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STUDIES ON SYNTHESIS OF OSW-1 ANALOGUE WITH THIAZOLE RING AT SIDE CHAIN EMPLOYING WITTIG REARRANGEMENT

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Abstract – OSW-1 analogue with thiazole at the side chain was synthesized employing a tandem Williamson etherification - [2,3]-Wittig rearrangement, which provided a one-pot producer for the formation of (20*S*)-22-hydroxy steroids **6** and **7** from the known allylic alcohol **4** and 2-bromomethylthiazole as a key step. Glycosylation of steroid aglycone **17** with donors was investigated under various conditions.

INTRODUCTION

The naturally occurring steroidal saponin OSW-1 (**1**) is found in the bulbs of *Ornithogalum saudersiae*[1] and is highly cytotoxic against tumor cell lines.[2](Figure 1) OSW-1 exhibited extremely potent cytotoxic activity against various human malignant tumor cells *in vitro*.[2] The activity of OSW-1 is much more potent than that of some well-known anticancer agents in clinical use, such as mitomycin C, adriamycin, cisplatin, camptothecin, and taxol. OSW-1 has been paid particular attention because of its structural novelty and its extremely potent activity. Although a number of synthetic studies of OSW-1 and its analogues,[3] including its total syntheses,[4] have been reported, the precise mechanism by which OSW-1 exerts its effect remains unclear. Recently, we have succeeded in the synthesis of OSW-1 and its analogue **2** with thiophene at side chain utilizing Wittig rearrangement of 17(20)-ethylidene-16-thiophene-methyloxy steroid.[5] In this regard, we have been interested in the application of the Wittig rearrangement[6] to synthesis of OSW-1 analogue **3** with thiazole at side chain, which could be a potential candidate for a new antitumor agent. In this paper, we wish to report a synthesis of the aglycone **17** of the OSW-1 analogue **3** and an investigation into its glycosylation with donors.

This paper is dedicated to Professor Dr. Ryoji Noyori on the occasion of his 70th birthday.

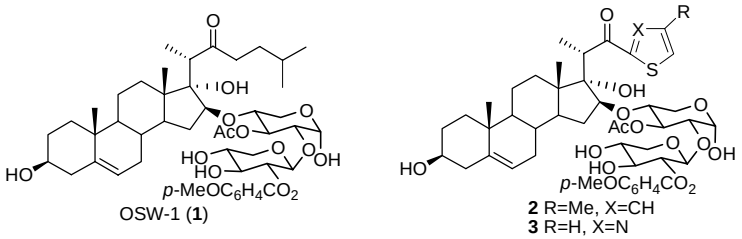


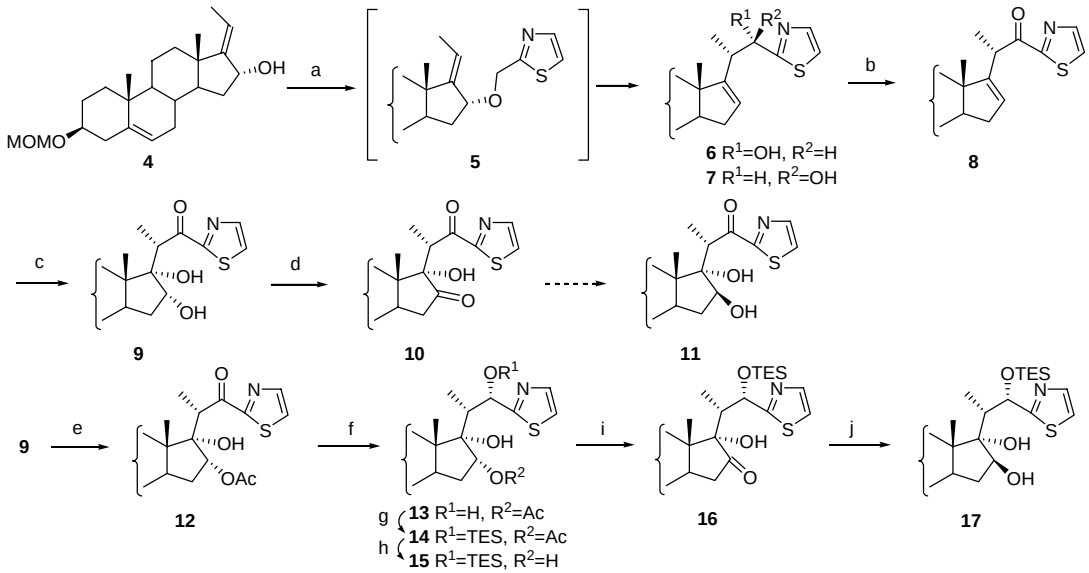
Figure 1. Structure of OSW-1 and its analogues

