December, 1989] © *1989 The Chemical Society of Japan* NOTES *Bull. Chem. Soc. Jpn., 62, 4075—4077 (1989)* 4075

Synthesis of a 24-Epimeric Mixture of 24-Methyl-19,29-dinorlanost-9(11)-en-3-one[1)]

Tetsuya Makino, Tatsushi Murae, Takahiko Tsuyuki,* and Takeyoshi Takahashi
Department of Chemistry, Faculty of Science, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

(Received August 8, 1989)

Synopsis. A 24-epimeric mixture of 24-methyl-19,29-dinorlanost-9(11)-en-3-one was synthesized from 24-methylenecycloartanol. The synthesis comprises acid-cleavage of the cyclopropane ring, 4β-demethylation, the Barton reaction of the 3-nitrile, dehydration of the 11β-hydroxy derivative, and oxidation of the 19-hydroxy derivative followed by photolysis.

As an authentic sample for identification of a triterpene isolated from the plant fossile,[2)] a 24-epimeric mixture of 24-methyl-19,29-dinorlanost-9(11)-en-3-one (=4α,14α,24-trimethyl-19-norcholest-9(11)-en-3-one) (**1**) was prepared from 24-methylene-9,19-cyclo-lanostan-3β-yl acetate (=24-methylenecycloartenyl acetate) (**2**). The synthetic route is given in Fig. 1.

Experimental[3)]

Isolation of the Starting Compound (2). Rice bran oil contains phenolic compounds, named oryzanol A and C, which were reported to be cycloartenyl ferulate and 24-methylenecycloartenyl ferulate, respectively.[4)] Alkaline hydrolysis of a powdery oryzanol mixture[5)] (16 g) followed by acetylation yielded a mixture (10 g), which was shown to be a 1 : 1 mixture of **2** and 9,19-cyclolanost-24-en-3β-yl acetate (cycloartenyl acetate) (**3**) by the gas chromatography-mass spectrometry (GC-MS)[6)] and the proton nuclear magnetic resonance (^{1}H NMR) spectrometry. Since the mixture (**2** and **3**) showed a single spot on the thin-layer chromatography (TLC), the mixture (40.0 g) in CH_2Cl_2 (800 ml) was subjected to selective epoxidation and the reaction was mon-

