Studies on Steroidal Plant-growth Regulators.† A New Route for the Efficient Synthesis of the 2α,3α-Dihydroxy-7-oxa-6-oxo-B-homo Structural Unit of Brassinolide

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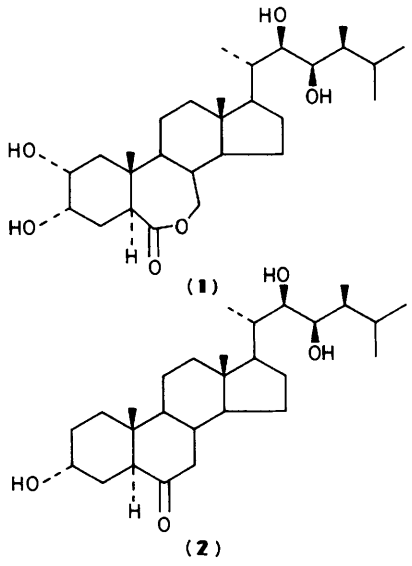
A highly regioselective formation of steroidal 7-oxa lactone rings *via* ozone oxidation of enol silyl ethers is described.

Brassinosteroids, *e.g.* brassinolide (**1**)[1] and typhasterol (**2**),[2] are steroidal plant growth regulators. Their remarkable biological activities and novel structural features have led to various syntheses of these substances and their analogues.[3] Baeyer–Villiger oxidation has been used successfully for the construction of the 7-oxa lactone from the 2α,3α-dihydroxy-6-oxo moiety. However, in the case of 3α(β)-hydroxy-5α(β)-6-oxo steroids, only a mixture of the 6- and 7-oxa lactones in a ratio of *ca.* 1 : 2[4] or 4 : 2[5] was obtained.

We have previously reported[5] the regioselective prepara-

† For Part 9 of the series, see W. S. Tian, W. S. Zhou, B. Jiang, and X. F. Pan, *Acta Chem. Sinica*, submitted for publication.



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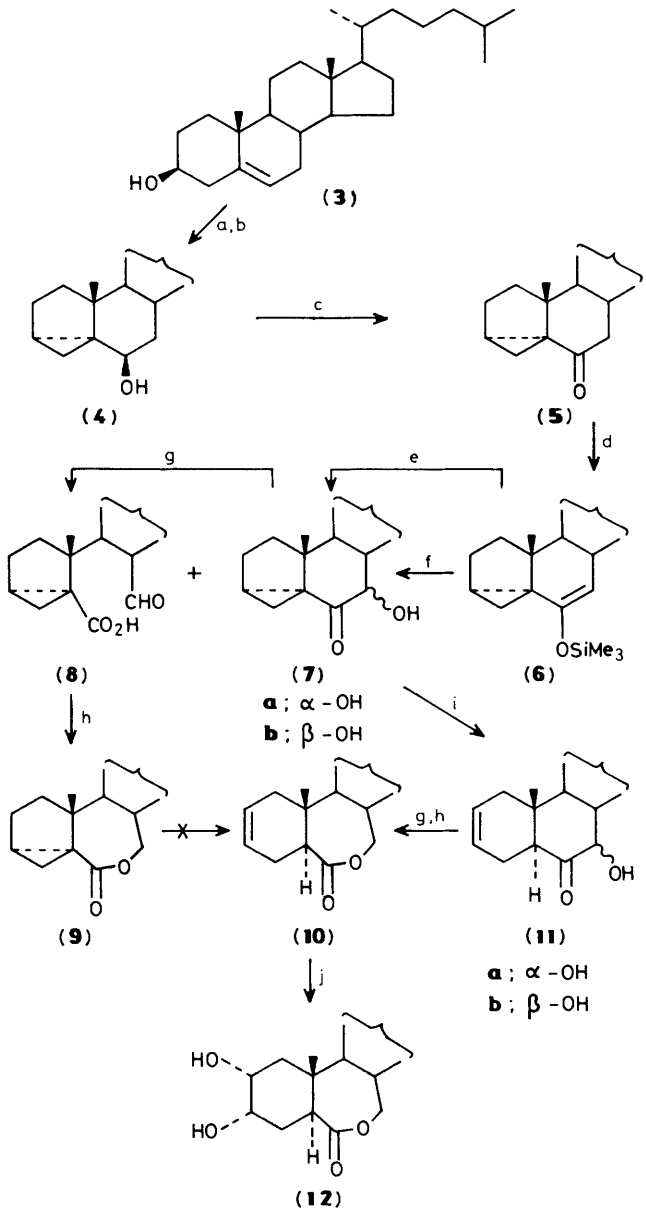
tion of the 7-oxa lactone from methyl 3α-hydroxy-6-oxo-5α-cholanate by oxidation of an enol silyl ether with ozone. We now report an extension of this reaction to 3,5-cyclocholestanone-6-one (**5**). Oxidation of 3,5-cyclocholesterol (**4**), obtained from cholesterol (**3**), with Jones reagent gave 3,5-cyclocholestanone (**5**) in 87.5% yield. Kinetic deprotonation of (**5**) with triethylamine in the presence of trimethylsilyl trifluoromethanesulphonate[6] provided the enol trimethylsilyl ether (**6**),‡ m.p. 126—127 °C, quantitatively. Ozonization of (**6**) in dichloromethane–methanol followed by reduction with Me_2S and acidification gave a 3 : 1 : 4 mixture of (**7a,b**) and (**8**) in 90% yield, which was separated by flash chromatography. Oxidation of (**7a,b**) with periodic acid furnished (**8**) quantitatively, reduction of which with $NaBH_4$ followed by acidification gave the 7-oxa lactone (**9**) {m.p. 137—138 °C, $[\alpha]_D$ −78.9° (*c* 1.05, $CHCl_3$)} in 97% yield. The overall yield was 87% in four steps from (**5**). All attempts to open the cyclopropane ring of (**9**) to form compound (**10**) failed. However, the cyclopropane ring of the ketone (**7**) could be smoothly opened



