2′,3′,5′-Tri-*O*-benzoyl[4-^{13}C]uridine, 1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2,4-dihydroxy[4-^{13}C]pyrimidine (11). To a solution at 10 °C containing 4.68 g (9.3 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside[25] and 2.0 g (8.6 mmol) of bis(*O*-trimethylsilyl)[4-^{13}C]uracil (**10**) in 100 mL of dry acetonitrile under a dry nitrogen atmosphere was added 1.6 g (6.1 mmol) of freshly distilled (from P_2O_5) stannic chloride in 50 mL of dry acetonitrile. The resulting solution was stirred at room temperature (22 °C) for 16 h and the solvent was removed at 22 °C under reduced pressure. The residue was dissolved in 300 mL of 1,2-dichloroethane and shaken with 250 mL of a saturated sodium bicarbonate solution. The resulting emulsion was allowed to settle and as much of the clear organic layer as possible was removed. A further 100 mL of 1,2-dichloroethane was added to the emulsion and the process was repeated. After the fifth extraction, the remaining bicarbonate layer was filtered through Whatman No. 1 filter paper to break up the emulsion and the resulting clear bicarbonate layer was extracted twice more with 50 mL of organic solvent. The combined organic extract was dried (sodium sulfate and magnesium sulfate) and the solvent was removed to afford 4.81 g of a light, creamy white crystalline solid. Medium-pressure chromatography on silica gel (ICN, 0.032–0.063 mm or 230–400 mesh) using methylene chloride–2% methanol as the eluant afforded 4.30 g (7.74 mmol, 90%) of 2′,3′,5′-tri-*O*-benzoyl[4-^{13}C]uridine as a white crystalline solid: mp 142–143 °C (lit.[35] 142–143 °C).

Acknowledgments. We wish to thank Mr. Clyde L. Livingston for assistance in obtaining ^{13}C NMR spectra.

Registry No.—**10**, 65102-77-4; **12**, 1563-79-7; **13**, 65138-36-5; trifluoroacetic acid anhydride, 407-25-0; 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside, 6974-32-9.

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(1) This work was supported by the National Institutes of Health, CA 16824.
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(40) Allowance must be made for the water (39 mmol) initially in the [1-^{13}C]-acetic acid. The amount of water used allows for a 5% excess over the theoretical.
(41) The amount of material which azeotroped over is effected by the amount of water present in the mixture. Hence, the amount of water added for the hydrolysis was carefully calculated to minimize the water left after hydrolysis.
(42) It is necessary to use anhydrous acetic acid to obtain the reported yield. We have not used this procedure with [1-^{13}C]acetic acid because of the high cost of the labeled material.

Steroid Total Synthesis. 11.[1,2] (+)-Estr-4-ene-3,17-dione from a Chiral Lactone

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Optically pure (+)-estr-4-ene-3,17-dione and (−)-estra-4,9-diene-3,17-dione have been synthesized from the prochiral 5,9-diketoheptanoic acid via the lactone **11**. The selective microbiological reduction of **10** produced optically pure **11**, which was converted to the masked Mannich base **16** and subsequently condensed with 2-methylcyclopentane-1,3-dione to give predominantly the trans diene **17**. This key intermediate was then transformed into (+)-estr-4-ene-3,17-dione via **24** and also to (−)-estra-4,9-diene-3,17-dione by the cyclization of the polyketone **20**.

An asymmetric synthesis of (+)-estr-4-ene-3,17-dione (**27**) is described starting from the chiral lactone **11** (Scheme I) obtained by the selective microbiological reduction of 5,9-diketoheptanoic acid. Condensation of the amine **16**,

