A Simple Synthesis of Steroidal 3α,5-Cyclo-6-ones and their Efficient Transformation to Steroidal 2-En-6-ones[1]

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Sterols **1** were converted to 3α-5-cyclo-6-ones **4** via their mesylates and subsequent oxidation. Refluxing **4** with sodium bromide/*p*-toluene sulfonic acid in dimethylformamide gave steroidal 2-en-6-ones **5**, among which **5d** is an important brassinolide intermediate.

Brassinolide [(2*R*,3*S*,22*R*,23*R*,24*S*)-2,3,22,23-tetrahydroxy-*B*-homo-7-oxa-5α-ergostan-6-one] is a naturally occurring steroid known to have potent plant-growth promoting activity and is expected to present a wide variety of application in agriculture.[2] A number of attempts have been made to develop an efficient process for the preparation of brassinolide.[3-10] One of the promising methods for a large-scale preparation of brassinolide is that reported by Mori et al,[6] in which abundantly available stigmasterol **1a** is used as the starting material. In that method, (22*E*,24*S*)-5α-stigmasta-2,22-dien-6-one **5a** is an important intermediate.

In this paper, we report a general and simple synthesis of steroidal 3α-5-cyclo-6-ones **4** from sterols **1**, and their efficient transformation to steroidal 2-en-6-ones **5** with catalytic amount of both acid and salt in dimethylformamide. In addition, we also report the synthesis of (22*R*,23*R*,24*S*)-22,23-isopropylidenedioxy-5α-ergost-2-en-6-one **(5d)** which is known as an important brassinolide intermediate.[3,4]

We first tried an easy method to prepare 3,5-cyclo-6-ones **4**. The conventional method for the synthesis of 3,5-cyclo-6-ones **4a–c** is the solvolysis of the tosylates of **1** to the 3,5-cyclo-6-ols **3** in aqueous acetone and oxidation in acetone. The solvents used are water-soluble so the extraction by other solvents and subsequent concentration are indispensable on each step. We circumvented this by using methyl ethyl ketone as the solvent and simplyfying the procedure (experimental). In the solvolysis reaction, we found that, sodium bicabonate or sodium carbonate could be used as a base in place of potassium bicarbonate. (Table 1).

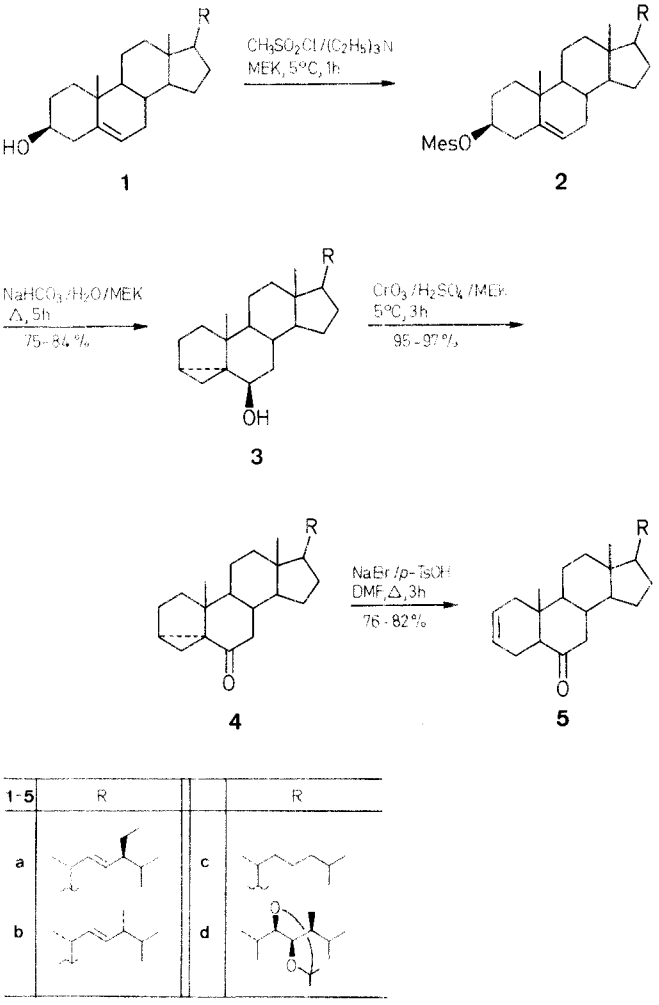
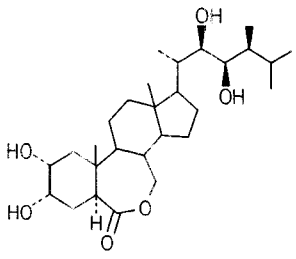


