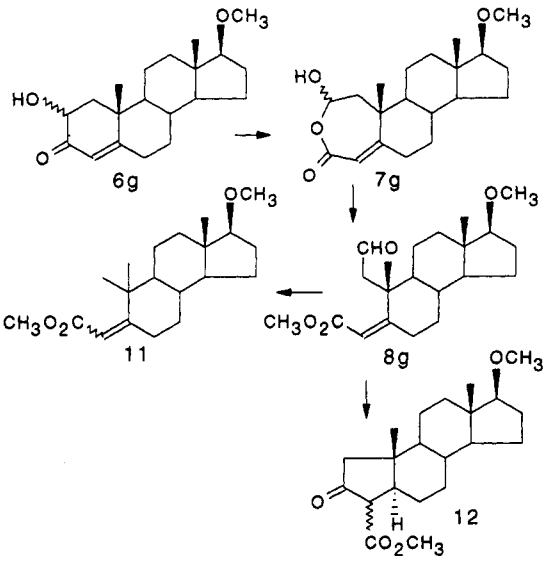

Figure 4.

Experimental Section

6-Hydroxy-3-methyl-2-cyclohexen-1-one (6b). To 4.4 g (40 mmol) of 3-methyl-2-cyclohexen-1-one (**4b**) (Aldrich) in 100 mL of anhydrous benzene under a Dean–Stark trap was added 41.7 g (180 mmol) of $Mn(OAc)_3$ in three portions over 5-h intervals. The mixture was refluxed under a N_2 atmosphere for 10 h. The mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed successively with 1 N HCl solution, H_2O, and brine, and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using 1:3 EtOAc–hexane to give 4.7 g (70%) of **5b**:[11] IR (KBr) 3032 (vinylic CH), 1739 (O(C=O)-CH_3), 1687 (C=O), 1634 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99 (s, 3, CH_3), 2.18 (s, 3, $OCOCH_3$), 5.32 (dd, J = 7.4 and 13 Hz, 1, C*H*($OCOCH_3$)), 5.90–5.98 (m, 1, vinylic H); ^{13}C NMR ($CDCl_3$) δ 21.0, 24.3, 28.4, 30.6, 73.3 (C-6), 125.9 (C-2), 163.0 (C-3), 170.9 (ester C=O), 194.3 (C=O).

To 1.0 g (6.0 mmol) of **5b** in 60 mL of MeOH was added 823 mg (6.0 mmol) of anhydrous K_2CO_3. The mixture was stirred for 2 h at 25 °C. The mixture was diluted with EtOAc, washed successively with 1 N HCl and brine, and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using 1:3 EtOAc–hexane to afford 526 mg (70%) of **6b**:[14] IR (KBr) 3470 (OH), 3033 (vinylic CH), 1672 (C=O), 1633 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99 (s, 3, CH_3), 3.80 (s, 1, OH), 4.13 (dd, J = 8 and 13.4 Hz, 1, C*H*OH), 5.90–5.98 (m, 1, vinylic H); ^{13}C NMR ($CDCl_3$) δ 24.3, 30.6, 30.9, 72.0 (C-6), 123.5 (C-2), 164.6 (C-3), 199.8 (C=O).

6-Hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one (6c). To 5.2 g (37 mmol) of 3,5,5-trimethyl-2-cyclohexen-1-one (**4c**) (Aldrich) in 182 mL of anhydrous benzene under a Dean–Stark trap was added 52.2 g (225 mmol) of $Mn(OAc)_3$ in three portions over 5-h intervals. The mixture was refluxed under N_2 for 10 h. The mixture was diluted with EtOAc and filtered through Celite. The filtrate was washed successively with 1 N HCl solution, H_2O, and brine and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using 1:3 EtOAc–hexane to give 4.96 g (68%) of **5c**:[15] IR (KBr) 1740 (ester C=O), 1675 (C=O), 1631 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (s, 3, CH_3), 1.10 (s, 3, CH_3), 1.96 (s, 3, CH_3), 2.22 (s, 3, $OCOCH_3$), 2.19 (d, J = 18.4 Hz, 1, H_a of CH_2), 2.55 (d, J = 18.4 Hz, 1, H_b of CH_2), 5.22 (s,

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1, C*H*OCOCH$_3$), 5.87–5.92 (m, 1, vinylic H); ^{13}C NMR ($CDCl_3$) δ 19.8, 20.6, 24.2, 27.2, 37.6, 46.0, 80.4 (C-6), 124.6 (C-2), 159.3 (C-3), 170.4 (ester C=O), 193.0 (C=O).

To 692 mg (16.5 mmol) of LiOH monohydrate in 150 mL of aqueous MeOH was added 2.85 g (15 mmol) of **5c**. The mixture was stirred for 1 h at 25 °C. The mixture was concentrated and diluted with EtOAc. The mixture was washed successively with 1 N HCl solution and brine and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using 1:3 EtOAc–hexane to afford 1.61 g (70%) of **6c**:[14] IR (KBr) 3381 (OH), 1668 (C=O), 1634 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3, CH_3), 1.21 (s, 3, CH_3), 1.97 (s, 3, CH_3), 2.15 (d, J = 18.6 Hz, 1, H_a of CH_2), 2.47 (d, J = 18.6 Hz, H_b of CH_2), 3.70 (d, J = 2 Hz, 1, OH), 3.96 (d, J = 2 Hz, 1, C*H*OH), 5.95–6.00 (m, 1, vinylic H); ^{13}C NMR ($CDCl_3$) δ 18.4, 24.5, 27.6, 39.4, 45.8, 79.7 (C-6), 123.0 (C-2), 161.7 (C-3), 199.5 (C=O).

