Notes

[Chem. Pharm. Bull. 30(11)4181—4185(1982)]

Synthesis of (22*R*,23*R*)-28-Homobrassinolide

Suguru Takatsuto and Nobuo Ikekawa*

Department of Chemistry, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152, Japan

(Received April 26, 1982)

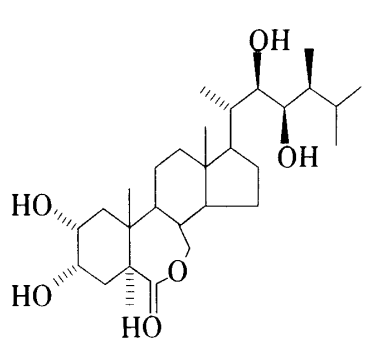
(22*R*,23*R*)-28-Homobrassinolide (**18**), an analog of brassinolide (**1**), was synthesized from stigmasterol (**3**).

Keywords——brassinolide; plant growth-promoting substance; active analogs of brassinolide; structure–activity relationship; stigmasterol; plant hormones; Baeyer–Villiger oxidation

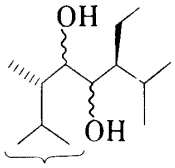
Recently, a novel plant growth-promoting substance named brassinolide (**1**) has been isolated from the pollen of rape (*Brassica napus* L.), and its structure was determined as (22*R*,23*R*,24*S*)-2α,3α,22,23-tetrahydroxy-24-methyl-B-homo-7-oxa-5α-cholestan-6-one by X-ray crystallography.[1] Brassinolide (**1**) is a steroid having a seven-membered B-ring lactone and α_F configuration of the hydroxyl group at C-22; such structural features are unprecedented in natural products. Brassinolide (**1**) shows strong activity in the lamina inclination assay[2] and possesses a broad spectrum of biological activities compared with the known plant hormones.[3] It may therefore find practical applications in the agricultural field in future. Because of its unique structural features and remarkable biological activities, special attention has been focussed on the synthesis of brassinolide (**1**), which has already been achieved by us[4] and other groups.[5,6] Several active analogs of brassinolide (**1**) have also been synthesized.[7–10] Although (22*S*,23*S*)-28-homobrassinolide (**17**)[10] and a mixture of (22*R*,23*R*)- and (22*S*,23*S*)-stereoisomers (**2**)[8] have already been synthesized, the (22*R*,23*R*)-isomer (**18**), which has the same configuration as natural brassinolide (**1**), has not yet been prepared in an isomerically pure state. (22*R*,23*R*)-28-homobrassinolide (**18**) is essential for further investigation of the structure–activity relationship of brassinolide (**1**). We describe here a simple synthesis of (22*R*,23*R*,24*S*)-2α,3α,22,23-tetrahydroxy-24-ethyl-B-homo-7-oxa-5α-cholestan-6-one (**18**).

The key intermediate, (24*S*)-2α,3α-diacetoxy-24-ethyl-5α-cholest-22-en-6-one (**8**) was prepared from stigmasterol (**3**) in 47% yield as follows. Mesylation of stigmasterol (**3**), followed by solvolysis with $KHCO_3$ in aqueous acetone under reflux gave the 3,5-cyclo-6β-ol, which was oxidized with Jones reagent to afford the 6-ketone **4**. Treatment of **4** with 5 N H_2SO_4 in acetic acid under reflux, followed by saponification, yielded the 3β-hydroxy-6-ketone **5**. Tosylation of **5**, followed by treatment with lithium bromide in dimethyl-formamide under reflux[12] afforded the 2-ene **7**. Osmium tetroxide oxidation[13,14] of **7** in the presence of *N*-methylmorpholine *N*-oxide in aqueous tetrahydrofuran, followed by acetylation, afforded, after chromatographic purification, the 2α,3α-diacetate **8**, mp 193—194°C.