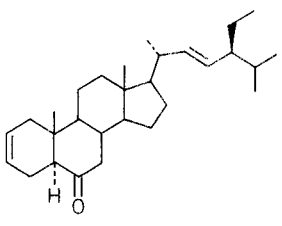
Table 1. Steroidal 3α, 5-Cyclo-6β-ols **3** Prepared

Entry	Product No.	Base/Mol[a]	Ratio[b] 3	Ratio[b] 1	Yield[c] (%)
1	**3a**	$KHCO_3$/2.0	91	8	–
2	**3a**	$NaHCO_3$/2.0	90	9	84
3	**3a**	K_2CO_3/1.0	91	8	–
4	**3a**	Li_2CO_3/1.0	91	8	–
5	**3b**	$KHCO_3$/3.0	85	12	–
6	**3b**	$NaHCO_3$/2.0	86	12	81
7	**3c**	$NaHCO_3$/2.0	86	13	81
8	**3d**	$NaHCO_3$/2.0	86	13	75

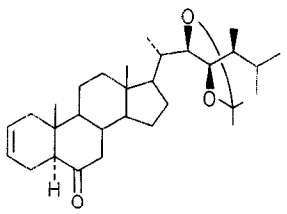
[a] Mol based on steroidal 3-methanesulfonyloxy-5-enes **2**.
[b] Determined by TLC scan; TLC: Merck silica gel F_{254} developed with benzene/*n*-hexane (1:2) or ethyl acetate/benzene (1:10).
[c] Yield of products isolated by column chromatography.



Brassinolide



5a



5d

Several methods have been reported to give 2-en-6-ones **5** from 3,5-cyclo-6-ones **4**. Thompson et al prepared it in four steps;[11] while Fiecchi et al obtained the same *via* the steroidal 3-chloro-6-one in two steps.[12] The single step of Mori[13] was simple but involved the use sulfolane which is not a general solvent; the 2-en-6-one **5a** was obtained in 66% yield from 3,5-cyclo-6-one **4a**.

The transformation of 3,5-cyclo-6-one **4a** to **5a** with a catalytic amount of *p*-toluenesulfonic acid in dimethylformamide at reflux temperature proved unsuccessful. However, addition of a catalytic amount of lithium bromide to the reaction mixture gave 2-en-6-one **5a** in good yield (Table 2).

Table 2. Steroidal 2-En-6-ones **5** Prepared

Entry	Product No.	Catalyst[a]		Ratio[b]			Yield (%)[c]
		Acid/Mol	Base/Mol	**5**	**4**	**6**	
1	**5a**	*p*-TsOH/0.1	LiBr/0.2	90	4	6	–
2	**5a**	*p*-TsOH/0.1	LiBr/0.5	92	2	4	79
3	**5a**	*p*-TsOH/0.1	NaBr/0.5	92	4	5	–
4	**5a**	*p*-TsOH/0.1	KBr/0.5	37	57	3	–
5	**5a**	*p*-TsOH/0.1	LiCl/0.5	15	84	–	–
6	**5a**	*p*-TsOH/0.1	NaCl/0.5	10	85	–	–
7	**5a**	*p*-TsOH/0.1	KCl/0.5	8	92	–	–
8	**5a**	*p*-TsOH/0.1	LiI/0.5	74	19	–	–
9	**5a**	*p*-TsOH/0.1	NaI/0.5	89	4	5	78
10	**5a**	*p*-TsOH/0.1	KI/0.5	7	92	–	–
11	**5a**	conc. HCl/0.3	NaBr/0.5	79	9	11	–
12	**5a**	conc. HBr/0.2	NaBr/0.2	88	4	7	80
13	**5a**	conc. HCl/0.2	$MgBr_2$/0.2				81
14	**5a**	*p*-TsOH/0.2	NaBr/0.5				82
15	**5b**	*p*-TsOH/0.2	NaBr/0.5				79
16	**5c**	*p*-TsOH/0.2	NaBr/0.5				77
17	**5d**	*p*-TsOH/0.2	NaBr/0.5				76

[a] Mole based on 3,5-cyclo-6-ones **4**.
[b] Determined by TLC scan; TLC: Merck silica gel F_{254} developed with benzene/*n*-hexane (1:4). Compounds **6** are by-products (steroidal 4-en-6-ones).
[c] Yield of products isolated by column chromatography.