4-Hydroxyspiro[5.5]undec-1-en-3-one (6d). To a solution of 1.7 g (7.8 mmol) of α′-4-acetoxyspiro[5.5]undec-1-en-3-one (**5d**)[11] in 78 mL of 1:3 THF–H_2O was added 489 mg (11.6 mmol) of LiOH monohydrate. The mixture was stirred at 25 °C for 30 min and neutralized with 6 N HCl solution. The organic layer was separated, and the aqueous layer extracted with EtOAc. The combined layers were washed with brine and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using 1:8 EtOAc–hexane to give 1.1 g (80%) of **1d** as colorless oil that solidified on storage at −5 °C: IR (TF) 3482 (OH), 1690 (C=O), 1610 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40–1.70 (m, 11, CH_2), 2.45–2.59 (m, 1, C-5 H), 3.51 (d, J = 1.8 Hz, 1, OH), 4.32 (two dd, J = 5.8 and 1.8 Hz, 1, C*H*OH), 5.97 (d, J = 10.2 Hz, 1, C-2 vinylic H), 6.83 (dd, J = 10.2 and 2.1 Hz, 1, C-1 vinylic H); ^{13}C NMR ($CDCl_3$) δ 20.7, 22.2, 25.7, 33.3, 38.0, 39.2, 40.5, 69.3 (CHOH), 123.8 (C-1), 160.1 (C-2), 200.6 (C=O). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: C, 73.21; H, 8.97.

7-Hydroxy-2-cyclohepten-1-one (6e). To 1.6 g (14.5 mmol) of 2-cyclohepten-2-one (**4e**) (Aldrich) in 50 mL of anhydrous benzene was added 7.9 g (17.8 mmol) of $Pb(OAc)_4$.[12] The mixture was refluxed under N_2 for 15 h. The mixture was filtered, and the filtrate was washed successively with 10% aqueous KI solution, 10% aqueous $Na_2S_2O_3$ solution, and brine. The organic layer was dried over anhydrous $MgSO_4$ and chromatographed on silica gel using 1:6 EtOAc–hexane to give 2.2 g (88%) of **5e**: IR (TF) 3028 (vinylic CH), 1740 (OAc), 1684 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.55–2.35 (m, 4, $(CH_2)_2$), 2.17 (s, 3, OCH_3), 2.41–2.64 (m, 2, C*H*$_2$CH=CH), 5.32 (dd, J = 3.8 and 10.2 Hz, 1, C*H*OAc), 6.05–6.18 (m, 1, CH=C*H*CO), 6.70–6.85 (m, 1, C*H*=CHCO); ^{13}C NMR ($CDCl_3$) δ 20.6, 27.9, 28.9, 78.2 (C-7), 130.1 (C-2), 147.6 (C-3), 170.4 (ester C=O), 197.0 (C=O). Anal. Calcd for $C_{19}H_{12}O_3$: C, 64.29; H, 7.14. Found: C, 64.26; H, 7.20.

To 2.16 g (12.8 mmol) of **5e** in 75 mL of 67% aqueous THF was added 2.73 g (19.2 mmol) of LiOH monohydrate. The mixture was stirred for 2 h at 25 °C. The pH was adjusted to 4–6 using 3 N HCl and THF evaporated under reduced pressure. The solution was extracted with EtOAc, and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using 1:4 EtOAc–hexane to afford 683 mg (55%) of **6e**:[15] IR (TF) 3460 (OH), 3025 (vinylic CH), 1706 (C=O), 1662 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.55–2.15 (m, 3, C-5 H), 2.20–2.40 (m, 1, C-6 H), 2.40–2.55 (m, 2, C*H*$_2$CH=CH), 3.95 (s, 1, OH), 4.25 (dd, J = 5 and 10 Hz, 1, C*H*OH), 6.12–2.25 (m, 1, CH=C*H*CO), 6.72–6.88 (m, 1, C*H*=CH-CO); ^{13}C NMR ($CDCl_3$) δ 22.7, 29.5, 30.9, 76.9 (CHOH), 128.5 (C-3), 147.6 (C-2), 202.7 (C=O).

