The Reactivity of Hydroxyl Groups of Grayanotoxin-II

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On microbial oxidation with Pseudomonas pseudo-mallei, Grayanotoxin (G)-II (1) was transformed to 3-dehydro G-II (2) as the main product, and the structure was elucidated on the basis of the spectral data.1 In this report, we wish to describe the investigation of the reactivity of three secondary hydroxyl groups toward acetylation and alkaline hydrolysis, and chemical transformation of G-II (1) into 3-dehydro G-II (2), on the basis of preliminary evidence.

On mild acetylation (Py. 1 ml, Ac2O 1 ml, at 0°C, for 4 hr), G-II (1) (100 mg) gave 3,6-diacetate (3) (46 mg, 37.1 % yield) and 3-acetate (4), mp 83°C (40 mg, 35.7% yield) (preparative TLC: C6H6: Et2O: EtOH = 5:2:0.5). Similarly, ethylidene G-II (5) (78 mg), obtained as below, gave ethylidene G-II-3,6-diacetate (6) (27 mg, 28.3 % yield), ethylidene G-II-3-acetate (7) (33 mg, 38.1 % yield), mp 150°C, ethylidene G-II-6-acetate (8) (10 mg, 11.5% yield), mp 203°C, and 5 (5 mg, 6.4 % yield) on mild acetylation at 8°C for 12 hr. Ethylidene G-II (5) was obtained on heating G-II-3,6-diacetate (3) in isopropyl ether and acetal with catalytic amounts of p-toluenesulfonic acid and successive alkaline hydrolysis (58% yield). From these facts, the C3-hydroxyl group was the most reactive toward acetylation.

On the other hand, the C6-acetoxyl group was the most reactive toward alkaline hydrolysis. On ammonolysis, G-II tetraacetate (9) gave G-II triacetate (10) and ethylidene G-II-3,6-diacetate (6) gave ethylidene G-II-3-acetate (7) (84.5 % yield). The easier hydrolysis of the C5-acetoxyl group is explained by the stronger neighboring group effect of the Cg-hydroxyl group, as described by T. C. Bruice.3 On the basis of these findings, G-II (1) was transformed to 3-dehydro G-II (2) as below. G-II triacetate (10) (50 mg) was allowed to react with dihydropyrane (0.5 ml) to give tetrahydropyranyl ether (11) (56 mg, 96% yield), mp 156°C. Triacetyl tetrahydropyranyl ether (11) (45 mg) was partially hydrolyzed with 5 % K2CO3-70 % MeOH (15 ml) at 0-5°C for 18 hr, to give 14,16-diacetyl tetrahydropyranyl ether (12) (43 mg, quantitative yield), mp 178°C. The C6-hydroxyl group of 12 (25 mg) was oxidized with CrO3 (50 mg)-pyridine (1 ml) complex to give the 3-dehydro compound (33) (20 mg, 80% yield). The protective groups of the ketone (13) (19 mg) were hydrolyzed successively in 50% EtOH (4 ml) with p-toluene sulfonic acid (20 mg) at 30°C for 24 hr to give the diacetate (14) (17 mg, quantitative yield), mp 182°C, and in 5 % NaOH-EtOH at 30°C for 30 min to give 3-dehydro G-II (2) (8 mg, quantitative yield), mp 233°C. By IR spectroscopy, the microbial oxidation product of G-II (1) was identified with 3-dehydro G-II.5

Spectral data

G-II (1). NMR (pyr.-d5+1H2O) 3: 0.95, 1.41, 1.47 (3H, s, CH3), 3.85 (1H, q, J=6 & 3, C3-H), 4.29 (1H, s, C14-H), 4.45 (1H, t, J=6, C6-H), 5.09 (2H, s, C=CH2-H). IR vcm-1: 3520 (OH), 1725, 1250, 1630, 900 (C=CH2), 875 (THP). NMR (CDCl3) δ: 1.08 (6H, s, CH3 x 2), 1.65 (bs, CH3+THP), 1.98 (3H, s, OAc), 2.18 (6H, s, OAc x 2), 4.05 (3H, m, C6-C=H+THP), 4.08 (1H, m, THP), 5.15 (4H, m, C=CH2+CH=H+C14-H). MS m/e: 502 (M+-AcOH), 418 (M+-H2O), 352 (352-2OAc), 340 (352-AcOH), 298 (298-H2O), 270, 255, 252.

Tetrahydropyranyl ether of 10.

C23H42O6; 516. IR vcm-1: 3500 (OH), 1725 (C=O+OAc), 1250, 1630, 900 (C=CH2), 870 (THP). NMR (CDCl3+D2O) δ: 0.99, 1.09 (3H, s, CH3), 1.62 (bs, CH3+THP), 1.92, 2.01 (3H, s, OAc), 3.48 (1H, d, C3-H), 3.9 (6H, m, C6-C=H+THP), 4.61 (bs, THP+HOD), 4.99 (1H, m, C=CH2+C14-H+C14-H). MS m/e: 502 (M+), 434 (M+-H2O), 416 (434-2OAc), 316 (316-C2H4O), 298, 299 (298-AcOH), 282, 280 (282-H2O), 270, 255, 252.

