A New Strategy for the Stereoselective Introduction of Steroid Side Chain via α-Alkoxy Vinyl Cuprates: Total Synthesis of a Highly Potent Antitumor Natural Product OSW-1[1]

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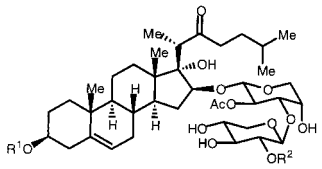
Introduction of a steroid side chain into tetracyclic steroid starting materials has been one of the most important aspects in steroid synthesis, and it has been the subject of many investigations.[2,3]1,4-Addition of an acyl anion equivalent to 17(20)-en-16-one steroids is an attractive strategy to install a steroid side chain. Although this strategy was recognized by Kessar,[4] its application in the synthesis of steroids is still in its infancy.[5] The reason for limited application of this strategy is that hard acyl anion equivalents often prefer 1,2-addition over 1,4-addition, whereas soft acyl anion equivalents afford an equilibrium between 17(20)-en-16-one steroids and 1,4-addition products.[6]

Recently, we reported a new methodology for the general preparation of α-alkoxy vinyl anions.[7] We also demonstrated that α-alkoxy vinyl cuprates can undergo facile 1,4-addition to α,*β*-unsaturated ketones.[7] On the basis of these results, a new convergent strategy for the introduction of the steroid side chain was designed (Scheme 1). TMSCl-activated[8] stereoselective 1,4-addition of the α-alkoxy vinyl cuprate to steroid 17(20)-en-16-one should afford the silyl enol ether, which can further undergo oxidation, alkylation, or condensation at C-17. We were particularly interested in the oxidation reaction because it allows the stereoselective introduction of a hydroxy group to C-17, avoiding the use of osmium tetroxide, which is commonly employed to introduce the 16,17-diol.[9,12]

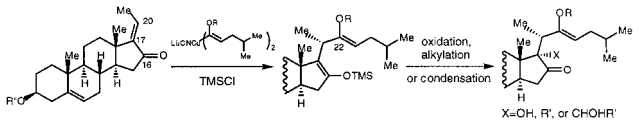
To demonstrate our new strategy, the total synthesis of a naturally occurring saponin, OSW-1 (**1**), was investigated. OSW-1 (**1**) and its four natural analogues (**2**−**5**) are five highly potent antitumor saponins that were recently isolated from the bulbs of *Ornithogalum saundersiae*, a perennial grown in southern Africa.[10]



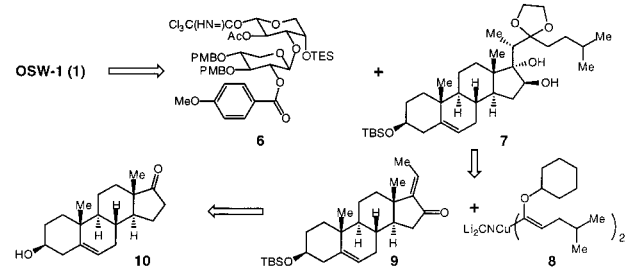
	R^1	R^2	
1	H	*p*-methoxybenzoyl	**OSW-1**
2	H	3,4-dimethoxybenzoyl	
3	H	(*E*)-cinnamoyl	
4	Glc	*p*-methoxybenzoyl	
5	Glc	(*E*)-cinnamoyl	

The IC_{50} values of these compounds against human promyelocytic leukemia HL-60 cells range from between 0.1 and 0.3 nM.[11] Their anticancer activities are from 10 to 100 times more potent than other well-known anticancer agents in clinical use, including mitomycin C, adriamycin, cisplatin, camptothecin, and taxol. OSW-1 (**1**), the main constituent of *Ornithogalum saundersiae* bulbs, is highly cytostatic in the NCI 60-cell in vitro screen, with a mean IC_{50} of 0.78 nM.[11] Due to these extraordinary antitumor activities, OSW-1 is an attractive synthetic target.[12] Fuchs reported the first synthesis of the protected aglycone of OSW-1 in 1998.[12a] By employing the same approach, Yu, Hui, and their co-workers reported the first total synthesis of OSW-1 in 1999.[12b] In this paper, we report a total synthesis of OSW-1(**1**) based on our proposed new strategy.

