11.2 Hz, PhCHCH*H*OAc), 4.23 (dd, J = 4.5, 11.8 Hz, C-4 H), 3.96 (dd, J = 8.0, 11.7 Hz, $CMe_2CHCHHOAc$), 3.36 (dd, J = 4.4, 8.0 Hz, $CMe_2CHCHHOAc$), 2.09 (s, $COCH_3$), 2.00 (s, $COCH_3$), 1.30 (s, C-3 CH_3), 1.20 (s, C-3 CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 173.8, 170.6, 170.2, 136.3, 128.9, 128.3, 127.4, 64.0, 63.8, 61.6, 56.7, 51.9, 22.4, 20.7, 20.6, 16.5; IR (CCl_4) 1755, 1752 cm^{-1}; MS (CI) m/z 334 (MH^+, 100), 274 (11), 264 (10), 163 (8), 128 (12).

3,3-Dimethyl-4(*S)-(hydroxymethyl)-1-[2-hydroxy-1-(*S**)-phenylethyl]-2-azetidinone (12).** According to the method of Mori,[13] a solution of diacetate **11** (17 mg, 0.051 mmol), EtOH (1 mL), and a catalytic amount of KCN (~1 mg) was stirred at 23 °C for 7 h. This solution was then diluted with CH_2Cl_2 (5 mL), filtered through Florisil, and concentrated. The residue was purified by flash chromatography (silica gel, 9:1 $CHCl_3$-EtOH) to give 12 mg (92%) of **12** as an oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.40 (m, Ph), 4.61 (dd, J = 3.8, 8.0 Hz, NC*H*Ph), 4.40 (br s, OH), 4.06-4.13 (m, PhCHC*H*HOH), 3.92-3.99 (m, PhCHCH*H*OH), 3.51-3.62 (m, $CMe_2CHCHHOH$), 3.43-3.49 (m, $CMe_2CHCHHOH$), 3.34 (dd, J = 4.6, 5.6 Hz, C-4 H), 2.05 (br s, OH), 1.30 (s, CH_3), 1.26 (s, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 175.6, 137.6, 129.0, 128.4, 127.4, 65.6, 64.3, 62.0, 61.4, 51.2, 22.7, 16.6; IR (film) 3387, 1718 cm^{-1}.

1-[2-[(*p*-Bromobenzoyl)oxy]-1(*S)-phenylethyl]-3,3-dimethyl-4(*S**)-[[(*p*-bromobenzoyl)oxy]methyl]-2-azetidinone (13).** A solution of **12** (7 mg, 0.028 mmol), *p*-bromobenzoyl chloride (34 mg, 0.16 mmol), and pyridine (0.5 mL) was stirred at 23 °C for 10 h. The resulting slurry was diluted with H_2O (2 mL) and extracted with Et_2O (3 × 2 mL). The combined organic extracts were washed with 1 M HCl (3 mL), 1 M $KHCO_3$ (3 mL), saturated aqueous $CuSO_4$ (3 mL), and saturated aqueous NaCl (3 mL). After drying (Na_2SO_4) and concentration, the residue was purified by flash chromatography (silica gel, 3:1 hexanes-EtOAc) to give 15 mg (88%) of **13** as a colorless crystalline solid.

An analytical sample of this material prepared from (*R*)-(-)-2-phenylglycine afforded X-ray quality crystals from a mixture of EtOAc-hexane-EtOH: mp 82-83 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.54-7.91 (m, 8 H, C_6H_4), 7.27-7.34 (m, Ph), 5.02 (dd, J = 4.8, 10.0 Hz, NC*H*Ph), 4.92 (app t, J = 10.0 Hz, CHC*H*HO), 4.69 (dd, J = 4.9, 10.7 Hz, CHCH*H*O), 4.44 (dd, J = 4.5, 12.0 Hz, CHC*H*HO), 4.22 (dd, J = 7.1, 12.0 Hz, CHCH*H*O), 3.50 (dd, J = 4.5, 7.1 Hz, C-4 H), 1.32 (s, CH_3), 1.25 (s, CH_3); IR (CCl_4) 1730, 1760 cm^{-1}. Anal. Calcd for $C_{28}H_{25}NO_5Br_2$: C, 54.66; H, 4.10; N, 2.28; Br, 25.97. Found: C, 54.58; H, 4.15; N, 2.28; Br, 25.87.