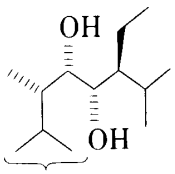
The first method to obtain the (22*R*,23*R*)-tetra-acetate **10** is by way of osmium tetroxide oxidation of the 22-olefin **8**. Treatment of **8** with a catalytic amount of OsO_4 in the presence of *N*-methylmorpholine *N*-oxide in aqueous tetrahydrofuran,[13] followed by acetylation with acetic anhydride in pyridine at 60°C, gave the less polar (22*S*,23*S*)-tetra-acetate **9** and the more polar (22*R*,23*R*)-tetra-acetate **10** in 70% yield in a ratio of 96 : 4. This assignment is based on the stereochemistry of OsO_4 oxidation at the C-22 (23) double bond of the stigmasterol side chain[10] and the similarity of proton nuclear magnetic resonance (^{1}H-NMR)



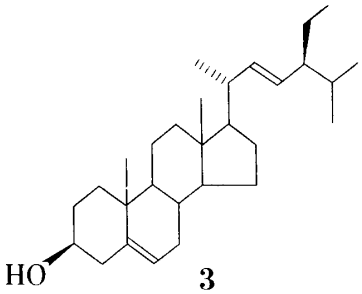
1



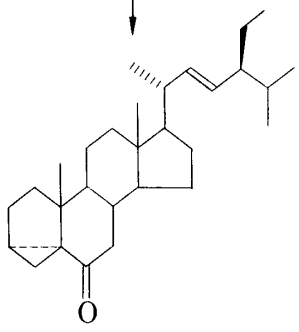
2



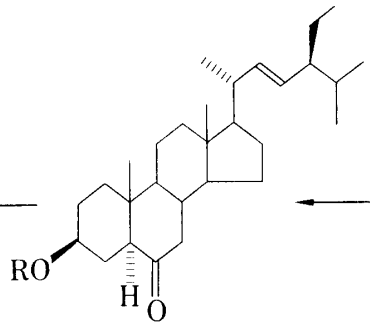
17



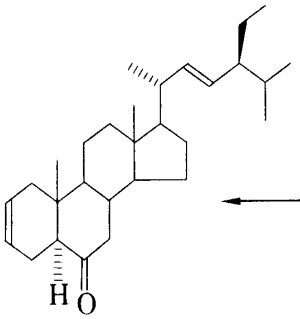
3



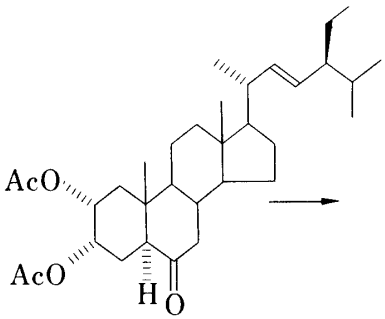
4



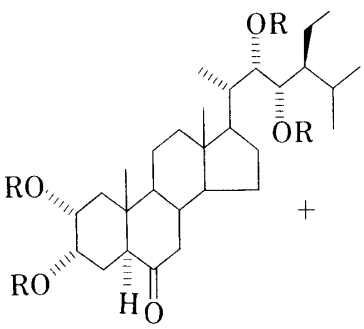
5 : R=H
6 : R=Ts



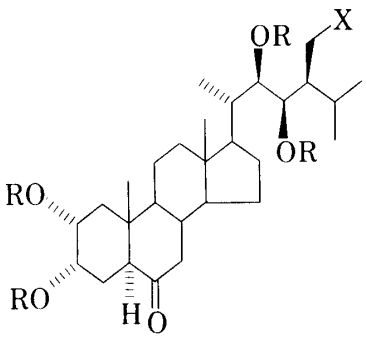
7



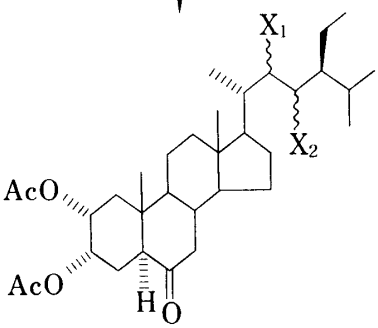
8



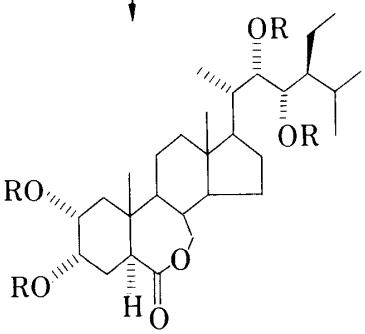
9 : R=Ac
11 : R=H



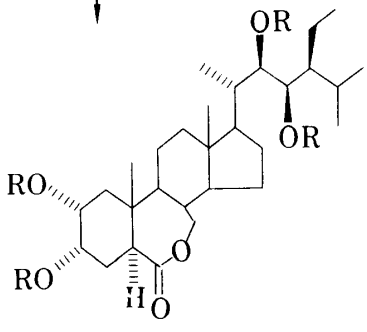
10 : R=Ac, X=Me
12 : R=H, X=Me
13 : R=Ac, X=H



