ORGANIC LETTERS

2006
Vol. 8, No. 13
2679−2682

Facile Conversion of Spirostan Saponin into Furostan Saponin: Synthesis of Methyl Protodioscin and Its 26-Thio-analogue

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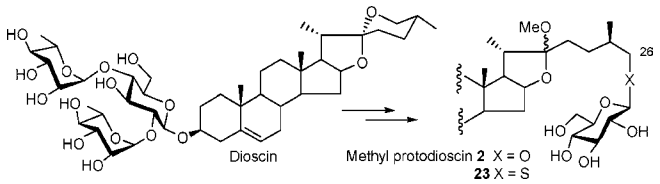
Received March 11, 2006

ABSTRACT



A facile approach for the conversion of a spirostan saponin into its furostan counterpart, as illustrated by the transformation of dioscin to methyl protodioscin (and its 26-thio-analogue), has been developed.

Steroidal saponins constitute an extremely diverse and abundant family of plant metabolites, with a broad range of biological activities. They are usually divided into three classes, i.e., spirostan saponins, furostan saponins, and cholestan saponins, and are biosynthetically interrelated.[1] Dioscin (**1**) and methyl protodioscin (**2**), which bear an identical *β*-chacotriosyl (α-L-rhamnopyranosyl-(1→2)-[α-L-rhamnopyranosyl-(1→4)]-*β*-D-glucopyranosyl) moiety at the 3-OH of the steroidal aglycones, illustrate the classification of spirostan and furostan saponins (Figure 1). Dioscin is one of the most common steroidal saponins that occur in plants. It was first characterized from the rhizome of *Dioscorea tokoro* Makino in 1904[2] and has since been isolated from about 20 genera. Methyl protodioscin (**2**) was first identified from the fresh rhizomes *Dioscorea gracillima* MiQ. in 1974[3] and was later found often co-occurring with dioscin.[4] Its methoxy group in the 22-ketal function could be either artificial[3] or genuine.[5] Among the wide range of bioactivities

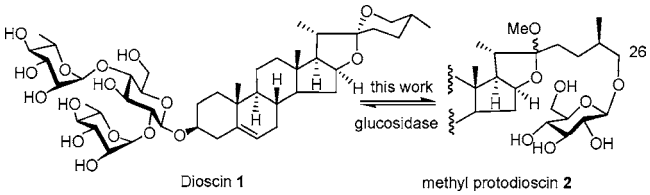


Figure 1. Conversion between dioscin and methyl protodioscin.

that spirostan saponins display, hemolysis and cytotoxicity are the most common ones observed. Recent studies have shown that dioscin can induce apoptosis within tumor cells and that it might be a potentially useful anticancer agent.[6] Methyl protodioscin shows no hemolytic effects but displays a level of antitumor potency similar to that of dioscin.[7] Interestingly, their profiles against the NCI 60 cell line panel are completely different, implying different mechanisms of antitumor action.[7b]

Because of the microheterogeneous nature of the plant saponins, the isolation of homogeneous saponins is often

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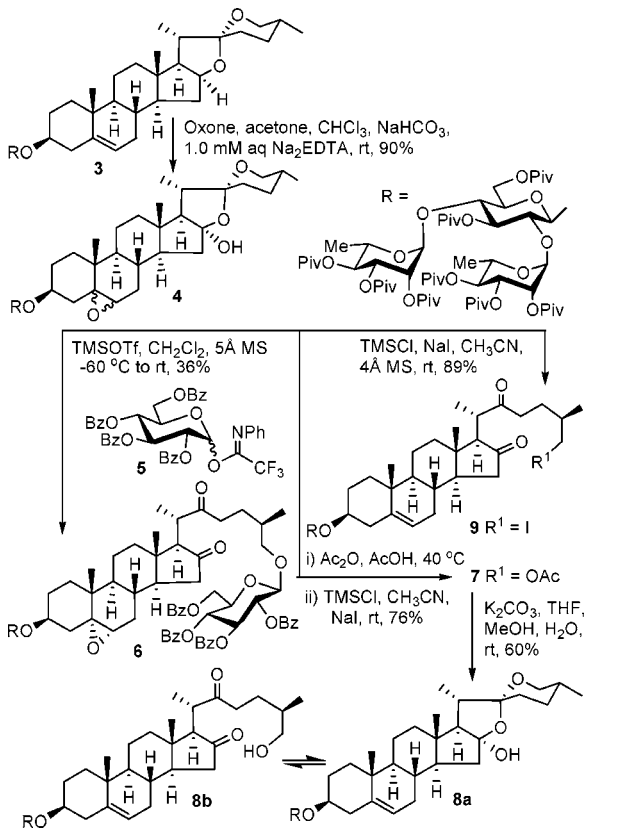
10.1021/ol060594w CCC: $33.50
Published on Web 05/27/2006