RESULTS AND DISCUSSION

We first examined the synthesis of the aglycone of OSW-1 analogue **3** along with our previous result.[5] (Scheme 1) Reaction of the known 16α-allylic alcohol **4**[7] with 2-bromomethylthiazole[8] in the presence of NaH (10 equiv) and 18-crown-6 (10 equiv) resulted in a tandem Williamson etherification - [2,3]-Wittig rearrangement of 2-thiazolylmethyl ether **5**, generated *in situ*, to afford 22α- and 22β-hydroxy steroids **6** and **7** in 62% and 21% yields, respectively. The stereochemistries at the C-20 and C-22 positions in both **6** and **7** were tentatively assigned to be (20*S*,22*S*)-*threo* and (20*S*,22*R*)-*erythro* isomers, respectively, from our previous results.[5,9] The ^{1}H NMR signal to H-22 in *threo* **6** is observed further upfield than that of *erythro* **7**. The similar relationship between *threo*- and *erythro*-22-hydroxy steroids are also observed in the corresponding steroids with modified side chains.[5,9] Although there is one example[10] of Wittig rearrangement of allyl thiazolylmethyl ether under the standard condition, *n*-BuLi as a base, this is the first report on a facile one-pot Williamson etherification - [2,3]-Wittig rearrangement.

Oxidation of **6** with Dess-Martin periodinane[11] gave ketone **8**, which was further converted into diketone **10** by successive dihydroxylation of alkene **8** using a stoichiometric amount of OsO_4 and TPAP oxidation[12] of diol **9** in 92% overall yield from **6**. Disappointingly, reduction of diketone **10** with $NaBH_4$ did not give the desired 16β,17α-diol **11** but complex mixtures, probably due to the almost same reactivity of carbonyl groups at the 16- and 22-positions. Attempts to protect ketone **9** as the corresponding ketal failed under various conditions.

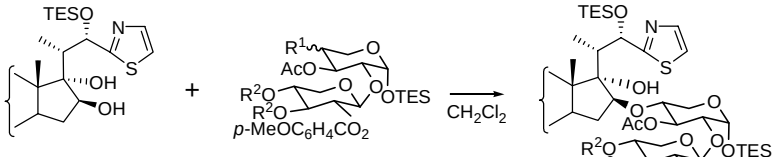
We next examined the synthesis of 22-hydroxylated 16β,17α-diol **17**, although some extra steps would be required. Acetylation of diol **9** gave acetate **12**, which was reduced with $NaBH_4$ to give diol **13** in 91% yield (2 steps). Since hydride reduction of 22-arylated 22-oxo steroids gave the Cram product 22α-hydroxy steroids exclusively,[9a] the stereochemistry at the C-22 position in **13** was deduced to be (22*S*) configuration. Protection of diol **13** with TESOTf gave silyl ether **14**, which was converted to 16β,17α-diol **17** by successive hydrolysis of acetate **14** with DIBAL, TPAP oxidation of diol **15**, and stereoselective reduction of **16** with $NaBH_4$ in 75% overall yield from **13**.



Scheme 1. Reagents and conditions: (a) NaH (10 equiv), 18-crown-6 (10 equiv), 2-bromomethylthiazole (2 equiv), bezene, reflux, 8 h, 62% for **6**, 21% for **7**; (b) Dess-Martin periodinane (1.2 equiv), CH_2Cl_2, rt, 2 h, 97%; (c) OsO_4, pyridine, CH_2Cl_2, -78°C, 12 h, 98%; (d) TPAP (0.1 equiv), NMO (10 equiv), CH_2Cl_2, rt, 6 h, 97%; (e) Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 2.5 h, 100%; (f) $NaBH_4$ (1.2equiv), MeOH-CH_2Cl_2 (1/1), -18°C, 1 h, 91%; (g) TESOTf (1.1 equiv), 2,6-lutidine (2 equiv), CH_2Cl_2, -78°C, 1 h, 93%; (h) DIBAL (3 equiv), THF, -78°C→rt, 3.5 h, 97%; (i) TPAP (0.1 equiv), NMO (10 equiv), CH_2Cl_2, rt, 4 h, 89%; (j) $NaBH_4$ (1.1 equiv), MeOH, -18°C, 1 h, 94%.

With the aglycone **17** of OSW-1 analogue **3** in hand, we investigated the glycosylation of **17** with donors as follows. (Table 1) An initial attempt to perform glycosylation of **17** with disaccharide trichloroacetimidate **18**[4a] by use of TMSOTf as a promoter in the presence of MS 4A, the standard condition employed in most OSW-1 syntheses, failed. (entries 1 and 2) We also tried other promoters, such as TBSOTf, $TiCl_4$, and $BF_3{\cdot}Et_2O$, no coupling product was obtained. (entries 3-5) We assumed that thiazole moiety would bind to TMSOTf and therefore prevent activation of the donor **18**. We next examined the

