Pergamon

Tetrahedron Letters 42 (2001) 77–79

TETRAHEDRON LETTERS

The first synthetic route to furostan saponins

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Received 15 August 2000; revised 9 October 2000; accepted 26 October 2000

Abstract—26-*O*-β-D-Glucopyranosyl-22-methoxy-25(*R*)-furost-5-en-3β-ol 3-*O*-β-D-glucopyranoside is synthesized from diosgenin in 11 steps and 26% overall yield. The present synthetic route represents the first one to furostan saponins.

Steroidal saponins comprise a diverse class of plant glycosides that possess a broad range of interesting biological activities.[1] According to the structure of sapogenins, steroidal saponins can be divided into three classes, i.e. cholestan saponins, spirostan saponins, and furostan saponins[1] (Fig. 1). Furostan saponins have a β-D-glucopyranose substituent at the 26-OH and another sugar chain attached, usually, at the 3-OH with few exceptions.[2] The 22-*O*-methyl group is thought to be introduced during extraction with methanol and can be converted to a 22-OH in refluxing aqueous acetone.[3] The 26-*O*-glucopyranosyl residue is readily cleaved by enzymes present in plants, and under the acidic conditions of isolation, this leads to the closure of the F ring. Therefore, furostan saponins are regarded as precursors of the corresponding spirostan saponins in plants.[2] This is also the reason why recognition of their existence was much later than that of cholestan and spirostan saponins. Marker et al. postulated the existence of furostan saponins in 1947,[4] and Schreiber and Ripperger isolated the first furostan saponin, jurubune, 20 years later.[5] We have recently synthesized cholestan saponin OSW-1[6] and a number of spirostan saponins.[7] Herein we report the synthesis of a simple furostan saponin **1**, namely 26-*O*-β-D-glucopyranosyl-22-methoxy-25(*R*)-furost-5-en-3β-ol 3-*O*-β-D-glucopyranoside, which has been isolated from the rhizomes of *Costus spicatus*.[8]

Employing a similar procedure to that developed by Bovicelli et al.,[9] the 3-*O*-*tert*-butyldiphenylsilyl ether of diosgenin (**2**) was converted into the 16,22-dione **6** in four steps and in 69% overall yield, i.e. protection of the C_5,C_6 double bond with bromide gave dibromide **3** (*trans* diastereoisomers); selective oxyfunctionalization of the ethereal C_{16} with dimethyldioxirane generated in situ[10] led to hemiketal **4**; acetolytic opening of the ketal afforded dione **5**; and removal of the bromide protection using zinc and ammonium chloride in ethanol provided **6** (Scheme 1). Compounds **3**–**5** have not been purified and were directly subjected to the next reaction after the usual workup. Cleavage of the 26-*O*-acetyl group using K_2CO_3/THF/MeOH generated spiroketal **7** and dione **8** (total 94% yield). These two compounds

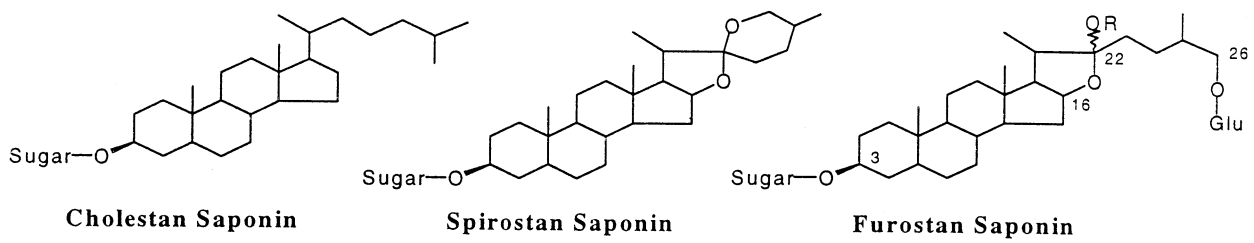

Figure 1. Typical structures of three classes of steroidal saponins.

Keywords: furostan saponin; synthesis; glycosidation.