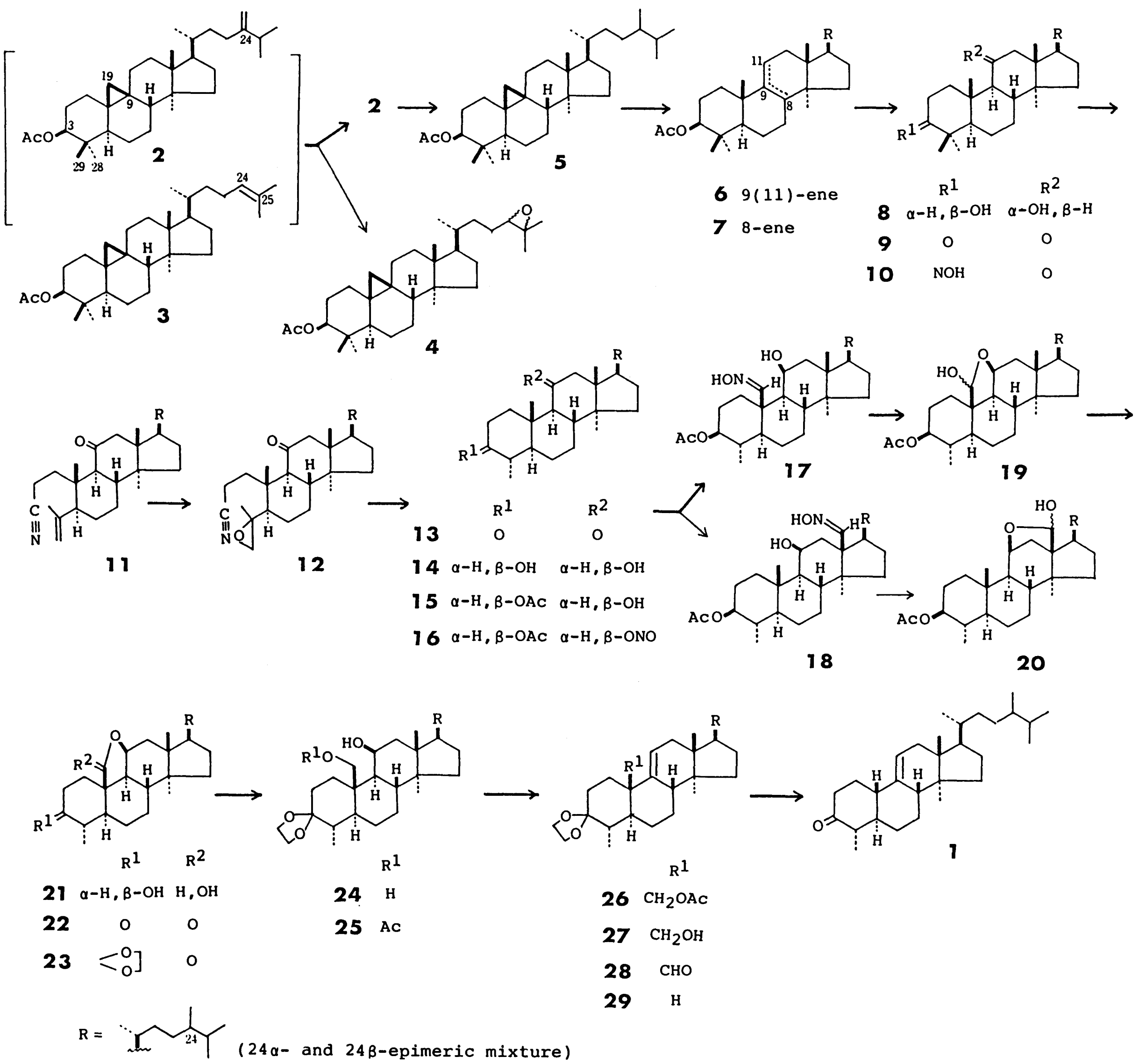

Fig. 1.

itored by GC. The epoxidation with *m*-chloroperbenzoic acid (mCPBA; 80%, 12.3 g) at −40 °C for 6 h gave an epoxide (**4**; 20.1 g) and the unchanged **2** (19.7 g) after column chromatography (SiO_2; 4—40% Et_2O in hexane). **2**: mp 108—109 °C (lit,[4] 116—117 °C); ^{1}H NMR δ=4.43—4.77 (3H, m; 3α-H and $C_{(24)}$=CH_2).

Hydrogenation of 2. The 24-methylene derivative (**2**; 29.2 g) in ether (1 l) was subjected to catalytic hydrogenation to give a 24-epimeric mixture of 24-methyl-9,19-cyclolanostan-3β-yl acetate[7] (**5**; 29.3 g), mp 125—126 °C; ^{1}H NMR; δ=0.34 (1H, d, *J*=4 Hz; 19-H), 0.59 (1H, d, *J*=4 Hz; 19′-H), 0.75 (3H, s; Me), 0.87—0.93 (6×Me), 0.97 (3H, s; Me), 2.04 (3H, s; OAc), and 4.43—4.70 (1H, m; 3α-H); MS *m/z* (%) 484 (M^+; 21), 469 (13), 444 (12), 424 (100), 409 (46), 385 (20), 382 (22), 356 (20), 302 (37), and 296 (32).

24-Methyllanostane-3,11-dione (9). Dry hydrogen chloride was introduced into a solution of **5** (11.5 g) in $CHCl_3$ (300 ml) for 2 h.[8] The usual work-up gave a mixture (11.2 g) of 24-methyl-9(11)-lanosten-3β-yl acetate (**6**) and its 8-ene isomer (**7**) in a ratio of 7 : 3, ^{1}H NMR δ=0.64—1.07 (9×Me), 2.04 (3H, s; OAc), 4.33—4.60 (1H, m; 3α-H), and 5.11—5.30 (0.7H, m; 11-H of **6**).

To a solution of the mixture (65.4 mg) in THF (4 ml) kept at 0 °C, diborane in THF (1.1 mmol^{-1} ml, 0.15 ml) was added and the solution was stirred for 2 d at 40 °C. After addition of water (3 ml), 3 M (1 M=1 mol dm^{-3}) NaOH (0.2 ml), and 30% H_2O_2 (0.2 ml), the reaction mixture was worked up as usual to afford 24-methyllanostane-3β,11α-diol (**8**; 26.5 mg), mp 202—204 °C; ^{1}H NMR δ=0.75 (3H, s; Me), 0.82—0.92 (6×Me), 0.98 and 1.01 (each 3H, s; Me), 3.08—3.35 (1H, m; 3α-H), and 3.73—4.12 (1H, m; 11β-H); MS *m/z* (%) 460 (M^+; 11), 442 (29), 427 (30), 424 (14), 409 (31), 399 (13), 238 (86), 223 (100), and 84 (>100).