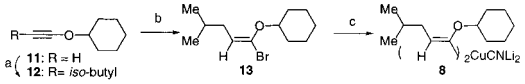
Scheme 1



Scheme 2



Scheme 3[a]



[a] a. (i) *n*-BuLi, −20−0 °C, 20 min; (ii) *iso*-butyl triflate, −30−25 °C, 12 h, 85%; b. TMSBr, MeOH, CH_2Cl_2, −40−25 °C, 15 min, 99%; c. (i) *t*-BuLi (2 equiv), ether, −78 °C, 30 min; (ii) CuCN, LiCl, THF, −78 °C, 15 min.

The retrosynthetic analysis is outlined in Scheme 2. OSW-1 (**1**) was disconnected into the dissacharide **6** and the steroid aglycone **7**. **7** was envisaged to be prepared by the 1,4-addition of the α-alkoxy vinyl cuprate **8** to **9** which was from commercially available 5-androsten-3*β*-ol-17-one **10**.

Scheme 3 outlines the synthesis of the requisite α-alkoxy vinyl cuprate **8**. The acetylenic ether **11** was prepared according to the literature procedure.[13] The α-bromo vinyl ether **13** was prepared regio- and stereoselectively according to our procedures,[7] which was converted in situ to the high-order cuprate **8**.[14]

Compound **15** was prepared from **10** according to literature procedure (Scheme 4).[15] Trost and co-workers have shown that selenium dioxide-mediated allylic oxidation can regio- and stereoselectively introduce a hydroxy group to the C-16 of the steroid 17(20)-en-16-ones.[15] However, in their examples the double bond in the B ring was protected. It is noteworthy that we were able to achieve complete chemo-, regio-, and stereose-

(1) Synthesis via α-halo vinyl ethers 2.
(2) Piatak, D. M.; Wicha, J.*Chem. Rev.* **1978**, *78*, 199 and references therein.
(3) Redpath, J.; Zeelen, F. J. *Chem. Soc. Rev.* **1983**, *12*, 75 and references therein.
(4) (a) Kessar, S. V.; Gupta, Y. P.; Mahajan, R. K.; Rampal, A. L. *Tetrahedron* **1968**, *24*, 893. (b) Kessar, S. V.; Gupta, Y. P.; Mahajan, R. K.; Joshi, G. S.; Rampal, A. L. *Tetrahedron* **1968**, *24*, 899.
(5) 1,4-addition of the soft anion derived from 1-acetoxy-5-nitro-2-methylpentane to 17(20)-en-16-one was very slow (one week). Furthermore, a mixture of diastereoisomers at C-20 was obtained.
(6) Yu, W.; Jin, Z. Unpublished results.
(7) Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2000**, *122*, 9840.
(8) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. (b) Alexakisss, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.
(9) (a) Bernstein, S.; Lenhard, R. H.; Allen, W. S.; Heller, M.; Littell, R.; Stolar, S. M.; Feldman, L. I.; Blank, R. H. *J. Am. Chem. Soc.* **1959**, *81*, 1689. (b) Wendler, N. L.; Taub, D. *J. Am. Chem. Soc.* **1960**, *82*, 2836. (c) Bernstein, S.; Littell, R. *J. Org. Chem.* **1959**, *24*, 429. (d) Brown, J. J.; Bernstein, S. *J. Org. Chem.* **1961**, *26*, 5033.
(10) Kubo, S.; Mimaki, Y.; Terao M.; Sashida, Y.; Nikaido, T.; Ohmoto, T. *Phytochemitstry* **1992**, *31*, 3969.
(11) Mimaki, Y.; Kuroda, M.; Kameyama, A.; Sashida, Y.; Hirano, T.; Oka, K.; Maekawa, R.; Wada, T.; Sugita, K.; Beutler, J. A. *Bioorganic Med. Chem. Lett.* **1997**, *7*, 633.
(12) (a) Guo, C.; Fuchs, P. *Tetrahedron Lett.* **1998**, *39*, 1099. (b) Deng, S.; Yu, B.; Lou, Y.; Hui, Y. *J. Org. Chem.* **1999**, *64*, 202. (c) Morzycki, J. W.; Gryszkiewicz, A.; Jastrzebska, I. *Tetrahedron Lett.* **2000**, *41*, 3751.
(13) Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919.
(14) Lipshutz, B. H. *Synthesis* **1987**, *87*, 325 and references therein.
(15) Schmuff, N. R.; Trost, B. M. *J. Org. Chem.* **1983**, *48*, 1404.