Table 1. Reaction of aglycone **17** with glycosyl donors



17

18 R^1=OC(=NH)CCl_3, R^2=TES
19 R^1=PhS(O), R^2=PMB
20 R^1=PhS, R^2=PMB

21

entry	donor	condition	temp.	yield (%)
1	**18**	TMSOTf (0.2 equiv)	-78°C	0
2	**18**	TMSOTf (1.2 equiv)	-78°C	0
3	**18**	TBSOTf (0.2 equiv)	-78°C	0
4	**18**	$TiCl_4$ (0.4 equiv)	0°C	decomp.
5	**18**	$BF_3{\cdot}Et_2O$ (0.2 equiv)	-78°C	0
6	**19**	Ph_2SO (1 equiv),Tf_2O (1 equiv) TTBP (2.4 equiv)	-78°C	0
7	**20**	Ph_2SO (1 equiv),Tf_2O (1 equiv) TTBP (2.4 equiv)[a]	-78°C	31
8	**20**	Ph_2SO (1 equiv),Tf_2O (1 equiv) TTBP (2.4 equiv)[b]	-78°C	33
9	**20**	Ph_2SO (1 equiv),Tf_2O (1 equiv) TTBP (2.4 equiv)[c]	-78°C	55

a) Quenched with Et_3N. b) Quenched with sat. aq. $NaHCO_3$.
c) Quenched with MeOH.
TTBP: 2,4,6-tri-*tert*-butylpyrimidine

sulfoxide and sulfinate methods developed by Crich *et al*.,[13] which are typically conducted in the presence of base. Reaction of **17** with sulfoxide **19**[4b] by use of Tf_2O as an activating agent in the presence of 2,4,6-tri-*tert*-butylpyrimidine (TTBP) gave none of coupling product, while glycosylation of **17** with sulfinate **20**[4b] under the same condition as the sulfoxide method produced **21** in 31% yield. (entries 6 and 7) It is noteworthy that quenching with either aq. $NaHCO_3$ or MeOH instead of Et_3N was associated with improvement in yield, up to 55% (entries 8 and 9), although the reason for this observation was unclear. Removal of all the protecting groups (two TES, one MOM, and two PMB) was carried out under various conditions, such as TMSBr, DDQ, and CAN, unfortunately, none of the desired products was isolated.

CONCLUSION

Thus, we have disclosed the synthesis of OSW-1 analogue modified side chain with thiazole employing a concise one-pot Williamson etherification - [2,3]-Wittig rearrangement leading to (20*S*)-22-hydroxy-22-(2-thiazolyl) steroid as a key step. Although glycosylation of aglycone **17** with disaccharide trichloroactimidate **18** did not give the desired product, reaction of **17** with sulfinate **20** produced steroidal saponin derivative **21**. Studies on the synthesis of OSW-1 analogue modified side chain with thiazole and an investigation of its structure-activity relationship (SAR) are underway.

EXPERIMENTAL

IR spectra were obtained using a JASCO FT/IR-200 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on JEOL LAMBDA-270 (270 MHz ^1H, 67.5 MHz ^{13}C) or JEOL LAMBDA-500 (500 MHz ^1H, 125 MHz ^{13}C) or Brucker AV400 (400 MHz ^1H, 100 MHz ^{13}C) instruments in deuterochloroform ($CDCl_3$) as noted individually. Chemical shifts are reported on the δ scale from internal TMS. Mass spectra were measured with a JEOL JMS-D300 spectrometer. Optical rotations were taken with a JASCO DIP-360 polarimeter.

Reaction of alcohol 4 with 2-bromomethylthiazole

To a solution of 16α-allylic alcohol **4**[7] (2.9 g, 8.0 mmol), 18-crown-6 (21 g, 80 mmol), 50% NaH (3.8 g, 80 mmol) in benzene (540 mL) was added dropwise a solution of 2-bromomethylthiazole[8] (2.8 g, 16 mmol) in benzene (110 mL) over 4 h at reflux under Ar. After stirring for 8 h at the same temperature, the reaction mixture was quenched with sat. NH_4Cl aq. and the precipitate was filtered, extracted with Et_2O-pentane (1:1, v/v). The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by silica gel chromatography using hexane-AcOEt (19:1, v/v) as eluent to give the recovered starting material **4** (0.34 g). Second elution gave **(20*S*,22*R*)-22-hydroxy-3β-methoxymethyloxy-22-(2-thiazolyl)-23,24-bisnor-5,16-choladiene (7)** (0.69 g, 21% based on recovery of the starting material) as colorless powder. $[\alpha]^{24}_D$ -46.2°(*c* 0.91, $CHCl_3$); IRυmax 3420, 2930, 2460, 1460, 1090 cm^{-1}; ^1H-NMR ($CDCl_3$; 400 MHz) δ 0.82 (3H, s), 0.96 (3H, d, *J*= 7.0 Hz), 0.99 (3H, s), 2.73 (1H, brs) 2.95 (1H, dq, *J*=5.6, 6.6 Hz), 3.38-3.48 (4H, m), 4.70 (2H, s), 5.13 (1H, d, *J*= 3.3 Hz), 5.38 (1H, dd, *J*= 1.7, 3.3 Hz), 5.68 (1H, t, *J*= 1.6 Hz), 7.29 (1H, d, *J*=3.3 Hz), 7.66 (1H, d, *J*= 3.3 Hz); ^{13}C-NMR ($CDCl_3$; 67.8 MHz) δ14.5, 16.1, 19.2, 20.5, 28.7, 30.3, 31.2, 31.4, 34.6, 36.8, 37.0, 39.5, 46.9, 50.5, 55.1, 57.5, 73.5, 76.5, 94.5, 118.4, 121.4, 125.4, 140.9, 142.0, 156.7, 174.3; MS (EI): 114, 282, 424, 442, 457 (M^+); HRMS (EI) calcd for $C_{27}H_{39}NO_3S$: 457.2650. Found: 457.2621.
Further elution using the same soluvent gave **(20*S*,22*S*)-22-hydroxy-3β-methoxymethyloxy-22-**

