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# Total Synthesis of the Anticancer Natural Product OSW-1

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***Abstract:*** The highly potent anticancer natural saponin OSW-1 has been successfully synthesized from commercially available 5-androsten-3$\beta$-ol-17-one **79** in 10 operations with 28% overall yield. The key steps in the total synthesis included a highly regio- and stereoselective selenium dioxide-mediated allylic oxidation of **80** and a highly stereoselective 1,4-addition of $\alpha$-alkoxy vinyl cuprates **68** to steroid 17(20)-en-16-one **12E** to introduce the steroid side chain. This total synthesis demonstrated once again the versatile synthetic applications of $\alpha$-halo vinyl ether chemistry developed in our laboratories.

## Introduction

OSW-1 (**1**), a highly potent anticancer natural product, and its four natural analogues (**2**−**5**) have been isolated from the bulbs of *Ornithogalum saundersiae*, a perennial grown in southern Africa where it is cultivated as a cut flower and garden plant.[1] These natural products are members of the cholestane glycosides. Their absolute structures have been determined by extensive application of spectroscopic methods.[1] The structural novelty of compounds **1**−**5** is characterized by the attachment of a disaccharide to the C-16 position of the steroid aglycone, whereas compounds **4** and **5** have another glycosyl sugar associated with the C-3 alcohol position of the steroid (Figure 1).

Compounds **1**−**5** exhibited extremely potent cytostatic activity against human promyelocytic leukemia HL-60 cells, showing $IC_{50}$ values ranging between 0.1 and 0.3 nM. The activity of OSW-1 (**1**) in this assay is much more potent than that of clinically used anticancer agents such as etoposide, adriamycin, and methotrexate.[2] OSW-1 (**1**), the main constituent of the bulbs, exhibited exceptionally potent cytostatic activities against various human malignant tumor cells.[2] Its cytostatic activities are from 10- to 100-fold more potent than some well-known anticancer agents in clinical use, such as mitomycin C, adriamycin, cisplatin, camptothecin, and even taxol, but it has significantly lower toxicity ($IC_{50}$ 1500 nM) to normal human pulmonary cells.[2] The surprising similarity of the cytotoxicity profile of OSW-1 to that of cephalostatins,[3] one of the most active anticancer agents tested by NIH, with correlation coefficient of 0.60−0.83, suggests they might have the same

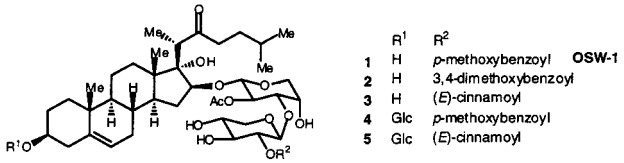


***Figure 1.***

mechanism of action.[4] It has been speculated by Fuchs that the C22-oxonium ions might be the active intermediate for the potent anticancer activity of OSW-1 (**1**) and cephalostatins.[5] This suggests that OSW-1 (**1**) might represent a new class of anticancer agents with a new mechanism of action. All of these factors make OSW-1 (**1**) a very attractive synthetic target.[4,6] As part of our program studying the chemistry and biology of anticancer natural products, we recently initiated a project directed toward the total synthesis of OSW-1 (**1**). We report herein our full account of our studies toward the total synthesis of this highly promising anticancer natural product.

## Results and Discussion

**Retrosynthetic Analysis.** The C-20 carbon of OSW-1 has the "normal" 20*S* configuration. Molecular mechanics calculations (MM2) have shown that compound **1** is about 3.1 kcal/mol more stable than its 20*R* epimer **6**, whereas **7** is about 2.4 kcal/mol more stable than **8** (Figure 2).[7] Therefore, we thought that it was not necessary to control the stereochemistry at C-20 during the synthesis and anticipated that compound **6** would eventually epimerize to the thermodynamically more stable **1** at the end of the synthesis.

Figure 3 outlines our retrosynthetic analysis of OSW-1 (**1**). Disconnection at the glycoside bond reveals the protected

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(7) MM2 calculation was performed using CS Chem Ultra program on a powerMac. The calculation results were consistent with experimental results, see ref 10.


**10.1021/ja012119t CCC: $22.00** 

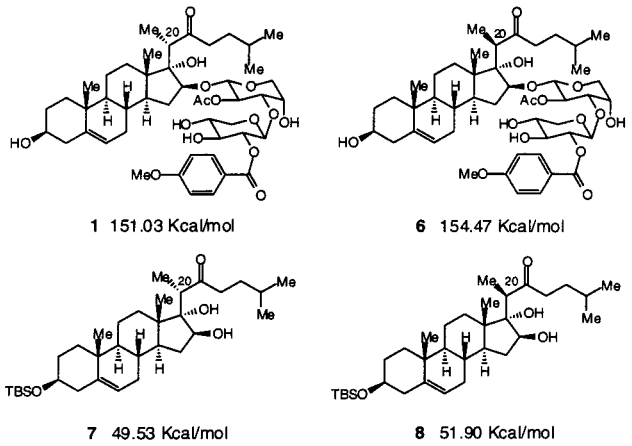



***Figure 2.***

aglycone **9** and the disaccharide **10** as the potential key fragments for the construction of the target molecule. Compound **9** was envisioned to be formed via a triply convergent strategy which would involve 1,4-addition of acyl anion equivalent **11** to enone **12** followed by in situ stereoselective oxidation of the resulting enolate. Enone **12** was envisaged to be prepared from the commercially available steroid **14**. Further disconnection at the glycoside bond of the disaccharide fragment **10** shows two monosaccharide units **15** and **16** which could be derived from L-arabinose and D-xylose, respectively.