3ξ-Hydroxy-5β-methoxy-4aβ-methylind-1(7α)-en-2-one (6f). To 3.8 g (21.2 mmol) of 5β-methoxy-4aβ-methylind-1(7α)-en-2-one (**4f**) in 50 mL of anhydrous benzene was added 14.1 g (31.8 mmol) of $Pb(OAc)_4$.[12] The mixture was refluxed for 40 h under a N_2 atmosphere. The mixture was filtered, and the filtrate was washed successively with 10% KI solution, 10% $Na_2S_2O_3$ solution, and brine. The organic layer was dried over anhydrous $MgSO_4$, concentrated, and chromatographed on silica gel using 1:3 EtOAc–hexane to give 4.0 g (80%) of 3ξ-acetoxy-5β-methoxy-4aβ-methylind-1(7α)-en-2-one (**5f**) as a mixture of C-2 epimers: IR (TF) 1748 (ester C=O), 1682 (C=O), 1642 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 and 1.27 (s, 3, CH_3), 1.70–2.85 (m, 6, CH_2), 2.11 and 2.18 (two s, 3, $OCOCH_3$), 3.40 (s, 3, OCH_3), 3.35–3.50 (m, 1, C*H*OCH_3), 5.20–5.28 and 5.50–5.62 (m, 1, C*H*OAc), 5.81–5.86 and 5.88–5.95 (m, 1, vinylic H); ^{13}C NMR ($CDCl_3$) δ 16.6, 19.8, 21.0, 21.2, 26.2, 26.6, 27.1, 39.5, 41.3, 44.6, 46.7, 58.1, 69.6, 70.5, 88.9 (*C*$HOCH_3$), 121.9, 122.2, 169.9, 170.3, 174.4 (ester C=O), 176.9 (ester C=O), 192.5 (C=O), 193.2 (C=O). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.55; H, 7.56. Found: C, 65.27; H, 7.58.

To 1.8 g (7.6 mmol) of **5f** in 75 mL of 95% EtOH was added 494 mg (7.6 mmol) of KCN. The mixture was stirred at 25 °C for 10 h. The mixture was concentrated and diluted with EtOAc. The solution was washed with brine and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using 1:3 EtOAc–hexane to give 734 mg (50%) of **6f** as a mixture of C-2 epimers. The principal C-2α isomer had the following spectral data: IR (TF) 3472 (OH), 1674 (C=O), 1639 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 3, CH_3), 1.65–2.85 (m, 6, CH_2), 3.42 (s, 3, OCH_3), 3.43 (dd, J = 2.6 and 7.6 Hz, 1, C*H*OCH_3), 3.60 (s, 1, OH), 4.36 (dd, J = 5.6 and 13.2 Hz, 1, C*H*OH), 5.88 (t, J = 2 Hz, 1, vinylic H); ^{13}C NMR ($CDCl_3$) δ 16.3, 25.9, 26.9, 44.9, 46.7, 58.1, 69.1, 89.0 (*C*$HOCH_3$), 120.4 (*C*=CHC=O), 176.4 (C=*C*HC=O), 199.4 (C=O); exact mass spectrum calcd for $C_{11}H_{16}O_3$ 196.1099, found 196.1100.

2ξ-Hydroxy-17β-methoxy-4-androsten-3-one (1g). To 120 mL of DMF was added 10 g (34.7 mmol) of testosterone (**4g**) (Sigma) and 108 mL (1.73 mol, 50 equiv) of CH_3I under a N_2 atmosphere. The solution was cooled in an ice–salt bath for 15 min, and 2.08 g (52.0 mmol, 1.5 equiv) of NaH (washed with anhydrous hexane) was added. The mixture was stirred for 5 h. The mixture was quenched with MeOH and poured into H_2O. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined layers were washed with brine, dried over anhydrous $MgSO_4$, and chromatographed on silica gel using 1:2 EtOAc–hexane to afford 9.2 g (88%) of 17β-methoxy-4-androsten-3-one: mp 121–122 °C; IR (KBr) 3025 (vinylic CH), 1667 (C=O), 1609 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.81 (s, 3, C-18 CH_3), 1.19 (s, 3, C-19 CH_3), 3.24 (t, J = 7.8 Hz, 1, C*H*OCH_3), 3.35 (s, 3, OCH_3), 5.74 (s, 1, vinylic H); ^{13}C NMR ($CDCl_3$) δ 11.0, 14.3, 15.6, 18.9, 20.3, 24.1, 25.7, 29.3, 31.1, 36.1, 43.2, 45.3, 54.2, 58.0, 68.2, 69.4 (OCH_3), 90.6 (C-17), 120.2 (C-4), 175.2 (C-5), 195.1 (C-3). Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.47; H, 9.93. Found: C, 79.24; H, 9.96.

The procedure of Arseniyadis[12] was repeated using 3.7 g (12.3 mmol) of 17β-methoxy-4-androsten-3-one in 25 mL of anhydrous benzene under N_2 and 6.8 g (15.4 mmol) of $Pb(OAc)_4$ to afford, after refluxing under a Dean–Stark trap for 36 h and chromatography on silica gel using 6:1 hexane–EtOAc, 3.1 g (70%) of 2ξ-acetoxy-17β-methoxy-4-androsten-3-one (**5g**) as a 1:1 mixture of C-2 epimers: IR (KBr) 1747 (ester C=O), 1684 (C=O), 1614 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80 (s, 3, CH_3), 1.21 and 1.33 (two s, 3, CH_3), 2.16 and 2.17 (two s, 3, $OCOCH_3$), 3.18–3.30 (m, 1, C*H*OCH_3), 3.35 (s, 3, OCH_3), 5.26–5.51 (m, 1, C-2 H), 5.73–5.82 (m, 1, vinylic H); ^{13}C NMR ($CDCl_3$) δ 11.2, 11.3, 17.8, 20.3, 20.6, 20.7, 21.9, 22.0, 22.3, 22.9, 23.0, 27.4, 31.2, 32.1, 32.6, 33.8, 34.6, 35.3, 37.16, 37.22, 40.4, 40.9, 41.2, 42.5, 43.0, 50.4, 54.1, 57.7, 70.3, 71.1, 90.3 (C-17), 120.5 (C-4), 121.8 (C-4), 170.5 (C-5), 171.2 (C-5), 173.4 (ester C=O), 193.9 (C=O), 194.0 (C=O). Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.33; H, 8.89. Found: C, 73.20; H, 8.94.