A solution of **8** (8.45 g) in acetone (500 ml) was treated with Jones reagent (10 ml) for 5 min at 0 °C. The reaction mixture was worked up and chromatographed (SiO_2; 5% Et_2O in C_6H_6) to yield 24-methyllanostane-3,11-dione (**9**; 7.10 g), mp 158—159 °C; ^{1}H NMR δ=0.75—0.83 (4×Me), 0.89 (3H, s; Me), 1.05—1.09 (3×Me), 1.20 (3H, s; Me), and 2.78—3.13 (1H, m); MS (%) 456 (M^+; 100), 442 (8), 428 (44), 413 (18), 317 (96), and 219 (100).

4β-Demethylation of 9 According to the Pinhey's Procedure.[9] The dione (**9**) was converted into 24-methyl-29-norlanostane-3,11-dione (**13**) by the same procedure as before[1] through 3-hydroxyimino-24-methyllanostan-11-one (**10**), 24-methyl-11-oxo-3,4-secolanost-4(29)-ene-3-nitrile[10] (**11**), and 4,29-epoxy-24-methyl-11-oxo-3,4-secolanostane-3-nitrile[10] (**12**) in 48% overall yield. **10:** mp 215.5—216 °C; IR (KBr) 3320, 1700, and 930 cm^{-1}; ^{1}H NMR δ=0.73—0.90 (5×Me), 1.07 (6H, s; 2×Me), 1.13 and 1.17 (each 3H, s; Me); MS *m/z* (%) 471 (M^+; 76), 454 (46), and 140 (100). **11:** as a pale yellow oil, IR (neat) 2250, 1700, 890, and 680 cm^{-1}; ^{1}H NMR δ=0.75—0.89 (5×Me), 1.10 (6H, s; 2×Me), 1.73 (3H, br s; Me), 4.69 and 4.90 (each 1H, br s; C=CH_2); MS *m/z* (%) 453 (M^+; 100), 439 (14), 413 (15), and 372 (49). **12:** as a pale yellow oil, IR (neat) 2250, 1700, 820, and 660 cm^{-1}; ^{1}H NMR δ=0.75—0.89 (5×Me), 1.05, 1.14, and 1.28 (each 3H, s; Me), 2.43, and 2.68 (each 1H, br s); MS *m/z* (%) 469 (M^+; 43), 455 (12), 441 (100), 370 (55), 317 (42), 291 (53), and 264 (49). **13:** an amorphous solid, IR (KBr) 1710 and 1700 cm^{-1}; ^{1}H NMR δ=0.76—0.83 (4×Me), 0.90 (3H, s; Me), 0.99 (3H, d, *J*=6.5 Hz), 1.09, 1.26 (each 3H, s; Me), and 3.05 (1H, ddd, *J*=13, 6, and 3 Hz); MS *m/z* (%) 442 (M^+: 100), 428 (13), 414 (11), 317 (40), 288 (23), 274 (27), 221 (29), and 205 (100).

Photolysis of 3β-Acetoxy-24-methyl-29-norlanostan-11β-yl Nitrite (16). The 3,11-dione (**13**; 236 mg) in ether (100 ml) was reduced with LAH (200 mg) to yield 24-methyl-29-norlanostane-3β,11β-diol (**14**; 148 mg), mp 208—209 °C; ^{1}H NMR δ=0.78—0.93 (6×Me), 1.01, 1.11 (each 3H, s; Me), 2.83—3.25 (1H, m; 3α-H), and 4.10—4.31 (1H, m; 11α-H); MS *m/z* (%) 464 (M^+; 11), 428 (33), 413 (21), 410 (7), 274 (69), 238 (100), and 208 (78). Acetylation of the diol (**14**; 148 mg) gave 11β-hydroxy-24-methyl-29-norlanostan-3β-yl acetate (**15**; 150 mg), mp 170—171 °C; ^{1}H NMR δ=0.78—0.87 (6×Me), 0.98, 1.10 (each 3H, s; Me), 2.00 (3H, s: OAc), and 4.07—4.55 (2H, m; 3α-H and 11α-H); MS *m/z* (%) 488 (M^+; 11), 470 (65), 455 (80), 410 (17), 395 (53), and 238 (100).