**Synthesis of the Disaccharide 10.** The first monosaccharide **15** was prepared from tetraacetyl-L-arabinose **17** as illustrated in Figure 4. Thioglycoside **18** was prepared according to the standard methods[8] followed by deacetylation to give compound **19** in excellent yield. Regioselective protection of the *cis* diol of **19** followed by protection of the C-2 hydroxyl group gave **20** in 90% yield. Deprotection of the acetonide afforded diol **21**. It is well-known that the equatorial C-3 hydroxyl group in many sugars is more reactive than C-4 axial hydroxyl group. To our surprise, high selectivity at C-4 hydroxyl group was observed when **21** was treated with TESOTf and lutidine at low temperature affording the desired product **15** in 90% yield.

The second monosaccharide **16** was prepared from tetraacetyl-D-xylose **22**. The thio ortho ester **24** was prepared via the glycoside bromide **23** according to the literature procedures (Figure 5).[8] Protecting-group manipulations followed by zinc chloride-promoted intramolecular ring opening of the thio ortho ester **26** gave thioglycoside **27** in excellent yield. After deacety-

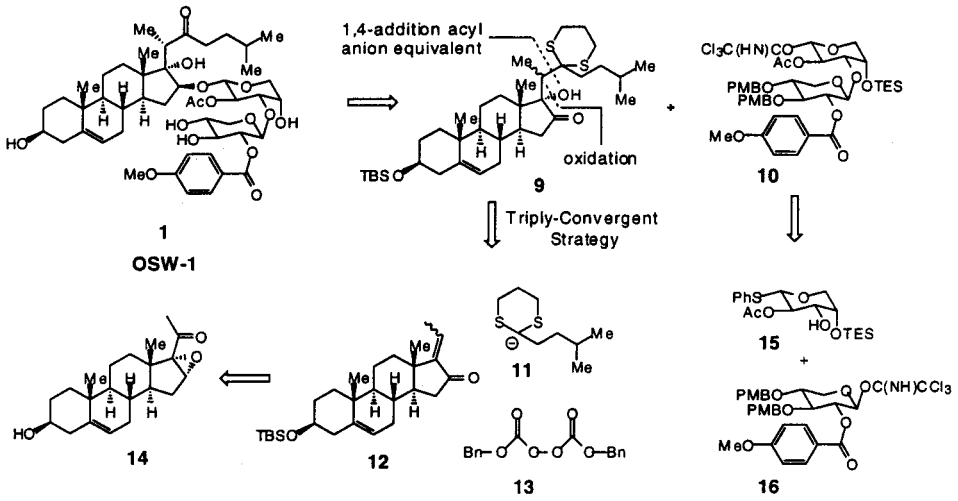
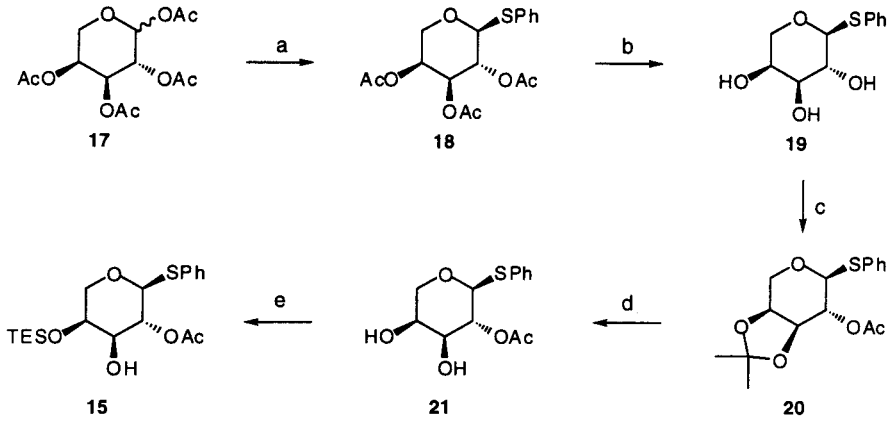
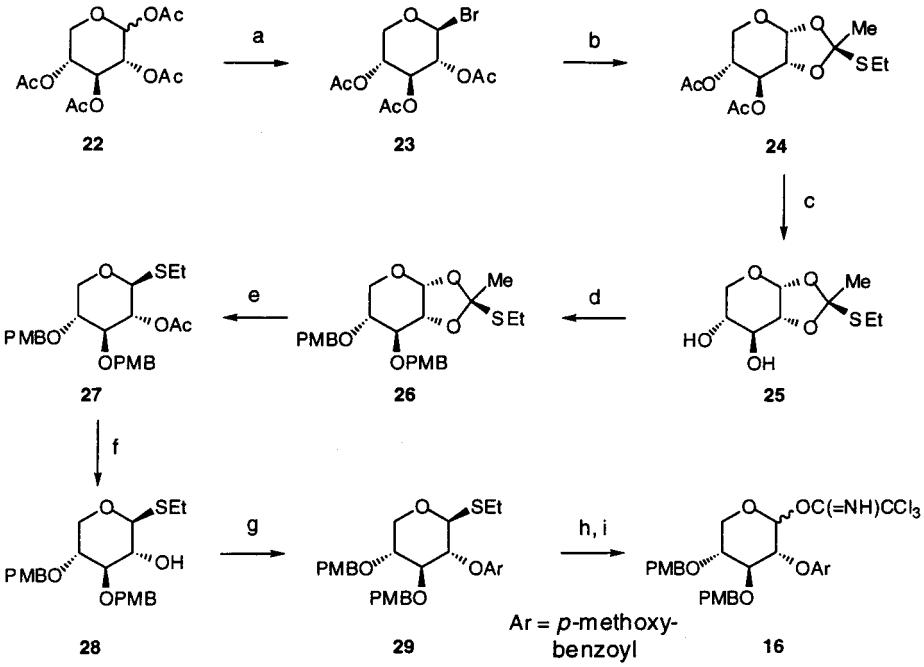