To 4.0 g (11 mmol) of **5g** in 75 mL of MeOH was added 753 mg (5.5 mmol, 0.5 equiv) of anhydrous K_2CO_3. The mixture was stirred at 25 °C for 40 min. The solution was diluted with EtOAc, washed with dilute HCl, and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using 4:1 hexane–EtOAc to afford 2.3 g (60%) of **6g**: IR (KBr) 3432 (OH), 1686 (C=O), 1614 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.80 (s, 3, CH_3), 1.18 and 1.30 (two s, 3, CH_3), 3.23 and 3.24 (two t, J = 9.1 Hz, 1, C*H*OCH_3), 3.35 (s, 3, OCH_3), 3.61 and 3.65 (two d, J = 1.7 Hz, 1, OH), 4.22 and 4.25 (two dt, J = 13.9 and 1.5 Hz, 1, C*H*OH), 5.79 and 5.80 (two s, 1, vinylic H); ^{13}C NMR ($CDCl_3$) δ 11.1, 11.3, 17.7, 20.1, 22.3, 22.5, 22.85, 22.94, 27.3, 27.4, 31.2, 32.3, 32.7, 34.3, 34.5, 35.3, 37.2, 37.3, 39.2, 40.3, 41.1, 42.4, 43.0, 43.8, 49.9, 50.3, 50.4, 54.2, 57.7, 63.4, 69.3, 90.2 (C-17), 118.7 (C-4), 120.2 (C-4), 173.2 (C-5), 175.3 (C-5), 200.0 (C=O for both epimers). Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.47; H, 9.43. Found: C, 75.39; H, 9.48.

6-Oxohexanoic Acid (7a) from 6a Using Lead Tetraacetate. To 114 mg (1 mmol) of **6a** in 10 mL of HOAc was added 665 mg (1.5 mmol) of $Pb(OAc)_4$. The mixture was stirred for 30 min at 25 °C under a N_2 atmosphere. The mixture was diluted with EtOAc and washed successively with 10% KI solution, 10%

$Na_2S_2O_3$ solution, H_2O, and brine. The organic layer was dried over anhydrous $MgSO_4$. The product was chromatographed on a silica gel column using 1:1 EtOAc–hexane to afford 91 mg (70%) of **7a**: IR (TF) 3600–2300 (CO_2H), 1715 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65–1.80 (m, 4, $(CH_2)_2$), 2.35–2.55 (m, 4, CH_2CO_2H and CH_2CHO), 9.79 (t, J = 1.6 Hz, 1, CHO); ^{13}C NMR ($CDCl_3$) δ 21.2, 23.8, 33.5, 43.3, 179.8 (CO_2H), 202.5 (C=O). Repetition of this experiment using benzene in place of HOAc gave only a 5% yield of **7a**.[9]

Methyl 6-oxohexanoate (8a): IR (TF) 1735 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.58–1.68 (m, 4, CH_2), 2.30–2.50 (m, 4, $CH_2CO_2CH_3$ and CH_2CHO), 3.68 (s, 3, CO_2CH_3), 9.78 (t, 1, J = 1.5 Hz, CHO); ^{13}C NMR ($CDCl_3$) δ 21.5, 24.3, 33.7, 43.5, 51.6, 173.7 (CO_2CH_3), 202.0 (C=O).

6-Oxohexanoic Acid (7a) from 6a Using Sodium Periodate. To 114 mg (1 mmol) of **6a** in 10 mL of 60% aqueous THF was added 214 mg (1 mmol) of $NaIO_4$. The mixture was stirred at 25 °C for 10 h, and an additional 107 mg (0.5 mmol) of $NaIO_4$ was added. The mixture was stirred for an additional 6 h, diluted with EtOAc, washed successively with H_2O and brine, and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using 1:1 EtOAc–hexane to afford 105 mg (81%) of **7a** which had spectral data identical to that described above.

6-Oxohexanoic Acid (7a) from 6a Using Sodium Bismuthate. To 114 mg (1 mmol) of **6a** in 10 mL of 50% aqueous HOAc was added 308 mg (1.1 mmol) of $NaBiO_3$. The mixture was stirred at 25 °C for 12 h, diluted with EtOAc, washed successively with 10% $NaHSO_3$ solution, H_2O, and brine, and dried over anhydrous $MgSO_4$. The product was chromatographed on silica gel using 1:1 EtOAc–hexane to afford 93 mg (72%) of **7a** which had spectral data identical to that above.

