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Convergent synthesis and cytotoxic activities of 26-thio- and selenodioscin

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ABSTRACT

Convergent block syntheses of 26-thio- and selenodioscin have been achieved by developing the highly stereoselective 1,2-*trans* glycosylations of chacotriosyl imidate without recourse to neighboring group assistance. Both thiodioscin and selenodioscin possess cytotoxic activities similar to dioscin, a natural spirostanol glycoside.

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1. Introduction

Spirostanol glycosides, consisting of an aglycone of spirostan type with a sugar chain generally attached at position C-3, are abundant naturally occurring secondary metabolites [1]. Dioscin (Fig. 1), a representive of spirostan saponin, is composed by diosgenin and β-chacotriosyl moiety (α-L-rhamnopyranosyl-(1 → 2)-[α-L-rhamno-pyranosyl-(1 → 4)]-β-D-glucopyranoside), has been isolated from various plants [2–5]. It displays a broad spectrum of bioactivities such as antitumor [6–8], antiviral [9], antifungal [3,10], anti-inflammatory [11–13], and immunostimulant activities [14]. Additionally, dioscin is an active component of DI'AO XINXUEKANG, a clinic medicine for treatment of cardiovascular disease in China [15,16]. These properties make dioscin as an interesting lead for drug development. Various approaches to dioscin have been developed [17–23], and intensive efforts have been devoted to research on its structure–activity relationship including: (i) replacement of diosgenin with cholesterol [21,23], glycyrrhetic acid [22], hecogenin [24], or oleanic acid [25]; (ii) substitution of chacotriosyl group with other oligosaccharide moieties, or its decoration with functional groups at 4‴-OH and 6′-OH [26,27]; (iii) a change of original β-ether likage by α-glycosidic bond [21,23], or a triazole group [28]. Taken together, these results indicate that bioactivities of dioscin depend on both aglycone and sugar moiety. Recently, "key polar hydroxy groups" of dioscin against tumor cell lines have been determined based on syntheses of its eight monomethylated analogues [29]. In medicinal chemistry both divalent sulfur and selenium as bioisosteres [30] of oxygen are usually utilized in lead modifications. Organosulfides [31,32] and organoselenides [33] display a wide arrange of interesting bioactivities such as antioxidation, antivirus and antitumor. Consequently, we would like to substitute sulfur and selenium for oxygen at position 26 in dioscin skeleton to make 26-thio- and selenodioscin **1** and **2** (Fig. 1), and to evaluate their cytotoxicities. So far little information is available regarding the influence of spiroketal functionality of dioscin on its antitumor activities. Herein, we report our findings on 26-thio- and selenodioscin **1** and **2** (Fig. 1).

2. Experimental

2.1. General

Reagents were purchased and used without further purification. Dichloromethane (CH_2Cl_2), *N*, *N*–dimethylformamide (DMF) and pyridine were dried over calcium hydride. Methanol (MeOH) was distilled over magnesium. All reactions were carried out under argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Reactions were monitored with analytical TLC on silica gel 60-F254 precoated glass plates and visualized under UV (254 nm) and/or by staining with 8% H_2SO_4 in methanol. Column chromatography was carried out on 300–400 mesh of silica Gel 60. ^1H and ^{13}C NMR spectra were

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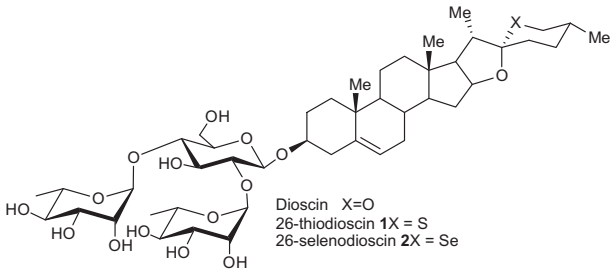

Fig. 1. Structures of dioscin, 26-thio- and selenodioscin **1** and **2**.

recorded on Jeol JNM-ECP 600 (600 MHz), and chemical shifts were reported in parts per million (δ) downfield from tetramethylsilane as an internal standard. The peak patterns are shown as the following abbreviations: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. Mass spectra (MS) were measured by a Thermo Electron LCQ Classic or Micromass ZQ of Waters (ESI). High resolution mass spectra (HRMS) were recorded by a Micromass Q-Tof Ultima API mass spectrometer. Optical rotations were determined with a JASCOP-1020 polarimeter.