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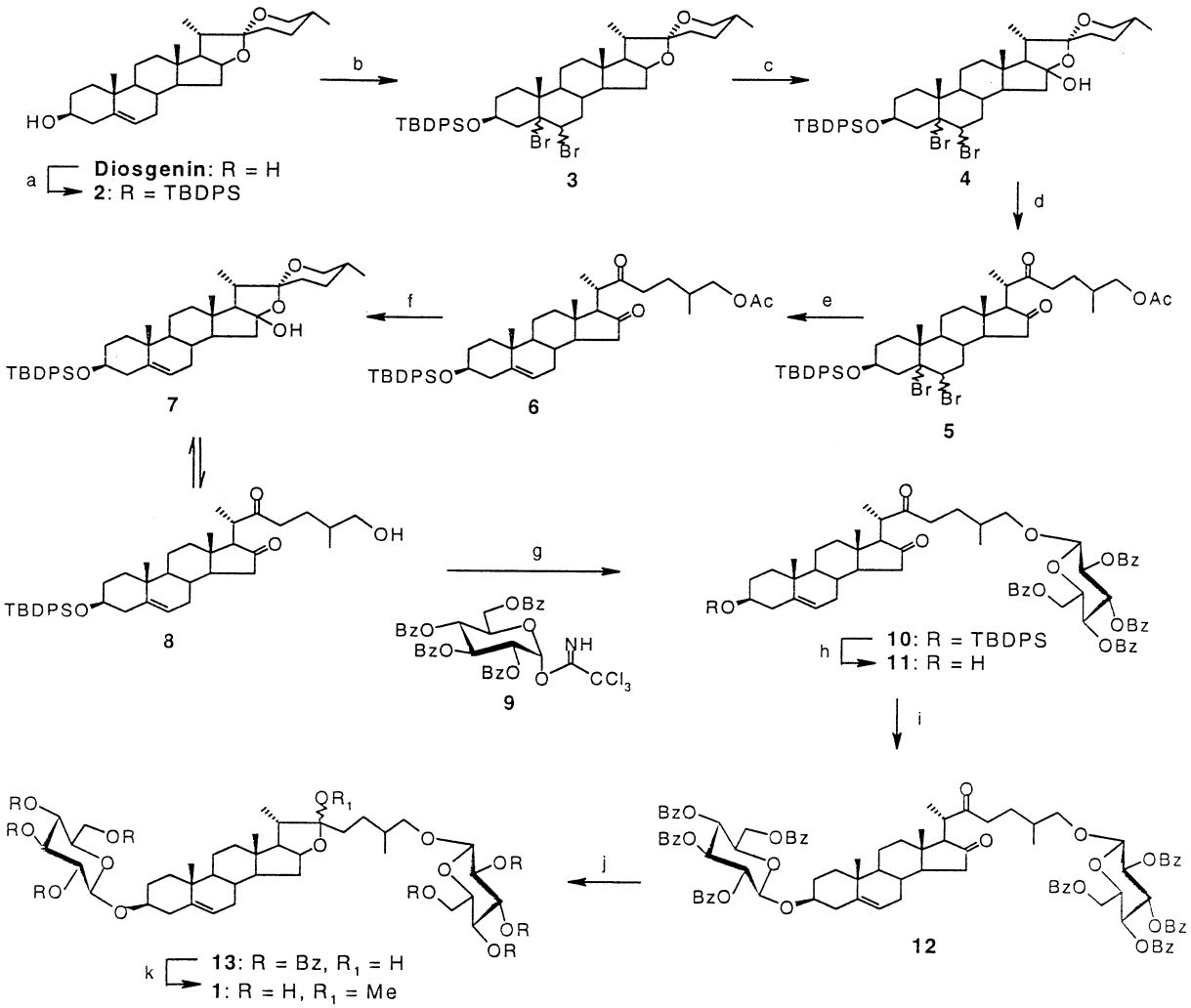
0040-4039/01/$ - see front matter
PII: S0040-4039(00)01889-X