A solution of the hydroxy acetate (**15**; 250 mg) in pyridine (25 ml) was treated with NOCl at −30 °C and worked up in the usual manner to afford 3β-acetoxy-24-methyl-29-norlanostan-11β-yl nitrite (**16**; 261 mg) as a pale yellow oil, IR (neat) 1735, 1630, 1600, 1250, 820, 775, and 755 cm^{-1}; ^{1}H NMR δ=0.77—0.88 (8×Me), 2.02 (3H, s; OAc), 4.12—4.53 (1H, m; 3α-H), and 5.83—6.05 (1H, m; 11α-H); MS *m/z* (%) 487 (M^+−NO; 2), 470 (7), 455 (20), 433 (9), 426 (15), 395 (20), 249 (23), and 95 (100).

A solution of the nitrite (**16**; 567 mg) in toluene (40 ml) and *t*-butylamine (2 ml) was photoirradiated with a 400 W-high-pressure mercury lamp for 10 min under nitrogen. The usual work-up and chromatographic separation (SiO_2; 4% Et_2O in C_6H_6) gave a mixture (246 mg) of 11β-hydroxy-19-hydroxyimino-24-methyl-29-norlanostan-3β-yl acetate (**17**) and its 18-hydroxyimino isomer (**18**) together with **15** (248 mg). The mixture showed two singlet signals due to olefinic protons attached to carbon bearing hydroxyimino groups at δ=7.75 (0.7H) and δ=7.43 (0.3H), the major product being the 19-hydroxyimino isomer (**17**).[11] MS of the mixture: *m/z* (%) 517 (M^+; 1), 499 (23), 440 (91), and 57 (100).

24-Methyl-3-oxo-29-norlanostan-19,11β-olide (22). The mixture (159.2 mg) of **17** and **18** in acetone (10 ml) was stirred with concd HCl (4 drops) overnight at room temperature. The reaction product was chromatographed (SiO_2; 4—10% Et_2O in hexane) to give 11,19-epoxy-19-hydroxy-24-methyl-29-norlanostan-3β-yl acetate (**19**; 62.4 mg) and its 11,18-epoxy-18-hydroxyimino isomer (**20**; 30.9 mg). **19:** IR (KBr) 1740 and 1250 cm^{-1}; ^{1}H NMR δ=0.70 (3H, s; Me), 0.76—0.90 (5×Me), 1.04 (3H, s; Me), 2.06 (3H, s; OAc), 4.07—4.27 (1H, m; 11α-H), 4.27—4.64 (1H, m; 3α-H), and 5.35 and 5.63 (total 1H, br s; 19-H's of 19-epimeric mixture of **19**); MS *m/z* (%) 502 (M^+; 0.4), 484 (1.6), 469 (1.3), 456 (23), 441 (14), 396 (100), and 381 (38). **20:** IR (KBr) 1730 and 1260 cm^{-1}; ^{1}H NMR δ=0.77 (3H, s; Me), 0.82—1.00 (6×Me), 2.04 (3H, s; OAc), 4.13—4.51 (1H, m; 3α-H), 4.42 (1H, d-like, *J*=6 Hz; 11α-H), 5.10 (0.7H, d, *J*=6 Hz; 18-H), and 5.48 (0.3H, d, *J*=5 Hz; 18-H of the other epimer); MS *m/z* (%) 484 (M^+ −H_2O; 28), 469 (8), 456 (42), 441 (14), 381 (12), 356 (11), 329 (100), 269 (46), and 207 (82).

The acetate (**19**; 156 mg) in EtOH (50 ml) containing KOH (600 mg) was refluxed for 3 h to afford a hemiacetal, 11,19-epoxy-24-methyl-29-norlanostane-3β, 19-diol (**21**; 161 mg), MS *m/z* (%) 442 (M^+ −H_2O; 100), 428 (22), 425 (11), 415 (38), 400 (35), 397 (51), 387 (15), and 382 (32). The hemiacetal (**21**; 161 mg) in acetone (30 ml) was treated with Jones reagent (2 ml) and the reaction product was chromatographed (SiO_2; 5% Et_2O in C_6H_6) to afford 24-methyl-3-oxo-29-norlanostan-19,11β-olide (**22**; 86.8 mg), mp 209—210 °C; IR (KBr) 1750 and 1730 cm^{-1}: ^{1}H NMR δ=0.73—0.94 (6×Me), 1.00 (3H, d, *J*=6 Hz), 3.30—3.77 (1H, m), 4.67—4.83 (1H, m; 11α-H); MS *m/z* (%) 456 (M^+; 100), 442 (21), 428 (5), 412 (15), and 397 (6).

