

A Highly Stereoselective Synthesis of α -Halo Vinyl Ethers and Their Applications in Organic Synthesis¹

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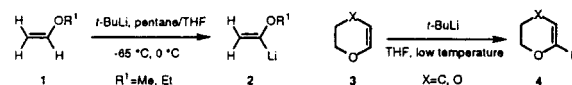
The use of acyl anion equivalents in the formation of C–C bonds is a powerful strategy in the development of new synthetic methods.² Among all the acyl anion equivalents, the α -alkoxy vinyl anions are notable for their low cost, high reactivity, and easy deprotection of the resultant vinyl ether functionality. α -Alkoxyvinylolithiums can be prepared by metalation of the commercially available methyl vinyl ether or ethyl vinyl ether using *t*-BuLi or super base (BuLi/KO-*t*-Bu).³ This methodology was subsequently extended to cyclic systems (Scheme 1) by Boeckman.⁴ In addition, metalation of 1,3-dienyl ethers, 1,3,5-trienyl ethers, and alkoxyallenes was also realized under the similar conditions.⁵

Chemical applications of more substituted acyclic α -alkoxy vinyl anions is still in its infancy compared to other acyl anion equivalents. The reason for the underdevelopment in this field is that clean metalation of a variety of acyclic vinyl ethers with β -alkyl substituents is quite difficult.⁶ Although (*Z*)-1-propenyl 2-tetrahydropyranyl ether and 2-methyl-1-propenyl 2-tetrahydropyranyl ether react with *s*-BuLi/KO-*t*-Bu to give the corresponding anions, it only works in the case of tetrahydropyranyl ether for additional chelation and stability of such reagents.⁷ Metalation of (*Z*)-1-ethoxy-propene required 24 h at -30 °C and gave only 70% yield of the corresponding anion. Metalation of compounds bearing more sterically demanding alkyl groups were uniformly unsuccessful even employing super bases.⁶

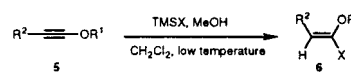
To solve this problem, Kocienski and co-workers developed a procedure to prepare α -alkoxy vinylstannanes as the precursor of α -alkoxy vinyl anions.⁶ However, this method suffered from low yields due to the formation of the undesired regioisomer and the decomposition of the products during column chromatography.

In connection with a project in our laboratories, we required to generate β -alkyl substituted α -alkoxy vinyl cuprates. α -Alkoxy vinylolithium was envisaged to be generated by lithium–halogen exchange between butyllithium and α -halo vinyl ether. However, we were surprised to find that there was no general literature procedure for the regio- and stereoselective preparation of α -halo vinyl ethers. Thus, our first task was to secure a new method for the preparation of α -halo vinyl ethers.

Scheme 1



Scheme 2



It is known that many reagents can undergo electrophilic addition to acetylenic ethers.⁸ However, the addition of HX to acetylenic ethers has not been systematically studied. The problem associated with this type of reactions lies in the difficulty of accurate addition of commercially available HX and the formation of a mixture of stereoisomers and side products caused by excess of HX.^{8c,18d} In addition, α -halo vinyl ethers are quite labile and are prone to decomposition during aqueous workup and silica gel column chromatography. We have found that hydrogen halide generated *in situ* by addition of 0.99 equiv of trimethylsilyl halide⁹ to a solution of 1.0 equiv of acetylenic ether¹⁰ and 0.99 equiv of MeOH in CH_2Cl_2 at low temperature exclusively gave α -halo vinyl ether in a completely regio- and stereospecific manner (Scheme 2). The yield was nearly quantitative (excess of acid resulted in poorer selectivity). Since MeOTMS could be evaporated easily, neither work up nor column chromatography was necessary.

Table 1 summarized the preparation of a variety of α -halo vinyl ethers using our procedure. It should be noted that the reaction employing *in situ* generation of HCl was not only faster than that using commercially available HCl in ether (entries 4 and 5), but also gave better stereoselectivity (entry 3). We believe that this is due to the solvent effect. In addition, higher temperature gave better stereoselectivity (entries 3 and 5). Although α -halo vinyl ethers are prone to decomposition to the corresponding esters, they can be stored in frozen benzene for a month. Because of the simplicity of our procedure, we often prepare them before use.

We next examined the reaction between α -bromo vinyl ethers and BuLi.¹¹ *t*-BuLi reacted with α -bromo vinyl ethers very quickly at -78 °C and afforded α -alkoxy vinylolithiums quantitatively.¹² The geometry of the double bond was fully retained in all instances. Entries 1–4 in Table 2 are several examples of the application of this type of acyl anions for organic synthesis.

The quantitative generation of the α -alkoxy vinylolithium enabled us to study the formation of organo copper reagents.¹³ Low-order,¹³ high-order,¹⁴ and mixed-high-order cuprates¹⁵ have

(1) Synthesis via α -halo vinyl ethers 1.

(2) For recent reviews on acyl anion equivalents, see: (a) Albright, J. D. *Tetrahedron* **1983**, 39, 3207. (b) Otera, J. *Synthesis* **1988**, 88, 95. (c) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, 18, 239. (d) Hase, T. A.; Koskimies, J. K. *Aldrichimica Acta* **1982**, 15, 35 and references therein.

(3) (a) Schollkopf, U.; Hanssle, P. *Justus Liebigs Ann. Chem.* **1972**, 763, 208. (b) Baldwin, J. E.; Hofle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, 96, 7125. (c) Verkruisje, H. D.; Brandsma, L.; Schleyer, P. V. R. *J. Organomet. Chem.* **1987**, 332, 99.