were found to be interconvertible during isolation and analysis. Consequently, the mixture of **7** and **8** was treated directly with 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate (**9**) in the presence of a catalytic amount of TMSOTf (0.05 equiv.) in methylene chloride, providing the 26-*O*-glycosylated product **10** in good yield (86%), with a trace amount of the F-ring closure product being detected. These glycosylation conditions have been optimized for coupling with sapogenins.[11] Compound **10** was then treated with tetrabutylammonium fluoride to remove the 3-OTBDPS ether to give **11** (86%), which was subjected to the second glycosylation under similar conditions to those employed above, giving the coupled product **12** in excellent yield (96%). Selective reduction of the 16-ketone of the cholestan-16,22-dione with $NaBH_4$ in *i*-PrOH, followed by concurrent intramolecular hemiketal formation, to provide the corresponding furostan has been well documented.[12] Subjecting dione **12** to similar conditions provided hemiketal **13** in moderate yield (64%). Removal of the benzoyl protecting groups using NaOMe in $MeOH/CH_2Cl_2$ afforded the target furostan saponin **1** in 90% yield. The 22-OH was meanwhile converted into the 22-OMe. All the isolated compounds gave satisfactory analytical data,[13] and those of compound **1** were virtually identical to those reported for the natural product.[8]

In conclusion, the furostan saponin **1** was synthesized from a spirostan sapogenin (diosgenin) in 11 steps and 26% overall yield. The present synthetic route represents the first one to furostan saponins. The stepwise manner of introduction of the C_{26} and C_3 sugar moieties demonstrates the generality of the present approach to the synthesis of furostan saponins.

Acknowledgements

This work is supported by the Ministry of Science and Technology of China (G1998051104) and the National Natural Science Foundation of China (29925203 and 29802008).



Scheme 1. Reagents and conditions: (a) TBDPSCl, imidazole, DMF, rt, 99%; (b) Br_2, $CHCl_3$, 0°C→rt; (c) $KHSO_5$, $NaHCO_3$, acetone/CH_2Cl_2, rt; (d) Ac_2O/HOAc (v:v, 1:1), 35°C; (e) Zn, NH_4Cl, EtOH, reflux, 69% (for four steps); (f) K_2CO_3, THF/MeOH (1:1), rt, 94%; (g) TMSOTf (0.05 equiv.), CH_2Cl_2, −78°C→rt, 86%; (h) TBAF, THF, rt, 86%; (i) TMSOTf (0.1 equiv.), CH_2Cl_2, rt, 96%; (j) $NaBH_4$, *i*-PrOH, rt, 64%; (k) MeONa, $MeOH/CH_2Cl_2$ (1:1), rt, 90%.