***Figure 3.***



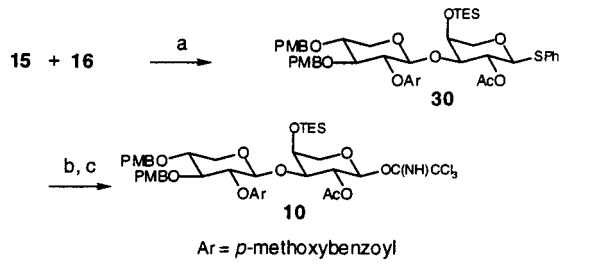

a. PhSH, $SnCl_4$, $CH_2Cl_2$, -78 to 25 °C, 80%; b. NaOMe, MeOH, 6 h, 95%; c. i) $Me_2C(OMe)_2$, CSA, $CH_2Cl_2$, 12 h; ii) $Ac_2O$, DMAP, $Et_3N$, $CH_2Cl_2$, 2 h; d. Amberlite IR-118H, MeOH, 12 h, 90% from **19**; e. TESOTf, lutidine, $CH_2Cl_2$, -60 to -70 °C, 2 h, 90%.

***Figure 4.***




a. 30% HBr-AcOH, $CH_2Cl_2$, 0 to 25 °C, 4 h, 93%; b. EtSH, 2,6-lutidine, $MeNO_2$, 12 h, 82%; c. NaOMe, MeOH, 25°C, 3 h; d. i) NaH, THF; ii) PMBCl, reflux, 4 h, 94% from **24**; e. $ZnCl_2$ (5%), $CH_2Cl_2$, -60 to 0 °C; f. NaOMe, MeOH, 25 °C, 4 h, 95% for 2 steps; g. *p*-anisoyl chloride, DMAP, $NEt_3$, $CH_2Cl_2$, 24 h, 97%; h. NBS, $H_2O$, $CH_2Cl_2$, 1 h, 88%; i. $CCl_3CN$, DBU, $CH_2Cl_2$, 3 h, 95%.

***Figure 5.***




a. $BF_3$•$Et_2O$, 4Å MS, $CH_2Cl_2$, -78 to -20°C, 4 h, 93%; b. NBS, $CH_2Cl_2$-$H_2O$ (9:1), 25 °C, 2 h, 81%; c. $CCl_3CN$, DBU, $CH_2Cl_2$, 12 h, 88%.

***Figure 6.***

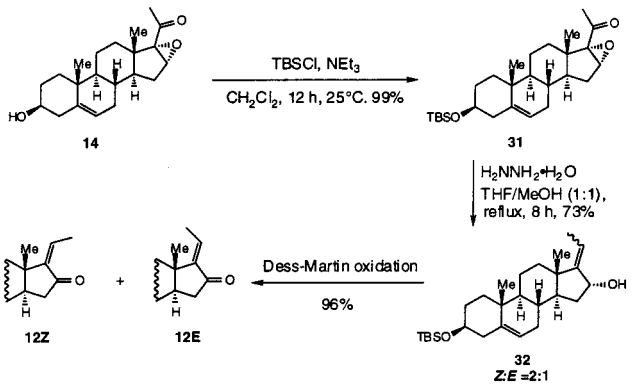



***Figure 7.***

lation, the *p*-methoxy benzoyl group was introduced at the C-2 position to afford **29**, which was subsequently converted to **16** in 95% yield.[9]

Glycosylation of **15** with **16** in the presence of $BF_3$•$Et_2O$ afforded the $\beta$-disaccharide **30** in 93% yield (Figure 6). Disaccharide **30** was then converted to the trichloroacetimidate **10**, which was then ready to couple with the protected steroid aglycone.