3,3-Ethylenedioxy-24-methyl-29-norlanost-9(11)-en-19-al (28). The keto lactone (**22**; 19 mg) was converted into the ethylenedioxy derivative (**23**; 20 mg), mp 211—212 °C, IR (KBr) 1755 cm^{-1}; ^{1}H NMR δ=0.76—0.92 (7×Me), 2.60—3.05 (1H, m), 3.93 (4H, br s; -OCH_2CH_2O-), and 4.56—4.78 (1H, m; 11α-H); MS *m/z* (%) 500 (M^+; 16), 485 (2), 472 (8), 100 (100), and 99 (>100). The lactone (**23**; 56.1 mg) in THF (20 ml) was treated with LAH (47 mg) to afford 3,3-ethylenedioxy-24-methyl-29-norlanostane-11β,19-diol (**24**; 60.7 mg), mp 174—175 °C; ^{1}H NMR δ=0.75—0.90 (6×Me), 1.04 (3H, s; Me), 3.58 and 3.91 (2H, ABq, J=12 Hz; 19-H_2), 3.95 (4H, br s; $-OCH_2CH_2O-$), and 4.17 (1H, m; 11α-H); MS m/z (%) 504 (M^+; 0.5), 486 (4), 468 (15), 385 (68), 100 (100), and 99 (>100).

The diol (**24**; 60.7 mg) was acetylated to give 3,3-ethylenedioxy-11β-hydroxy-24-methyl-29-norlanostan-19-yl acetate (**25**; 43.3 mg), mp 105—107 °C; IR (KBr) 3470, 1735, and 1260 cm^{-1}; ^{1}H NMR δ=0.77—0.84 (4×Me), 0.88 (6H, s; 2×Me), 1.00 (3H, s; Me), 2.05 (3H, s; OAc), 3.94 (4H, br s; $-OCH_2CH_2O-$), 4.07—4.28 (1H, m; 11α-H), and 4.37 (2H, br s; 19-H_2); MS m/z (%) 546 (M^+; 10), 528 (4), 486 (32), 454 (15), 444 (48), 385 (100), 384 (>100), and 99 (>100).

The 11β-hydroxy acetate (**25**; 54.1 mg) in pyridine (10 ml) was treated with phosphoryl chloride (0.05 ml) under nitrogen. After the solution was heated at 80 °C for 3 h, the reaction product was chromatographed (SiO_2; 5% Et_2O in C_6H_6) to give 3,3-ethylenedioxy-24-methyl-29-norlanost-9(11)-en-19-yl acetate (**26**; 45.6 mg), mp 170—171 °C; IR (KBr) 1745 and 1240 cm^{-1}; ^{1}H NMR δ=0.60 (3H, s; Me), 0.77—0.89 (6×Me), 1.97 (3H, s; OAc), 3.95 (4H, br s; $-OCH_2CH_2O-$), 4.27 (2H, br s; 19-H_2), and 5.28—5.48 (1H, m; 11-H). Alkaline hydrolysis of **26** (4.8 mg) gave 3,3-ethylenedioxy-24-methyl-29-norlanost-9(11)-en-19-ol (**27**; 4.3 mg), mp 154—155 °C; ^{1}H NMR δ=0.66 (3H, s; Me), 0.75—0.90 (6×Me), 3.56 and 3.74 (2H, ABq, J=11 Hz; 19-H_2), 3.95 (4H, br s; $-OCH_2CH_2O-$), and 5.37—5.53 (1H, m; 11-H); MS m/z (%) 486 (M^+; 11), 471 (9), 455 (42), 441 (9), and 99 (100).

To the Collins reagent prepared from CrO_3 (35 mg) and pyridine (0.12 ml) in CH_2Cl_2 (6 ml) was added **27** (29.3 mg) in CH_2Cl_2. After the usual work-up, chromatographic separation (SiO_2; 5% Et_2O in C_6H_6) afforded 3,3-ethylenedioxy-24-methyl-29-norlanost-9(11)-en-19-al (**28**; 29.0 mg), mp 131—133 °C; IR (KBr) 1720 cm^{-1}; ^{1}H NMR δ=0.57 (3H, s; Me), 0.77—0.90 (6×Me), 3.93 (4H, br s; $-OCH_2CH_2O-$), 5.50—5.73 (1H, m; 11-H), and 9.11 (1H, br s; CHO); MS m/z (%) 484 (M^+; 3), 469 (2), 455 (85), 441 (12), 411 (4), 393 (12), and 99 (100).

