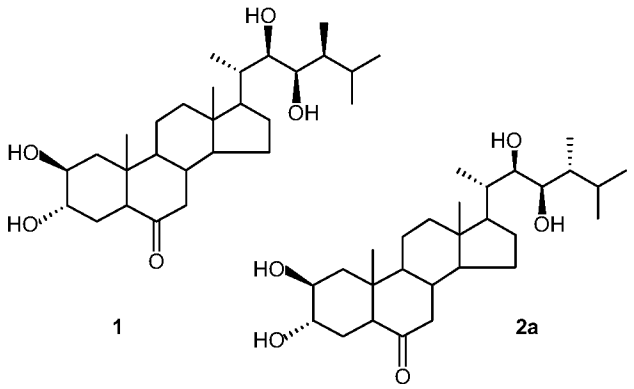
Synthesis of 2,24-Diepicastasterone and its 22*S*,23*S*-Isomer: Novel Brassinosteroids with a *trans*-2,3-Diol Function

Edward E. Levinson, Natal'ya A. Kuznetsova, Natal'ya Ya. Podkhalyuzina and Valery F. Traven*

D. I. Mendeleev Russian Chemico-Technological University, 125820 Moscow, Russian Federation. Fax: +7 095 200 4204

(22*R*,23*R*,24*R*)-2β,3α,22,23-Tetrahydroxy-5α-ergostane-6-one and its (22*S*,23*S*)-isomer, the novel brassinosteroids, containing a *trans*-2,3-diol function, have been synthesized from ergosterol in eight steps.

The brassinosteroids are a new class of highly active plant growth promotors and biochemical studies on them are currently of great interest. Nevertheless, brassinosteroids are scarcely accessible by isolation from natural material on account of their poor content in it. Therefore, numerous investigations[1] have been made on the directed syntheses of these compounds. The brassinosteroids, containing a *trans*-2,3-diol function, and in particular the naturally occurring 2-epicastasterone[2] **1** and its 24*R*-isomer 2,24-diepicastasterone **2a**, have not yet been synthesized.† In this report, we develop a synthetic pathway for this steroidal phytohormone **2a**.



(22*E*,24*R*)-3α,5-Cyclo-5α-ergost-22-en-6-one **3**, the key intermediate, was elaborated by common[5] transformations from ergosterol **4** in four steps: tosylation, solvolysis with rearrangement to 3α,5-cyclo-6β-ol, oxidation of that alcohol to 6-ketone and reduction of the 7(8) double bond of the conjugated ketone by Li in liquid ammonia, in 56% yield.[6] Having this intermediate one can introduce *cis*-22,23- and *trans*-2,3-diol functions separately. With this aim ketone **3** was hydroxylated with osmium tetraoxide (OsO_4) and *N*-methylmorpholine *N*-oxide (NMMO) in a tetrahydrofuran–*tert*-butanol–water (4:1:1) solution. (22*R*,23*R*,24*R*)-22,23-Dihydroxy-3α,5-cyclo-5α-ergostane-6-one **5a** and its (22*S*,23*S*)-isomer **5b** have been isolated by column chromatography in 33% and 43% yield, respectively (Scheme 1). The further transformation of the 3α,5-cyclopropane ring to a 2(3) double bond by heating diol **5a** in dimethylformamide with pyridinium hydrobromide at 140 °C during 2 h gave compound **6a** in 58% yield. Epoxidation of **6a** with trifluoroperacetic acid (CF_3CO_3H) in dichloromethane in the presence of Na_2CO_3 at 0 °C gave (22*R*,23*R*,24*R*)-22,23-dihydroxy-2α,3-epoxy-5α-ergostane-6-one **7a** in 97% yield. Acid catalysed hydrolysis of the oxirane ring in aqueous dioxane allowed us to retrieve diaxial *trans*-2β,3α-diol **2a** (2,24-diepicastasterone **2a**) in 81% yield. The total yield of compound **2a** from ergosterol **4** is 9%.

The transformation of (22*S*,23*S*,24*R*)-22,23-dihydroxy-3α,5-cyclo-5α-ergostane-6-one **5b** in analogous reactions gave us compounds **6b**, **7b** and **2b** in 61%, 96% and 83% (12% from ergosterol **4**) yields, respectively. The melting points of all compounds have been measured.‡ The structures of newly sythesized steroids have been confirmed by NMR, IR and mass spectroscopy and elemental analysis data.§

† The synthesis of the *trans*-2,3-diol function of cholestane[3] and stigmastane derivatives[4] has been described.

‡ Melting points/°C for: **5a** 190–191, **5b** 173–174, **6a** 155–156, **6b** 153–154 (lit.,[7] m.p. 148–149), **7a** 169–170, **7b** 171–172, **2a** 254–255, **2b** 189–190.