3-Dehydro-6-THP ether diacetate (13). C23H36O7; 516. IR vcm-1: 3500 (OH), 1725 (C=O+OAc), 1250 (OAc), 1630, 900 (C=CH2), 870 (THP). NMR (CDCl3+D2O) δ: 0.99, 1.09 (3H, s, CH3), 1.62 (bs, CH3+THP), 1.93, 2.01 (3H, s, OAc), 3.85 (5H, m, C6-C=H+THP), 4.16 (1H, m, THP), 4.8 ~ 5.2 (5H, m, C=CH2+C14-H+C14-H). MS m/e: 518 (M+), 434 (M+-H2O), 374 (374-AcOH), 356 (356-C2H4O), 297, 296 (296-H2O), 268, 119.

3-Dehydro G-II diacetate (14). C24H34O7; 434. IR vcm-1: 3460 (OH), 1720 (C=O+OAc), 1250 (OAc), 1630, 900 (C=CH2). NMR (CDCl3+D2O) δ: 0.99, 1.19, 1.63 (3H, s, CH3), 1.94, 2.06 (OAc), 3.72 (1H, t, J=6, C3-H), 4.92 (1H, s, C14-H), 5.15, 5.19 (1H, s, C=CH2). MS m/e: 434 (M+), 374 (M+-AcOH),

3-Dehydro G-II⁺ (2). C₁₀₈H₃₀O₉; 350.

G-II diacetate (3). C₆₀H₅₂O₁₄; 436. IR ν̂max cm⁻¹⁻¹: 3440 (OH), 1710, 1250 (OAc), 1630, 895 (C=CH₂). NMR (CDCl₃+D₂O) δ: 1.03, 1.08, 1.35 (3H, s, CH₃), 2.07, 2.12 (3H, s, OAc), 4.42 (1H, s, C₆-H), 4.60 (1H, q, J= 7 & 5.5, C₆-H), 4.95, 5.05 (1H, s, C=CH₂). MS m/e: 376 (M⁺-AcOH), 360, 358 (376-H₂O), 316 (336-C₂H₂O), 300, 298 (316-H₂O), 280 (298-H₂O), 240, 119.

3-Acetate (4). C₁₀₈H₃₆O₁₄; 394. IR ν̂max cm⁻¹⁻¹: 3400 (OH), 1700, 1255 (OAc), 1630, 890 (C=CH₂). NMR (CDCl₃+D₂O) δ: 0.94, 1.20, 1.35 (3H, s, CH₃), 2.13 (3H, s, OAc), 3.16 (1H, q, J= 7 & 3, C₃-H), 4.40 (1H, s, C₆-H), 4.75 (1H, q, J= 9 & 2, C₆-H), 4.95, 5.12 (1H, s, C=CH₂). MS m/e: 376 (M⁺-H₂O), 358 (376-H₂O), 318, 316 (336-C₂H₂O), 298 (316-H₂O), 280 (298-H₂O), 258, 240 (258-H₂O), 197.

Ethylidene G-II diacetate (6). C₁₀₈H₃₀O₉; 462. IR ν̂max cm⁻¹⁻¹: 3500 (OH), 1720, 1240 (OAc), 1625, 905 (C=CH₂). NMR (CDCl₃+D₂O) δ: 0.94, 1.20, 1.35 (3H, s, CH₃), 1.19 (3H, d, J= 7 & 3, CH₂), 2.05 (6H, s, OAc), 4.44 (1H, s, C₆-H), 4.70-5.10 (4H, m, CH₂), 4.80 (1H, s, C=CH₂). MS m/e: 402 (M⁺-AcOH), 359, 358 (402-C₂H₄O), 342 (402-AcOH), 299, 298 (358-AcOH), 280 (298-H₂O), 258, 240 (258-H₂O), 197.

Ethylidene G-II (5). C₁₀₈H₃₄O₁₄; 378. IR ν̂max cm⁻¹⁻¹: 3300 (OH), 1625, 900 (C=CH₂). NMR (CDCl₃+D₂O) δ: 1.07, 1.26, 1.31 (3H, s, CH₃), 1.17 (3H, d, J= 7 & 3, CH₃), 4.45 (1H, s, C₆-H), 4.70-5.10 (4H, m, C₆-H), 4.95, 5.12 (1H, s, C=CH₂). MS m/e: 316 (M⁺-C₂H₂O-H₂O), 298 (316-H₂O), 189, 175, 149, 133, 119, 105, 93, 81, 41.

Ethylidene G-II-3-acetate (7). C₁₀₈H₃₆O₁₄; 420. IR ν̂max cm⁻¹⁻¹: 3490 (OH), 1720, 1250 (OAc), 1630, 900 (C=CH₂). NMR (CDCl₃+D₂O) δ: 1.11, 1.14, 1.30 (3H, s, CH₃), 2.03 (3H, s, OAc), 4.06 (1H, m, C₆-H), 4.40 (1H, d, J= 7, C₆-H), 4.85 (1H, q, J= 7.6 & 5.6, C₆-H), 4.90, 5.07 (1H, s, C=CH₂).

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REFERENCES