(2*Z*)-6-Oxo-3-methyl-2-hexenoic Acid (7b). To 126 mg (1 mmol) of **6b** in 10 mL of H_2O was added 214 mg (1.0 mmol) of $NaIO_4$. The mixture was stirred for 8 h at 25 °C. An additional 107 mg (0.5 mmol) of $NaIO_4$ was added, and the mixture was stirred for an additional 4 h. The mixture was saturated with NaCl and extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The product was chromatographed on a preparative silica gel plate using 1:1 EtOAc–hexane to afford 119 mg (84%) of **7b**: IR (KBr) 2500–3400 (CO_2H), 1726 (C=O), 1686 (acid C=O), 1636 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (d, J = 1.3 Hz, 3, CH_3), 2.60–2.72 (m, 2, CH_2CHO), 2.92 (t, J = 7.6 Hz, 2, $CH_2C(CH_3)$=CH), 5.76 (d, J = 1.2 Hz, 1, $CH_2C(CH_3)$=CH), 9.81 (t, J = 1.4 Hz, 1, CHO); ^{13}C NMR ($CDCl_3$) δ 25.5, 26.2, 42.1, 116.8 (C-3), 161.3 (C-2), 171.0 (CO_2H), 201.3 (C=O). Anal. Calcd for $C_7H_{10}O_3$: C, 59.16; H, 7.04. Found: C, 59.03; H, 7.07.

(2*Z*)-6-Oxo-3,5,5-trimethyl-2-hexenoic Acid (7c) Using $NaIO_4$. To 154 mg (1 mmol) of **6c** in 10 mL of H_2O was added 321 mg (1.5 mmol) of $NaIO_4$. The mixture was stirred for 15 h at 25 °C. The mixture was chilled in an ice bath to crystallize the product. The white precipitate was collected by filtration and dried under high vacuum to give 112 mg (70%) of **7c**. An analytical sample was prepared by recrystallization from CH_2Cl_2–hexane: mp 58–59 °C; IR (KBr) 2500–3400 (CO_2H), 1718 (C=O), 1693 (acid C=O), 1627 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 6, C-5 CH_3), 1.85 (s, 3, C-3 CH_3), 2.98 (s, 2, CH_2), 5.81 (s, 1, vinylic H), 9.56 (s, 1, CHO); ^{13}C NMR ($CDCl_3$) δ 21.8, 27.1, 39.4, 46.6, 119.0 (C-3), 158.9 (C-2), 171.5 (CO_2H), 205.5 (C=O). Anal. Calcd for $C_9H_{14}O_3$: C, 63.53; H, 8.24. Found: C, 63.56; H, 8.25.

(2*Z*)-6-Oxo-3,5,5-trimethyl-2-hexenoic Acid (7c) Using $NaBiO_3$. To a solution of 50 mg (0.3 mmol) of **6c** in 5 mL of 1,4-dioxane was added 115 mg (0.35 mmol) of $NaBiO_3$ in 5 mL of H_2O. The solution was stirred at 25 °C for 5 min, and 3 mL of 68% of H_3PO_4 was added over a period of 10 min. The mixture was stirred for 30 min and filtered. The mixture was diluted with EtOAc, washed with brine, and dried over anhydrous $MgSO_4$. The product was chromatographed on a preparative layer silica gel plate using 1:3 EtOAc–hexane to afford 10 mg (20%) of **7c** which had spectral data identical to that described above.

Methyl (2*Z*)-6-Oxo-3,5,5-trimethyl-2-hexenoate (8c) Using $Pb(OAc)_4$. To 154 mg (1 mmol) of **6c** in 10 mL of anhydrous benzene was added 665 mg (1.5 mmol) of $Pb(OAc)_4$. The mixture was stirred at 25 °C for 2 h under N_2. The mixture was diluted with EtOAc and washed successively with 10% KI solution, 10% $Na_2S_2O_3$ solution, and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude product was treated with CH_2N_2, and the product was chromatographed on a preparative silica gel plate using 1:6 EtOAc–hexane to afford 110 mg (60%) of **8c**: IR (TF) 1715 (C=O), 1644 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, 6, C-5 CH_3), 1.81 (d, J = 1.2 Hz, 3, C-3 CH_3), 2.97 (s, 2, CH_2), 3.68 (s, 3, CO_2CH_3), 5.78 (s, 1, vinylic H), 9.57 (s, 1, CHO); ^{13}C NMR ($CDCl_3$) δ 21.8, 26.8, 39.5, 46.6, 50.9, 119.0 (C-3), 115.8 (C-2), 166.6 (CO_2CH_3), 205.6 (C=O).