(4) (a) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron Lett.* **1977**, 4187. (b) Boeckman, Jr. R. K.; Bruza, K. J. *Tetrahedron* **1981**, 37, 3997. (c) Riobe, O.; Lebouc, A.; Delaunay, J. C. R. *Hebd. Seances Acad. Sci.* **1977**, 284, 281. (d) Schlosser, M.; Schaub, B.; Spahie, B.; Sleiter, G. *Helv. Chim. Acta* **1973**, 36, 2166.

(5) (a) Everhardus, R.; Grafing, R.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1978**, 97, 69. (b) Soderquist, J. A.; Hassner, A. *J. Am. Chem. Soc.* **1980**, 102, 1577. (c) McDougal, P. G.; Rico, J. G. *J. Org. Chem.* **1987**, 52, 4817.

(6) Casson, S.; Kocienski, P. *Synthesis* **1993**, 1133.

(7) (a) Hartmann, J.; Stahle, M.; Schlosser, M. *Synthesis* **1974**, 888. (b) Schlosser, M. *Organometallics in Synthesis: A Manual*; Wiley: Chichester, 1994; pp 110–111.

(8) (a) Kazankova, M. A.; Satina, T. Ya.; Lun'kov, V. D.; Lutsenko, I. F. *J. Gen. Chem. USSR (Engl. Transl.)* **1978**, 48, 58. (b) Van Den Bosch, G.; Bos, H. J. T.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1970**, 89, 133. (c) Arth, G. E.; Poos, G. I.; Lukes, R. M.; Robinson, F. M.; Johns, W. F.; Feurer, M.; Sarett, L. H. *J. Am. Chem. Soc.* **1954**, 76, 1715. (d) Herrmann, M.; Böhlendorf, B.; Irschik, H.; Reichenbach, H.; Höfle, G. *Angew. Chem., Int. Ed.* **1998**, 37, 1253. (e) Regio- and stereoselective *syn*-monoaddition of gaseous HCl to alkynyl tosylates has been reported: Stang, P. J.; Roberts, K. A. *J. Org. Chem.* **1987**, 52, 5213.

(9) Both TMSCl and TMSBr were distilled and stored over polyvinyl pyridine in a flame-dried bottle. TMSI (purchased from Aldrich) was used without further purification.

(10) Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, 52, 2919 and references therein.

(11) For references of Li-halogen exchange of 2-bromofuran, 2-bromo-2,3-dihydrofuran, and 2-bromopyran see: (a) Knight, D. W.; Rustidge, D. C. *J. Chem. Soc., Perkin. Trans. 1* **1981**, 679. (b) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, 112, 1897.

(12) (a) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, 94, 7210. (b) Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, 107, 847.

(13) Boeckman, R. K., Jr.; Bruza, K. J.; Baldwin, J. E.; Lever, O. W., Jr. *Chem. Commun.* **1975**, 519.

(14) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, 40, 5005 and references therein.

(15) Lipshutz, B. H. *Synthesis* **1987**, 87, 325 and references therein.

Table 1. A Stereoselective Synthesis of α -Halo Vinyl Ethers

Entry	Substrates ^a	Conditions ^b	Products ^c	Yield ^d
1		Method A,		99%
2	7	Method B,	8-I X=I	97%
3	7	Method C,	8-Cl X=Cl	97%
4	7	HCl in ether, 25 °C, 30min	8-Cl	90%
5	7	HCl in ether, -30 °C, 7h	8-Cl	E:Z=2:1 99%
6	9	Method A		89%
7	9	Method B	10-I X=I	91%
8	11	Method A		99%
9	11	Method B	12-I X=I	99%
10	13	Method A		99%
11	13	Method B	14-I X=I	99%
12	15	Method A		96%
13	15	Method B	16-I X=I	98%

^a R³ = (-)-menthol, R⁴ = [(1*S*)-endo]-(-)-Borneol. ^b All reactions were run in CH₂Cl₂. ^c The geometry of double bonds were determined by NOESY spectra. ^d All yields are isolated yields. The *Z/E* ratios were measured by integration of well-resolved signals in the ¹H NMR. Method A: TMSBr (0.99 equiv), MeOH (0.99 equiv), -40 °C, 10 min; Method B: TMSI (0.99 equiv), MeOH (0.99 equiv), -78 °C, 10 min; Method C: TMSCl (0.99 equiv), MeOH (0.99 equiv).

been successfully prepared from α -alkoxy vinylolithium, and their conjugate additions to α,β -unsaturated ketones were examined (Table 2, entries 5–7). All reactions afforded excellent yields and retention of the stereochemistry of the double bond.

α -Halo vinyl ethers can undergo many important transformations catalyzed by transition metals such as palladium and nickel.¹⁶ In the presence of a catalytic amount of palladium catalyst, compound **8-Br** underwent Stille coupling¹⁷ with tributylvinyltin to provide functionalized 1,3-diene **22** which could not be easily access *via* known procedures, and can be used in asymmetric Diels–Alder reactions (Table 2, entry 8). It was interesting to observe that the geometry of the double bond was cleanly inverted. α -Bromo vinyl ether **10-Br** could also undergo Sonogashira coupling¹⁸ to give enyne **23** in excellent yield with complete retention of the geometry of the double bond (Table 2, entry 9). Palladium(0)-catalyzed carbonylation¹⁹ between α -bromo vinyl ether **12-Br** and CO in the presence of methanol gave α -methoxy- α,β -unsaturated ester **24** in nearly quantitative yield (Table 2, entry 10). In this case, the geometry of the double bond was stereospecifically inverted. α -Halo vinyl ethers also couple with Grignard reagents catalyzed by an organonickel catalyst. Compound **12-Br** reacted with EtMgBr in the presence of a catalytic amount of NiCl₂dpppp₂ to give **25** in 71% after hydrolysis the enol ether (Table 2, entry 11). The same reaction also worked with

(16) Ni(acac)₂ was in the coupling reaction between 1-bromo-1-ethoxy-ethene and a Grignard reagent, Glazunova, E. Yu.; Lutsenko, S. V.; Efimova, I. V.; Trostyanskaya, I. G.; Kazankova, M. A.; Beletskaya, I. P. *Russian J. Org. Chem.* **1969**, *34*, 4, 1104. In addition, both nickel and palladium catalysts have been used in the preparation of dialkylaminovinyl-phosphonates from 1-bromo-1-ethoxy-ethene, Kazankova, M. A.; Trostyanskaya, I. G.; Lutsenko, S. V.; Beletskaya, I. P. *Tetrahedron Lett.* **1999**, *40*, 569; Kazankova, M. A.; Chirkov, E. A.; Kochetkov, A. N.; Efimova, I. V.; Beletskaya, I. P. *Tetrahedron Lett.* **1999**, *40*, 573.