2.2. Synthesis

2.2.1. 26-Pseudodiosgenyl 4-methylbenzenesulfonate (**9**)

A solution of TsCl (1.73 g, 9.01 mmol) in dry $CHCl_3$ (15 mL) was slowly added to a chilled (−5 °C) solution of pseudodiosgenin **5** (2.51 g, 6.05 mmol), Et_3N (1.68 mL, 12.10 mmol) and $Me_3N{\cdot}HCl$ (58 mg, 0.61 mmol) in dry $CHCl_3$ (45 mL) over 2 h. After being stirred at −5 °C for 12 h, the mixture was successively washed with 0.5 M HCl (2 × 200 ml), saturated aqueous $NaHCO_3$ (2 × 200 mL) and brine (300 mL). The organic layers were dried over Na_2SO_4 and concentrated. The obtained residue was dissolved in acetone (42 mL) and H_2O (18 mL), and the resulting solution was stirred for 2 h at 60 °C, then the mixture was poured into ice-water (500 mL), the precipitate was collected by filtration and dissolved in CH_2Cl_2 (200 mL), the mixture was washed with brine (300 mL). The organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc/CH_2Cl_2 = 5/1/1,) to yield **9** (3.05 g, 89%) as a white solid $[\alpha]_D^{20}$–27.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 5.34 (d, *J* = 4.8 Hz, 1H), 4.71–4.66 (m, 1H), 3.88 (dd, *J* = 9.0, 4.8 Hz, 1H), 3.79 (dd, *J* = 9.6, 6.6 Hz, 1H), 3.51 (m, 1H), 2.44 (s, 3H), 1.52(s, 3H), 1.01 (s, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.64 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 150.8, 144.6, 140.8, 133.0, 129.77, 129.74, 127.9, 121.3, 104.1, 84.2, 74.9, 71.6, 64.1, 55.0, 50.0, 43.2, 42.2, 39.4, 37.2, 36.6, 34.0, 32.3, 32.1, 31.6, 31.2, 30.0, 22.9, 21.6, 20.9, 19.4, 16.4, 13.9, 11.6.

2.2.2. 26-pseudodiosgenyl thioacetate (**10**)

To a solution of **9** (369 mg, 0.65 mmol) in DMF (5 mL) was added $KSCOCH_3$ (222 mg, 1.95 mmol). The mixture was stirred for 10 h at room temperature, then the volatile was removed under reduced pressure. The resultant residue was diluted with CH_2Cl_2 (100 mL), and washed subsequently with H_2O (2 × 150 mL) and brine (300 mL). The organic layers were dried over Na_2SO_4 and concentrated to dryness. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 4/1,) to afford **10** (295 mg, 96%) as a white solid $[\alpha]_D^{20}$–22.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.32 (d, 1H, *J* = 5.4 Hz), 4.73–4.69 (m, 1H), 3.51–3.47 (m, 1H), 2.91 (dd, 1H, *J* = 13.2, 5.4 Hz), 2.75 (dd, 1H, *J* = 13.2, 7.2 Hz), 2.44 (d, 1H, *J* = 10.2 Hz), 2.30 (s, 3H), 1.56 (s, 3H), 1.00 (s, 3H), 0.93 (d, 3H, *J* = 6.6 Hz), 0.66 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 195.9, 151.3, 140.8, 121.3, 103.7, 84.2, 71.5, 64.1, 54.9, 50.0, 43.2, 42.2, 39.4, 37.2, 36.5, 35.6, 34.0, 33.2, 32.8, 32.1, 31.5, 31.2, 30.6, 23.2, 20.9, 19.3, 18.9, 13.9, 11.6; HRESIMS: $[M + H]^+$ cacld for $C_{29}H_{45}O_3S$: 473.3084; Found: 473.3090.