§ Spectroscopic data for: **5a** IR (KBr) ν/cm^{-1} 1670 (C=O), 3440 (–OH); *m/z* 430 (M^+); (Found: C, 78.17; H, 10.60. Calc. for $C_{28}H_{46}O_3$ C, 78.09; H, 10.76%); ^{1}H NMR ($CDCl_3$) δ 0.75 (s, 3H, 18-Me), 0.88 (d, *J* 7 Hz, 3H, 28-Me), 0.90 (d, *J* 7 Hz, 3H, 27-Me), 0.95 (d, 3H, *J* 7 Hz, 21-Me), 0.99 (d, *J* 7 Hz, 3H, 26-Me), 1.02 (s, 3H, 19-Me), 2.44 (m, 2H, C_7-2H), 3.43 (m, 1H, C_{23}-H), 3.72 (m, 1H, C_{22}-H).

5b IR (KBr) ν/cm^{-1} 1660 (C=O), 3380 (–OH); *m/z* 430 (M^+); (Found: C, 78.11; H, 10.65. Calc. for $C_{28}H_{46}O_3$ C, 78.09; H, 10.76%); ^{1}H NMR ($CDCl_3$) δ 0.74 (s, 3H, 18-Me), 0.87 (d, *J* 7 Hz, 3H, 27-Me), 0.90 (d, *J* 7 Hz, 3H, 28-Me), 0.96 (d, 3H, *J* 7 Hz, 26-Me), 1.00 (s, 3H, 19-Me), 1.02 (d, *J* 7 Hz, 3H, 21-Me), 2.41 (m, 2H, C_7-2H), 3.59 (m, 1H, C_{23}-H), 3.72 (m, 1H, C_{22}-H).

6a ^{1}H NMR ($CDCl_3$) δ 0.70 (s, 3H, 18-Me), 0.72 (s, 3H, 19-Me), 0.86 (d, 3H, *J* 7 Hz, 28-Me), 0.88 (d, *J* 7 Hz, 3H, 27-Me), 0.93 (d, *J* 7 Hz, 3H, 21-Me), 0,99 (d, *J* 7 Hz, 3H, 26-Me), 2.35 (m, 2H, $C_{5\alpha}$-H and $C_{7\beta}$-H), 3.42 (m, 1H, C_{23}-H), 3.71 (m, 1H, C_{22}-H), 5.53–5.75 (m, 2H, C_2-H and C_3-H).

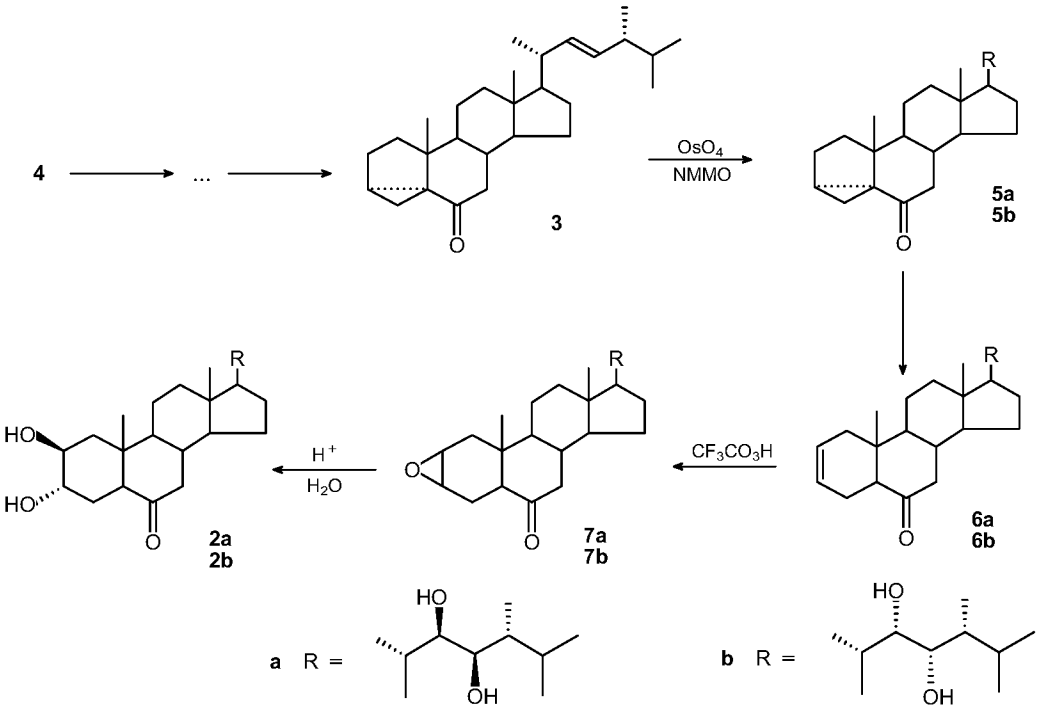
6b ^{1}H NMR ($CDCl_3$) δ 0.71 (s, 3H, 18-Me), 0.72 (s, 3H, 19-Me), 0.88 (d, 3H, *J* 7 Hz, 27-Me), 0.91 (d, *J* 7 Hz, 3H, 28-Me), 0.98 (d, *J* 7 Hz, 3H, 26-Me), 1.03 (d, *J* 7 Hz, 3H, 21-Me), 2.37 (m, 2H, $C_{5\alpha}$-H and $C_{7\beta}$-H), 3.61 (m, 1H, C_{23}-H), 3.73 (m, 1H, C_{22}-H), 5.53–5.75 (m, 2H, C_2-H and C_3-H). The other spectral data for compounds **6a**, **6b** were identical with those of the authentic samples.[7]