(17) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.

(18) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467

(19) Tour, J. M.; Negishi, E.-I. *J. Am. Chem. Soc.* **1985**, *107*, 8289.

(20) Tamao, K.; Zembayashi, M.; Kumada, M. *Chem. Lett.* **1976**, *76*, 1237.

Table 2. Application of α -Halo Vinyl Ethers in Organic Synthesis

Entry	Substrates ^a	Conditions	Products ^b	Yield ^c
1	10-Br	1) <i>n</i> -BuLi, THF, -78 °C 2) PhCHO, 3) Ac ₂ O		99%
2	16-Br	1) <i>t</i> -BuLi, THF, -78 °C 2) ClCO ₂ Bn		87%
3	8-Br	1) <i>t</i> -BuLi, THF, -78 °C 2) TMSCl		97%
4	8-Br	1) <i>t</i> -BuLi, THF, -78 °C 2) Me ₃ SnCl		98%
5	14-Br	1) <i>t</i> -BuLi, ether, -78 °C 2) CuI, Me ₂ S, -40 °C, 3) 2-cyclohexen-1-one, -78 °C,		78%
6	14-Br	Method A	21	88%
7	14-Br	Method B	21	84%
8	8-Br	PdCl ₂ (PPh ₃) ₂ , CH ₃ CN, Bu ₃ Sn-, reflux,		91%
9	10-Br	≡Me, PdCl ₂ (PPh ₃) ₂ , CuI, piperidine, THF, 0–25 °C,		94%
10	12-Br	Pd(OAc) ₂ , PPh ₃ , Et ₃ N, CO, MeOH, DMF, 70 °C		98%
11	12-Br	1) NiCl ₂ dpppp ₂ , EtMgBr, 25 °C, C ₆ H ₆ , 2) H ₃ O ⁺		71%
12	8-Br	NiCl ₂ dpppp ₂ , PhMgBr, 25 °C, C ₆ H ₆		86%

^a R³ = (-)-menthol, R⁴ = [(1*S*)-endo]-(-)-Borneol. ^b The geometry of double bonds were determined by NOE or NOESY spectra. ^c All yields are isolated yields. Method A: (1) *t*-BuLi (2 equiv., ether, -78 °C). (2) CuCN, LiCl (2 equiv), THF, -40 °C, 30 min. (3) 2-cyclohexen-1-one, -78 °C, 5 min. Method B: (1) *t*-BuLi, ether, -78 °C. (2) CuCN, MeLi, THF, -40 °C, 30 min. (3) 2-cyclohexen-1-one, -78 °C, 5 min.

PhMgBr to afford **26** with retention of the geometry of the double bond (Table 2, entry 12).²⁰

In summary, we have successfully developed a highly regio- and stereoselective method for the synthesis of α -halo vinyl ethers. We have demonstrated that α -halo vinyl ethers can serve as excellent latent acyl anions for carbon–carbon bond formation. The quantitative generation of α -alkoxyvinylolithium enables the formation of a variety of cuprates that were not accessible via the previous known literature procedures. Furthermore, we have also discovered that α -halo vinyl ethers are highly versatile substrates for transition metal catalyzed cross-coupling reactions. Currently, we are studying the asymmetric reactions employing the substrates bearing a chiral R¹ group as chiral auxiliary. Application of these methodologies to the total synthesis of natural products is underway, and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data for all the compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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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 β -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 α -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 α -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 IC₅₀ 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 (IC₅₀ 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

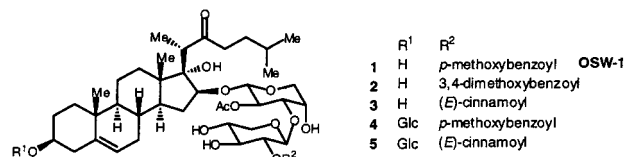


Figure 1.

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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(1) Kubo, S.; Mimaki, Y.; Terao, M.; Sashida, Y.; Nikaido, T.; Ohmoto, T. *Phytochemistry* **1992**, *31*, 3969.
 (2) Mimaki, Y.; Kuroda, M.; Kameyama, A.; Sashida, Y.; Hirano, T.; Oka, K.; Maekawa, R.; Wada, T.; Sugita, K.; Beutler, J. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 633.
 (3) (a) Pettit, G. R.; Inoue, M.; Kamano, Y.; Herald, D. L.; Arm, C.; Dufresne, C.; Christie, N. D.; Schmidt, J. M.; Doubek, D. L.; Krupa, T. S. *J. Am. Chem. Soc.* **1988**, *110*, 2006. (b) LaCour, T. G.; Guo, C.; Bhandaru, S.; Boyd, M. R.; Fuchs, P. L. *J. Am. Chem. Soc.* **1998**, *120*, 692.

(4) Guo, C.; Fuchs, P. L. *Tetrahedron Lett.* **1998**, *39*, 1099.
 (5) Guo, C.; LaCour, T. G.; Fuchs, P. L. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 419.
 (6) (a) Deng, S.; Yu, B.; Lou, Y.; Hui, Y. *J. Org. Chem.* **1999**, *64*, 202. (b) Morzycki, J. W.; Gryszkiewicz, A.; Jastrzebska, I. *Tetrahedron Lett.* **2000**, *41*, 3751. (c) Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2001**, *123*, 3369.
 (7) MM2 calculation was performed using CS Chem Ultra program on a powerMac. The calculation results were consistent with experimental results, see ref 10.