(2-thiazolyl)-23,24-bisnor-5,16-choladiene (6) (2.0 g, 62% based on recovery of the starting material) as colorless powder. $[\alpha]^{24}_D$ -86.1°(*c* 0.93, $CHCl_3$); IRυmax 3360, 2930, 2460, 1460, 1090 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 400 MHz) δ 0.81 (3H, s), 1.05 (3H, d, *J*=7.8 Hz), 1.06 (3H, s), 2.64 (1H, quant, *J*=7.1, 7.8 Hz), 2.84 (1H, d, *J*= 2.6 Hz), 3.38-3.48 (4H, m), 4.70 (2H, s), 4.99 (1H, dd, *J*=2.2, 8.5 Hz), 5.38 (1H, d, *J*= 1.9 Hz), 5.69 (1H, d, *J*=2.2 Hz), 7.33 (1H, d, *J*= 3.2 Hz), 7.75 (1H, d, *J*=3.2 Hz); ^{13}C-NMR ($CDCl_3$; 67.8 MHz) δ 15.9, 18.2, 19.2, 20.6, 28.8, 30.4, 31.3, 31.5, 34.6, 36.8, 37.1, 39.5, 41.9, 47.1, 50.3, 55.1, 57.4, 74.6, 76.8, 94.6, 118.9, 121.4, 125.4, 140.9, 141.7, 156.4, 173.5; MS (EI): 114, 282, 442, 457 (M^+); HRMS (EI) calcd for $C_{27}H_{39}NO_3S$: 457.2650. Found: 457.2660.

(20*S*)- 3β-Methoxymethyloxy-22-(2-thiazolyl)- 23,24-bisnor-5,16-choladien-22-one (8)
To a solution of alcohol **6** (1.3 g, 2.8 mmol) in CH_2Cl_2 (28 mL) was added Dess-Martin periodinane[11] (1.4 g, 3.4 mmol) at 0 °C. After stirring at rt for 2 h, the reaction mixture was quenched with sat. aq. NH_4Cl solution and the solvent was extracted with Et_2O- CH_2Cl_2 (1:1, v/v). The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by silica gel chromatography using hexane-AcOEt (9:1, v/v) as eluent to give ketone **8** (1.2 g, 97%) as colorless powder. $[\alpha]^{24}_D$ +74.1°(*c* 1.10, $CHCl_3$); IRυmax 2970, 2930, 2900, 2850, 1690 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 270 MHz) δ 0.78 (3H, s), 0.88-1.12 (6H, m), 1.35 (3H, d, *J*= 6.9 Hz), 3.37-3.47 (4H, m), 4.58 (q, *J*= 6.9 Hz), 4.69 (2H, s), 5.36 (1H, d, *J*= 4.9 Hz) , 5.50 (1H, brs), 7.65 (1H, d, *J*= 3.1 Hz), 7.96 (1H, d, *J*= 3.1 Hz); ^{13}C-NMR ($CDCl_3$; 67.8 MHz) δ15.8, 17.4, 19.1, 20.6, 28.7, 30.3, 31.1, 31.3, 34.6, 36.7, 37.0, 39.4, 47.5, 50.5, 54.9, 56.9, 76.6, 94.5, 121.3, 125.6, 126.2, 140.7, 144.2, 153.5, 166.8, 194.0; MS (EI): 112, 412, 427, 440, 455 (M^+); HRMS (EI) calcd for $C_{27}H_{37}NO_3S$: 455.2494. Found: 455.2466.