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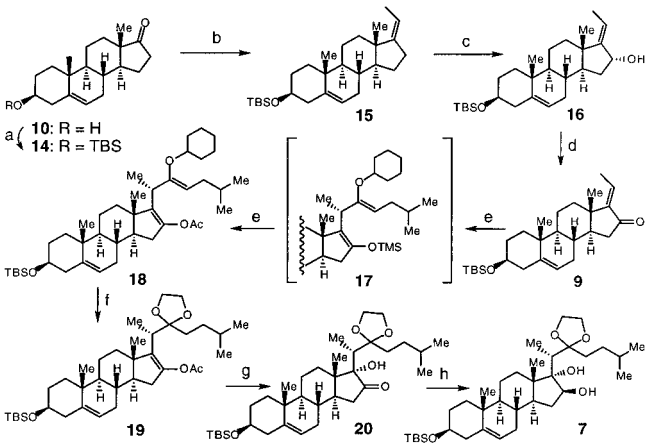
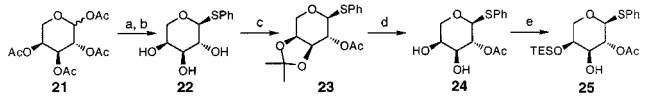
Scheme 4[a]



[a] a. TBSCl, imidazole, CH_2Cl_2, 25 °C, 12 h, 99%; b. $CH_3CH_2P^+Ph_3Br^-$, KO-*t*-Bu, THF, reflux, 36 h, 95%; c. SeO_2 (0.5 equiv), TBHP (1.2 equiv), 0 °C, 2 h, 97%; d. Swern oxidation, 96%; e. (i) TMSCl, **8**, −78 °C, 0.5 h; (ii) EtOK, THF, 0 °C, (iii) AcCl; f. $(CH_2OH)_2$, PPTS, CH_2Cl_2, 25 °C, 5 h, 75% from **9**; g. KO-*t*-Bu, THF, 0 °C, Davis reagent, −78 °C; 76%; h. $LiAlH_4$, −78 °C, THF, 0.5 h, 97%.

Scheme 5[a]



[a] a. PhSH, $SnCl_4$, CH_2Cl_2, −78−25 °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 **22**; e. TESOTf, lutidine, CH_2Cl_2, −50 to −70 °C, 2 h, 90%.

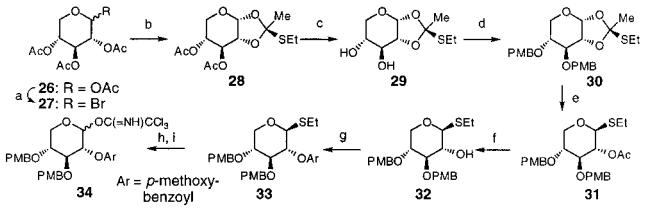
lective allylic oxidation at C-16 under the same reaction conditions without the protection of the 5(6) double bond. Swern oxidation of **16** afforded enone **9** in nearly quantitative yield.[15] TMSCl-activated[8] 1,4-addition of α-alkoxy vinyl cuprate **8** to enone **9** went smoothly to give silyl enol ether intermediate **17**, which was converted to enol acetate **18** in a single operation without the isolation of **17**.[16] The conversion of silyl enol ether **17** to enol acetate **18** enabled us to achieve chemoselective transformation of the enol ether to cyclic acetal **19**. Generation of the enolate from **19** by potassium ethoxide or potassium *tert*-butoxide[17] followed by in situ oxidation by Davis reagent[18] stereoselectively gave α-hydroxy ketone **20** in 76% yield. Stereoselective reduction of compound **20** by $LiAlH_4$ at −78 °C provided the requisite *trans*-16*β*,17α-diol **7** in 97% yield.[19] Thus, the protected aglycone of OSW-1 (**1**) was synthesized with eight operations in 48.4% overall yield.