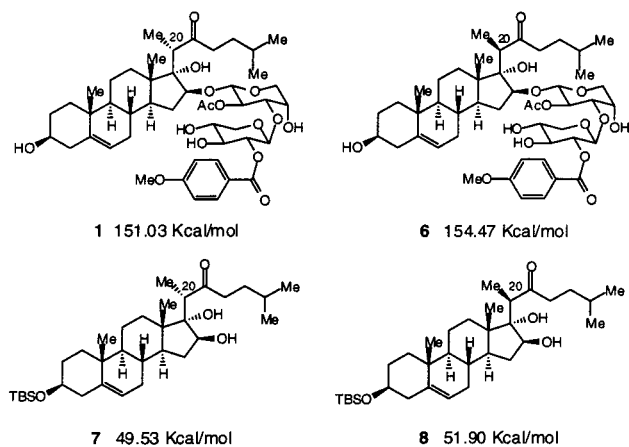


Figure 2.

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 methods⁸ 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-

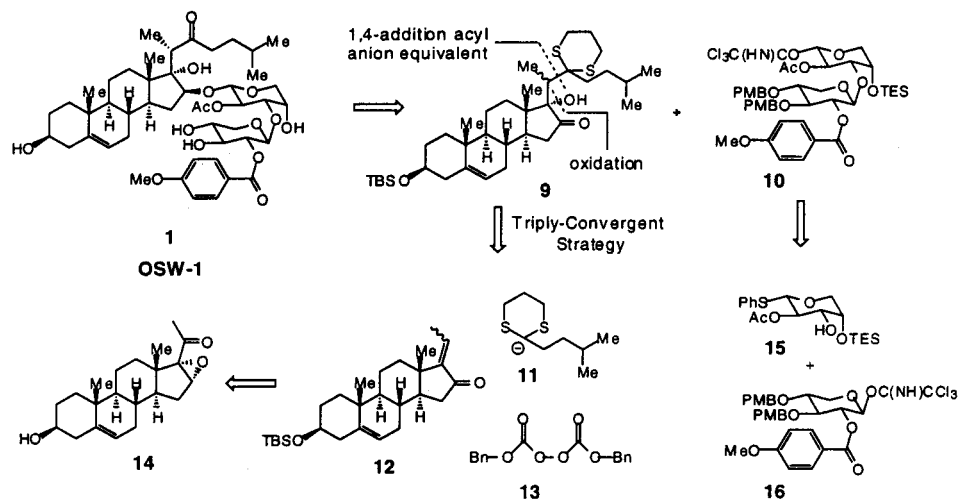
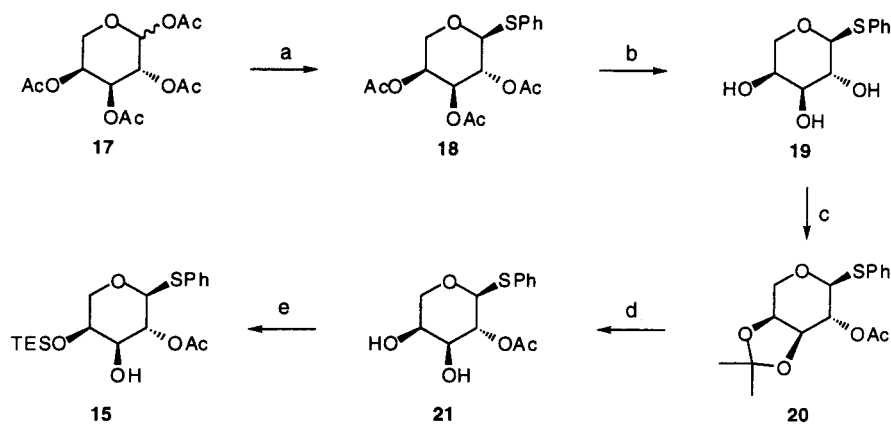
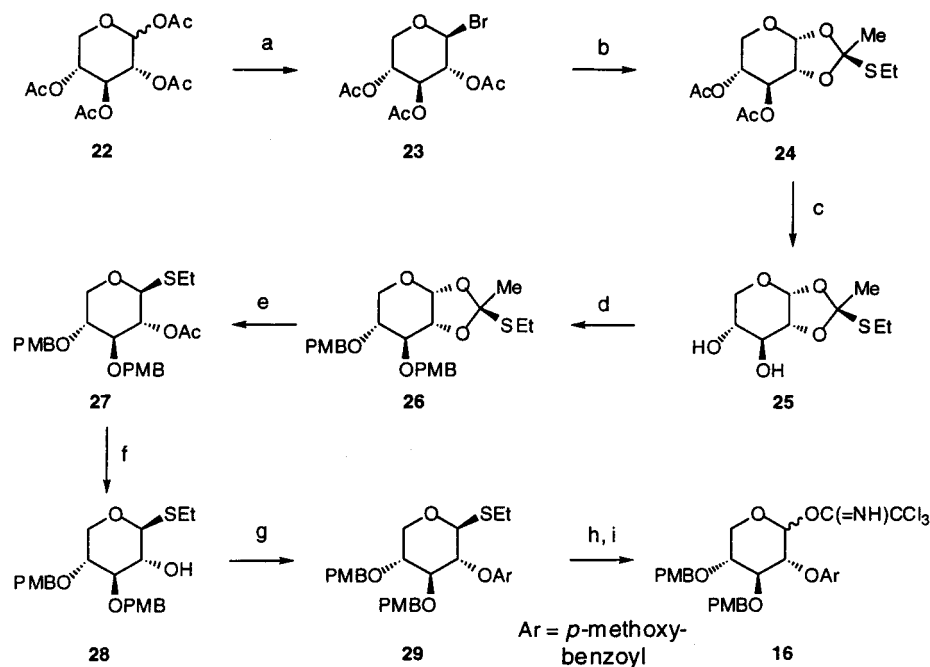


Figure 3.