14 : X_1=AcO, X_2=Br
14 : X_1=Br, X_2=AcO



15 : R=Ac
17 : R=H



16 : R=Ac
18 : R=H

spectral data between the more polar tetraacetate (**10**) and our previously reported (22*R*,23*R*, 24*S*)-24-methyl-tetra-acetate (**13**).[4] This assignment was finally confirmed by conversion of the less polar tetra-acetate (**9**) into the known (22*S*,23*S*)-28-homobrassinolide (**17**).[10]

The second method, which was expected to give a higher ratio of **10** to **9**, relied on our previous observation[11] that oxidation of a stigmasterol derivative with *m*-chloroperbenzoic acid produced the (22*R*,23*R*)- and (22*S*,23*S*)-epoxides in a ratio of 5:3. Epoxidation of **8** with *m*-chloroperbenzoic acid, followed by *trans* ring opening of the resulting epoxide with 47% HBr in chloroform–acetic acid and subsequent acetylation gave a regio- and stereoisomeric mixture of the bromoacetates (**14**). Refluxing of **14** in aqueous acetic acid (S_N2 reaction at the carbon bearing bromine) and subsequent acetylation at 60°C afforded, in 20% yield, a mixture of the less polar (22*S*,23*S*)-tetra-acetate (**9**) and the more polar (22*R*,23*R*)-tetra-acetate (**10**) in a ratio of 9:10. Separation of **9** and **10** was easily carried out by silica gel column chromatography. Saponification of **9** and **10** with 5% KOH/MeOH under reflux for 1 h furnished the (22*S*,23*S*)-tetra-ol (**11**), mp 200—204°C, and (22*R*,23*R*)-tetra-ol (**12**), mp 253—255°C, respectively, in *ca.* 90% yield.

Treatment of the 6-oxo-tetra-acetates (**9**) and (**10**) with trifluoroperacetic acid in dichloromethane in the presence of disodium hydrogen phosphate at 0°C afforded, after chromatographic purification, the 7-oxalactones (**15**) and (**16**), respectively, in *ca.* 80% yield. Saponification of **15** and **16** with 5% KOH/MeOH under reflux for 1 h and acidification with conc. HCl furnished (22*S*,23*S*)-28-homobrassinolide (**17**), mp 197—198°C (lit.[10] mp 197—198°C) and (22*R*,23*R*)-28-homobrassinolide (**18**), mp 268—271°C (dec.), respectively, in *ca.* 90% yield.

Biological activities of the synthetic (22*R*,23*R*)-28-homobrassinolide (**18**) and other analogs **11**, **12** and **17** are now under investigation and will be reported in a forthcoming paper.

Experimental

Melting points were determined on a hot stage microscope and are uncorrected. ^{1}H-NMR spectra were run on a JEOL JNM-4H-100 spectrometer and a Hitachi R-24A spectrometer with $CDCl_3$ as a solvent and with tetramethylsilane as an internal reference. Mass spectra were taken on a Shimadzu LKB-9000 mass spectrometer and a Hitachi M-80 mass spectrometer. IR spectra were obtained with a Hitachi Model 260-10 spectrometer. Column chromatography was normally effected with Merck silica gel Kieselgel 60 (70—230 mesh). Merck silica gel 60 F_{254} (0.25 mm thick) was used for TLC. The following abbreviations apply to ^{1}H-NMR data; s=singlet; d=doublet; dd=double doublet; br s=broaden singlet.