difficult. Fortunately, chemical synthesis has shown promise as a practical alternative to access the spirostan saponins.[8,9] In contrast, the synthesis of furostan saponins is still a difficult task. A previous route for their synthesis started from the spirostan diosgenin and oxidatively opened the E and F rings and subsequently introduced the sugar moieties onto the 26-OH and the 3-OH of the aglycone.[10] Thus, for the synthesis of methyl protodioscin, the stereocontrolled installation of a chacotriosyl moiety (which lacks a neighboring participatory group) onto the steroidal 3-OH was required.[10c] To avoid this problem, we planned to access the furostan saponins directly from their spirostan counterparts (Figure 1) and herein report our results.

We first attempted to oxidatively ring open the spirostan E and F rings on dioscin pivalate **3** using in situ generated DMDO (Scheme 1). The reaction (in acetone−CH_2Cl_2−H_2O, 1:4:5) proceeded slowly but cleanly,[10] affording the desired 5,6-epoxy-16α-ol hemiketal **4** in 80% yield over 96 h. The epoxidation on the 5,6-double bond was poorly stereoselective, producing the 5α,6α-epoxide as the major component of a 3:1 mixture of epoxide diastereomers. As anticipated, the glycosidic linkages remained intact. Significantly, when compound **3** was exposed to a solution of $NaHCO_3$ in acetone−$CHCl_3$−1.0 mM aqueous Na_2EDTA (1:1:1) followed by dropwise addition of Oxone in 1.0 mM aqueous Na_2EDTA, the reaction was complete within 10 h (90%). This phenomenon might be ascribed to the increased solubility of DMDO in $CHCl_3$[11] and the avoidance of peroxide decomposition in the presence of Na_2EDTA.[12]

Scheme 1. Oxidative Opening of the E,F Rings of Dioscin Pivalate **3**



Because we considered that the 16-hemiketal **4** might undergo ring-chain tautomerization to give a 16,22-dione-26-ol (as in **8a** ↔ **8b**), we directly subjected **4** to glycosidation (Scheme 1). Unfortunately, the treatment of **4** with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl trifluoroacetimidate **5**[9b] under a variety of conditions furnished the desired glycoside **6** in no more than 36% yield (0.25 equiv of TMSOTf in CH_2Cl_2 at −60 °C to room temperature). Replacement of the promoter TMSOTf with AgOTf, TfOH, or $Zn(OTf)_2$ provided no better results. It was thought that the 5,6-epoxy group on **4** might be playing a detrimental role in the reaction, as the steroidal 5β,6β-epoxide is known to undergo rearrangement to give the corresponding 5α-cholestan-6-one under acidic conditions.[13] In this regard, starting with the mixture of 5β,6β- and 5α,6α-epoxide **4**, we only obtained the 5α,6α-product **6**.

We next decided to remove the 5,6-epoxide (on **4**) prior to glycosylation. TMSI, which can be prepared conveniently in situ from TMSCl and NaI in CH_3CN, is an effective reagent for conversion of the steroidal 5,6-epoxide into a double bond.[14] Thus, treatment of the 5,6-epoxide **4** with Ac_2O in AcOH (to open the hemiketal) followed with TMSI afforded the desired $\Delta^{5,6}$-26-acetate **7** in 76% yield. Removal of the 26-*O*-acetyl group in **7** with K_2CO_3 was found not to be as clean and complete as expected, providing **8a** and **8b** in 60% yield in a ratio of 2:1. Unexpectedly, treatment of epoxyhemiketal **4** directly with TMSI afforded $\Delta^{5,6}$-26-iodide **9** (72%), where iodination took place concurrently at C-26 (Scheme 1).