(20*S*)-16α,17α-Dihydroxy-3β-methoxymethyloxy-22-(2-thiazolyl)-23,24-bisnor-5-cholen-22-one (9)
To a solution of alkene **8** (500 mg, 1.1 mmol) in CH_2Cl_2 (10 mL) was added a solution of OsO_4 (330 mg, 1.3 mmol) in pyridine (1.8 mL) at -78 °C under Ar. After stirring for 12 h at the same temperature, sat. aq. $NaHSO_3$ was added and the resulting mixture was stirred at rt for 8 h. The reaction mixture was extracted with Et_2O- CH_2Cl_2 (1:1, v/v). The extract was washed with 1N HCl and then brine, and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by silica gel chromatography using hexane-AcOEt (4:1, v/v) as eluent to give diol **9** (521 mg, 98%) as colorless powder. $[\alpha]^{24}_D$ -13.7°(*c* 0.95, $CHCl_3$); IRυmax 3400, 2940, 2900, 1670 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 270 MHz) δ 0.95 (3H, s), 1.02 (3H, s), 1.34 (3H, d, *J*= 6.9 Hz), 3.37-3.47 (4H, m), 4.14 (1H, brd, *J*= 7.4 Hz), 4.20 (1H, q, *J*= 6.9 Hz), 4.69 (2H, s), 5.34 (1H, d, *J*= 5.1 Hz), 7.72 (1H, d, *J*= 3.1 Hz), 8.01 (1H, d, *J*= 3.1) ; ^{13}C-NMR ($CDCl_3$; 67.8 MHz) δ 12.5, 14.8, 19.2, 20.2, 28.7, 31.6, 31.6, 32.2, 35.1, 36.5, 36.9, 39.3, 45.2, 48.4, 48.5, 49.1, 55.0, 75.7, 76.7, 83.2, 94.5, 121.3, 127.6, 140.5, 144.3, 167.4, 197.7; MS (EI): 69, 142, 286, 489 (M^+); HRMS (EI) calcd for $C_{27}H_{39}NO_5S$: 489.2549. Found: 489.2574.

(20*S*)-17α-Hydroxy-3β-methoxymethyloxy-22-(2-thiazolyl)-23,24-bisnor-5-cholene-16,22-dione (10)
A suspension of diol **9** (25 mg, 0.05 mmol), TPAP (1.8 mg, 5 μmmol), NMO (58 mg, 0.5 mmol), and MS4A (58 mg) in CH_2Cl_2 (5 mL) was stirred at rt for 1 h. The insoluble materials were filtered off and the filtrate was evaporated off to give an oil, which was purified by silica gel chromatography using hexane-AcOEt (9:1, v/v) as eluent to give diketone **10** (24.2 mg, 97%) as colorless powder. $[\alpha]^{24}_D$ -100.1°(*c* 0.75, $CHCl_3$); IRυmax 3430, 2930, 2900, 1740, 1670 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 270 MHz) δ 0.92 (3H, s), 1.06-1.15 (4H, m), 1.34 (3H, d, *J*= 7.2 Hz), 1.47-1.80 (6H, m), 1.88-2.18 (3H, m), 2.24-2.84 (4H, m), 3.38-3.49 (4H, m), 3.99 (1H, brs), 4.70 (2H, s), 5.35 (1H, d, *J*= 4.9 Hz), 7.72 (1H, d, *J*= 3.0 Hz), 7.99 (1H, d, *J*= 3.0) ; ^{13}C-NMR ($CDCl_3$; 67.8 MHz) δ 12.2, 14.3, 19.3, 20.1, 28.8, 30.2, 31.1, 31.8, 35.3, 36.7, 36.9, 39.4, 45.4, 45.5, 49.3, 55.1, 76.7, 77.2, 86.3, 94.7, 121.0, 126.7, 140.8, 144.4, 166.6, 200.3, 216.5; MS (EI): 393, 443, 455, 487 (M^+); HRMS (EI) calcd for $C_{27}H_{37}NO_5S$: 487.2392. Found: 487.2411.

(20*S*)-16α-Acetoxy-17α-hydroxy-3β-methoxymethyloxy-22-(2-thiazolyl)-23,24-bisnor-5-cholen-22-one (12)

A solution of diol **9** (315 mg, 0.64 mmol), acetic anhydride (0.91 mL, 0.97 mmol), DMAP (78 mg, 0.64 mmol), and pyridine (0.15 mL, 1.9 mmol) in CH_2Cl_2 (7 mL) was stirred at rt for 2.5 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and the solvent was extracted with Et_2O- CH_2Cl_2 (1:1, v/v). The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by silica gel chromatography using hexane-AcOEt (5:2, v/v) as eluent to give acetate **12** (336 mg, 100%) as colorless powder. $[\alpha]^{24}_D$ -40.8°(*c* 0.54, $CHCl_3$); IRυmax 3520, 2940, 2900, 1730, 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 270 MHz) δ1.00 (3H, s), 1.03 (3H, s), 1.32 (3H, d, *J*= 7.1 Hz), 1.76 (3H, s), 3.37-3.49 (4H, m), 3.79 (1H, brs), 4.69 (1H, q, *J*= 7.1 Hz), 5.07 (1H, dd, *J*= 3.0, 9.6 Hz), 5.33 (1H, d, *J*= 5.1 Hz), 7.71 (1H, d, *J*= 3.1 Hz), 8.03 (1H, d, *J*= 3.1 Hz); ^{13}C-NMR ($CDCl_3$; 67.8 MHz) δ 12.4, 14.9, 19.3, 20.3, 20.7, 28.8, 31.5, 31.8, 31.9, 32.8, 36.6, 37.0, 39.5, 44.9, 48.4, 48.8, 49.5, 55.2, 76.7, 78.7, 82.7, 94.6, 121.3, 127.2, 140.7, 144.9, 167.0, 169.7, 197.1; MS (EI): 142, 240, 329, 391, 435, 470, 532 (M^+); HRMS (CI) calcd for $C_{29}H_{41}NO_6S$+H: 532.2732. Found: 532.2731.