In the reaction, sodium bromide, sodium iodide, lithium iodide or magnesium bromide can also be used in place of lithium bromide and hydrochloric acid or hydrobromic acid can be used in place of *p*-toluenesulfonic acid (Table 2). (22*E*,24*S*)-5α-Stigmasta-2,22-dien-6-one (**5a**) was obtained in 82% yield from 3,5-cyclo-6-one **4a** and in 67% yield from stigmasterol (**1a**) without purification of the intermediate 3,5-cyclo-6-one **4a**.

Similarly brassicasterol (**1b**) and choreserol (**1c**) gave (22*E*,24*R*)-5α-ergsta-2,22-dien-6-one (**5b**)[12-14] and 5α-cholest-2-en-6-one (**5c**),[15] respectively.

The preparation of (22*R*,23*R*,24*S*)-22,23-isopropylidenedioxy-5α-ergost-2-en-6-one (**5d**) having 22,23-vicinal diol functions has been reported by Siddall et al[3] and Ikekawa et al[4] at about the same time. Their method involved derivatization of sterol **1d**, followed by hydroboration-oxidation at C-6, oxidation of 6-ol and elimination of sulfonic acid with lithium carbonate or lithium bromide.

We found that 2-en-6-one **5d** could be derived from sterol **1d**[17] in the same manner as **5a**. This method was readily accomplished by use of the conventional reagents and could be executed with simple processes to the stage of 3,5-cyclo-6-one **4d**. The steroidal 2-en-6-one **5d** was obtained in a 57% yield from sterol **1d**. If the crude 3,5-cyclo-6-ol **3d** was purified by column chromatography, the pure 3,5-cyclo-6-ol **3d** was obtained in 75% and sterol **1d** was recovered in 18% yield (Table 3).

Melting points were determined with a Yanagimoto hot-stage microscope and uncorrected. Infrared spectra were obtained with a Jasco A-102 spectrometer. ^{1}H-NMR spectra were recorded on a Varian XL-200 spectrometer. EI/MS spectra were taken on a Jeol JMS-D300. A Shimadzu CS-930 TLC scanner was used for the TLC analyses.

Steroidal 3α,5-Cyclo-6-ones 4a–d; General Procedure:
Methyl ethyl ketone (100 ml) and triethyl amine (2.8 ml) are added to sterol **1** (10 mmol) and the mixture is cooled to 5°C. Methanesulfonyl chloride (1.72 g, 1.16 ml, 15 mmol) is added dropwise to it at 5°C. After stirring for 1 h, 15% aqueous sodium chloride solution (20 ml) is added to the mixture, the organic layer is separated and washed with aqueous sodium bicarbonate solution (20 ml). The organic layer is stirred with water (20 ml) and sodium hydrogen carbonate (1.68 g) and heated under reflux for 5 h. Jones reagent (2.75 ml) is added dropwise to the stirred and cooled organic layer, and the stirring is continued for 3 h at