**The Attempted Synthesis of the Protected Steroid Aglycone.** The commercially available 5-pregnen-16,17-epoxy-3$\beta$-ol-20-one **14** was protected by a TBS group to give compound **31** (Figure 7). Reduction of the $\alpha,\beta$-epoxy ketone **31** by hydrazine hydrate gave the allyl alcohol **32** in 73% yield.[10] Dess−Martin oxidation[11] of the allyl alcohol afforded 96% yield of enone **12** as a mixture of *Z*- and *E*-stereoisomers with a ratio of 2:1.[12]

1,4-Addition of an acyl anion synthon to enone **12** was the key reaction to install the side chain of the aglycon in our strategy. Our studies on the addition of various α-thioacetal anions to enone **12** are summarized in Figure 8.

The reaction between 1,3-dithiane anion **33** and enone **12** gave exclusively 1,2-addition product **35** even in the presence of HMPA and at room temperature (Figure 8).[13] The softer anion **36** reacted with enone **12** in 1,2-fashion at −78 °C and then, in the presence of HMPA, rearranged to the 1,4-addition product

(8) Nicolaou, K. C.; Trujillo, J. I.; Chibale, K. *Tetrahedron* **1997**, *53*, 8751.
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(11) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(12) The stereochemistry of the double bond was determined by NOESY spectrum.

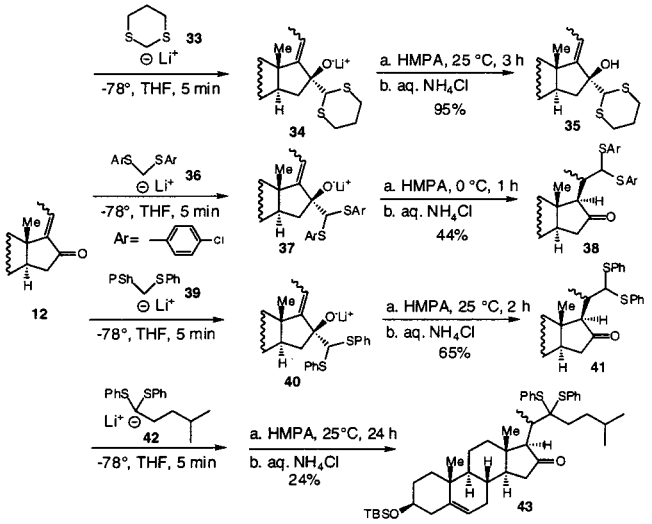


***Figure 8.***

**38** upon warming up the reaction mixture. However, the yield was quite low, and 20% of the starting material enone was recovered due to the equilibrium. Anion **39** appeared to be the best choice, as it gave 65% yield of compound **41**. Unfortunately, due to the steric hindrance of the tertiary anion **42**, the reaction was too slow and the yield was quite low. Therefore we decided to introduce the side chain in two steps via the addition of anion **39**.

1,4-Addition of anion **39** to enone **12** afforded enolate intermediate **44**, which was easily oxidized by dibenzyl peroxydicarbonate **13**[14] at −78 °C to give compound **45** in 63% yield (Figure 9). It appeared that the oxidation of the thioacetal by dibenzyl peroxydicarbonate **13** was much slower than the oxidation of the enolate at −78 °C, and no sulfoxide product was isolated. Hydrolysis followed by stereoselective reduction by $LiAlH_4$ afforded three diastereoisomers **47**, **48**, and **49**. The stereochemistry of the C-21 methyl group and the C-16 hydroxyl group were determined by analysis of the corresponding ROESY spectra. The desired products **47** and **48** which have $\beta$C-16 hydroxyl groups were obtained in a combined yield of 86%.

The metalation of both **47** and **48** proved to be quite difficult. After screening a few strong bases with or without additives such as HMPA or TMEDA, α-thioacetal anions **50** and **51** were successfully generated from **47** and **48** by treatment with super base (*n*-BuLi/*t*-BuOK) (Figure 10).[15] The formation of these anions was confirmed by deuterium incorporation after the reaction was quenched with $D_2O$ at −78 °C. Unfortunately, the attempt to quench them with electrophiles such as methyl iodide or allyl bromide resulted in quick decomposition of the anions **50** and **51**. Although it is still not clear exactly what happened, we speculate that the addition of electrophiles might accelerate the α-elimination of the highly bulky tertiary anions **50** and **51**. This speculation is supported by the fact that the reaction mixture smelled like thiophenol in the metalation step, and the odor of the thiophenol intensified immediately after the addition of an electrophile.

The unexpected difficulty in the alkylation of α-thioacetal anions **50** and **51**, coupled with the difficulties in the 1,4-addition of the sterically hindered tertiary α-thioacetal anions, led us to modify our original approach.

**The Attempted Synthesis of OSW-1.** An α-alkoxy vinyl anion, such as anion **56**, is another kind of acyl anion equivalent, which is more reactive and smaller compared to α-thioacetal anion **42** (Figure 11). This suggests a new approach in which α-alkoxy vinyl anion will be employed as the acyl anion equivalent.