(24*S*)-2α,3α-Diacetoxy-24-ethyl-5α-cholest-22-en-6-one (8)——Stigmasterol (**3**) (14 g, 33.98 mmol) was dissolved in pyridine (50 ml) and tetrahydrofuran (50 ml), and methanesulfonyl chloride (7 ml) was added at 0°C. This mixture was stirred at 0°C for 3 h, then ice-water was added and the whole was extracted with ether. The organic layer was washed with conc. HCl, sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude mesylate (15 g). A mixture of the crude mesylate (15 g), $KHCO_3$ (3 g) and water (180 ml) in acetone (750 ml) was refluxed for 8 h. The solvent was removed under reduced pressure and the residue was extracted with ether. The organic layer was washed with brine, and dried over $MgSO_4$. Evaporation of the solvent gave the crude 3,5-cyclo-6β-ol (13 g), which was dissolved in acetone (300 ml). Jones reagent was added at 0°C. When the reaction mixture became reddish, water (200 ml) was added, and the mixture was extracted with ether. The organic layer was washed with water and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the ketone (**4**) (12 g). A mixture of **4** (12 g) and 5 N H_2SO_4 (10 ml) in acetic acid (100 ml) was refluxed for 1 h. Evaporation of the solvent under reduced pressure gave the residue, which was extracted with ether. The organic layer was washed with sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent gave a crude product (13 g), which was treated with 2 N NaOH/MeOH (100 ml) in ether (100 ml) at room temperature for 2 h. The solvent was evaporated off under reduced pressure and the residue was extracted with ether. The organic layer was washed with brine, 2 N HCl, and brine, then dried over $MgSO_4$. Removal of the solvent gave crude 3β-hydroxy-6-ketone (**5**) (12 g). A mixture of **5** (12 g) and *p*-toluenesulfonyl chloride (1.5 eq) in pyridine (70 ml) in the presence of 4-dimethylaminopyridine (100 mg) was stirred at 0°C for 3 h. Ice-water was added to this reaction mixture and the whole was extracted with ether. The organic layer was washed with conc. HCl, sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent gave the crude tosylate (**6**) (13.5 g). Recrystallization from acetone afforded crystals, mp 185—186°C (lit.[10] mp 185—186°C). MS *m/z*: 582 (M^+). NMR ($CDCl_3$) δ: 0.67 (3H, s, 18-H_3), 0.72 (3H, s, 19-H), 1.02 (3H, d, J=6 Hz, 21-H_3), 2.46 (3H, s, tosyl), 4.50 (1H, m, 3-H), 5.08 (2H, m, 22-H and 23-H), 7.32 (2H, d, J=8 Hz, tosyl), 7.80 (2H, d, J=8 Hz, tosyl). A mixture of the tosylate (**6**) (13.5 g) and lithium bromide (5 g) in dimethylform-

amide (70 ml) was refluxed for 1 h, then cooled to room temperature, and water was added. This mixture was extracted with ethyl acetate. The organic layer was washed with 2 N HCl, sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the 2-ene (**7**) (9 g). Recrystallization from methanol gave crystals, mp 112—113°C (lit.[8] mp 111—112°C). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710. NMR ($CDCl_3$) δ: 0.70 (6H, s, 18-H_3 and 19-H_3), 1.02 (3H, d, J=6 Hz, 21-H_3), 5.07 (2H, m, 22-H, and 23-H), 5.58 (2H, m, 2-H and 3-H). A mixture of **7** (9 g), osmium tetroxide (200 mg) and *N*-methylmorpholine *N*-oxide (5 g) in aqueous tetrahydrofuran (150 ml) was stirred at room temperature for 6 h, then $NaHSO_3$ (5 g) and water (100 ml) were added and stirring was continued for 2 h. This mixture was extracted with dichloromethane and the organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude 2α,3α-diol (10 g). A mixture of this diol (10 g) and acetic anhydride (50 ml) in pyridine (50 ml) was stirred at 60°C for 17 h, then water was added. This mixture was extracted with ethyl acetate and the organic layer was washed with conc. HCl, sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a crude product (12 g). Chromatography on silica gel (100 g) with benzene–ethyl acetate (100: 1) afforded pure 2α,3α-diacetate (**8**) (8.47 g, 47% from stigmasterol (**3**), mp 193—194°C (from methanol). NMR ($CDCl_3$) δ: 0.69 (3H, s, 18-H_3), 0.82 (3H, s, 19-H_3), 1.01 (3H, d, J=6 Hz, 21-H_3), 1.98 (3H, s, acetyl), 2.03 (3H, s, acetyl), 5.07 (3H, m, 2-H, 22-H and 23-H), 5.35 (1H, m, 3-H). *Anal.* Calcd for $C_{33}H_{52}O_5$: C, 74.96; H, 9.91. Found: C, 74.82; H, 9.85.