(20*S*,22*S*)-16α-Acetoxy-17α,22-dihydroxy-3β-methoxymethyloxy-22-(2-thiazolyl)-23,24-bisnor-5-cholene (13)

To a solution of ketone **12** (750 mg, 1.41 mmol) in MeOH- CH_2Cl_2 (1:1, v/v, 47 mL) was added $NaBH_4$ (65 mg, 1.7 mmol) at -18 °C. After stirring for 1 h at the same temperature, the reaction mixture was quenched with sat. aq. NH_4Cl solution and the solvent was extracted with Et_2O- CH_2Cl_2 (1:1, v/v). The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by silica gel chromatography using hexane-AcOEt (85:15, v/v) as eluent to give desired diol **13** (686 mg, 91%) as colorless powder. $[\alpha]^{24}_D$ -39.0°(*c* 0.40, $CHCl_3$); IRυmax 3400, 2930, 2360, 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 270 MHz) δ 0.89-0.92 (6H, m), 1.02 (3H, s), 1.88 (3H, s), 3.37-3.48 (4H, m), 4.69 (2H, s), 5.00 (1H, brs), 5.25 (1H, dd, *J*= 2.0, 9.2 Hz), 5.35 (1H, d, *J*= 4.8 Hz), 6.88 (1H, s), 7.31 (1H, d, *J*= 3.3 Hz), 7.73 (1H, d, *J*= 3.3 Hz) ; ^{13}C-NMR ($CDCl_3$; 67.8 MHz) δ 8.2, 15.2, 19.3, 20.4, 21.2, 28.8, 31.6, 31.8, 32.1, 33.6, 36.6, 37.0, 39.4, 45.8, 48.1, 48.7, 49.5, 55.1, 73.2, 76.8, 79.3, 83.3, 94.6, 119.0, 121.4, 140.6, 141.5, 171.5, 175.4; MS (EI): 142, 340, 453, 533 (M^+); HRMS (CI) calcd for $C_{29}H_{43}NO_6S$+H: 534.2889. Found: 534.2888.

(20*S*,22*S*)-16α-Acetoxy-17α-hydroxy-3β-methoxymethyloxy-22-(2-thiazolyl)-22-triethylsiloxy-23,24-bisnor-5-cholene (14)

To a solution of diol **13** (685 mg, 1.28 mmol) and lutidine (0.30 mL, 2.6 mmol) in CH_2Cl_2 (13 mL) was added TESOTf (0.32 mL, 1.4 mmol) at -78 °C. After stirring for 1 h at the same temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ solution and the solvent was extracted with Et_2O-CH_2Cl_2 (1:1, v/v). The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by silica gel chromatography using hexane-AcOEt (3:1, v/v) as eluent to give desired silyl ether **14** (770 mg, 93%) as colorless powder. $[\alpha]^{24}_D$ -52.4°(*c* 0.30, $CHCl_3$); IRυmax 3300, 2960, 2950 , 2360, 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 270 MHz) δ 0.68 (6H, q, *J*= 7.7 Hz), 0.83-0.87 (14H, m), 1.90 (3H, s), 3.37-3.48 (4H, m), 4.69 (2H, s), 5.25 (1H, dd, *J*= 2.1, 9.2 Hz), 5.37 (1H, brd),6.81 (1H, s), 7.26 (1H, d, *J*= 3.1 Hz), 7.72 (1H, d, *J*= 3.1 Hz) ; ^{13}C-NMR ($CDCl_3$; 67.8 MHz) δ 4.7, 6.7, 8.1, 15.1, 19.3, 20.4, 21.1, 28.8, 31.6, 31.9, 32.0, 33.6, 36.6, 37.0, 39.5, 45.9, 48.1, 48.7, 49.5, 55.1, 73.9, 76.7, 79.2, 83.2, 94.6, 118.9, 121.5, 140.6, 141.6, 170.7, 177.1; MS (EI): 126, 229, 256, 456, 588, 619, 648 (M+1); HRMS (CI) calcd for $C_{35}H_{57}NO_5SSi$+H: 648.3754. Found:648.3761.

(20*S*,22*S*)-16α,17α-Dihydroxy-3β-methoxymethyloxy-22-(2-thiazolyl)-22-triethylsiloxy-23,24-bisnor-5-cholene (15)

To a solution of acetate **14** (770 mg, 1.2 mmol) in THF (12 mL) was added DIBAL (0.97 M in THF, 3.6 mL, 3.6 mmol) at -78 °C. The reaction mixture was allowed to warm to rt over 3.5 h and sat. aq. potassium sodium tartrate solution was added. After stirring for 1h, the reaction mixture was extracted with Et_2O- CH_2Cl_2 (1:1, v/v). The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by silica gel chromatography using hexane-AcOEt (5:1, v/v) as eluent to give desired diol **15** (697 mg, 97%) as colorless powder. $[\alpha]^{24}_D$ -42.3°(*c* 0.56, $CHCl_3$);