Photo-decarbonylation of 28. Photo-decarbonylation of homoallylic aldehydes was carried out according to the procedure described in literatures.[12a,b] A solution of **28** (29.0 mg) in EtOH (50 ml) was photoirradiated for 30 min using a 400 W-high-pressure mercury lamp. Evaporation of the solvent followed by chromatography (SiO_2; C_6H_6) afforded 3,3-ethylenedioxy-24-methyl-19,29-dinorlanost-9(11)-ene (**29**; 25.9 mg), mp 153—154 °C; ^{1}H NMR δ=0.67 (3H, s; Me), 0.77—0.92 (6×Me), 3.93 (4H, br s; $-OCH_2CH_2O-$), and 5.13—5.33 (1H, m; 11-H); MS m/z (%) 456 (M^+; 100), 441 (26), 427 (7), 412 (9), 394 (49), 380 (18), 100 (92), and 99 (>100).

24-Methyl-19,29-dinorlanost-9(11)-en-3-one (1). A solution of **29** (24.3 mg) in acetone was treated with p-TsOH (30 mg) overnight and the reaction product was chromatographed (SiO_2; C_6H_6) to give 24-methyl-19,29-dinorlanost-9(11)-en-3-one (**1**; 16.3 mg), mp 126—128 °C; $[\alpha]_D^{25}$ +70° (c 0.2, $CHCl_3$); $[\theta]_{290}$ +5350 (peak); IR (KBr) 1715 cm^{-1}; ^{1}H NMR (Brucker AM-500, 500 MHz, $CDCl_3$) δ=0.70 (3H, br s), 0.755 (3H, s), 0.786 (3H, d, J=6.9 Hz), 0.790, 0.811 (total 3H, each d, J=6.8 Hz), 0.857, 0.860 (total 3H, each d, J=6.8 Hz), 0.884, 0.893 (total 3H, d, J=6.5 Hz), 1.03 (3H, d, J=6.5 Hz), 2.34—2.50 (3H, m), and 5.30 (1H, d, J=4.5 Hz); MS m/z (%) 412 (M^+; 73), 397 (100), 383 (14), 285 (29), 271 (8), 258 (12), 243 (20), 229 (23), 217 (33), and 149 (36); Found: m/z 412.3692. Calcd for $C_{29}H_{48}O$: M, 412.3703.

References

1) The previous papers: M. Naora, T. Murae, T. Tsuyuki, and T. Takahashi, *Bull. Chem. Soc. Jpn.*, **59**, 1767 (1986); M. Yamashita, M. Naora, T. Murae, T. Tsuyuki, and T. Takahashi, *ibid.*, **60**, 1383 (1987).

2) T. Murae, M. Namikawa, K. Hosokawa, H. Miyazaki, M. Ishibashi, T. Tsuyuki, and T. Takahashi, "21st Symposium on the Chemistry of Natural Products," Sapporo 1978, Symposium paper, p.568.

3) General procedures were the same as those described in Ref. 1. ^{1}H NMR spectra were measured using a JEOL FX90 (90 MHz, FT) in $CDCl_3$ solution unless otherwise stated. Gas chromatography was carried out on a Shimadzu GC-6A.

4) G. Ohta, *Chem. Pharm. Bull.*, **8**, 5 and 9 (1960).

5) The authors wish to express their thanks to Boso-yushi Co. Ltd. for generous gift of the powdery oryzanol mixture.

6) T. Itoh, T. Tamura, and T. Matsumoto, *Steroids*, **27**, 275 (1976); H. E. Audier, R. Berugelwans, and B. C. Das, *Tetrahedron Lett.*, **1966**, 4341.

7) All 24-methyl derivatives obtained by the preparation described below in this paper refer to 24-epimeric mixtures, respectively.

8) D. S. Irvine, J. A. Henry, and F. S. Spring, *J. Chem. Soc.*, **1955**, 1316.

9) K. F. Cohen, R. Kazluskas, and J. T. Pinhey, *J. Chem. Soc. D*, **1971**, 1419.

10) The carbon number at C-29 was given tentatively.

11) D. H. R. Barton, R. P. Budhiraja, and J. F. McGhie, *J. Chem. Soc. C*, **1969**, 336.

12) a) C. W. Shoppee, J. C. Coll, and R. E. Lack, *J. Chem. Soc. C*, **1968**, 1581. b) J. Iriarte, J. Hill, K. Schaffner, and O. Jeger, *Proc. Chem. Soc.*, **1963**, 114.