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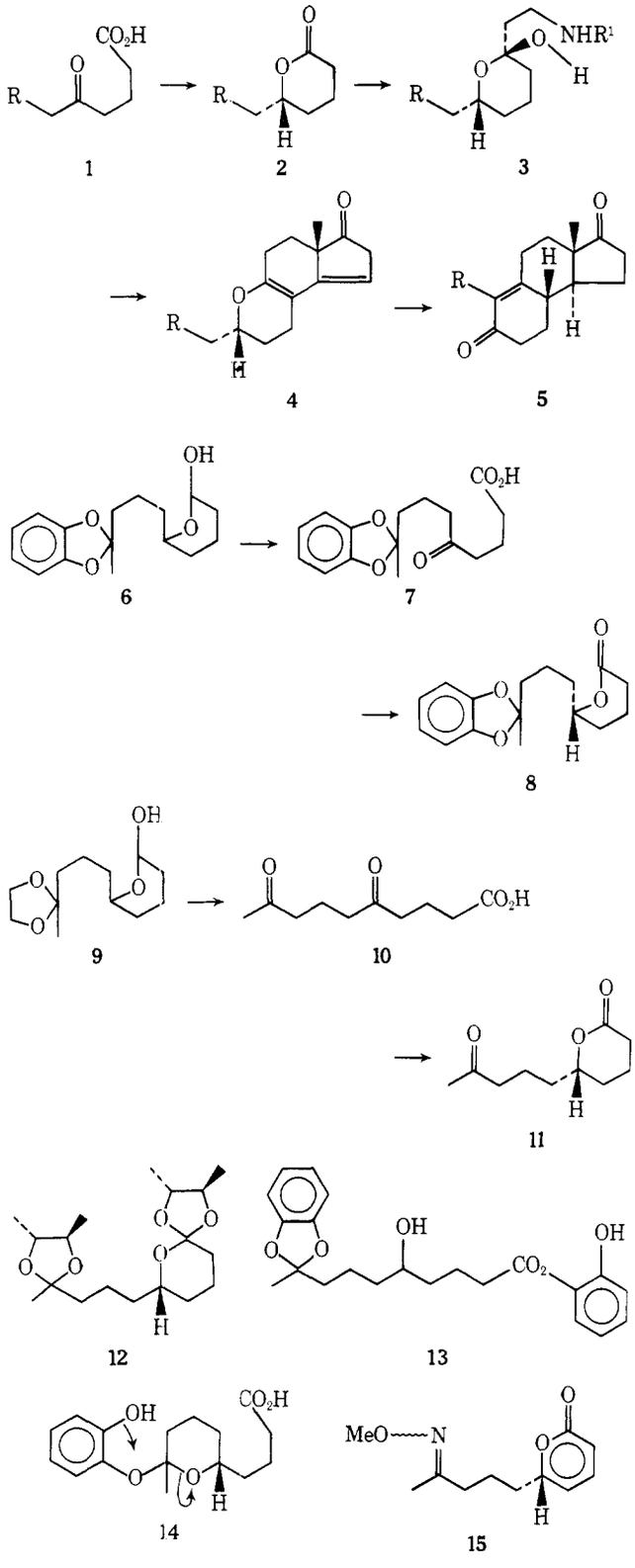
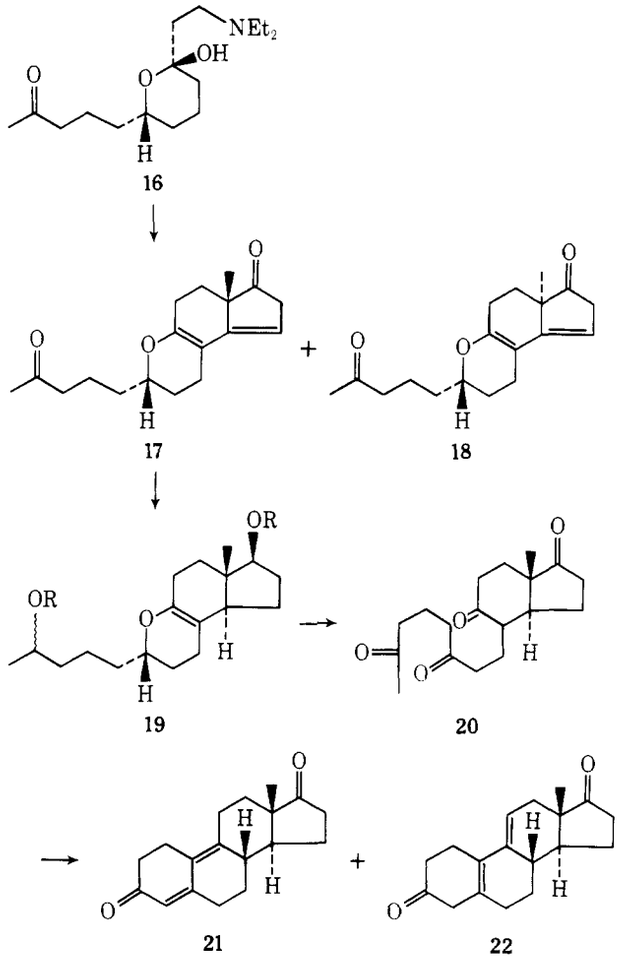
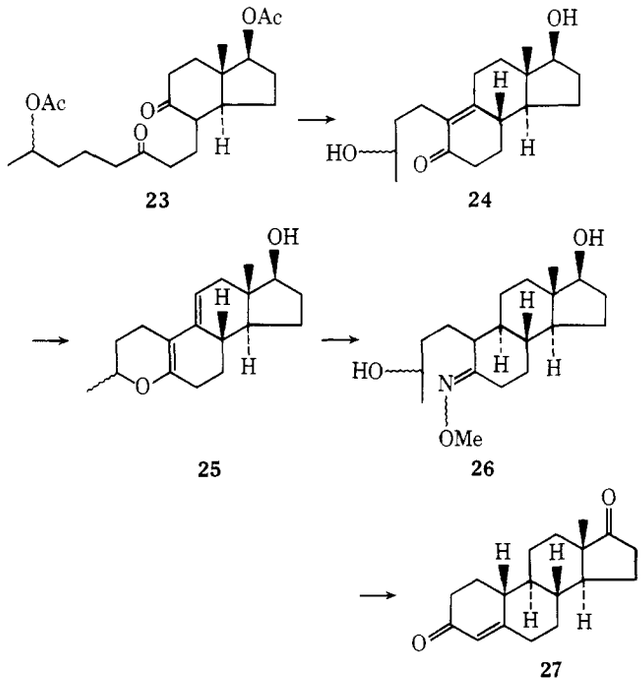
Scheme I



Scheme II



Scheme III



(Scheme II), derived from this lactone, with 2-methylcyclopentane-1,3-dione gave predominantly the 13β trans diene **17**, indicative of a highly diastereoselective process. Suitable manipulations of this key substrate **17** then generated the target compounds **21**, **22**, and **27** (Scheme III).

Previous publications[3,4] from our laboratories have described routes to optically pure 19-nor steroids (e.g., **27**) which involve a classical resolution of masked Mannich bases, of the type **3**, to introduce the controlling chiral carbon (*pro*-C_5). These bases on condensation with 2-methylcyclopentane-1,3-dione then lead to the versatile dienes **4**, with high asymmetric induction, giving mainly the 13β arrangement.

This paper describes a related route based on some of our earlier work[5] in which asymmetry was introduced early in the synthesis via optically active lactones which are generated by the microbiological reduction of δ-keto acids.

Results and Discussion

The microbiological reduction of δ-keto acids to the corresponding hydroxy acids[6] of high optical purity is a simple and efficient method and has proved useful in our total synthesis of retro-steroids.[5] Extension of this reduction to keto acids with suitably functionalized side chains had not been described previously and seemed to us to offer an excellent entry into natural 19-nor steroids.