The steroidal 26-iodides (e.g., **9**) are potentially valuable intermediates for further transformations into various ste-

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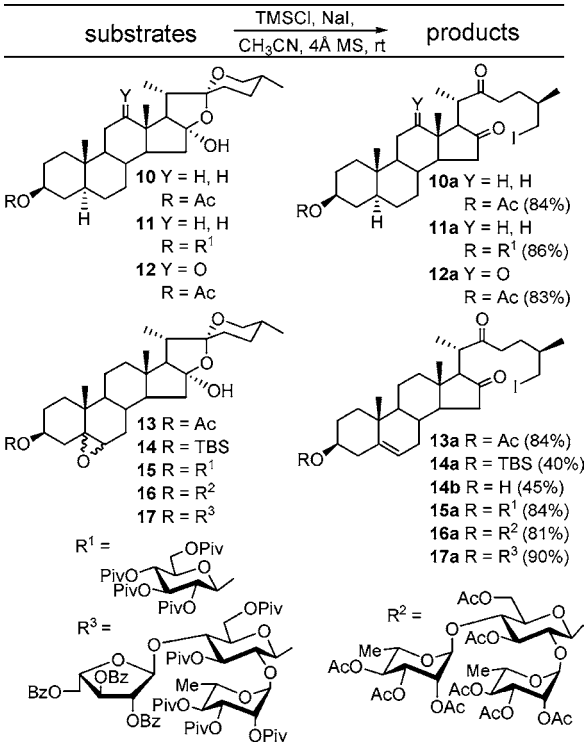
roidal derivatives.[15] Thus, we further optimized the reaction conditions and examined briefly the scope of this novel transformation. We found that the reagent combination of TMSCl (5 equiv) and NaI (20 equiv) with 4 Å molecular sieves as an additive could convert epoxyhemiketal **4** into iodide **9** in 89% yield. Related reagents such as AlI_3,[16] Ph_3P/I_2,[17] and $ZrCl_4/NaI$[18] did not effect this transformation. Under the present conditions, steroidal 16-hemiketals **10**−**17** were converted readily into the corresponding 26-iodides **10a**−**17a** in excellent yields (81∼90%) (Table 1). The glycosidic linkages and the global acyl groups (acetyl, benzoyl, and pivaloyl groups) remained untouched in these reactions. The 3-*O*-TBS group in **14** was labile, however, and it was partially cleaved to give a mixture of **14a** and **14b**.[15a] For the hecogenin derivative **12**, no intramolecular aldol condensation (between the 12-carbonyl group and 23-methylene) was detected.[19] The ^1H and ^{13}C NMR spectra of the 26-iodides (in $CDCl_3$) gave rise to a characteristic doublet at around δ 3.25 ppm (J = 4.8 Hz) for the 26-methylene protons and an upfield signal at around δ 17.6 ppm for the C-26. Single-crystal diffraction analysis of iodides **10a**, **12a**, and **13a** confirmed the structural assignments.[20]