(22*S*,23*S*,24*S*)-2α,3α,22,23-Tetrahydroxy-24-ethyl-5α-cholestan-6-one (9) and (22*R*,22*R*,24*S*)-2α,3α,22,23-Tetrahydroxy-24-ethyl-5α-cholestan-6-one (10)——Method A: The mixture of **8** (5 g, 9.47 mmol), osmium tetroxide (200 mg) and *N*-methylmorpholine *N*-oxide (2 g, 14.81 mmol) in aqueous tetrahydrofuran (100 ml) was stirred at room temperature for 3 d, then $NaHSO_3$ (2.5 g) and water (30 ml) were added and stirring was continued for 2 h. This mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a crude product (5.5 g). A mixture of this product (5.5 g) and acetic anhydride (30 ml) in pyridine (35 ml) was stirred at 60°C for 19 h, then ice was added and the whole was extracted with ethyl acetate. The organic layer was washed with conc. HCl, sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was evaporated off under reduced pressure to give crude tetraacetate (6.1 g). Chromatography on silica gel (100 g) with benzene–ethyl acetate (20: 1) afforded the starting material (**8**) (1.28 g), the less polar (22*S*,23*S*)-tetraacetate (**9**) (3.15 g, 51.5%), oil. NMR ($CDCl_3$) δ: 0.69 (3H, s, 18-H_3), 0.84 (3H, s, 19-H_3), 2.00 (3H, s, acetyl), 2.07 (3H, s, acetyl), 2.09 (6H, s, two acetyls), 4.96 (1H, m, 2-H), 5.04 (1H, m, 22-H or 23-H), 5.26 (1H, m, 22-H, or 23-H), 5.38 (1H, m, 3-H) and the more polar (22*R*,23*R*)-tetraacetate (**10**) (131 mg, 2.2%); oil. NMR ($CDCl_3$) δ: 0.70 (3H, s, 18-H_3), 0.84 (3H, s, 19-H_3), 1.97 (3H, s, acetyl), 1.99 (3H, s, acetyl), 2.02 (3H, s, acetyl), 2.08 (3H, s, acetyl), 4.96 (1H, m, 2-H), 5.13 (1H, br s, 22-H or 23-H), 5.19 (1H, br s, 22-H or 23-H), 5.39 (1H, m, 3-H). Compound **9** (300 mg, 0.463 mmol) was refluxed with 5% KOH/MeOH (10 ml) for 1 h. The solution was cooled to room temperature, then 2 N HCl was added. The mixture was extracted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded the (22*S*,23*S*)-tetra-ol (**11**) (200 mg, 90%), mp 200—204°C (from ethyl acetate). IR ν_{max}^{KBr} cm^{-1}: 3400, 2960, 2880, 1722, 1472, 1390, 1090, 1055, 1022, 1005. FD-MS *m/z*: 479 (M+1), 461 (M+1−18), 393 (M−85, C_{23}–C_{24} fission), 363 (M−115, C_{22}–C_{23} fission), 333 (M−145, C_{20}–C_{22} fission), 145, 115. EI-MS *m/z*: 460 (M−18), 393 (M−85, C_{23}–C_{24} fission), 364 (M−115+H, C_{22}–C_{23} fission), 345 (363−18), 327, 287 (C_{14}–C_{15} and C_{13}–C_{17} fissions+H), 2.63, 245, 175, 173, 145, 115, 85. Compound **10** (155 mg, 0.240 mmol) was saponified in the same manner to yield the (22*R*,23*R*)-tetraol (**12**) (105 mg, 92%), mp 253—255°C (from ethyl acetate), IR ν_{max}^{KBr} cm^{-1}: 3430, 2950, 2875, 1710, 1468, 1390, 1085, 1043, 1018, 997. FD-MS *m/z*: 479 (M+1), 461, 393, 363, 333, 145, 115. EI-MS *m/z*: 460 (M−18), 393, 364, 345, 327, 287, 263, 245, 175, 173, 145, 115, 85.