Table 3. Spectral Data of Compounds **1–5**

Product No.	m.p. (°C)	Molecular Formula[a] or Lit. m.p. (°C)	MS (70 eV) *m/e*	IR (KBr) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
4a	110–111	102–103[6]	–	1685, 1460, 1370, 1295, 1160, 1120, 975, 875, 810, 630	–
5a	120–121	112–113[14]	412 (M^+), 411, 410, 395, 367, 312, 149	1710, 1655, 1460, 1390, 1300, 1230, 1070, 1000, 970, 670	0.71 (s, 3H); 0.73 (s, 3H); 5.0–5.3 (m, 2H, H-22, H-23); 5.55–5.84 (m, 2H, H-2, H-3)
4b	105–107	109–111[14]	–	1685, 1460, 1410, 1370, 1295, 1160, 1120, 970, 875, 810, 630	–
5b	119–121	123–124[14]	398 (M^+), 397, 396, 381, 368, 353, 149	1710, 1655, 1460, 1385, 1370, 1300, 1230, 1075, 965, 670	0.69 (s, 3H); 0.72 (s, 3H); 5.22 (m, 2H, H-22, H-23); 5.55–5.84 (m, 2H, H-2, H-3)
4c	98–99.5	101–102[15]	–	1685, 1470, 1410, 1370, 1295, 1165, 1080, 965, 920, 875, 810	–
5c	104–106	105.5–106.5[15]	384 (M^+), 369, 356	1710, 1460, 1425, 1380, 1365, 1235, 1075, 1000, 670	0.68 (s, 3H); 0.72 (s, 3H); 5.55–5.84 (m, 2H, H-2, H-3)
1d	141–142	134–135[9]	417 (M^+ – 1), 457, 401, 357, 271, 171, 142	1460, 1380, 1370, 1240, 1175, 1025, 885	0.70 (s, 3H); 3.45–3.7 (m, 1H, H-3); 3.77 (q, 1H, J = 4 Hz); 3.88 (d, 1H, J = 8 Hz); 5.39 (d, 1H, J = 4 Hz, H-6)
3d	187–189	$C_{31}H_{52}O_3$ (472.8)	472 (M^+), 458, 457, 357, 229, 171, 142	1460, 1385, 1370, 1250, 1240, 1220, 1175, 1030, 880, 810	0.3 (q, 1H, J = 4 Hz); 0.53 (t, 1H, J = 4 Hz); 0.73 (s, 3H); 3.29 (br s, 1H, H-6); 3.77 (q, 1H, J = 4 Hz); 3.89 (d, 1H, J = 8 Hz)
4d	159–161	$C_{31}H_{50}O_3$ (470.7)	471 (M^+ – 1), 455, 412, 399, 355, 312, 271	1685, 1460, 1375, 1365, 1295, 1250, 1210, 1170, 1140, 885	0.73 (s, 3H); 3.77 (q, 1H, J = 4 Hz); 3.88 (d, 1H, J = 8 Hz)
5d	236–238	235–237[4]	471 (M^+ – 1), 455, 413, 399, 355, 297, 171	1710, 1460, 1390, 1380, 1370, 1235, 1180, 1030, 880, 820	0.69 (s, 3H); 0.73 (s, 3H); 3.77 (q, 1H, J = 4 Hz); 3.89 (d, 1H, J = 8 Hz); 5.4–5.8 (m, 2H, H-2, H-3)

[a] Satisfactory microanalyses obtained: C ±0.26, H ±0.09.

5°C. After adding 15% aqueous sodium chloride solution (20 ml) the organic layer is separated and washed with aqueous sodium hydrogen carbonate solution (20 ml) and aqueous sodium chloride solution (10 ml). The organic layer is dried with magnesium sulfate and concentrated *in vacuo*. The crude 3,5-cyclo-6-one **4** is chromatographed over silica gel with benzene/*n*-hexane or *n*-hexane/ethyl acetate ($\frac{1}{2}$ or $\frac{1}{20}$) as eluent; yield from sterol **1**: **4a**, 81%; **4b**, 77%; **4c**, 78%; **4d**, 73%.

Steroidal 2-En-6-ones 5a–5d; General Procedure:
p-Toluenesulfonic acid (76 mg) and sodium bromide (103 mg) are added to 3,5-cyclo-6-one **4** (2.0 mmol) in dimethylformamide (8 ml). The mixture is stirred and heated under reflux for 3 h. Ethyl acetate (50 ml) is added to the cooled reaction mixture, the organic layer is washed successively water (3 × 25 ml) and aqueous sodium chloride solution (10 ml). The organic layer is dried with magnesium sulfate and concentrated *in vacuo*. The crude 2-en-6-one **5** is chromatographed over silica gel with ethyl acetate/*n*-hexane or ethyl acetate/benzene ($\frac{1}{20}$ or $\frac{1}{50}$) as eluent; yield: 76–82%.

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