Our previous success with catechol as a ketone-protecting group[7] made the keto acid **7** our first choice for reduction. This material is readily available from the hemiacetal **6**[8] by simple oxidation with chromic acid,[9] or by direct addition of the Grignard reagent, derived from the catechol ketal of 1-chloro-4-pentanone, to glutaric anhydride.

While the microbiological reduction of **7** to the lactone **8** was observed, the conversions were low due to the toxic effects of the substrate or the generated hydroxy acid on the microorganism. With the diketo acid **10**,[10] however, a selective reduction and excellent conversion to the lactone **11** was observed. On the basis of molecular rotation comparison with **2** (R = methyl and *n*-butyl), the new lactone was also of high optical purity. To confirm the optical purity of our material we made use of a new method for determining the enantiomeric purity of chiral δ-lactones[11] which involves the formation of an ortho ester derivative with (−) -(2*R*,3*R*)-butanediol and subsequent analysis by GC. Exposure of the keto lactone **11** to the butanediol generated the expected ketal ortho ester **12** which showed only one peak on GC analysis, whereas with the racemic keto lactone the ketal ortho ester mixture of diastereomers showed two cleanly resolved peaks.

As we had already shown in a model study with racemic material that the keto lactone **11** could be converted to the ketalized material **8** via the adduct **13** by simple pyrolysis, we anticipated no problems for the optically active substrate. However, this failed to be the case, and when the lactone **11** was ketalized as before, examination of the protected lactone **8** showed that extensive racemization had occurred. This could be the result of an intermediate such as **14** being formed in which the pyran oxygen is derived from the carbonyl group, leading to inversion at C_5. Subsequent closing of the ketal results in the formation of the enantiomeric alcohol, and if such a process occurs at the same time as normal ketalization, then the overall effect is racemization.

The protection of the ketopentyl side chain, however, is possible by the formation of the oxime ether **15**. These oxime ethers are easily formed, are stable to acidic and basic environments, and have proved moderately useful to us[12] and others.[13]

Exposure of the keto lactone **11** to methoxylamine produces the protected product **15**, without apparent racemization, as a mixture of syn and anti isomers. This mixture was not separated but used directly and treated with vinylmagnesium chloride[5] to furnish a vinyl ketone. This was trapped with diethylamine to yield a Mannich base, which on mild acid treatment gave **16**. This acid treatment, which was designed to separate neutral impurities formed in this reaction, yielded an added bonus in removing the oxime ether protecting group. These mild conditions for ketone regeneration must be a result of internal assistance by the hydroxyl group, as in general more vigorous hydrolysis conditions have to be employed.[12]

With the pure material **16** in hand, the key condensation with 2-methylcyclopentane-1,3-dione in a mixture of toluene and acetic acid at reflux yielded the two dienes **17** and **18** in approximately a 3:1 ratio from which the required (trans) 13β isomer was readily obtained by direct crystallization. Reduction of both carbonyl groups with lithium aluminum hydride formed the diol which on stereoselective hydrogenation gave **19** (R = H), which was processed in two ways.

One sequence of reactions involved the hydration and subsequent oxidation of **19** (R = H) to the tetraketone **20**, which we then hoped to cyclize to the 19-nor steroid **21**. There is some precedent in the literature[14] that such a cyclization could be possible; however, when the reaction conditions described by these authors were applied to **20**, complex mixtures resulted which contained little of the desired material. In contrast, when heated at reflux in toluene with piperidinium acetate,[15] **20** gave a mixture of the two ketones **21** and **22** in approximately 70% yield. Exposure of isomer **22** to *p*-toluenesulfonic acid in toluene at reflux resulted in a 60% yield of the conjugated isomer **21**. The physical data for compound **21** compare well with the reports in the literature;[16] however, **22** could not be compared with previously synthesized material as no data are given,[17] and the structure rests solely on our ^1H NMR, IR, and UV spectra (see Experimental Section). Whether ring A forms first in the cyclization of **20** and this then reacts further to give the above mixture of ketones is not known.

The other set of transformations carried out on substrate **19** (R = H) involved protection of the diol as a diacetate (**19**, R = Ac), followed by hydration of the enol ether and subsequent oxidation to the diketone **23**. Exposure of this material to dilute methanolic base then brought about cyclization and hydrolysis to yield the tricyclic compound **24**, which on acid treatment afforded the mixture of diastereomers **25**. Conversion of this material to optically pure (+)-estr-4-ene-3,17-dione (**27**) then followed the course previously described by us.[12] Selective hydrogenation of **25** followed by treatment with methoxylamine generated the diol **26**, which on oxidation and cyclization gave **27**, identical in all respects with material synthesized previously by us[3] and others.[18]

In summary, the work described herein offers an efficient route to optically pure 19-nor steroids in relatively few steps starting with the easily prepared lactone **11**. There are no separation problems, and the overall yields to the key intermediates **17**, **20**, and the mixture of **21** and **22** from the lactone **11** are 45, 34, and 27%, respectively.