In this new approach, we needed to prepare the $\beta$-isobutyl substituted α-methoxy vinyl cuprate **58** (Figure 12). However, there was no literature procedure for the quantitative generation of the requisite $\beta$-isobutyl substituted α-methoxy vinyl anion. To solve this problem, we developed a new methodology for the regio- and stereoselective synthesis of α-halo vinyl ether that could serve as the precursor of the α-alkoxy vinyl anion.[16] The acetylenic ether **59** was prepared according to a literature procedure.[17] The α-bromovinyl ether **60** and the required

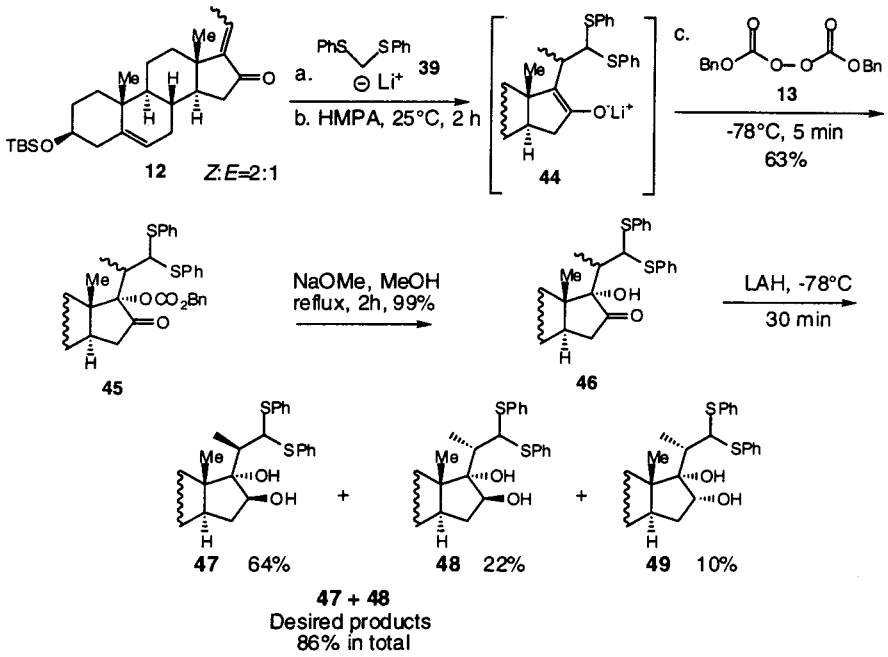


***Figure 9.***

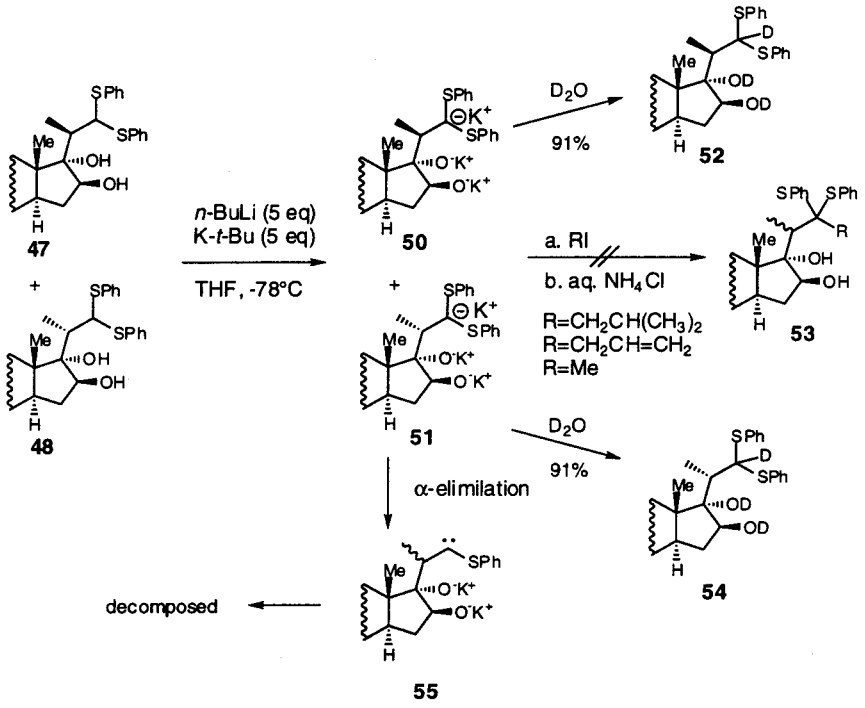
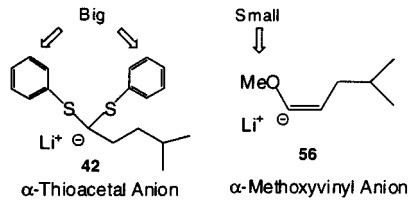



***Figure 10.***

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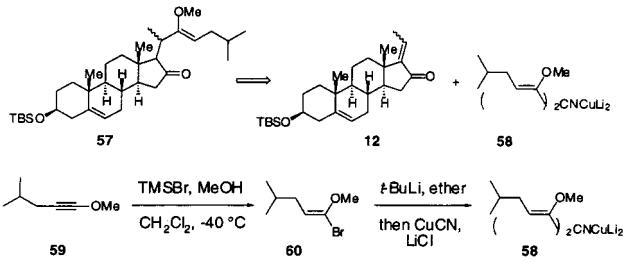