3(*S)-(Acetylamino)-1-[2-(benzyloxy)-1(*S**)-phenylethyl]-4(*S**)-[(1,1-dimethylethoxy)methyl]-2-azetidinone (16) and 3(*R**)-(Acetylamino)-1-[2-(benzyloxy)-1(*S**)-phenylethyl]-4(*S**)-[(1,1-dimethylethoxy)methyl]-2-azetidinone (17).** To a solution of LDA (2.0 mmol, formed as described for the preparation of **10**) were added dropwise at -20 °C a solution of silyl glycinate **15**[3] (0.46 g 1.9 mmol) and 6 mL of THF. After 2 h at -20 °C, a solution of imine **14** (0.56 g, 1.7 mmol) and 2 mL of THF was added dropwise. The reaction mixture was allowed to warm to 23 °C and after 10 h was quenched with AcOH (2 mL of a 1.0 M THF solution), and AcCl (0.60 g, 7.6 mmol) was then added. After 10 h at 23 °C the solvent was removed in vacuo, and the residue was partitioned between saturated $KHCO_3$ (5 mL) and EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give a 1:5 mixture (by GLC analysis) of β-lactams **16** and **17**, respectively. Flash chromatography (silica gel, EtOAc) gave 124 mg (17%) of pure **16** as a clear oil and 305 mg (42%) of pure **17** also as a clear oil.

16: ^1H NMR (250 MHz, $CDCl_3$) δ 7.27-7.42 (m, Ph), 6.58 (br d, J = 8.5 Hz, NH), 5.45 (dd, J = 5.2, 9.5 Hz, C-3 H), 4.52 (AB q, J = 11.7 Hz, $\Delta\nu$ = 28 Hz, CH_2Ph), 4.55-4.59 (m, NC*H*Ph), 4.23 (app t, J = 9.5 Hz, C*H*HOBn), 3.81 (app quintet, J = 2.7 Hz, C-4 H), 3.74 (dd, J = 5.9, 10 Hz, CH*H*OBn), 3.49 (dd, J = 2.2, 10.4 Hz, C*H*HOBu^t), 3.29 (dd, J = 2.9, 10.4 Hz, CH*H*OBu^t), 1.93 (s, $COCH_3$), 1.02 (s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 169.7, 167.2, 137.9, 137.4, 128.5, 128.4, 127.9, 127.8, 73.3, 70.8, 59.2, 58.5, 58.3, 56.5, 27.2, 27.1, 23.3; IR (CCl_4) 1758, 1740, 1691 cm^{-1}; HRMS (EI) m/z 424.2354 (424.2362 calcd for $C_{25}H_{32}N_2O_4$).

17: ^1H NMR (250 MHz, $CDCl_3$) δ 7.27-7.44 (m, Ph), 6.02 (br d, J = 6.3 Hz, NH), 4.82 (dd, J = 5.9, 9.4 Hz, NC*H*Ph), 4.61 (dd, J = 2.1, 6.3 Hz, C-3 H), 4.59 (s, CH_2Ph), 4.24 (app t, J = 9.6 Hz, C*H*HOBn), 3.80 (dd, J = 5.9, 9.8 Hz, CH*H*OBn), 3.64 (dd, J = 2.5, 9.57 Hz, C*H*HOBu^t), 3.52 (app dt, J ~ 2, 7 Hz, C-4 H), 3.36 (dd, J = 7.3, 9.5 Hz, CH*H*OBu^t), 1.93 (s, $COCH_3$), 1.02 (s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 170.4, 166.6, 138.1, 137.2, 128.4, 128.3, 127.8, 127.8, 127.6, 73.0, 70.8, 62.6, 62.1, 58.7, 57.2, 27.1, 27.1, 22.7; IR (CCl_4) 1744, 1683 cm^{-1}; HRMS (EI) m/z 424.2384 (424.2364 calcd for $C_{25}H_{32}N_2O_4$).