Experimental Section[19]

8-(2-Methyl-1,3-benzodioxol-2-yl)-5-oxooctanoic Acid (7). The crude hemiacetal[8] **6** (29 g) dissolved in acetone (380 mL) was cooled to −10 °C, treated over a period of 30 min with a fresh solution of Jones chromic acid mixture,[9] and then stirred overnight at room temperature. aqueous sodium bisulfite solution (50 mL, 20%) was added, and the products were extracted into ether to yield the crude keto acid. This material was partitioned between ether and aqueous sodium hydroxide solution (5%), and the aqueous phase was then acidified (6 N H_2SO_4) and extracted with ether. Removal of the solvents followed by distillation (oil-jacketed flask) yielded the pure material (16.7 g): bp 185–195 °C (0.1 mm); ^1H NMR ($CDCl_3$) δ 9.7 (s, 1, CO_2H), 6.8 (s, 4, C_6H_4), 2.5 (m, 6, CH_2CO), 1.9 (m, 6, CH_2), 1.6 (s, 3, CH_3); mass spectrum, *m/e* 292 (M^+). Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.9. Found: C, 65.63; H, 7.1.

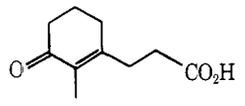
5,9-Diketodecanoic Acid (10). The hemiacetal[8] **9** (30 g; crude material containing 5–8% toluene) was dissolved in acetone (150 mL), treated with aqueous sulfuric acid (0.5 N, 75 mL), and left at room temperature for 2 h. Brine (1 L) was added, and the crude keto hemiacetal was extracted into dichloromethane (21.9 g). This material was dissolved in acetone (110 mL), cooled to 5 °C, and treated over 20 min with Jones chromic acid mixture (88.5 mL), followed by stirring at room temperature for 18 h and then quenching with aqueous sodium bisulfite solution (20%, 50 mL). Extraction with more acetone (4 × 200 mL) yielded the crude diketo acid on removal of the solvents. This material was then dissolved in dichloromethane, washed with brine, and dried. Crystallization of the solid residue (22.1 g) from isopropyl ether gave pure **10** (13.6 g): mp 78–80 °C; ^1H NMR ($CDCl_3$) δ 10.9 (s, 1, CO_2H), 2.5 (m, 8, CH_2CO), 2.17 (s, 3, $COCH_3$), 2.0 (m, 4, CH_2). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 60.15; H, 7.96.

(*S*)-Tetrahydro-6-[3-(2-methyl-1,3-benzodioxol-2-yl)propyl]-2*H*-pyran-2-one (8). The culture of *Margarinomyces bubaki* 459 M was grown aerobically as previously described,[6] dosed with the keto acid **7** (12 g, ~0.5 g/L) in ethanol, and then agitated anaerobically for

24 h. The total mixture was extracted to yield a crude extract (8.6 g) which was distilled (Kugelrohr) to give one major fraction (2.9 g), bp 165–195 °C (0.1 mm). This product was dissolved in ether and extracted with aqueous sodium carbonate solution (10%) to yield a neutral fraction (1.1 g) which was chromatographed on silica (50 g). Elution with a benzene–ethyl acetate mixture (9:1) yielded the lactone (485 mg), which was distilled to give pure material (446 mg): bp ~200 °C (0.02 mm); $[\alpha]^{20}_D$ −36.8° (*c* 1, dioxane). The ^{1}H NMR and IR spectra were identical with those of racemic material.[8]

(*S*)-Tetrahydro-6-(4-oxopentyl)-2*H*-pyran-2-one (11). The broth was prepared as before, the diketo acid was fed (1 g/L, 30 g), and the mixture was stirred anaerobically for 24 h. The pH of the medium was adjusted to 2, and the products were extracted into dichloromethane. Removal of the solvents and distillation of the residue (28.5 g) through a 4 in vacuum-jacketed Vigreaux column yielded one major fraction (17.4 g): bp 130–132 °C (0.1 mm); $[\alpha]^{20}_D$ −45.5° (*c* 0.091, dioxane); IR (film) 1725 and 1710 (keto lactone) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.4 (m, 1, CHO), 2.5 (m, 4, CH_2CO), 2.0 (s, 3, $COCH_3$), 1.7 (m, 8, CH_2). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.02; H, 8.94.

A simple assay for the progress of the fermentation was based on the reaction of **10** with aqueous base when the cyclohexenone A was



A

formed. This material had bp 130–140 °C (0.02 mm) (Kugel-Rohr); UV max (95% ethanol) 242 nm (ε 12 800). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.87; H, 7.54.

Thus aliquots from the broth were brought to pH 12 with aqueous sodium hydroxide solution, filtered, and assayed by UV spectroscopy.

Enantiomeric Purity Determination of 11. A solution of the keto lactone **11** (1.8 g), (−)-(2*R*,3*R*)-butanediol (3 g), and *p*-toluenesulfonic acid (100 mg) in benzene (50 mL) was heated at reflux in conjunction with a Dean and Stark water trap for 4 h. After this time the total reaction mixture was absorbed onto an alumina column (Woelm neutral, grade III, 100 g) and developed with a mixture of ether and hexane (1:9). Fractions 10–55 (10 mL each) were collected and concentrated to yield the pure ketal ortho ester (2.23 g). Anal. Calcd for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82. Found: C, 65.83; H, 9.81.

The racemic keto lactone (1.8 g) was treated as above to yield the pure mixture of diastereomers (2.66 g) after chromatography. GC analysis of these samples was performed with an HP5710A gas chromatograph on a 1 m × 4 mm glass column containing 5% OV-210 supported on GCQ 100–120 mesh. It is of interest that the ortho esters of both **11** and **2** (R = CH_3)[11] in the 5*S* series have the higher retention times as in the case of **12**.

(*R,S*)-Tetrahydro-6-(4-oxopentyl)-2*H*-pyran-2-one. (*RS*)-Tetrahydro-6-[3-(2-methyl-1,3-ethylenedioxol-2-yl)propyl]-2*H*-pyran-2-one (52.4 g)[8] was dissolved in acetone (150 mL), treated with aqueous sulfuric acid (2 N, 45 mL), and left at room temperature for 16 h. Brine was added and the keto lactone was isolated with benzene. Distillation gave the pure material (26 g), bp 134 °C (0.05 mm). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.35; H, 8.59.