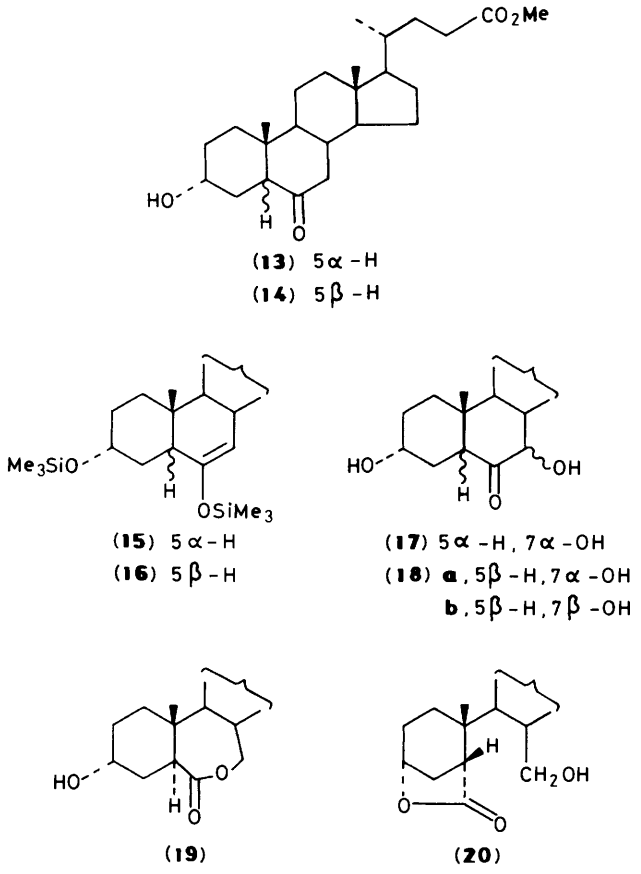
Scheme 1. *Reagents*:§ a, *p*-$MeC_6H_4SO_2Cl$, pyridine, room temp., 24 h; b, KOAc, aq. acetone, reflux, 2 h; c, Jones oxidation; d, $CF_3SO_2SiMe_3$, Et_3N, 0 °C, 5 min; e, O_3, CH_2Cl_2, pyridine, −78 °C, then 5% HCl; f, O_3, CH_2Cl_2–MeOH, −78 °C, then Me_2S, room temp., 2 h, then 5% HCl; g, $HIO_4 \cdot 2H_2O$, Et_2O, 0 °C, 2 h; h, $NaBH_4$, MeOH, 0 °C, 4 h, then 6 M HCl–THF (1 : 1), 24 h; i, *p*-$MeC_6H_4SO_3H$, $LiBr \cdot 2H_2O$, DMF, reflux, 8 h; j, *N*-methylmorpholine *N*-oxide, cat. OsO_4, THF, room temp., 24 h.

to give the Δ^2-α-ketol (**11**) in 85% yield. Treatment of (**11**) as in the steps (**7**)—(**9**) gave the 7-oxa lactone (**10**) {m.p. 138—140 °C, $[\alpha]_D$ −34° (*c* 0.42, $CHCl_3$)} in 93% yield, which was converted to the known compound (**12**) (Scheme 1).