Alternatively, with toluene as the solvent, **14** (0.56 g, 1.7 mmol) and **15** (0.46 g, 1.9 mmol) gave a 1:10 ratio of **16** and **17**, respectively (determined by GC analysis).

Epimerization of the Cis β-Lactam 16. To a solution of LDA (0.36 mmol, ca. 0.5 M in THF) at -70 °C was added a solution of β-lactam **16** (73 mg, 0.17 mmol) and THF (0.5 mL). After 1 h at -70 °C, Me_3SiCl (~30 μL, 0.24 mmol) was added dropwise, and the reaction was allowed to warm to 0 °C over 1 h. The reaction was then recooled to -70 °C and quenched with AcOH (0.3 mL of a 1.3 M solution in THF, 0.39 mmol). Upon warming to 23 °C, H_2O (2 mL) was added, and the mixture was extracted with EtOAc (3 × 1 mL). The combined organic extracts were washed with saturated aqueous K_2CO_3 (2 mL), dried (Na_2SO_4), and concentrated. The crude residue contained a 2:1 mixture of **17** and **16** as well as two other low boiling products (determined by GC analysis). This crude mixture was dissolved in EtOAc (2 mL) and stirred with 1 M HCl (2 mL) for 1 h. The aqueous layer was removed and washed with EtOAc (2 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give 44 mg (60%) of a 2.2:1 mixture of **17** and **16** as the only products observable by GC and ^1H NMR analysis.

3(*S)-(Acetylamino)-4(*S**)-[(1,1-dimethylethoxy)methyl]-1-(2-hydroxy-1(*S**)-phenylethyl)-2-azetidinone (18).** A mixture of **16** (54 mg, 0.13 mmol), 10% Pd/C (~10 mg), and EtOH (2 mL) was rapidly stirred under an atmosphere of H_2 for 12 h and then filtered through a bed of Celite. Concentration and purification of the residue by flash chromatography (silica gel, 20:1 CH_3Cl-EtOH) gave 28 mg (65%) of **18** as a colorless crystalline solid. An analytical sample was obtained by recrystallization from CH_2Cl_2-hexane: mp 147 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.37 (m, Ph), 6.98 (br d, J = 9.5 Hz, NH), 5.45 (dd, J = 5.3, 9.5 Hz, C-3 H), 4.83 (dd, J = 3.9, 8.6 Hz, NC*H*Ph), 3.97-4.07 (m, C*H*HO*H*), 3.88-3.93 (m, C-4 H and CH*H*OH), 3.57 (dd, J = 2.8, 10.6 Hz, C*H*HOBu^t), 3.43 (dd, J = 2.7, 10.6 Hz, CH*H*OBu^t), 2.00 (s, $COCH_3$), 1.15 (s, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 170.0, 168.5, 136.0, 128.8, 128.2, 127.7, 74.6, 63.4, 60.0, 58.5, 57.5, 56.7, 27.2, 23.1; IR (CCl_4) 3317, 3306, 2875, 1744, 1667 cm^{-1}; MS (CI) m/z 335 (MH^+, 100), 279 (10), 236 (12). Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.58; H, 7.86; N, 8.34.

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Supplementary Material Available: Details of the single-crystal X-ray analyses of **13** and **18** (13 pages). Ordering information is given on any current masthead page.