(*R,S*)-Tetrahydro-6-[3-(2-methyl-1,3-benzodioxol-2-yl)propyl]-2*H*-pyran-2-one. The keto lactone (15 g) in benzene (300 mL) was treated with catechol (20 g) and *p*-toluenesulfonic acid (0.6 g) and heated at reflux in conjunction with a Soxhlet extractor containing calcium hydride in the thimble. After 18 h the mixture was cooled and chromatographed directly on silica gel (650 g). Elution with 5, 10, and 15% ethyl acetate–benzene mixtures yielded the ketal ester **8** (28 g) as an oil: ^{1}H NMR ($CDCl_3$) δ 6.8 (m, 8, $(C_6H_4)_2$), 6.1 (s, 1, OH), 4.5 (m, 1, CHO), 1.6 (s, 3, CH_3); IR (film) 3300 (phenolic and aliphatic OH), 1700 (ester C=O), 1480, 1275, 740 (catechol ketal) cm^{-1}. Short-path destructive distillation yielded catechol (12.11 g) and the lactone (12.2 g), bp 157–162 °C (0.2 mm). This material was identical in all respects with a sample prepared from **6** by oxidation.[8] Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.3. Found: C, 69.84; H, 7.34.

When the above sequence was applied to the optically active keto lactone **11** (7.8 g; $[\alpha]^{20}_D$ −46°), the chemically pure ketal **8** (5.5 g), bp 170 °C (0.5 mm), was obtained. This was identical in all respects with the racemic material and had a specific rotation of $[\alpha]^{20}_D$ −7° (*c* 0.5, dioxane), indicating extensive racemization.

***syn,anti*-(*S*)-Tetrahydro-6-(4-methoxyiminopentyl)-2*H*-pyran-2-one (15).** An ice cold solution of lactone **11** (39.1 g) in pyridine (240 mL) was treated with a cold solution (10 °C) of methoxylamine hydrochloride (35.6 g) in pyridine (200 mL) and stirred 30 min more at 10 °C. The mixture was then cooled to 0 °C, treated with triethylamine (61 mL), stirred 15 min more, and filtered free of solids. The residue was washed with benzene, and the combined filtrates (benzene and pyridine) were concentrated to yield the oxime ether **15** (44.4 g) as a pale yellow oil.

A sample distilled for analysis had bp 110–120 °C (0.05 mm); $[\alpha]^{25}_D$ −44.6° (*c* 1.0817, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.3 (m, 1, OCH), 3.88 and 3.86 (two s, total of 3, OCH_3), 1.92 and 1.89 (two s, total of 3, N=CHCH_3). Anal. Calcd for $C_{11}H_{19}O_3N$: C, 61.94; H, 8.98; N, 6.57. Found: C, 62.18; H, 8.83; N, 6.52.

(2*S*,6*S*)-2-Diethylaminoethyl-6-(4-oxopentyl)-tetrahydropyran-2-ol (16). A solution of the crude oxime ether **15** (44.4 g) in tetrahydrofuran (THF, 850 mL) was cooled to −60 °C and treated over 10 min with a solution of vinylmagnesium chloride (2.2 M, 159 mL), the temperature being held between −50 and −55 °C. After complete addition, stirring was continued at −60 °C for 20 min followed by cooling to −70 °C. Methanol (24 mL) was carefully added, and the reaction mixture was then poured onto a mixture of saturated aqueous ammonium chloride solution (250 mL), ether (500 mL), and ice (100 g). The aqueous phase was reextracted several times with ether, and the combined ether extracts were washed with brine, dried over sodium sulfate, treated with diethylamine, and left at room temperature for 1 h. Removal of the solvents gave the crude Mannich base (62.5 g), which can be purified by acid extraction. To remove the oxime ether protecting group the base was dissolved in acetone (850 mL), treated with aqueous sulfuric acid (2 N, 610 mL) at 0 °C, and then left at room temperature for 24 h.

Most of the acetone was then removed at 30 °C and 20 mm pressure, and the residue was extracted with ether to yield the neutral material (7 g) which was discarded. The aqueous phase was cooled to 0 °C, treated with a sodium hydroxide solution (10 N, 155 mL), and extracted with ether. Removal of the solvents gave the base **16** (45.5 g) as an oil. A sample chromatographed on alumina furnished the analytical sample: IR ($CHCl_3$) 3100 (bonded OH), 1725 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{31}NO_3$: C, 67.33; H, 10.94; N, 4.91. Found: C, 67.38; H, 10.66; N, 4.88.

[2*S*-(2α,7aβ)]-2,3,4,7a,8,9-Hexahydro-7a-methyl-2-(4-oxopentyl)-6*H*-cyclopenta[*f*]-1-benzopyran-7-one (17). A mixture of 2-methylcyclopentane-1,3-dione (22 g), toluene (700 mL), and acetic acid (250 mL) was heated to 110 °C, treated over 10 min with a solution of the base **16** (45 g) in more toluene (200 mL), and then stirred 30 min more at this temperature. The temperature was then raised (bath to 130 °C), water was separated with a Dean–Stark trap for 1 h, and the mixture was cooled to room temperature. The cooled mixture was washed with water and saturated sodium bicarbonate solution and dried over sodium sulfate. Removal of the solvents yielded the mixture of dienes **17** and **18** (44 g) as a solid. Crystallization from aqueous methanol gave pure trans material **17** (27.6 g): mp 74–76 °C; $[\alpha]^{25}_D$ −162° (*c* 1.21, $CHCl_3$); UV max (95% ethanol) 252 nm (ε 18 750); IR ($CHCl_3$) 1740 (cyclopentanone), 1712 (C=O), 1642 (dienol ether) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.45 (t, *J* = 2 Hz, C_9–H), 3.77 (m, 1, C_3–H), 2.15 (s, 3, CH_3CO), 1.13 (s, 3, C_{7a}–CH_3). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.96; H, 8.39. Found: C, 74.76; H, 8.38.