(2*Z*)-7-Oxo-2-heptenoic Acid (7e) Using Sodium Periodate. To 126 mg (1 mmol) of **6e** in 10 mL of H_2O was added 235 mg (1.1 mmol) of $NaIO_4$. The mixture was stirred at 25 °C for 12 h. The mixture was saturated with NaCl and extracted with EtOAc. The product was chromatographed on a preparative silica gel plate using 1:1 EtOAc–hexane to give 85 mg (60%) of **7e**: IR (TF) 2500–3600 (CO_2H), 1722 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81 (p, J = 7.2 Hz, 2, CH_2CH_2CHO), 2.54 (dt, J = 1.4 and 7.2 Hz, 2, CH_2CH_2CHO), 2.64–2.85 (m, 2, CH_2CH=CH), 5.79–6.00 (m, 1, CH=CHCO), 6.35 (dt, J = 7.8 and 11.6 Hz, 1, CH=CHCO), 9.80 (t, J = 1.4 Hz, 1, CHO); ^{13}C NMR ($CDCl_3$) δ 20.9, 28.1, 43.0, 120.3 (C-2), 151.8 (C-3), 172.1 (CO_2H), 202.6 (C=O).

A derivative was prepared by treating the aldehyde with dimedone in 50% aqueous EtOH. The precipitate was recrystallized from 50% aqueous EtOH: mp 135–137 °C. Anal. Calcd for $C_{23}H_{32}O_6$: C, 68.32, H, 7.92. Found: C, 68.08; H, 7.98.

Methyl (2*Z*)-3-(1′-(Formylmethyl)-1′-cyclohexyl)acrylate (8d). To 180 mg (1 mmol) of **6d** in 10 mL of H_2O was added 256 mg (1.2 mmol) of $NaIO_4$. The mixture stirred for 12 h at 25 °C. The mixture was saturated with NaCl and extracted with EtOAc. The organic layer was washed with 5% $Na_2S_2O_3$, dried over anhydrous $MgSO_4$, and concentrated. The crude product was treated with CH_2N_2 and chromatographed on a preparative silica gel plate using 1:5 EtOAc–hexane to give 158 mg (75%) of **8d**: IR (TF) 1722 (C=O), 1632 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25–1.60 (m, 8, CH_2), 1.95–2.15 (m, 2, CH_2), 3.00 (d, J = 2.1 Hz, 2, CH_2CHO), 3.71 (s, 3, CO_2CH_3), 5.89 (d, J = 13.1 Hz, 1, vinylic H), 6.27 (d, J = 13.1 Hz, 1, vinylic H), 9.69 (t, J = 2.1 Hz, 1, CHO); ^{13}C NMR ($CDCl_3$) δ 22.4, 25.7, 36.8, 38.8, 51.4, 53.9, 120.3, (CH=CHC=O), 154.1 (CH=CHC=O), 166.3 (CO_2CH_3), 202.3 (C=O).

Methyl (2*Z*)-7-Oxo-2-heptenoate (8e). To 126 mg (1 mmol) of **6e** in 10 mL of anhydrous benzene was added 665 mg (1.5 mmol) of $Pb(OAc)_4$. The mixture was stirred at 25 °C for 2 h under a N_2 atmosphere. The mixture was diluted with EtOAc and washed successively with 10% KI solution, 10% $Na_2S_2O_3$ solution, and brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude product was treated with CH_2N_2 and chromatographed on a preparative silica gel plate using 1:5 EtOAc–hexane to afford 47 mg (30%) of **8e**: IR (TF) 1723 (C=O), 1645 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (p, J = 7.5 Hz, 2, C-5 H), 2.50 (dt, J = 1.1 and 7.3 Hz, 2, CH_2CHO), 2.64–2.78 (m, 2, CH_2CH=CH), 3.71 (s, 3, CO_2CH_3), 5.75–5.88 (m, 1, CH=CHCO$_2$CH$_3$), 6.21 (dt, J = 7.5 and 11.5 Hz, 1, CH=CHCO$_2$CH$_3$), 9.79 (t, J = 1.1 Hz, 1, CHO); ^{13}C NMR ($CDCl_3$) δ 21.2, 28.1, 43.1, 51.0, 120.3 (CH=CHC=O), 148.9 (CH=CHC=O), 166.6 (CO_2CH_3), 202.0 (C=O).

(1*S*,2*S*,3*Z*)-3-(Carbomethoxymethylene)-2-(formylmethyl)-2-methyl-1-cyclopentyl Methyl Ether (8f). To 212 mg (1 mmol) of **6f** in 10 mL of H_2O was added 214 mg (1 mmol) of $NaIO_4$. The mixture was stirred at 25 °C for 6 h and an additional 214 mg (1 mmol) of $NaIO_4$ was added twice at 6-h intervals. The mixture was stirred for a total of 18 h. The mixture was saturated with NaCl and extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated, and the residue was dissolved in anhydrous ether. To the crude acid was added CH_2N_2, and the solution was stirred for 30 min. The product was chromatographed on a preparative silica gel plate using 1:4 EtOAc–hexane to give 136 mg (60%) of **8f**: IR (TF) 1716 (C=O), 1650 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (s, 3, CH_3), 1.42–1.63 (m, 1, C-5 H), 2.02–2.18 (m, 1, C-5 H), 3.01 (dd, J = 17.4 and 1.6 Hz, 1, CHCHO), 3.35 (s, 3, OCH_3), 3.48 (dd, J = 17.4 and 1.5 Hz, 1, CHCHO), 3.66 (s, 3, $COOCH_3$), 5.76 (t, J = 2.3 Hz, 1, vinylic H), 9.68 (t, J = 1.6 Hz, 1, CHO); ^{13}C NMR ($CDCl_3$) δ 17.8, 25.7, 32.5, 46.5, 50.6, 51.0, 57.8, 87.3 ($COCH_3$), 113.3 (C=CHC=O), 165.8 (C=CHC=O), 169.6 (CO_2-

CH_3), 202.1 (C=O); exact mass spectrum calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1161.