A Convenient Method for the Synthesis of 3β-Hydroxy 4-En-6-one Steroids

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In view of the synthetic utility of the title compounds and their multistep syntheses,[1] we report a convenient and

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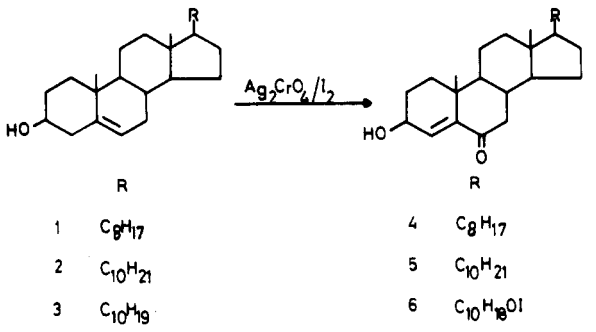
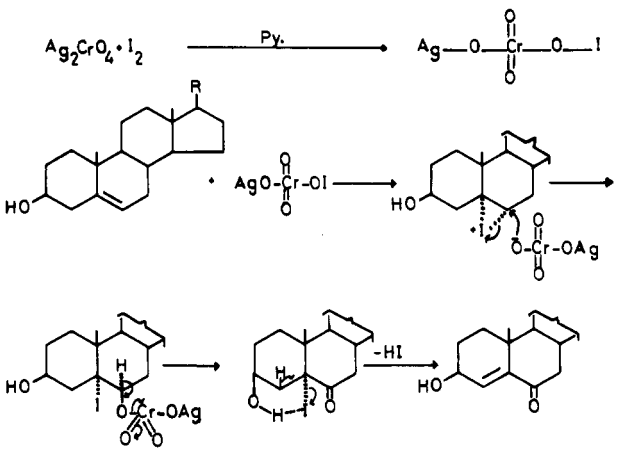
Scheme I



Scheme II



single-step preparation of the title compounds with quantitative yields. Our synthetic strategy involves the reaction of silver chromate–iodine and pyridine with cholesterol (1), β-sitosterol (2) and stigmasterol (3) affording 3β-hydroxycholest-4-en-6-one (4), 3β-hydroxystigmast-4-en-6-one (5), and 3β-hydroxy-22/23-iodostigmast-4-en-6,23/22-dione (6), respectively (Scheme I). The novelty of this reaction lies in its simplicity and its clean, one-step character (Scheme II). The formation of hydroxy iodo ketones from olefins is rationalized according to the mechanism described by Cardillo and Shimizu.[2] In these hydroxy iodo ketones a n-σ charge transfer takes place from the nonbonding electrons of oxygen (C3–OH) to the bond C5-I,[3] increasing the bond length[4] and heteropolarity[5] of this bond. As a consequence of this, the hydrogen atom of the hydroxyl group chelates to the iodine atom. The stability of the complex so formed is further increased by back donation[6] of electron density from the C5–I bond, increasing the positive charge at C5. All of these processes weaken the C–I bond, leading to its rupture to give I^- and a carbocation, which leads to the formation of the α,β-unsaturated ketone (Scheme II). The role of pyridine is presumably that of facilitating the formation of the supposed hypoiodous chromic acid mixed anhydride. In fact, addition of pyridine to a silver chromate–iodine mixture caused an immediate change of color.

Some other steroidal olefins, such as the 3β-acetoxy and 3β-chloro analogues of cholesterol and β-sitosterol, were subjected to the same treatment, but they instead provided the respective α-iodo ketones.

Thus, the above results as well as the mild reaction conditions, which provide 3β-hydroxy 4-en-6-one steroids (4, 5, and 6) in quantitative yields from their respective olefins (1, 2, and 3), make the present method highly useful for the synthesis of these unsaturated ketones which otherwise have been obtained by many steps.

Experimental Section

Melting points were recorded on a Kofler hot block apparatus and are uncorrected. IR data were obtained on a Pye-Unicam SP3-100 spectrometer. ^1H NMR were run in $CDCl_3$ on a Varian A60-D instrument with TMS as the internal standard, and its values are given in ppm (δ). Mass spectra were recorded by using a JMS-300 spectrometer. Elemental analysis was carried out at the Instrumentation Centre of the Department. Methylene chloride was freshly dried over calcium hydride.