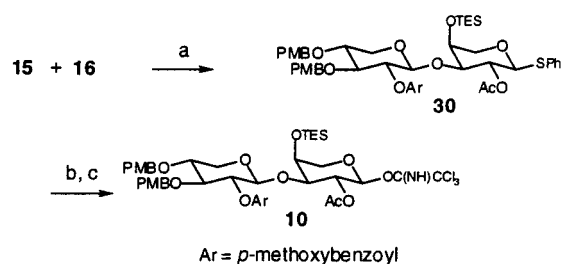
a. PhSH, SnCl₄, CH₂Cl₂, -78 to 25 °C, 80%; b. NaOMe, MeOH, 6 h, 95%; c. i) Me₂C(OMe)₂, CSA, CH₂Cl₂, 12 h; ii) Ac₂O, DMAP, Et₃N, CH₂Cl₂, 2 h; d. Amberlite IR-118H, MeOH, 12 h, 90% from **19**; e. TESOTf, lutidine, CH₂Cl₂, -60 to -70 °C, 2 h, 90%.

Figure 4.



a. 30% HBr-AcOH, CH₂Cl₂, 0 to 25 °C, 4 h, 93%; b. EtSH, 2,6-lutidine, MeNO₂, 12 h, 82%; c. NaOMe, MeOH, 25 °C, 3 h; d. i) NaH, THF; ii) PMBCl, reflux, 4 h, 94% from **24**; e. ZnCl₂ (5%), CH₂Cl₂, -60 to 0 °C; f. NaOMe, MeOH, 25 °C, 4 h, 95% for 2 steps; g. *p*-anisoyl chloride, DMAP, NEt₃, CH₂Cl₂, 24 h, 97%; h. NBS, H₂O, CH₂Cl₂, 1 h, 88%; i. CCl₃CN, DBU, CH₂Cl₂, 3 h, 95%.

Figure 5.



a. BF₃·Et₂O, 4 Å MS, CH₂Cl₂, -78 to -20 °C, 4 h, 93%; b. NBS, CH₂Cl₂-H₂O (9:1), 25 °C, 2 h, 81%; c. CCl₃CN, DBU, CH₂Cl₂, 12 h, 88%.

Figure 6.

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 BF₃·Et₂O afforded the β-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-3β-ol-20-one **14** was protected by a TBS group to give compound **31** (Figure 7). Reduction of the α,β-epoxy ketone **31** by hydrazine hydrate gave the allyl alcohol **32** in 73% yield.¹⁰

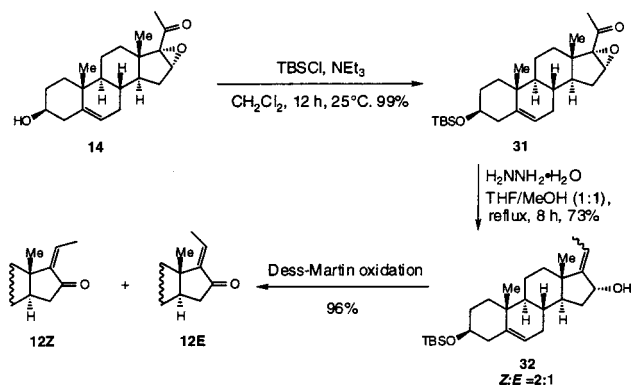


Figure 7.

Dess–Martin oxidation¹¹ 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.
(9) Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; Delft, F. L. van; Vourloumis, D.; et al. *J. Am. Chem. Soc.* **1998**, *120*, 8674.

(10) (a) Kessar, S. V.; Rampal, A. L. *Tetrahedron*, **1968**, *24*, 887. (b) Kessar, S. V.; Gupta, Y. P.; Mahajan, R. K.; Rampal, A. L. *Tetrahedron* **1968**, *24*, 893.

(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.

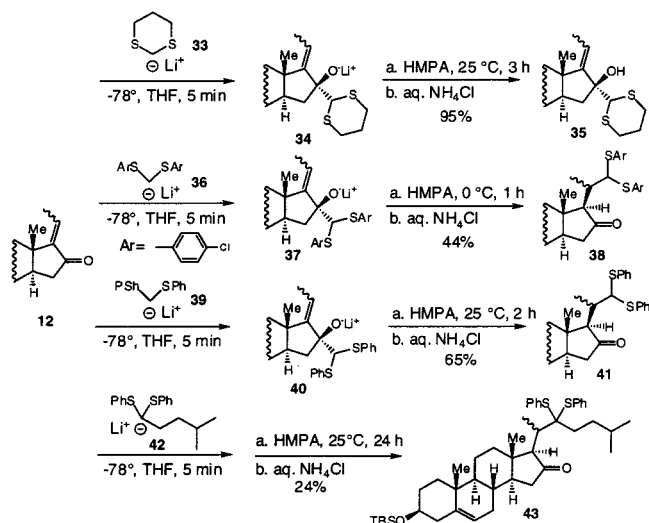


Figure 8.