2.2.3. 26-thiodiosgenin (**3**)

To a solution of **10** (295 mg, 0.62 mmol) in methanol (20 mL) was added 5 mL of H_2O/MeOH (v/v = 1/9) containing KOH (70 mg, 1.25 mmol). After stirring for 15 min. at room temperature, 6 M HCl (320 μL, 1.87 mmol) was added and the resultant mixture was stirred for another 30 min at room temperature, then kept for 12 h at 0 °C. The solid was collected by filtration and dried *in vacuo* to afford **10a** in quantitative yield. A solution of **10a** (239 mg, 0.55 mmol) in 20 ml of aqueous ethanolic HCl (0.3 M, v/v = 1/19) was refluxed for 5 h, then cooled to room temperature, diluted with water (200 mL) to result in the formation of a precipitate, which was collected by filtration, washed with water, died *in vacuo* followed by silica gel column chromatography (petroleum ether/EtOAc = 5/1) to give **3** (209 mg, 87% over two steps) as a white solid $[\alpha]_D^{20}$–162.7 (*c* 1.10, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.34 (d, 1H, *J* = 4,8 Hz), 4.62 (dd, 1H, *J* = 15.0, 7.2 Hz), 3.55–3.48 (m, 1H), 2.52 (t, 1H, *J* = 13.2 Hz), 2.28 (d, 2H, *J* = 13.2 Hz), 2.22 (t, 1H, *J* = 12.6 Hz), 1.01 (s, 3H), 1.00 (d, 3H, *J* = 8.4 Hz), 0.92 (d, 3H, *J* = 6.6 Hz), 0.80 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 140.8, 121.4, 97.5, 81.6, 71.7, 62.8, 56.6, 50.0, 44.4, 42.2, 40.3, 39.7, 38.5, 37.2, 36.6, 33.3, 32.1, 32.0, 31.7, 31.6, 31.41, 31.38, 22.4, 20.8, 19.4, 16.5, 16.2; HRESIMS: cacld for $C_{27}H_{43}O_2S$, $[M + H^+]$, 431.2978. Found: 431.2983.

2.2.4. 26, 26′-(Bispseudodiosgenyl) diselenide (**11**)

To a suspension of $CsOH{\cdot}H_2O$ (75.6 mg, 0.45 mmol) and activated selenium power (23.7 mg, 0.30 mmol) in DMF (2 mL) was added $N_2H_4{\cdot}H_2O$ (55 μL, 0.90 mmol) under N_2 atmosphere. After being stirred for 2 h at r.t., **9** (170.6 mg, 0.30 mmol) was added. The mixture was continued to stir for another 4 h at 60 °C, then evaporated under reduced pressure to give a residue, which was taken into CH_2Cl_2 (100 mL). The mixture was washed successively with H_2O (2 × 150 mL), brine (300 mL). The collected organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc = 3/1) to give **11** (131.9 mg, 92%) as a yellow solid $[\alpha]_D^{20}$ 34.2 (*c* 1.21, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.34 (d, 2H, *J* = 4.8 Hz), 4.75–4.70 (m, 2H), 3.53–3.49 (m, 2H), 3.02 (dd, 2H, *J* = 12.0, 5.4 Hz), 2.82 (dd, 2H, *J* = 12.0, 7.8 Hz), 2.45 (d, 2H, *J* = 10.2 Hz), 2.30 (m, 4H), 2.22 (t, 4H, *J* = 10.8 Hz) 1.58 (s, 6H), 1.01 (s, 6H), 0.99 (d, 6H, *J* = 6.6 Hz), 0.68 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.5, 140.8, 121.3, 103.7, 84.3, 71.6, 64.2, 55.0, 50.0, 43.2, 42.2, 39.5, 39.1, 37.2, 36.6, 34.1, 33.9, 33.8, 32.2, 31.6, 31.2, 23.4, 21.0, 19.5, 19.4, 14.0, 11.7.

2.2.5. 26-selenodiosgenin (**4**)

To a solution of **11** (286 mg, 0.30 mmol) in acetic acid (30 mL) was added zinc powder (59 mg, 0.90 mmol). After refluxing for 24 h at 150 °C, the mixture was cooled to room temperature and the solid was filtered off. The filtrate was removed under reduced pressure to give a residue, which was dissolved in dioxane (15 mL), then 20 mL of 10% KOH in EtOH/H_2O (v/v = 1/1) was added. After being stirred for 2 h at room temperature, the solution was poured into ice-water (300 mL) and extracted with dichloromethane (2 × 100 mL). The organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was applied to silica gel column chromatography eluting with petroleum ether and EtOAc (v/v = 6/1) to afford **4** (250 mg, 92%) as a white solid $[\alpha]_D^{20}$–192.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 5.34 (d, 1H, *J* = 4.8 Hz), 4.64 (dd, 1H, *J* = 15.6, 7.8 Hz), 3.53–3.50 (m, 1H), 2.58 (t, 1H, *J* = 12.0 Hz), 2.37–2.34 (m, 1H), 2.31–2.28 (m, 1H),

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