Method B: Mixture of **8** (1.8 g, 3.41 mmol) and *m*-chloroperbenzoic acid (650 mg, 3.76 mmol) in chloroform (10 ml) was stirred at room temperature for 18 h, then sat. $NaHCO_3$ was added and the whole was extracted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude epoxide (1.85 g). A mixture of this epoxide (1.85 g) and 45% HBr (1.5 ml) in acetic acid (4 ml) and chloroform (20 ml) was stirred at room temperature for 15 h, then sat. $NaHCO_3$ was added and the mixture was extracted with ether. The organic layer was washed with sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent at below 30°C gave the bromohydrin (1.92 g), which was acetylated with acetic anhydride (10 ml) and pyridine (10 ml) in the presence of 4-dimethylaminopyridine (20 mg) at room temperature for 17 h. Then ice was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with conc. HCl, sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent gave the bromoacetate (**14**) (2.2 g). A solution of **14** (2.2 g) in AcOH–H_2O (5: 1, 20 ml) was refluxed for 15 h then cooled to room temperature, and sat. $NaHCO_3$ was added. This mixture was extracted with ethyl acetate and the organic layer was washed with sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was evaporated off under reduced pressure to leave a residue, which was acetylated in the usual manner at 60°C for 15 h. Then ice was added and the mixture was extracted with ethyl acetate. The organic layer was washed with conc. HCl, sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent and chromatography of the residue on silica gel (50 g) with benzene–ethyl acetate (20: 1) afforded the less polar (22*S*,23*S*)-tetraacetate (**9**)

(210 mg, 9.5%) and the more polar (22*R*,23*R*)-tetraacetate (**10**) (230 mg, 10.5%). TLC and ^{1}H-NMR spectral data were identical with those of the products obtained by OsO_4 oxidation and acetylation. The saponified tetra-ols were also identical with corresponding products obtained by the above-described method A in terms of melting points, MS and IR spectral data.

(22*S*,23*S*,24*S*)-2α,3α,22,23-Tetrahydroxy-24-ethyl-B-homo-7-oxa-5α-cholestan-6-one (17)——A mixture of **9** (1.4 g, 2.17 mmol), Na_2HPO_4 (3 g) and trifluoroperacetic acid (7 eq) [prepared from 90% H_2O_2 and trifluoroacetic anhydride in dichloromethane] in dichloromethane (15 ml) was stirred at 0°C for 2 h, then sat. $NaHSO_3$ was added and the whole was extracted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solvent and chromatography on silica gel (50 g) with benzene–ethyl acetate (15: 1) afforded the 7-oxalactone (**15**) (1.16 g, 81%), mp 176—178°C (lit.[10] mp 176—178°C). NMR ($CDCl_3$) δ: 0.71 (3H, s, 18-H_3), 0.98 (3H, s, 19-H_3), 2.00 (3H, s, acetyl), 2.07 (3H, s, acetyl), 2.10 (3H, s, acetyl), 2.12 (3H, s, acetyl), 3.00 (1H, dd, J=6 and 13 Hz, 5-H), 4.10 (2H, m, 7-H_2), 4.70—5.40 (4H, m, 2-H, 3-H, 22-H and 23-H). A mixture of the tetraacetate (**15**) (1.16 g, 1.80 mmol) and 5% KOH/MeOH (20 ml) was refluxed for 1.5 h. The mixture was cooled to room temperature, then 2 N HCl (40 ml) was added and stirring was continued for 1 h. This mixture was extracted with ethyl acetate and the organic layer was washed with sat. $NaHCO_3$ and brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded **17** (798 mg, 90%), mp 197—198°C (lit.[18] mp 197—198°C) (from methanol). IR ν_{max}^{KBr} cm^{-1}: 3435, 2960, 2875, 1700, 1472, 1410, 1392, 1336, 1280, 1230, 1191, 1136, 1125, 1072, 1031, 1000. FD-MS *m/z*: 495 (M+1), 477 (M+1−18), 379 (M−115, C_{12}–C_{23} fission), 349 (M−145, C_{20}–C_{22} fission), 145, 115. EI-MS *m/z*: 476 (M−18), 461 (M−18−15), 409 (M−85, C_{23}–C_{24} fission), 380 (M−115+H, C_{22}–C_{23} fission), 379 (M−115, C_{22}–C_{23} fission), 361, 350 (M−145+H, C_{20}–C_{23} fission), 177, 145, 115, 85.