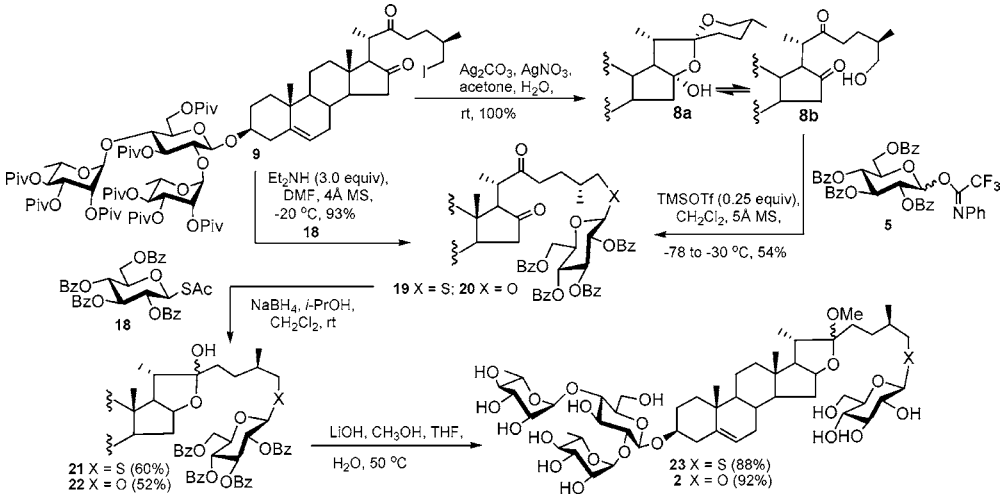
Continuation of the present synthesis of methyl protodioscin (**2**) called for introduction of a β-D-glucopyranosyloxy residue onto the C-26 of iodide **9**; this was realized via an anomeric O-alkylation reaction.[21] However, treatment of the 26-iodide **9** with 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranose[22] under a variety of conditions (e.g., NaH or Ag_2O)[23] failed to provide the desired product. On the other hand, displacement of the 26-iodide in **9** with a more nucleophilic glucose 1-thiolate, derived in situ from 2,3,4,6-tetra-*O*-benzoyl-1-thio-acetyl-β-D-glucopyranose **18** in the presence of Et_2NH in DMF at −20 °C,[24] succeeded, affording 26-thio-glucopyranoside **19** in an excellent yield (93%) (Scheme 2). Hydrolysis of the 26-iodide in **9** was efficient under the action of Ag_2CO_3 and a catalytic amount of $AgNO_3$,[25] furnishing rapidly and quantitatively 26-ol **8b** which was in equilibrium with the more favored hemiketal **8a** (1:4). Coupling of the resulting mixture of **8a** and **8b** with glucosyl trifluoroacetimidate **5** (0.25 equiv of TMSOTf, CH_2Cl_2, −78 to −30 °C) produced the desired glycoside **20** in 54% yield. Selective reduction of the 16-carbonyl group in **19** and **20** with $NaBH_4$ provided the hemiketal **21** and **22** in 60% and 52% yield, respectively.[10,15a] Finally, removal of the pivaloyl and benzoyl groups of **22** and **21** with LiOH in CH_3OH−THF−H_2O (8:8:1) at 50 °C furnished methyl protodioscin **2** and its 26-thio-analogue **23** in excellent yields.

Table 1. Synthesis of 26-Iodo-cholestan Derivatives



In summary, conversion of the readily available dioscin pivalate **3** into methyl protodioscin **2** has been achieved in six steps and 21% overall yield. This illustrates an effective

Scheme 2. Synthesis of Methyl Protodioscin (**2**) and Its 26-Thio-analogue (**23**)



approach for the conversion of spirostan saponins into furostan saponins; the latter is otherwise a biosynthetic precursor of the former.[26] The 26-thio-analogue of methyl protodioscin **23** was also prepared efficiently (five steps, 39% overall yield). Replacement of the 26-*O*-glycosidic linkage with the 26-*S* linkage (in **23**) should retain the native geometry of the furostan saponins but prevent its enzymatic cleavage of this sugar moiety. Thus, the 26-thio-analogue **23** should prove a valuable probe for the study of the biological processes involving the native furostan compound.[27] What should also be highlighted in the present work is the ready preparation of the steroidal 26-iodides (**9** and **10a**−**17a**), which are useful intermediates for further transformations.

Acknowledgment. This work is supported by the National Natural Science Foundation of China (20321202) and the Chinese Academy of Sciences (KGCX2-SW-213 and KGCX2-SW-209).

Supporting Information Available: Full experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060594W

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(20) Full crystallographic details of compounds **10a**, **12a**, and **13a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 600782, 600783, and 600784, respectively). Copies of these data may be obtained free of charge from the director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. (fax, +44-1223-336033; e-mail, deposit@ccdc.cam.ac.uk; or www, http://www.ccdc.cam.ac.uk).
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