General Procedure for Synthsis of 3β-Hydroxy 4-En-6-one Steroids from Their Respective Steroidal Olefins. To a suspension of silver chromate (3.3 mmol) in 15 mL of dichloromethane was added iodine (4.5 mmol) and a solution of pyridine (1.5 mmol) in 0.75 mL of dichloromethane at 0 °C, and the mixture was stirred for 5 min. A solution of steroidal olefin (2.0 mmol) in 5 mL of dichloromethane was added dropwise during 10 min to the ice-cooled suspension and was stirred for 20 min at 0 °C. Then the cooling bath was removed and the reaction mixture was stirred for an additional hour at room temperature. The reaction mixture was filtered, and the filtrate was successively washed with 5% aqueous $Na_2S_2O_3$ and saturated aqueous NaCl and dried over anhydrous sodium sulfate. The crude product obtained after removal of the solvent was purified by column chromatography (ca. 18 g of silica gel; elutant petroleum ether/ether, 4/1) to give the respective α,β-unsaturated ketones (4–6), recrystallized from petroleum ether (4 and 5).

3β-Hydroxycholest-4-en-6-one (4): yield 0.578 g (75%); mp 149–150 °C; IR (KBr) 3400 (OH), 1685, 1620 cm^{-1} (C=C—C=O); ^1H NMR ($CDCl_3$/TMS) δ 6.02 (d, 1 H, C4-H), 4.3 (mc, 1 H, C3α-H, $W_{1/2}$ = 12 Hz, axial), 2.18 (br, 1 H, OH), 1.15 (s, 3 H, C10-CH_3), 0.70 (s, 3 H, C13-CH_3), 0.91 and 0.81 (other methyl protons); MS (*m/e*, intensity), 400 ($M^{\cdot+}$, 100), 385 (13.75), 384 (15.0), 383 (5.5), 382 (12.5), 372 (7.0), 368 (5.0), 354 (5.5), 287 (17.5), 259 (7.5), 152 (15.4). Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.90; H, 10.98.

3β-Hydroxystigmast-4-en-6-one (5): yield 0.597 g (72%); mp 162 °C; IR (KBr) 3450 (OH), 1690, 1615 cm^{-1} (C=C—C=O); ^1H NMR ($CDCl_3$/TMS) δ 6.12 (d, 1 H, C4-H), 4.35 (mc, 1 H, C3α-H, $W_{1/2}$ = 15 Hz, axial), 2.2 (br, 1 H, OH), 1.12 (s, 3 H, C10-CH_3), 0.68 (s, 3 H, C13-CH_3), 0.94 and 0.82 (other methyl protons); MS (*m/e*, intensity) 428 ($M^{\cdot+}$, 100), 413 (10.0), 412 (13.5), 411 (9.2), 410 (15.5), 400 (8.4), 396 (7.0), 382 (6.5), 287 (21.5), 259 (6.5), 152 (17.4). Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.24; H, 11.28. Found: C, 81.39; H, 11.22.

3β-Hydroxy-22/23-iodostigmast-4-ene-6,23/22-dione (6): yield 0.668 g (81%) semisolid; IR (Nujol) 3420 (OH), 1720 (C=O), 1680, 1610 (C=C—C=O), 520 cm^{-1} (C—I); ^1H NMR ($CDCl_3$/TMS) δ 6.2 (d, 1 H, C4-H), 4.4 (d, 1 H, C22/23-H), 4.1 (mc, 1 H, C3α-H, $W_{1/2}$ = 16 Hz, axial), 1.9 (br, 1 H, OH), 1.14 (s, 3 H, C10-CH_3), 0.71 (s, 3 H, C13-CH_3), 0.91 and 0.83 (other methyl protons); MS (*m/e* intensity) 568 ($M^{\cdot+}$, not observed), 441 (75.0), 440 (68.5), 424 (12.0), 423 (7.5), 422 (15.5), 413 (6.5), 412 (10.0), 395 (5.5), 394 (7.5), 343 (21.5), 287 (42.5), 152 (20.0). Anal. Calcd for $C_{29}H_{45}O_3I$: C, 61.25; H, 7.97. Found: C, 61.20; H, 7.93.

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