(22*R*,23*R*,24*S*)-2α,3α,22,23-Tetrahydroxy-24-ethyl-B-homo-7-oxa-5α-cholestan-6-one (18)——The (22*R*, 23*R*)-tetra-acetoxy-6-ketone (**10**) (120 mg, 0.186 mmol) was converted, in the same manner as described for **9**, into the 7-oxalactone (**16**) (101 mg, 82%), oil. NMR ($CDCl_3$) δ: 0.72 (3H, s, 18-H_3), 0.98 (3H, s, 19-H_3), 1.95 (3H, s, acetyl), 1.98 (6H, s, two acetyls), 2.08 (3H, s, acetyl), 2.98 (1H, dd, J=6 and 13 Hz, 5-H), 4.08 (2H, m, 7-H_2), 4.72 (1H, m, 2-H), 5.13 (1H, br s, 22-H or 23-H), 5.18 (1H, br s, 22-H or 23-H), 5.30 (1H, m, 3-H). Saponification of **16** (101 mg, 0.153 mmol) followed by acidification as described above afforded (22*R*,23*R*)-28-homobrassinolide (**18**) (69 mg, 91%), mp 268—271°C (dec.) (from ethyl acetate), IR ν_{max}^{KBr} cm^{-1}: 3450, 2970, 2945, 2875, 1701, 1470, 1410, 1388, 1337, 1282, 1230, 1190, 1148, 1130, 1068, 1030, 990. FD-MS *m/z*: 495 (M+1), 477, 379, 349, 145, 115. EI-MS *m/z*: 476 (M−18), 461, 409, 380, 379, 361, 350, 177, 145, 115, 85.

Acknowledgement The authors are grateful to Dr. K. Wada, Nagoya University, for the gift of (22*S*,23*S*)-28-homobrassinolide. This work was supported by a Grant-in-Aid from the Ministry of Education, Science and Culture, Japan.

References

1) M.D. Grove, G.F. Spencer, W.K. Rohwedder, N. Mandava, J.F. Worley. J.D. Warthen Jr., G.L. Steffens, J.L.F. Anderson, and J.C. Cook Jr., *Nature* (London), **281**, 216 (1979).
2) K. Wada, S. Marumo, N. Ikekawa, M. Morisaki, and K. Mori, *Plant and Cell Physiol.*, **22**, 323 (1981).
3) J.H. Yopp, N. Mandava, and J.M. Sasse, *Physiol. Plant.*, **53**, 445 (1981); N. Mandava, J.M. Sasse, and J.H. Yopp, *ibid.*, **53**, 453 (1981).
4) M. Ishiguro, S. Takatsuto, M. Morisaki, and N. Ikekawa, *J. Chem. Soc., Chem. Commun.*, **1980**, 962.
5) S. Fung and J.B. Siddall, *J. Am. Chem. Soc.*, **102**, 6580 (1980).
6) M.J. Thompson, N. Mandava, W.J. Meudt, W.R. Lusby, and D.W. Spaulding, *Steroids*, **38**, 567 (1981).
7) M.J. Thompson, N. Mandava, J.L.F. Anderson, J.F.Worley, S.R. Dutky, W.E. Robbins, and W. Lusby, *J. Org. Chem.*, **44**, 5002 (1979).
8) K. Mori, *Agric. Biol. Chem.*, **44**, 1211 (1980).
9) S. Takatsuto, B. Ying, M. Morisaki, and N. Ikekawa, *Chem. Pharm. Bull.*, **29**, 903 (1981).
10) K. Wada and S. Marumo, *Agric. Biol. Chem.*, **45**, 2579 (1981).
11) M. Nakane, M. Morisaki, and N. Ikekawa, *Tetrahedron*, **31**, 2755 (1975).
12) E. Lee, Y.T. Liu, P.H. Solomon, K. Nakanishi, *J. Am. Chem. Soc.*, **98**, 1634 (1976).
13) V. VanRheenen, R.C. Kelly, and D.Y. Cha, *Tetrahedron Lett.*, **1976**, 1973.
14) L. Fieser and M. Fieser, "Steroids," Reinhold, New York, 1959, p. 44.