(3*S*,6a*S*,7*S*)-3-[4(*R*,*S*)-Hydroxypentyl]-6a-methyl-1,2,3,5,6,6a,7,8,9,9a-decahydrocyclopenta[*f*][1]benzopyran-7-ol (19, R = H). The diene **17** (8.24 g) in tetrahydrofuran (170 mL) was added to a slurry of lithium aluminum hydride (4.35 g) in more tetrahydrofuran (430 mL) at 0–5 °C. The mixture was stirred for 30 min at room temperature and then treated carefully with a saturated aqueous solution of sodium sulfate. The solids were filtered off and washed with more tetrahydrofuran, and the solvents were then removed to yield the diol (8.9 g). A sample crystallized from an ether–isopropyl ether mixture had mp 95–102 °C; $[\alpha]^{25}_D$ −180° (*c* 1.0142, $CHCl_3$). Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.94; H, 9.66. Found: C, 73.66; H, 9.56.

The crude material (8.8 g) was dissolved in tetrahydrofuran (270 mL) and hydrogenated at room temperature and pressure over a palladium catalyst (1.2 g of AK4).[20] After 35 h the hydrogen uptake stopped (710 mL) and the solids were filtered off and washed with more solvent. The combined solvents were concentrated to give **19** (9.0 g) as an oil.

[2(*R,S*),6a*S*,7*S*]-2,3,4,6,6a,7,8,9,9a,10,11-Dodecahydro-2,6a-dimethylcyclopenta[5,6]naphtho[2,1-*b*]pyran-7-ol (25). The crude diol **19** (R = H) (9 g) was dissolved in a mixture of pyridine (80 mL) and acetic anhydride (40 mL) and then left for 18 h at room temperature. Removal of the solvents and extraction into benzene yielded the crude diacetate after washing with sodium bicarbonate solution and concentrating to dryness.

This product (**19**, R = Ac; 10 g) in acetone (170 mL) was exposed to dilute aqueous sulfuric acid (1 N, 50 mL), left to stand for 2.5 h, and

then cooled to 5 °C. To this mixture was added a fresh solution of Jones chromic acid mixture (14.2 mL), followed by stirring at room temperature for 2.5 h.

After cooling to 10 °C, sodium bisulfite was added to destroy the excess of oxidant, followed by a 10% aqueous sodium carbonate solution to pH 6–7. The majority of the acetone was then removed in vacuo at 35 °C, and the residue was extracted with benzene to yield the crude diketo diacetate **23** (9.45 g) as an oil.

This product was dissolved in methanol (87 mL) containing potassium hydroxide (2.6 g) and heated at reflux for 1.5 h. Water was then added, and the products were isolated with chloroform, yielding the tricyclic material **24** (7 g) as an oil.

A solution of this material (7 g) in benzene (140 mL) containing *p*-toluenesulfonic acid (200 mg) was heated at reflux for 2 h, cooled, washed with sodium bicarbonate solution and water, dried over sodium sulfate, and then taken to dryness to yield crude **25** (5.6 g) as an oil. Chromatography on silica gel (280 g) and elution with hexane–ether mixtures (2:1 and 1:1) afforded pure **25** (3.66 g) as a crystalline product: mp 60–71 °C; $[\alpha]^{25}_D$ +141.3° (*c* 1.42, $CHCl_3$); UV max (95% ethanol) 248 nm (ε 16 000); ^1H NMR ($CDCl_3$) δ 5.26 (m, 1, C_9–H), 1.27 and 1.25 (two d, total of 3, *J* = 6 Hz, C_2–CH_3), 0.85 (s, 3, C_{6a}–CH_3). Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.76; H, 9.5. Found: C, 78.58; H, 9.95.

(+)-Estr-4-ene-3,17-dione (27). The mixture of diastereomer **25** (3.75 g) dissolved in toluene (40 mL) containing triethylamine (0.37 mL) was hydrogenated in the presence of a palladium catalyst (0.550 g of AK4)[20] at room temperature and pressure until the uptake of hydrogen stopped (2 h, 350 mL uptake). The catalyst was filtered off, and the crude hydrogenation product (3.9 g) was dissolved in pyridine (75 mL) containing water (0.4 mL) and methoxylamine hydrochloride (2 g) and left at ambient temperature for 24 h. Dilution with dichloromethane and washing with brine yielded the crude oxime ether **26** (4.5 g), which was chromatographed on silica gel (110 g) to yield chemically pure material (3.97 g) on elution with hexane–ether (1:4) and ether–methanol (19:1) solvent mixtOres.

A solution of this material (1.21 g) in dimethylformamide (6 mL) was added over 10 min to a mixture of chromium trioxide (2.4 g) in more dimethylformamide (8 mL) containing sulfuric acid (0.75 mL)[12] at 0 °C and then stirred 2.5 h at room temperature. The mixture was cooled to 0 °C, treated with aqueous sodium hydroxide solution (10 N, 2.82 mL), and extracted with benzene.

The extract was washed with aqueous sodium bisulfite solution, dried, and concentrated to yield the crude diketone (1.18 g), which was dissolved in methanol (30 mL) containing hydrochloric acid (4 N, 9 mL) and heated in reflux for 2.5 h. After cooling to 0 °C, the mixture was made basic (10 N NaOH, 4.7 mL) and stirred for 2 h at room temperature.