***Figure 12.***

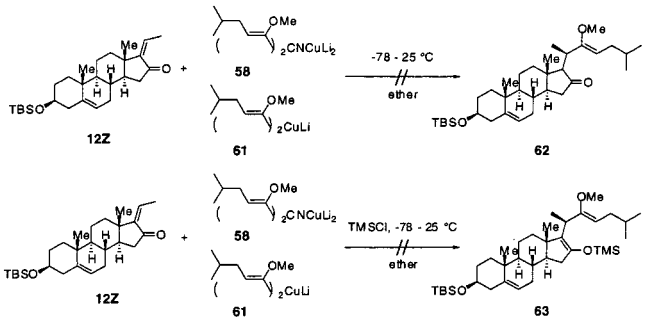


***Figure 13.***

***Figure 14.***

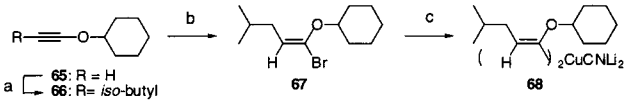


***Figure 15.***

α-methoxy vinyl cuprate **58** was prepared according to our newly developed methodology.[16]

We deliberately used compound **12Z** (the major isomer of the enone mixture **12**) to examine the proposed 1,4-addition reaction (Figure 13). It was anticipated that the **12Z** would be less reactive than the **12E** isomer. Although we had several successful model studies on the 1,4-addition of cuprate **58** to various simple α,β-unsaturated ketones,[18] to our surprise, the reaction between cuprate **58** and enone **12Z** did not lead to any desired product. Both low-order and high-order cuprates **61** and **58**, respectively, were carefully examined,[19] but no desired product was obtained even with TMSCl activation.[20,21] Enone **12Z** was recovered nearly quantitatively each time.

From the reaction mixture, a UV-active side product was isolated and it was found to be compound **64**, which had obviously been formed via the Würtz coupling of the α-methoxy

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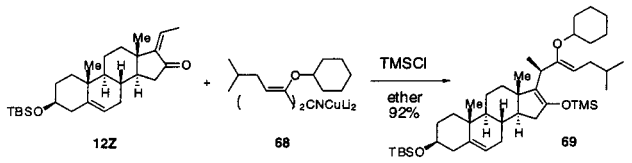



***Figure 16.***

vinyl cuprate **58** (Figure 14). The isolation of compound **64** suggested that the Würtz coupling was much faster than the desired 1,4-addition. Oxygen is normally considered to be the reason for the Würtz-coupling side reaction of organocuprates.[22] However, careful degassing of the reaction solvent and careful removal of possible traces of oxygen in argon by installing a Pyrogallol filter[23] still failed to stop the Würtz coupling.

The two neighboring methoxy groups in the Würtz-coupling product **64** are close to each other. We speculated that increasing the size of these two alkoxy groups might suppress the formation of the Würtz-coupling product. However, the alkoxy group should not be too bulky, otherwise the 1,4-addition would also be difficult. On the basis of the above analysis, α-cyclohexyloxy vinyl cuprate **68** was prepared. The size of the α-alkoxy group was increased from methoxy group to cyclohexyloxy group (Figure 15).

As expected, cuprate **68** underwent smooth 1,4-addition to enone **12Z** in the presence of TMSCl to afford the desired silyl enol ether **69** in 92% yield (Figure 16). However, 3 equiv of cuprate **68** was needed to drive the reaction to completion.

With the silyl enol ether **69** in hand, we needed to generate the enolate **70** and then oxidize the enolate **70** in situ to introduce the C-17 hydroxyl group (Figure 17). The literature procedure using MeLi to cleave the silyl enol ether **69** was found to be extremely slow.[24] Some dry fluoride reagents were also employed, but none of them gave any satisfactory results. To solve this problem, a new methodology for the generation of enolates from silyl enol ethers by using potassium ethoxide was developed.[25] Employing our new methodology, silyl enol ether **69** was cleaved in 5 min at 0 °C to give the potassium enolate **71** in quantitative yield.

Efforts to oxidize enolate **71** with Davis reagent,[26] molecular oxygen,[27] or dibenzyl peroxydicarbonate[14] were unsuccessful.