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 β -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 β -isobutyl substituted α -methoxy vinyl cuprate **58** (Figure 12). However, there was no literature procedure for the quantitative generation of the requisite β -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

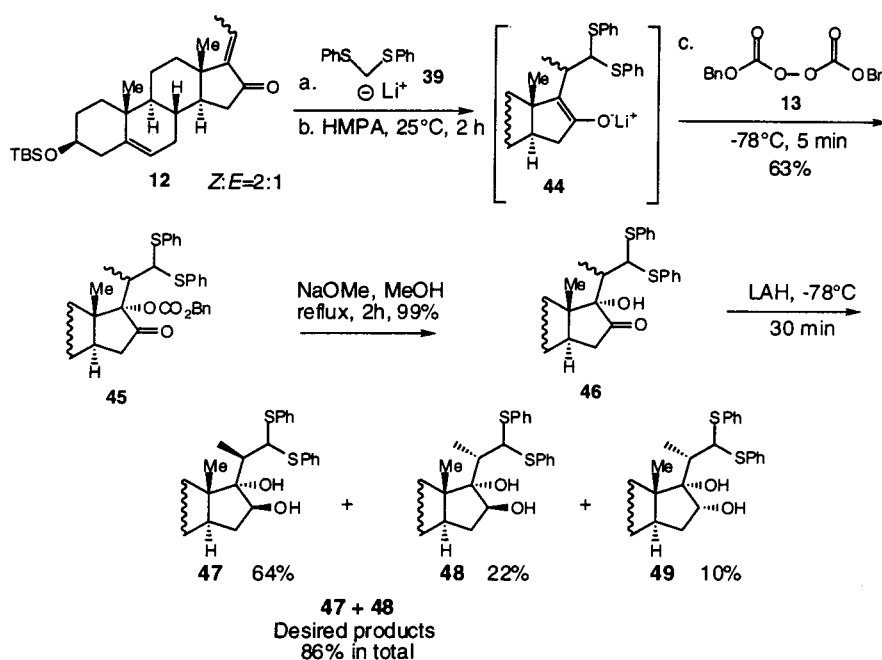


Figure 9.

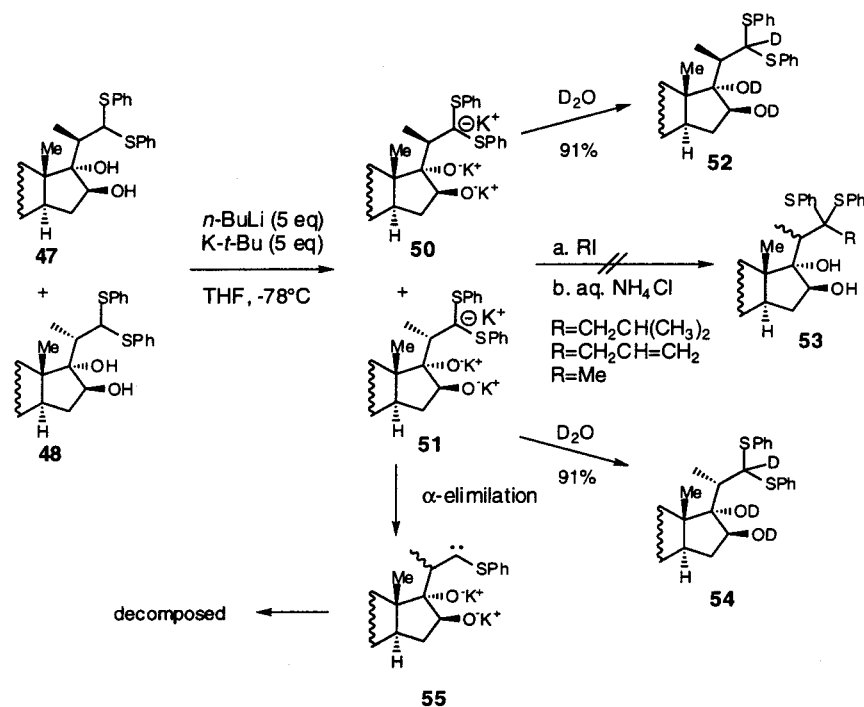


Figure 10.

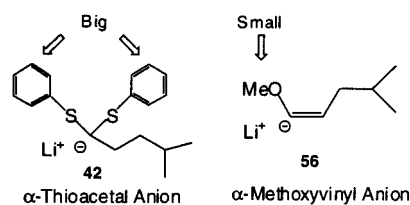


Figure 11.

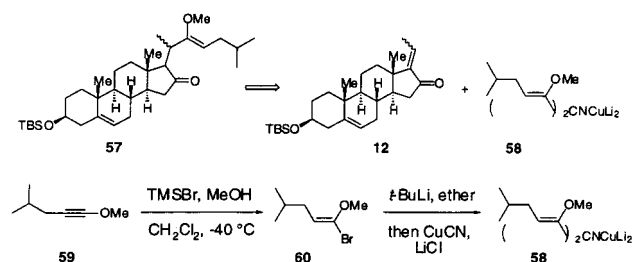


Figure 12.

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

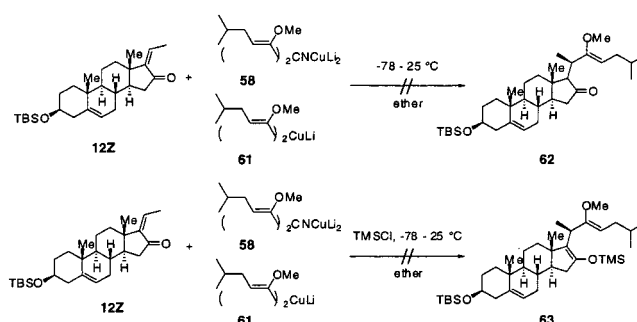


Figure 13.

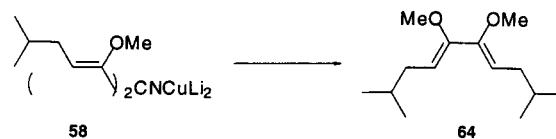


Figure 14.

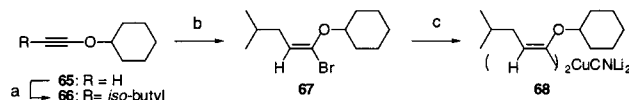


Figure 15.