(1*S*,3*Z*)-3-(Carbomethoxymethylene)-1-methoxy-2,2-dimethylcyclopentane (9). To 201 mg (0.89 mmol) of **8f** in 4.5 mL of anhydrous CH_2Cl_2 was added 824 mg (0.89 mmol, 1 equiv) of $RhCl(PPh_3)_3$. The mixture was refluxed for 20 h under N_2. The mixture was diluted with 1:1 EtOAc–hexane and filtered through a short silica gel column. The product was chromatographed on a preparative silica gel plate using 1:4 EtOAc–hexane to afford 133 mg (75%) of **9**: IR (TF) 1723 (C=O), 1650 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55–1.99 (m, 2, CH_2CHOCH_3), 2.30–2.70 (m, 2, allylic CH_2), 3.33 (dd, J = 2 and 6.6 Hz, 1, $CHOCH_3$), 3.38 (s, 3, C-1 OCH_3), 3.68 (s, 3, CO_2CH_3), 5.73 (t, J = 2 Hz, 1, vinylic H); ^{13}C NMR ($CDCl_3$) δ 18.8, 24.8, 26.0, 32.8, 46.4, 50.9, 57.8, 91.7 ($CHOCH_3$), 112.9 (C=$CHCO_2CH_3$), 166.0 (C=$CHCO_2CH_3$), 171.3 (C=$CHCO_2CH_3$).

1β-Formyl-3-oxo-7β-methoxy-7aβ-methyl-1,3,5,6,7,7a-hexahydrocyclopenta[*c*]pyran (10). To 300 mg (1.5 mmol) of **6f** in 7 mL of H_2O was added 327 mg (1.5 mmol) of $NaIO_4$. The mixture was stirred at 25 °C for 15 h under N_2. The mixture was extracted with EtOAc. The organic layer was washed with 5% $Na_2S_2O_3$ and brine solution, dried over anhydrous $MgSO_4$, and concentrated to give 201 mg (62%) of **10**. An analytical sample was prepared by recrystallization in EtOAc–hexane: mp 133–134 °C; IR (KBr) 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3, CH_3), 1.68–2.81 (m, 4, CH_2), 3.43 (s, 3, OCH_3), 3.83 (dd, J = 9.9 and 3.1 Hz, 1, $CHOCH_3$), 4.79 (d, J = 1.4 Hz, 1, (C=O)-$OCHCHO$), 5.80 (t, J = 2.0 Hz, 1, vinylic H), 9.78 (d, J = 1.4 Hz, 1, CHO); ^{13}C NMR ($CDCl_3$) δ 17.7, 25.3, 26.5, 47.4, 57.8, 81.2 ($CHOCH_3$), 86.2 ((C=O)$OCHCHO$), 113.4 (C=CHC=O), 161.9 (C=CHC=O), 167.4 (lactone C=O), 198.0 (CHO). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.86; H, 6.67. Found: C, 62.90, H, 6.70.

***A*-Homo-2ξ-hydroxy-17β-methoxy-4-oxo-3-oxaandrost-4a-ene (7g).** To a solution of 318 mg (1 mmol) of **6g** in 5 mL of 67% aqueous THF was added 428 mg (2 mmol) of $NaIO_4$. The solution was stirred at 25 °C for 10 h and an additional 428 mg (2 mmol) of $NaIO_4$ was added. The solution was stirred for an additional 10 h. The mixture was diluted with H_2O and extracted with EtOAc. The organic layers were washed with brine and dried over anhydrous $MgSO_4$. The product was chromatographed on preparative silica gel plates using 1:1 EtOAc–hexane to afford 284 mg (85%) of **7g** as an epimeric mixture of hemiacetals. The principal diastereomer had the following spectral data: IR (KBr) 3420, 3179 (OH), 1681 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (s, 3, C-18 CH_3), 1.26 (s, 3, C-19 CH_3), 3.22 (t, J = 7.7 Hz, $CHOCH_3$), 3.34 (s, 3, OCH_3), 4.68 (br s, 1, OH), 5.64 (d, J = 6.3 Hz, 1, acetal H), 5.81 (s, 1, vinylic H); ^{13}C NMR ($CDCl_3$) δ 11.5, 20.3, 21.3, 23.2, 27.6, 33.2, 34.9, 35.8, 37.5, 42.0, 42.8, 48.8, 50.4, 54.4, 57.8, 90.3, 94.6 ((C=O)$OCOH$), 115.5 (C=CHC=O), 165.2 (C=CHC=O), 166.3 (acetal C=O).