Extraction with benzene followed by chromatography on silica gel yielded pure **27** (354 mg): mp 168–171 °C; $[\alpha]^{25}_D$ +139.2° (*c* 1.0, $CHCl_3$); UV max (95% ethanol) 240 nm (ε 17 350).

(−)-Estra-4,9-diene-3,17-dione (21) and (+)-Estra-5(10),-9(11)-diene-3,17-dione (22). The crude reduction product **19** (R = H) (10.1 g, ~80–90% purity) dissolved in acetone at room temperature was treated with aqueous sulfuric acid (1 N, 25 mL), stirred for 2 h, and then cooled to 0 °C. To this mixture was added a fresh solution of Jones chromic acid mixture (37.5 mL) over 15 min followed by stirring at room temperature for 2 h. An aqueous solution of sodium bisulfite (1%, 300 mL) was added, and the tetraketone was extracted with benzene. Chromatography of the crude product on silica gel (420 g) yielded pure **20** (7.7 g) on elution with ether–benzene mixtures (2:1 and 4:1) and ether alone: IR ($CHCl_3$) 1740 (cyclopentanone), 1715 (cyclohexanone and dioxooctyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (s, 3, $COCH_3$), 1.17 (s, 3, C_{7a}–CH_3). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.88; H, 8.52.

A solution of **20** (7 g) in toluene (25 mL) was heated at reflux for 16 h with piperidinium acetate (200 mg) and then taken to dryness. The residue was dissolved in dichloromethane, washed with acid (1 N, H_2SO_4), and then chromatographed on silica gel (89 g) to yield pure **22** (319 mg) and pure **21** (323 mg), as judged by TLC.

Crystallization of the first fraction from an ether–hexane mixture gave analytically pure **22**: mp 107–108 °C; $[\alpha]^{25}_D$ +335° (*c* 1.0185, CH_3OH); UV max (95% ethanol) 250 nm (ε 20 000); IR ($CHCl_3$) 1730 (cyclopentanone and β,γ-unsaturated cyclohexenone) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.61 (t, *J* = 3 Hz, C_{11}–H), 0.87 (s, 3, C_{13}–CH_3). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.99; H, 8.25.

The later fraction on crystallization from an ethyl acetate–hexane mixture yielded analytically pure **21**: mp 143–144 °C; $[\alpha]^{25}_D$ −191.4° (*c* 0.4858, CH_3h); UV max (95% ethanol) 301 nm (ε 20 600); IR ($CHCl_3$) 1740 (cyclopentanone), 1660, 1610 (cyclohexenone) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.7 (s, 1, C_4–H), 1.02 (s, 3, C_{13}–CH_3). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.00; H, 7.95.

To isomerize **22** to **21** the pure diene **22** (500 mg) was dissolved in toluene (15 mL) containing *p*-toluenesulfonic acid (50 mg) and heated at reflux for 45 min. After this time the solution was washed successively with an aqueous sodium bicarbonate solution and brine and dried over anhydrous sodium sulfate. Chromatography of the crude product (510 mg) on silica gel (50 g) yielded chromatographically pure **21** (311 mg), mp 139–142 °C. Crystallization from a mixture of ethyl acetate–hexane yielded pure material: mp 142–143 °C; $[\alpha]^{25}_D$ −191 ° (*c* 0.556, CH_3OH).

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Registry No.—**6,** 30693-66-4; **7,** 65121-17-7: (*S*)-**8,** 65166-11-2; (±)-**8,** 30655-84-6; **9,** 23027-03-4; **10,** 34862-10-7; (*S*)-**11,** 36288-49-0; (±)-**11,** 30658-25-4; **12,** 65121-18-8; **15,** 35919-90-5; **16,** 35811-68-8; **17,** 36668-14-1; **18,** 65206-88-4; **19** (R = H) isomer I, 65166-12-3; **19** (R = H) isomer II, 65166-13-4; **19** (R = Ac) isomer I, 65166-14-5; **19** (R = Ac) isomer II, 65166-15-6; **20,** 65166-16-7; (−)-**21,** 5173-46-6; (+)-**22,** 2503-06-2; **23** isomer I, 65149-41-9; **23** isomer II, 65121-03-1; **24** isomer I, 65121-04-2; **24** isomer II, 65121-05-3; **25** isomer I, 65166-09-8; **25** isomer II, 65166-10-1; **26** isomer I, 65121-06-4; **26** isomer II, 65121-07-5; (+)-**27,** 734-32-7; 2-methyl-3-oxo-1-cyclohexenepropionic acid, 65121-08-6; (−)-(2*R*,3*R*)-butanediol, 24347-58-8; (*R*,*S*)-tetrahydro-6-[3-(2-methyl-1,2-ethylenedioxol-2-yl)propyl]-2*H*-pyran-2-one, 30655-83-5; catechol, 120-8-9; vinyl chloride, 75-01-4; 2-methylcyclopentane-1,3-dione, 765-69-5.

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silica gel (0.2–0.5 mm), and thin-layer chromatograms (TLC) were run on Brinkmann silica gel G plates with a UV indicator and developed in an ethyl acetate–benzene mixture (1:1). Spots were made visible by UV light, iodine vapor, or spraying with a 50% aqueous *p*-toluenesulfonic acid solution and heating at 120 °C. Varian HA-100 and A-60 spectrometers were employed to record proton magnetic resonance spectra (^{1}H NMR), and the chemical shifts are relative to tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Beckman IR-9 spectrometer, and ultraviolet (UV) spectra were recorded on a Cary Model 14M spectrophotometer.

(20) AK4 is a 5% palladium on carbon catalyst prepared at F. Hoffmann-La Roche & Co., AG, Basle, Switz.