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

(13) (a) Reich, H. J.; Sikorski, W. H. *J. Org. Chem.* **1999**, *64*, 14. (b) Brown, C. A.; Yamaichi, A. *Chem. Commun.* **1979**, 100.

(14) Gore, M. P.; Vederas, J. C. *J. Org. Chem.* **1986**, *51*, 3700.

(15) Schlosser, M.; Strunk, S. *Tetrahedron Lett.* **1984**, *25*, 741.

(16) Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2000**, *122*, 9840.

(17) Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2, 2919.

(18) Yu, W.; Jin, Z. Unpublished results.

(19) (a) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005 and references cited therein. (b) Lipshutz, B. H. *Synthesis* **1987**, *87*, 325 and references therein.

(20) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019.

(21) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.

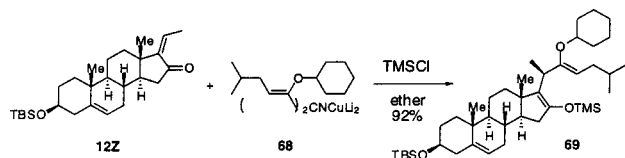


Figure 16.

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 filter²³ 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 peroxydicarbonate¹⁴ were unsuccessful.

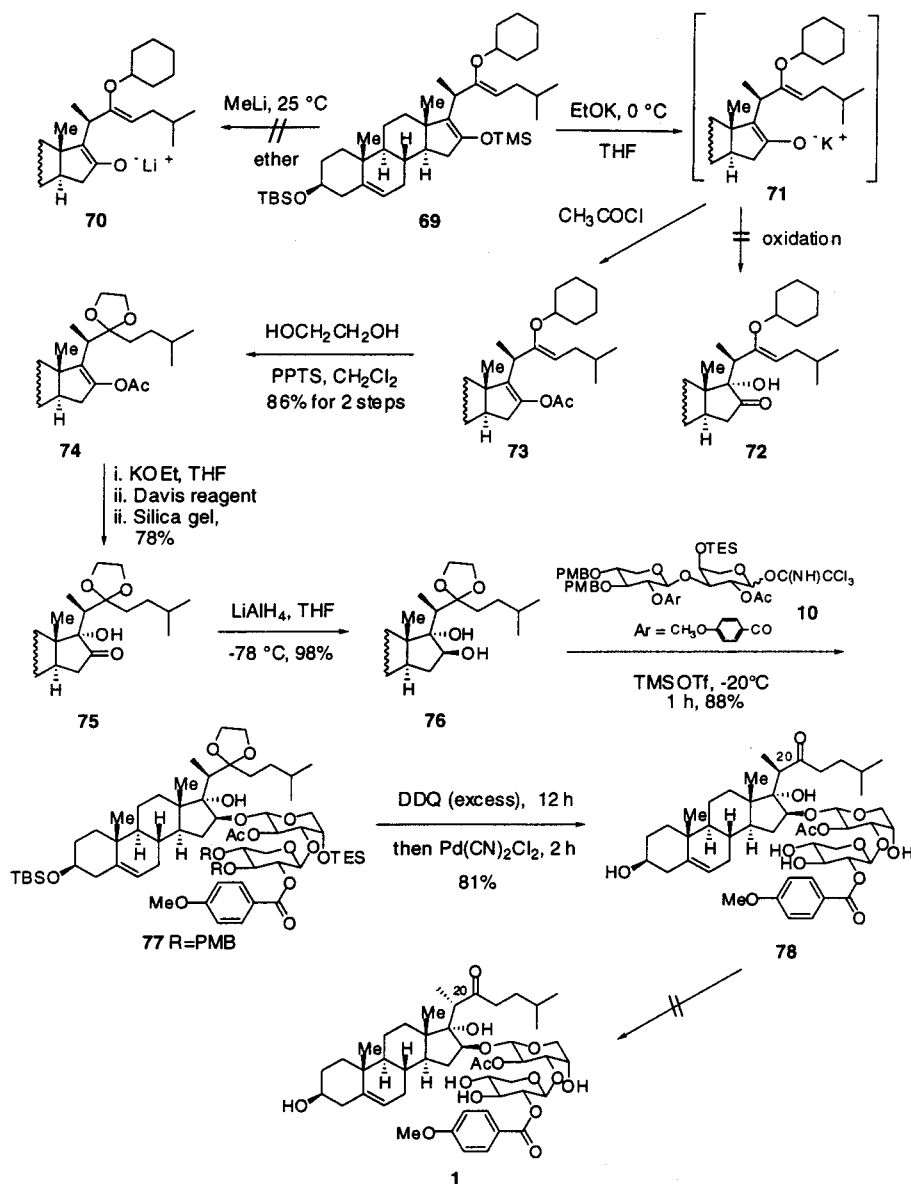


Figure 17.

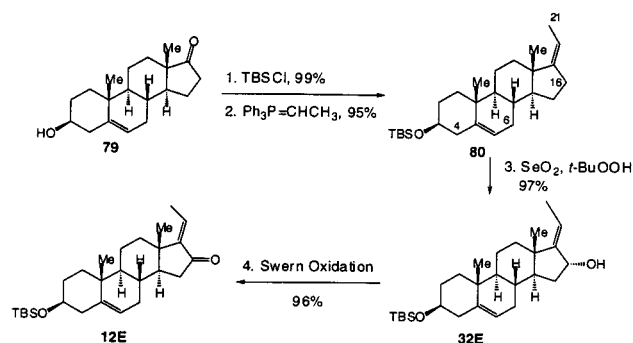
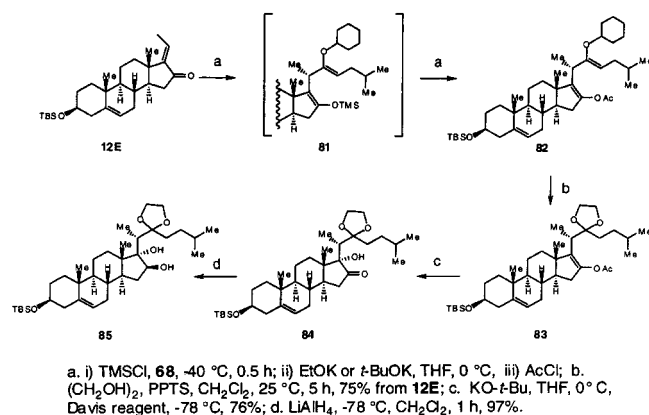