7a IR (KBr) ν/cm^{-1} 1720 (C=O), 3460 (–OH); *m/z* 446 (M^+), 428 (M^+-H_2O); (Found: C, 74.86; H, 10.54. Calc. for $C_{28}H_{46}O_4$ C, 75.29; H, 10.38%); ^{1}H NMR ($CDCl_3$) δ 0.66 (s, 3H, 18-Me), 0.71 (s, 3H, 19-Me), 0.84 (d, *J* 7 Hz, 3H, 28-Me), 0.86 (d, *J* 7 Hz, 3H, 27-Me), 0.91 (d, 3H, *J* 7 Hz, 21-Me), 0.97 (d, *J* 7 Hz, 3H, 26-Me), 3.12 (m, 1H, C_2-H), 3.27 (bs, 1H, C_3-H), 3.40 (m, 1H, C_{23}-H), 3.68 (m, 1H, C_{22}-H).

7b IR (KBr) ν/cm^{-1} 1700 (C=O), 3520 (–OH); *m/z* 446 (M^+), 428 (M^+-H_2O); (Found: C, 75.23; H, 10.50. Calc. for $C_{28}H_{46}O_4$ C, 75.29; H, 10.38%); ^{1}H NMR ($CDCl_3$) δ 0.69 (s, 3H, 18-Me), 0.71 (s, 3H, 19-Me), 0.88 (d, *J* 7 Hz, 3H, 27-Me), 0.90 (d, *J* 7 Hz, 3H, 28-Me), 0.96 (d, 3H, *J* 7 Hz, 26-Me), 1.02 (d, *J* 7 Hz, 3H, 21-Me), 3.11 (m, 1H, C_2-H), 3.26 (bs, 1H, C_3-H), 3.58 (m, 1H, C_{23}-H), 3.71 (m, 1H, C_{22}-H).

2a IR (KBr) ν/cm^{-1} 1700 (C=O), 3520 (–OH); *m/z* 464 (M^+), 446 (M^+-H_2O); (Found: C, 72.34; H, 10.67. Calc. for $C_{28}H_{48}O_5$ C, 72.37; H, 10.41%); ^{1}H NMR ($CDCl_3$) δ 0.67 (s, 3H, 18-Me), 0.85 (d, 3H, *J* 7 Hz, 28-Me), 0.86 (d, *J* 7 Hz, 3H, 27-Me), 0.92 (d, *J* 7 Hz, 3H, 21-Me), 0.96 (s, 3H, 19-Me), 0.98 (d, *J* 7 Hz, 3H, 26-Me), 2.31 (dd, J_1 12 Hz, J_2 5 Hz, 1H, $C_{7\beta}$-H), 2.73 (dd, J_1 13 Hz, J_2 3 Hz, 1H, C_5-H), 3.42 (m, 1H, C_{23}-H), 3.69 (m, 1H, C_{22}-H), 3.93 (m, 1H, C_2-H), 3.98 (m, 1H, C_3-H).

2b IR (KBr) ν/cm^{-1} 1710 (C=O), 3440 (–OH); *m/z* 464 (M^+), 446 (M^+-H_2O); (Found: C, 71.91; H, 10.55. Calc. for $C_{28}H_{48}O_5$ C, 72.37; H, 10.41%); ^{1}H NMR ($CDCl_3$) δ 0.70 (s, 3H, 18-Me), 0.89 (d, 3H, *J* 7 Hz, 27-Me), 0.92 (d, *J* 7 Hz, 3H, 28-Me), 0.97 (s, 3H, 19-Me), 0.98 (d, *J* 7 Hz, 3H, 26-Me), 1.03 (d, *J* 7 Hz, 3H, 21-Me), 2.32 (dd, J_1 12 Hz, J_2 5 Hz, 1H, $C_{7\beta}$-H), 2.73 (dd, J_1 13 Hz, J_2 3 Hz, 1H, C_5-H), 3.61 (m, 1H, C_{23}-H), 3.73 (m, 1H, C_{22}-H), 3.94 (m, 1H, C_2-H), 3.99 (m, 1H, C_3-H).



Scheme 1

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