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13. Selected analytical data: **6**: $[\alpha]_D^{30} = -140.2°$ (*c* 1.24, $CHCl_3$); ESI-MS: 733 (M+Na), 711 (M+1); ^{1}H NMR ($CDCl_3$, 300 MHz): 7.50–7.30 (m, 10 H), 5.10 (brs, 1 H, H-6), 3.93 (dd, 2 H, $J = 6.0$, 1.9, H-26), 3.53 (m, 1 H, H-3), 2.83–2.48 (m, 4 H), 2.04 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz): 217.9 (C = O), 213.2 (C = O), 171.2, 141.5 (C-5), 120.3 (C-6), 73.1 (C-3), 69.0 (C-26). **10**: $[\alpha]_D^{30} = -64.4°$ (*c* 1.24, $CHCl_3$); ESI-MS: 1270 (M+Na); ^{1}H NMR ($CDCl_3$, 300 MHz): 8.00–7.25 (m, 30 H), 5.87 (t, 1 H, $J = 9.6$), 5.61 (t, 1 H, $J = 9.6$), 5.51 (dd, 1 H, $J = 9.7$, 8.0), 5.09 (brs, 1 H, H-6), 4.86 (d, 1 H, $J = 7.9$, 26-*O*-Glc-H-1), 4.61 (dd, 1 H, $J = 12.1$, 3.2), 4.47 (dd, 1 H, $J = 12.1$, 5.2), 4.16 (m, 1 H), 3.69 (dd, 1 H, $J = 9.8$, 6.9), 3.53 (m, 1 H), 3.49 (dd, 1 H, $J = 9.8$, 5.2); ^{13}C NMR ($CDCl_3$, 75 MHz): 218.1, 213.5, 166.1, 165.8, 165.2, 163.6, 141.5, 120.3, 101.0 (26-*O*-Glc-C-1), 74.7, 73.1, 72.0, 70.1, 66.2, 63.3, 60.4. **12**: $[\alpha]_D^{30} = -35.8°$ (*c* 0.75, $CHCl_3$); ESI-MS: 1610 (M+Na), 1587 (M); ^{1}H NMR ($CDCl_3$, 300 MHz): 8.00–7.20 (m, 40 H), 5.90 (dt, 2 H, $J = 9.6$), 5.64 (dt, 2 H, $J = 9.6$), 5.50 (dd, 2 H, $J = 9.5$, 8.0), 5.20 (brs, 1 H, H-6), 4.94 (d, 1 H, $J = 8.0$, 3-*O*-Glc-H-1), 4.88 (d, 1 H, $J = 8.0$, 26-*O*-Glc-H-1), 4.46–4.66 (m, 4 H), 4.10–4.21 (m, 2 H), 3.71 (dd, 1 H, $J = 9.8$, 6.6), 3.53 (m, 1 H), 3.51 (dd, 1 H, $J = 9.8$, 5.2); ^{13}C NMR ($CDCl_3$, 75 MHz): 101.0 (26-*O*-Glc-C-1), 100.2 (3-*O*-Glc-C-1). **13**: $[\alpha]_D^{30} = +9.7°$ (*c* 0.80, $CHCl_3$); ESI-MS: 1572 (M+1−H_2O); ^{1}H NMR ($CDCl_3$, 300 MHz): 8.10–7.20 (m, 40 H), 5.91, 5.90 (t×2, 1 H each, $J = 9.6$), 5.64 (dt, 2 H, $J = 9.6$), 5.50 (dd, 2 H, $J = 9.4$, 7.7), 5.21 (brs, 1 H, H-6), 4.94 (d, 1 H, $J = 8.0$, 3-*O*-Glc-H-1), 4.81 (d, 1 H, $J = 8.0$, 26-*O*-Glc-H-1), 4.46–4.70 (m, 4 H), 4.20–4.32 (m, 2 H), 4.15 (m, 2 H), 3.83 (m, 1 H), 3.53 (m, 1 H), 3.31 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): 140.3 (C-5), 121.6 (C-6), 103.5 (C-22), 101.2 (26-*O*-Glc-C-1), 100.1 (3-*O*-Glc-C-1), 80.2 (C-16). **1**: $[\alpha]_D^{30} = -43.2°$ (*c* 0.60, CH_3OH); ESI-MS: 793 (M+K); ^{1}H NMR (pyridine-d_5, 300 MHz): 5.10 (brs, 1 H, H-6), 4.84 (d, 1 H, $J = 7.1$, 3-*O*-Glc-H-1), 4.63 (d, 1 H, $J = 7.7$, 26-*O*-Glc-H-1), 3.25 (s, 3 H, OMe), 1.18 (d, 3 H, $J = 6.6$), 1.01 (3 H, d, $J = 5.6$), 0.90 (s, 3 H, Me-19), 0.81 (s, 3 H, Me-18); ^{13}C NMR (pyridine-d_5, 75 MHz): 140.9, 121.7, 112.6, 104.9, 102.6, 81.3, 78.6 (2×C), 78.5 (2×C), 78.1, 75.3 (2×C), 75.2, 71.7 (2×C), 64.1, 62.8 (2×C), 56.3, 50.3, 47.2 (OMe), 40.8, 40.5, 39.8, 39.3, 37.4, 37.0, 34.2, 32.6, 32.2, 31.6, 30.8, 30.2, 28.2, 21.0, 19.1, 17.2, 16.5, 16.3.