IRυmax 3200, 2950, 2930, 2880, 2360, 2340 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 270 MHz) δ 0.71 (6H, q, *J*= 7.7 Hz), 0.81 (3H, d, *J*=7.1 Hz), 0.84(3H, s), 0.94-1.12 (14H, m), 1.34-1.66 (7H, m), 1.71-1.99 (6H, m), 2.22-2.39 (3H, m), 3.28 (1H, d, *J*= 10.5 Hz), 3.37-3.50 (4H, m), 4.18 (1H, dd, *J*=8.4, 9.1 Hz), 4.69 (2H, s), 5.36 (1H, d, *J*= 4.6 Hz), 5.58 (1H, d, *J*= 1.6 Hz), 7.23 (1H, d, *J*= 3.3 Hz), 7.38 (1H, brs), 7.68 (1H, d, *J*= 3.3 Hz); ^{13}C-NMR ($CDCl_3$; 125 MHz) δ4.9, 6.8, 8.8, 14.9, 19.4, 20.5, 28.9, 31.8, 31.8, 32.5, 36.4, 36.6, 37.1, 39.5, 46.3, 48.0, 48.4, 49.6, 55.1, 73.8, 76.8, 76.8, 83.3, 94.6, 118.8, 121.6, 140.6, 141.1, 178.3; MS (EI): 126, 229, 257, 606 (M+1); HRMS (CI) calcd for $C_{33}H_{55}NO_5SSi$+H: 606.3648. Found: 606.3667.

(20*S*,22*S*)-17α-Hydroxy-3β-methoxymethyloxy-22-(2-thiazolyl)-22-triethylsiloxy-23,24-bisnor-5-cholen-16-one (16)

A suspension of diol **15** (109 mg, 0.18 mmol), TPAP (7 mg, 0.02 mmol), NMO (211 mg, 1.8 mmol), and MS4A (211 mg) in CH_2Cl_2 (3.6 mL) was stirred at rt for 6h. The insoluble materials were filtered off and the filtrate was evaporated off to give an oil, which was purified by silica gel chromatography using hexane-AcOEt (10:1, v/v) as eluent to give ketone **16** (97 mg, 89%) as colorless powder. $[\alpha]^{24}_D$ -170.4°(*c* 0.61, $CHCl_3$); IRυmax 3180, 2950, 2880, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 270 MHz) δ 0.72 (6H, q, *J*= 7.7 Hz), 0.85 (3H, d, *J*= 7.1 Hz), 0.87 (3H, s), 1.00 (9H, t, *J*= 7.7 Hz), 1.04 (3H, s), 1.29-1.73 (6H, m), 1.79-2.05 (5H, m), 2.17-2.50 (5H, m), 3.37-3.49 (4H, m), 4.69 (2H, s), 5.37 (1H, d, *J*= 5.1 Hz), 6.69 (1H, d, *J*= 2.1 Hz), 7.23 (1H, d, *J*= 3.3 Hz), 7.66 (1H, d, *J*= 3.3 Hz), 7.95 (1H, s); ^{13}C-NMR ($CDCl_3$; 67.8 MHz) δ 4.7, 6.8, 8.5, 14.5, 19.3, 20.4, 28.8, 30.9, 31.2, 31.9, 36.7, 36.9, 37.7, 39.5, 42.1, 44.2, 46.5, 49.4, 55.2, 71.3, 76.7, 81.3, 94.7, 118.6, 121.2, 140.8, 141.1, 178.7, 219.0; MS (EI): 121, 186, 229, 256, 575, 604 (M+1); HRMS (EI) calcd for $C_{33}H_{53}NO_5SSi$: 603.3413. Found: 603.3389.

(20*S*,22*S*)-16β,17α-Dihydroxy-3β-methoxymethyloxy-22-(2-thiazolyl)-22-triethylsiloxy-23,24-bisnor-5-cholene (17)

To a solution of diketone **16** (9.8 mg, 16 μmol) in MeOH (1 mL) was added $NaBH_4$ (0.65 mg, 17 μmol) at -18 °C. After stirring for 1 h at the same temperature, the reaction mixture was quenched with sat. aq. NH_4Cl solution and the solvent was extracted with Et_2O-CH_2Cl_2 (1:1, v/v). The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave an oil, which was purified by silica gel chromatography using hexane-AcOEt (85:15, v/v) as eluent to give desired *trans*-diol **17** (9.2 mg, 94%) as colorless powder. $[\alpha]^{24}_D$ -59.6°(*c* 0.20, $CHCl_3$); IRυmax 3430, 2950, 2890, 2360, 2340 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 270 MHz) δ 0.57-0.60 (6H, m), 0.83 (3H, d, *J*= 7.1 Hz), 0.88-0.97 (16H, m), 1.03 (3H, s), 2.63 (1H, dq, *J*= 4.4, 7.1 Hz), 3.37-3.48 (4H, m), 4.19 (1H, brs), 4.69 (2H, s), 5.14 (1H, s), 5.36 (1H, d, *J*= 4.8 Hz), 5.59 (1H, d, *J*= 4.4 Hz), 7.27 (1H, d, 3.3 Hz), 7.66 (1H, d, *J*= 3.3 Hz); ^{13}C-NMR ($CDCl_3$; 67.8 MHz) δ 4.7, 6.8, 9.4, 13.4, 19.3, 20.5, 28.8, 31.9, 32.0, 32.9, 36.7, 36.9, 37.1, 39.5, 42.1, 47.4, 48.4, 49.7, 55.1, 74.7, 76.8, 81.1, 84.8, 94.6, 119.0, 121.6, 140.7, 141.3, 178.3; MS (EI): 119, 229, 431, 555, 605 (M^+); HRMS (EI) calcd for $C_{33}H_{55}NO_5SSi$: 605.3570. Found: 605.3581.