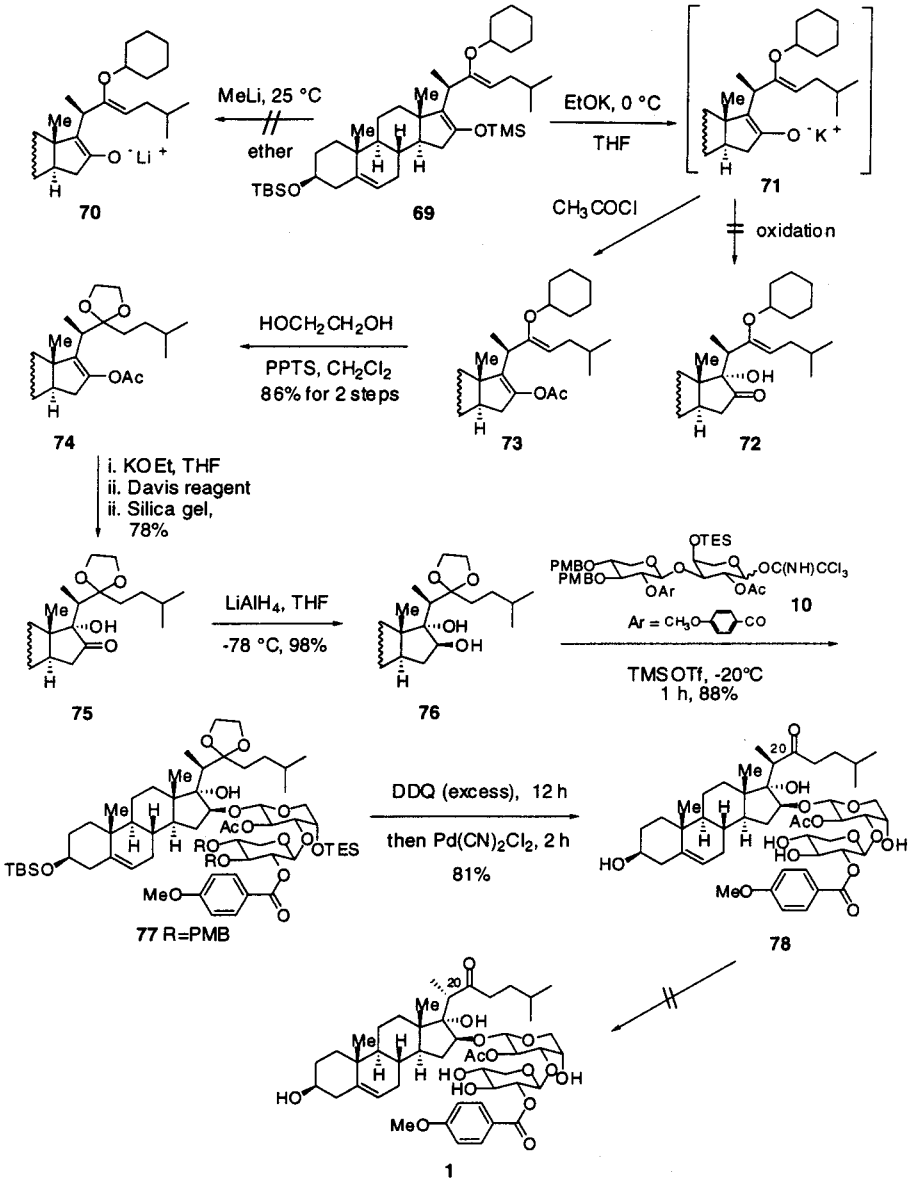
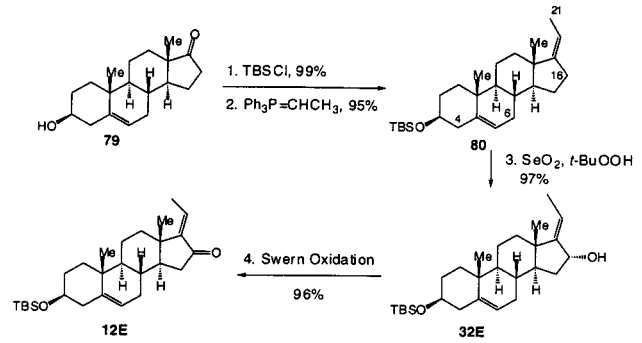



***Figure 17.***

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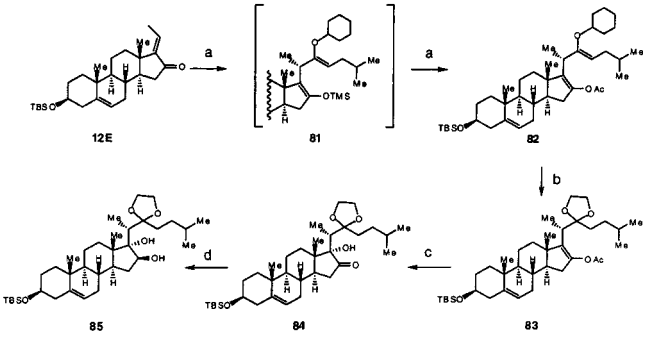