Synthesis of the disaccharide **6** is outlined in Schemes 5, 6, and 7. Thioglycoside **22** was prepared from tetraacetyl-L-arabinose **21** (Scheme 5). Regioselective protection of the *cis*-diol **22** followed by protection of the C-2 hydroxy group gave **23** in 90% yield. Deprotection of the acetonide afforded diol **24**. Although it is known that the equatorial C-3 hydroxy group in many sugars is more reactive than C-4 axial hydroxy group, to our surprise, high selectivity at the C-4 hydroxy group was observed when **24** was treated with TESOTf and lutidine at low temperature affording the desired product **25** in 90% yield.

The thio ortho ester **28** was prepared from tetraacetyl-D-xylose **26** (Scheme 6).[20] Protecting-group manipulations followed by zinc

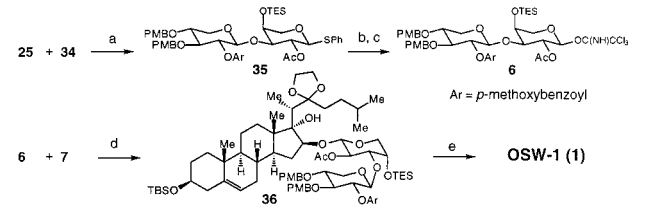
(16) The stereochemistry at C-16 and C-17 of compound **7** was determined by NOESY spectra.

Scheme 6[a]



[a] a. 30% HBr−AcOH, CH_2Cl_2, 0−25 °C, 4 h, 93%; b. EtSH, 2,6-lutidine, $MeNO_2$, 12 h, 82%; c. NaOMe, MeOH, 25 °C, 3 h, 99%; d. (i) NaH, THF; (ii) PMBCl, reflux, 4 h, 98%; e. $ZnCl_2$ (5%), CH_2Cl_2, −60−0 °C; f. NaOMe, MeOH, 25 °C, 4 h, 96% for two 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%.

Scheme 7[a]



[a] a. $BF_3{\cdot}Et_2O$, 4 Å MS, CH_2Cl_2, −78 to −20 °C, 2 h, 93%; b. NBS, pyr, acetone−H_2O (9:1), 25 °C, 2 h, 81%; c. CCl_3CN, DBU, CH_2Cl_2, 12 h, 88%; d. TMSOTf, 4 Å MS, CH_2Cl_2, −20−0 °C, 30 min, 71%; e. DDQ, CH_2Cl_2-H_2O, 25 °C, 12 h; then, $Pd(CN)_2Cl_2$, acetone−H_2O, 25 °C, 2 h, 81%.

chloride promoted intramolecular ring-opening of the thio ortho ester **30** gave thioglycoside **31** in excellent yield. After deacetylation, *p*-methoxy benzoyl group was introduced, and **33** was converted to **34** in 84%.[21]

Glycosylation of **25** with **34** afforded the *β*-disaccharide **35** which was converted to **6** (Scheme 7). Coupling of **6** with the steroid aglycone **7** under standard conditions[22] gave compound **36** in 71% yield. Removal of all of the protecting groups by sequential treatment of compound **36** with DDQ and bis-(acetonitrile)dichloropalladium(II) in one operation afforded OSW-1 (**1**) in 81% yield. The physical data of synthetic OSW-1 (**1**) are identical to those reported by Sashida.[10]

In conclusion, we have developed a new strategy for the stereoselective introduction of the steroid side via 1,4-addition of α-alkoxy vinyl cuprate to 17(20)-en-16-one steroids. On the basis of our new strategy, the highly potent antitumor natural product OSW-1 (**1**) has been successfully synthesized in only 10 linear operations from **10** in 28% overal yield.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Nicolaou, K. C.; Trujillo, J. I.; Chibale, K. *Tetrahedron* **1997,** *53*, 8751.
(18) Yu, W.; Jin, Z. *Tetrahydron Lett.* **2001**, *42*, 369.
(19) Duhamel, P.; Cahard, D.; Poirier, J. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, *21*, 2509.
(20) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.
(21) Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; van Delft, F. L.; Vourloumis, D.; Xu, J. Y.; Pfefferkorn, J.; Kimet, S. *J. Am. Chem. Soc.* **1998**, *120*, 8674.
(22) Jiang, Z. H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1992**, 975.