When (**6**) was ozonized in CH_2Cl_2 solution in the presence of a small amount of pyridine,[8] only (**7a**) and (**7b**) were obtained in a 3 : 2 ratio in 94% yield. Similarly, when the trimethylsilyl enol ethers (**15**) and (**16**), obtained from (**13**) and (**14**) (LDA, Me_3SiCl, TEA, THF, −78 °C), were ozo-

‡ All new compounds gave satisfactory analytical and spectral data. *Selected spectroscopic data* for (**6**): ^{1}H n.m.r., δ ($CDCl_3$) 0.91 (3H, s, 19-H), 4.70 (1H, s, 7-H); i.r., $\nu_{max.}$ ($CHCl_3$) 1645 cm^{-1}; m.s., *m/z* 456 (M^+), 441 (M^+ −Me), 367 (M^+ −$OSiMe_3$). (**9**): ^{1}H n.m.r., δ ($CDCl_3$) 0.87 (3H, s, 19-H), 4.03 (1H, d, *J* 12 Hz, 7β-H), 4.66 (1H, dd, *J* 12, 4 Hz, 7α-H); i.r., $\nu_{max.}$ ($CHCl_3$) 1720 cm^{-1}; m.s., *m/z* 401 (M^+ +1), 386 (M^+ −Me). (**10**): ^{1}H n.m.r., δ ($CDCl_3$) 0.89 (3H, s, 19-H), 4.06 (2H, m, 7-H), 5.63 (2H, m, 2 and 3-H); i.r., $\nu_{max.}$ ($CHCl_3$) 1730, 1681 cm^{-1}; m.s., *m/z* 400 (M^+), 385 (M^+ −Me). (**15**): ^{1}H n.m.r., δ ($CDCl_3$) 0.90 (3H, s, 19-H), 4.00 (1H, s, 3-H), 4.58 (1H, s, 7-H); i.r., $\nu_{max.}$ ($CHCl_3$) 1720, 1680 cm^{-1}; m.s., *m/z* 548 (M^+), 553 (M^+ −Me), 458 (M^+ −$OSiMe_3$). (**16**): ^{1}H n.m.r., δ ($CDCl_3$) 0.90 (3H, s, 19-H), 3.65 (1H, m, 3-H), 4.60 (1H, s, 7-H); i.r., $\nu_{max.}$ ($CHCl_3$) 1720, 1680 cm^{-1}; m.s., *m/z* 548 (M^+), 533 (M^+ −Me). (**17**):^{1}H n.m.r., δ ($CDCl_3$) 0.89 (3H, s, 19-H), 3.74 (1H, d, *J* 2.5 Hz, 7-H), 4.12 (1H, m, 3-H); i.r., $\nu_{max.}$ ($CHCl_3$) 3450, 1720, 1710 cm^{-1}; m.s., *m/z* 420 (M^+), 402 (M^+ −H_2O). (**18a**): ^{1}H n.m.r., δ ($CDCl_3$) 0.77 (3H s, 19-H), 3.60 (1H, m, 3-H), 3.85 (1H, d, *J* 2.5 Hz, 7β-H); i.r., $\nu_{max.}$ ($CHCl_3$) 3445, 1720, 1710 cm^{-1}; m.s., *m/z* 420 (M^+), 402 (M^+ −H_2O). (**18b**): ^{1}H n.m.r., δ ($CDCl_3$) 0.77 (3H, s, 19-H), 3.60 (1H, m, 3-H), 4.00 (1H, d, *J* 12 Hz, 7α-H); i.r., $\nu_{max.}$ ($CHCl_3$) 3450, 1720, 1710 cm^{-1}; m.s., *m/z* 420 (M^+). (**19**) ^{1}H n.m.r., δ ($CDCl_3$) 0.90 (3H, s, 19-H), 4.10 (2H, d, *J* 5 Hz, 7-H), 4.18 (1H, m, 3-H); i.r., $\nu_{max.}$ ($CHCl_3$) 3450, 1720 cm^{-1}; m.s., *m/z* 421 (M^+ +1), 403 (M^+ −H_2O). (**20**) ^{1}H n.m.r., δ ($CDCl_3$) 0.75 (3H, s, 19-H), 3.80 (2H, m, 7-H), 4.06 (1H, m, 3-H); i.r., $\nu_{max.}$ ($CHCl_3$) 3450, 1740, 1720 cm^{-1}; m.s., *m/z* 421 (M^+ +1).

§ THF = tetrahydrofuran; DMF = dimethylformamide; LDA = lithium di-isopropylamide; TEA = triethylamine.



Scheme 2

nized in CH_2Cl_2 solution in the presence of a small amount of pyridine (**17**) (90.5% yield) and (**18a,b**) (14 : 1; 96% yield), respectively, were obtained. Oxidation of (**17**) with periodic acid followed by reduction with $NaBH_4$ and acidification gave the 7-oxa lactone (**19**) {m.p. 140—141 °C, $[\alpha]_D$ +39.5° (*c* 0.75, $CHCl_3$)} in 90% yield, whereas similar treatment of (**18**) gave the γ-lactone (**20**) {m.p. 191—193 °C, $[\alpha]_D$ −2.5° (*c* 0.86, $CHCl_3$)}, which after isomerization with alkali (50% Bu^tOK/Bu^tOH, reflux, 2 h) followed by acidification and methylation with diazomethane also gave (**19**) in 88% overall yield in three steps (Scheme 2).

In conclusion, this highly regioselective formation of the 7-oxa lactone ring by ozone oxidation of an enol silyl ether is a complement to the Baeyer–Villiger oxidation.

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