(20*S*,22*S*)-16β,17α-Dihydroxy-22-(2-thiazolyl)-22-triethylsiloxy-3β-methoxymethyloxy-23,24-bisnor-5-cholene 16-*O*-{*O*-[(3,4-di-*O*-(4-methoxybenzyl)-2-*O*-(4-methoxybenzoyl)-β-D-xylopyranosyl]-(1→3)-2-*O*-acetyl-4-*O*-(triethylsilyl)-α-L-arabinopyranoside} (21)

A suspension of phenylthioglycoside **20**[4b] (36 mg, 0.040 mmol), Ph_2SO (6.6 mg, 0.033 mmol), TTBP (20 mg, 0.088 mmol) and MS4A (100 mg) in CH_2Cl_2 (0.5 mL) was stirred at rt for 1 h. Tf_2O (0.005 mL, 0.033 mmol) was added at -78 °C and the reaction mixture was stirred at the same temperature for 1 h. To the reaction mixture was added a solution of aglycone **17** (20 mg, 0.033 mmol) in CH_2Cl_2 (0.5 mL) at -78 °C. After stirring for 1 h at the same temperature, the reaction mixture was quenched with MeOH (0.05 mL). The solid was filtered and the solvent was removed gave an oil, which was purified by silica gel chromatography using hexane-AcOEt (9:1, v/v) as eluent to give β-glycoside **17** (25.2 mg, 55%) as colorless solid. $[\alpha]^{24}_D$ +2.6°(*c* 0.40, $CHCl_3$); IRυmax 3360, 2950, 2940, 2880, 1720, 1610, 1590, 1610, 1560, 1540, 1520 cm^{-1}; ^{1}H-NMR ($CDCl_3$; 500 MHz) δ 0.49-0.59 (6H, m), 0.65-0.72 (6H, m), 0.88-1.08 (30H, m), 1.19-1.26 (3H, m), 1.61 (3H, s), 1.40-1.73 (7H, m), 1.78-1.90 (4H, m), 2.26-2.49 (3H, m),

3.38 (3H, s), 3.29-3.48 (1H, m), 3.72 (3H, s), 3.80 (3H,s), 3.88 (3H,s), 3.77-3.95 (7H, m), 4.70 (2H, s), 4.53-4.72 (4H, m), 4.78 (1H, d, *J*= 7.3), 5.07 (1H, t, *J*= 7.9 Hz), 5.37 (1H, d, *J*= 4.9 Hz), 5.78 (1H, d, *J*= 3.1 Hz), 6.67 (2H, d, *J*= 8.5 Hz), 6.86 (2H, d, *J*= 8.2 Hz), 6.95 (2H, d, *J*= 8.5 Hz), , 7.08 (2H, d, *J*= 8.5 Hz), 7.24 (2H, d, *J*= 8.2 Hz), 7.25 (1H, d, *J*= 3.4 Hz), 7.80 (1H, d, *J*= 3.4 Hz), 8.01 (2H, d, *J*= 8.5 Hz); ^{13}C-NMR ($CDCl_3$; 125 MHz) δ 4.62, 4.80, 6.76, 6.80, 7.70, 13.35, 19.28, 20.72, 28.10, 28.85, 31.27, 32.07, 33.07, 36.61, 37.06, 37.27, 39.54, 41.13, 47.59, 47.93, 50.05, 55.04, 55.10, 55.20, 55.36, 6.375, 65.36, 71.99, 72.58, 72.81, 73.04, 74.28, 74.51, 76.89, 77.38, 80.55, 80.73, 82.00, 84.72, 94.59, 96.60, 102.23, 113.52, 113.52, 113.83, 113.83, 113.83, 113.83, 113.83, 113.83, 118.67, 121.85, 122.04, 124.22, 129.51, 129.51, 129.60, 129.60, 130.00, 130.14, 131.64, 140.58, 141.61, 159.03, 15.36, 163.30, 164.62, 180.00; MS (FAB): 162, 481.5, 673.9, 814.6, 1134.4, 1401.4 (M+1); HRMS (FAB) calcd for $C_{75}H_{110}NO_{18}SSi_2$: 1400.6982. Found: 1400.6964.

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