(4*Z*)-17β-Methoxy-2-oxo-2,3-secoandrost-4-en-3-oic Methyl Ester (8g). To a solution of 217 mg (0.65 mmol) of **7g** in 2 mL of anhydrous ether was added 5 mL of a solution of CH_2N_2 in ether. The mixture was stirred for 30 min at 25 °C. The product was chromatographed on a preparative silica gel plate using 1:4 EtOAc–hexane to afford 162 mg (72%) of **8g**: ^1H NMR ($CDCl_3$) δ 0.77 (s, 3, C-18 CH_3), 1.24 (s, 3, CH_3), 2.66 (dd, J = 18.2 and 3.2 Hz, 1, H_a of $CHCHO$), 3.22 (t, J = 7.8 Hz, 1, $CHOCH_3$), 3.34 (s, 3, C-17β OCH_3), 3.49 (d, J = 18.2 Hz, 1, H_b of $CHCHO$), 3.66 (s, 3, CO_2CH_3), 5.74 (s, 1, C-4 H), 9.96 (d, J = 3.4 Hz, 1, CHO); ^{13}C NMR ($CDCl_3$) δ 11.3, 20.6, 20.8, 23.0, 27.5, 29.1, 33.7, 35.8, 37.5, 41.6, 42.8, 47.4, 50.0, 50.9, 57.8, 90.4 (C-17), 115.1 (C-4), 161.9 (C-5), 168.0 ($COOCH_3$), 202.8 (C=O); exact mass spectrum calcd for $C_{21}H_{32}O_4$ 348.2301, found 348.2295.

17β-Methoxy-2-nor-2,3-secoandrost-4-en-3-oic Methyl Ester (11) and 4-Carbomethoxy-17β-methoxy-2-nor-5α-androstan-3-one (12). To 138 mg (0.40 mmol) of **8g** in 2.5 mL of anhydrous benzene was added 208 mg (0.40 mmol) of $RhCl(PPh_3)_3$. The mixture was refluxed for 20 h. The solution was diluted with 1:1 hexane–EtOAc and filtered through a short silica gel column. The product was chromatographed on a preparative silica gel plate using 20:1 hexane–EtOAc (three developments) to afford 51 mg (40%) of **11** as a 1:1 mixture of *E*/*Z* isomers and 57 mg (40%) of the addition product **12**.

Isomer A of 11: IR (KBr) 1722 (C=O), 1634 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.79 (s, 3, CH_3), 1.06 (s, 3, CH_3), 1.08 (s, 3, CH_3), 3.25 (t, J = 7.9 Hz, 1, $CHOCH_3$), 3.34 (s, 3, OCH_3), 3.69 (s, 3, CO_2CH_3), 3.84 (dt, J = 13.4 and 3.8 Hz, 1, CHC=$CHCOOCH_3$), 5.70 (s, 1, C-4 H); ^{13}C NMR ($CDCl_3$) δ 11.6, 21.5, 22.2, 23.3, 25.4, 25.7, 27.7, 32.7, 35.7, 37.9, 41.0, 42.9, 50.8, 50.9, 53.5, 57.8, 90.6 ($CHOCH_3$), 110.1 (C=CH-C=O), 168.1 (C=CHC=O), 171.1 (CO_2CH_3). Anal. Calcd for $C_{20}H_{32}O_3$: C, 75.00; H, 10.00. Found: C, 74.94; H, 10.12.

Isomer B of 11: IR (KBr) 1732 (C=O), 1644 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3, CH_3), 1.08 (s, 3, CH_3), 1.17 (s, 3, CH_3), 3.21 (t, J = 8.4 Hz, 1, $CHOCH_3$), 3.34 (s, 3, OCH_3), 3.70 (s, 3, CO_2CH_3), 5.52 (s, 1, C-4 H); ^{13}C NMR ($CDCl_3$) δ 11.6, 21.5, 21.6, 23.3, 25.0, 27.7, 32.4, 35.1, 35.5, 37.9, 40.5, 42.8, 51.0, 51.5, 52.5, 57.8, 90.6 ($CHOCH_3$), 112.9 (C=CHC=O), 156.4 (C=C,HC=O), 170.0 (CO_2CH_3). Anal. Calcd for $C_{20}H_{32}O_3$: C, 75.00; H, 10.00. Found: C, 74.88; H, 10.11.

4-Carbomethoxy-17β-methoxy-2-nor-5α-androstan-3-one (12): IR (KBr) 1722 (C=O), 1754 (ester C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (s, 3, CH_3), 0.88 (s, 3, CH_3), 3.06 (d, J = 13.4 Hz, 1, $CHCO_2CH_3$), 3.25 (t, J = 7.6 Hz, 1, $CHOCH_3$), 3.5 (s, 3, OCH_3), 3.75 (s, 3, CO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 11.7, 14.5, 23.2, 23.6, 27.5, 30.8, 35.4, 37.6, 40.2, 43.2, 50.8, 51.2, 52.4, 53.2, 53.9, 57.4, 57.8, 90.5 ($CHOCH_3$), 169.9 (CO_2CH_3), 210.7 (C=O). Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.41; H, 9.20. Found: C, 72.46; H, 9.24.

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Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra for compounds **7g** and **8d** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.