Formamidinesulfinic Acid Reduction of Dihydrocodeinone Derivatives

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Treatment of dihydrocodeinone (**1f**) with formamidinesulfinic acid afforded mixtures of dihydrothebainone (**3a**) and dihydroisothebainol (**4a**) under both homogeneous and heterogeneous conditions. Similar treatment of 14-hydroxydihydrocodeinone (**1g**) and 3-*O*-methylnatrexone (**1h**) gave predominantly the desired 6β-alcohols (**2g** and **2h**) under heterogeneous conditions. Under homogeneous conditions, **1g** and **1h** yielded mixtures of the 6β-alcohols and the dihydrothebainone derivatives **3b** and **3c**. Deuterium oxide studies established that ketone enolization was involved in the formamidinesulfinic acid reductions.

The reduction of dihydromorphinones **1a–e** to the corresponding 6β-alcohols **2a–e** using formamidinesulfinic acid was first reported by Chatterjie and co-workers.[1,2] Since the stereoselectivity of the new procedure was opposite to that of hydride reductions, its preparative potential was obvious.

In contrast, formamidinesulfinic acid reductions of dihydrocodeinone derivatives were less straightforward. Chatterjie and co-workers[2] reported the reduction of dihydrocodeinone (**1f**) to dihydroisocodeine (**2f**) in 63% yield. Due to the limited solubility of **1f** in the reaction medium,[3] ethanol was added as a cosolvent (homogeneous conditions)[4] in this experiment. However, our attempts to duplicate this reaction yielded dihydrothebainone (**3a**) as the major product.[5] In addition, Cone[6] reported the reduction of 14-hydroxydihydrocodeinone (**1g**) to 6β-alcohol **2g** with formamidinesulfinic acid in the absence of ethanol (heterogeneous conditions).[7]

As we had a need for the dihydroisocodeine compounds, we investigated the formamidinesulfinic acid reduction of dihydrocodeinones **1f–h** under various reaction conditions. During the course of our investigation, we discovered that use of deuterium oxide in the reaction mixture led to the polydeuterated 6β-alcohols.

Results and Discussion

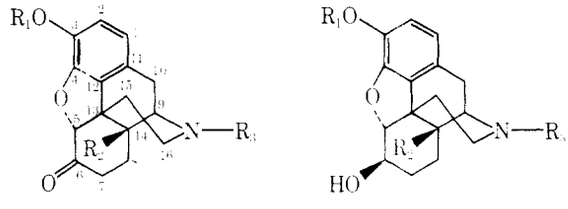
Compounds **1f–h** were treated with formamidinesulfinic acid under both homogeneous[4] and heterogeneous[6b] conditions. In addition, dihydrocodeinone (**1f**) was subjected to four additional experiments in attempts to prepare dihydroisocodeine (**2f**) directly. The results are summarized in Table I.

A comparison of the homogeneous and heterogeneous reactions showed that use of the organic cosolvent facilitated opening of the 4,5α-ether bridge. Moreover, the additional experiments on **1f** further demonstrated that bridge opening did not involve ethoxide formation (condition D) or the reaction temperature (condition E). The subsequent reduction of dihydrothebainone (**3a**) to dihydroisothebainol (**4a**)[8] could be forced to completion by use of a longer reaction time and excess reagent (condition F).

In the case of the dihydromorphinones, the 14-hydroxyl group was evidently nonessential for ketone reduction.[2,9] However, the results with the dihydrocodeinones indicated that the 14-hydroxyl group was necessary to obtain ketone reduction rather than 4,5α-ether bridge opening. For example, some 14-hydroxydihydroisocodeine (**2g**) and 3-*O*-methyl-6β-naltrexol (**2h**) were isolated even under the homogeneous conditions, while no dihydroisocodeine (**2f**) was ever obtained from **1f**. Further study is needed to elucidate the effect of the 14-hydroxyl group.

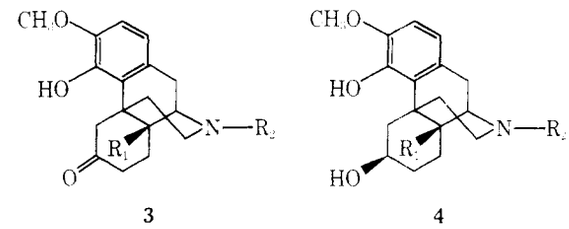
Dihydrocodeinone (**1f**) was also subjected to the heterogeneous reaction conditions with three further variations: (1) omission of the formamidinesulfinic acid, (2) use of sulfur dioxide in place of formamidinesulfinic acid, and (3) use of hydrochloric acid in place of sodium hydroxide. In each case the starting material was recovered unchanged in 98–100% yield. Attempts to reduce naltrexone (**1a**)[1] using variations (1) or (2) above also gave no reduction. These data indicated that both the formamidinesulfinic acid and the sodium hydroxide were necessary for reaction to occur.

Chart I



1 2

a, R_1 = H; R_2 = OH; R_3 = CH_2-c-C_3H_5
b, R_1 = H; R_2 = OH; R_3 = $CH_2CH{=}CH_2$
c, R_1 = H; R_2 = OH; R_3 = CH_2-c-C_4H_7
d, R_1 = H; R_2 = OH; R_3 = CH_3
e, R_1 = R_2 = H; R_3 = CH_3
f, R_1 = R_3 = CH_3; R_2 = H
g, R_1 = R_3 = CH_3; R_2 = OH
h, R_1 = CH_3; R_2 = OH; R_3 = CH_2-c-C_3H_5



3 4

a, R_1 = H; R_2 = CH_3
b, R_1 = OH; R_2 = CH_3
c, R_1 = OH; R_2 = CH_2-c-C_3H_5

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