*Figure 19.*

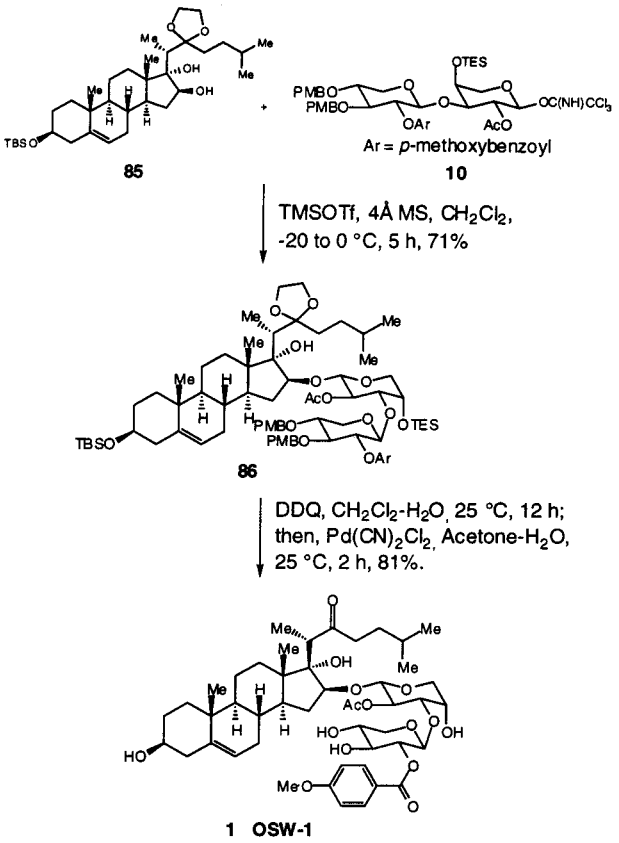


*Figure 20.*

This problem is probably due to the presence of another labile enol ether moiety on the steroid side chain which is also prone to various oxidative reaction conditions. Thus, silyl enol ether **69** was converted to enol acetate **73**, which enabled us to regiospecifically convert the enol ether functionality at C-22 to cycloketal **74**. Either EtOK or *t*-BuOK[28] was used to generate the enolate from enol acetate **74**, and the enolate was then oxidized in situ by Davis reagent to give the α-hydroxyl ketone **75** in 78% yield. Stereospecific reduction of the C-16 ketone by $LiAlH_4$ at −78 °C afforded the *trans* diol **76** in 98% yield. The stereospecificity of the $LiAlH_4$ reduction was presumably due to the directing effort of C-17 hydroxy group.[29]

Glycosylation of the diol **76** with the disaccharide **10** in the presence of TMSOTf provided β-glycoside **77** in 88% yield.[30] All the protecting groups, including two PMB, one TBS, one TES, and one cycloketal, were removed by sequential treatment with DDQ and $Pd(CN)_2Cl_2$[31] in a single operation to give **78** (C-20 epimer of OSW-1) in 81% yield.

To complete the total synthesis of OSW-1 (**1**), the stereochemistry of the C-20 methyl group needed to be epimerized to the requisite *S*-configuration. Unfortunately, our effort to epimerize the C-20 methyl group was not successful. Although various basic conditions (pyridine, DBU, phosphazene base $P_2$-*t*-Bu,[32] etc.) and acidic conditions were investigated, the epimerization of C-20 methyl group to the *S*-configuration was not observed.

The reason for this stereochemistry problem at C-20 was directly related to the enone **12**, a mixture of stereoisomers in favor of the undesired *Z*-isomer (Figure 7). Therefore, a new approach was needed to synthesize enone **12E** stereoselectively with the correct stereochemistry at C-20.

**Total Synthesis of OSW-1.** A new approach for the stereospecific synthesis of enone **12E** was developed (Figure 18). Compound **80** with the requisite *Z*-configuration was prepared according to a literature procedure from commercially available 5-androsten-3β-ol-17-one **79**.[33] Selenium dioxide-mediated allylic oxidation provided **32E** with complete chemo-, regio-, and stereoselectivity.[34] Swern oxidation of **32E** afforded enone **12E** in nearly quantitative yield.

With enone **12E** in hand, TMSCl-activated 1,4-addition of α-alkoxy vinyl cuprate **68** to enone **12E** went smoothly to give silyl enol ether intermediate **81**, which was further converted to enol acetate **82** without isolation of **81** (Figure 19). Compound **82** was then converted to compound **83** in excellent yield. Generation of the enolate from **83** by potassium ethoxide or *t*-BuOK[35] followed by in situ stereoselective oxidation by Davis reagent[36] gave α-hydroxyl ketone **84** in 76% yield. Stereose-

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lective reduction of **84** by $LiAlH_4$ at −78 °C provided the requisite *trans*-16$\beta$,17$\alpha$-diol **85** in 97% yield. The stereochemistry at C16 and C17 of compound **85** was determined by NOESY spectra. Thus, the protected aglycon of OSW-1 (**1**) was synthesized with eight operations in 48% overall yield.

Coupling of disaccharide **10** with the steroid aglycone **85** under the standard conditions[30] gave $\beta$-glycoside **86** in 71% yield. Removal of all the protecting groups by sequential treatment of compound **86** with DDQ and bis(acetonitrile)-dichloropalladium(II) in one operation afforded OSW-1 (**1**) in 81% yield (Figure 20). The physical data of synthetic OSW-1 (**1**) are identical to those reported by Sashida.[1]

## Conclusions

In conclusion, the highly potent anticancer natural product OSW-1 (**1**) has been successfully synthesized in only 10 linear operations from the commercially available starting material 5-androsten-3$\beta$-ol-17-one **79** in 28% overall yield. The highly convergent and stereoselective construction of the protected aglycon has verified that 1,4-addition of an acyl anion equivalent to 17(20)-en-16-one steroids is an attractive strategy to install a steroid side chain. This total synthesis demonstrated once again the versatile synthetic applications of $\alpha$-halo vinyl ether chemistry developed in our laboratories. Currently, synthesis of designed analogues of OSW-1 (**1**) and invesitgation of its structure−activity relationship are on the way in our laboratories and will be reported in due course.

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**Supporting Information Available:** Complete experimental procedures and spectroscopic and analytical data including copies of NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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