Figure 18.



a. i) TMSCl, **68**, -40 °C, 0.5 h; ii) EtOK or *t*-BuOK, THF, 0 °C, iii) AcCl; b. (CH₂OH)₂, PPTS, CH₂Cl₂, 25 °C, 5 h, 75% from **12E**; c. KO-*t*-Bu, THF, 0 °C, Davis reagent, -78 °C, 76%; d. LiAlH₄, -78 °C, CH₂Cl₂, 1 h, 97%.

Figure 19.

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 regioselectively convert the enol ether functionality at C-22 to cycloketal **74**. Either EtOK or *t*-BuOK²⁸ 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 LiAlH₄ at -78 °C afforded the *trans* diol **76** in 98% yield. The stereospecificity of the LiAlH₄ 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)₂Cl₂³¹ 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

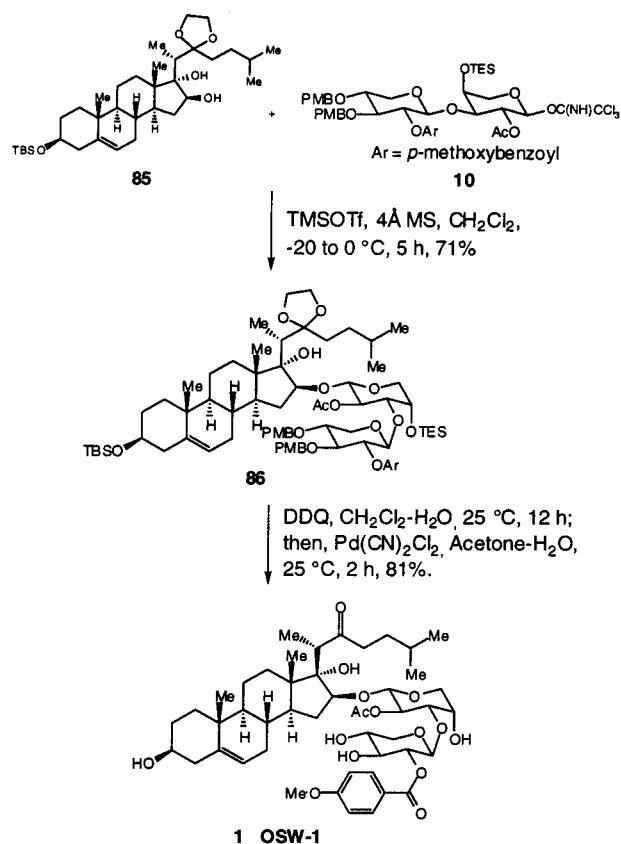


Figure 20.

various basic conditions (pyridine, DBU, phosphazene base P₂-*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*-BuOK³⁵ followed by in situ stereoselective oxidation by Davis reagent³⁶ gave α-hydroxyl ketone **84** in 76% yield. Stereose-

(22) Blanchot-Courtois, V.; Hanna, I. *Tetrahedron Lett.* **1992**, *33*, 8087.

(23) Kim, S.; Sutton, S. C.; Guo, C.; LaCour, T. G.; Fuchs, P. L. *J. Am. Chem. Soc.* **1999**, *121*, 2056.

(24) Stork, G.; Hudrik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464.

(25) Yu, W.; Jin, Z. *Tetrahedron Lett.* **2001**, *42*, 369.

(26) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.

(27) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

(28) (a) Duhamel, P.; Cahard, D.; Poirier, J. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, *21*, 2509. (b) Quesnel, Y.; Bidois-Sery, L.; Poirier, J.-M.; Duhamel, L. *Synlett* **1998**, 413.

(29) We found that LiAlH₄ reduction of an analogue of compound **75** without C-17 hydroxy group was very slow at low temperature. Yu, W.; Jin, Z. Unpublished results.

(30) Jiang, Z. H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1992**, 975.

(31) Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705.

(32) Schwesinger, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1164.

(33) Schmuft, N. R.; Trost, B. M. *J. Org. Chem.* **1983**, *48*, 1404.

(34) Snider, B. B.; Shi, B.; *Tetrahedron* **1999**, *55*, 14823.

(35) Duhamel, P.; Cahard, D.; Poirier, J. M. *J. Chem. Soc., Perkin Trans. 1* **1993**, *21*, 2509.

(36) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.

lective reduction of **84** by LiAlH_4 at $-78\text{ }^\circ\text{C}$ provided the requisite *trans*-16 β ,17 α -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 conditions³⁰ gave β -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 β -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 α -halo vinyl ether chemistry developed in our laboratories. Currently, synthesis of designed analogues of OSW-1 (**1**) and investigation of its structure–activity relationship are on the way in our laboratories and will be reported in due course.

Acknowledgment. This work was supported by a Research Project Grant RPG-00-030-01-CDD from the American Cancer Society, the Central Investment Fund for Research Enhancement at The University of Iowa. Thanks are due to the Center for Biocatalysis and Bioprocessing at The University of Iowa for providing a fellowship to W. Yu. We also express our appreciation to Ms. Johanne Ohannessian and Mr. Zhenmao Hua for their help in some of the experiments.

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>.

JA012119T

Total Synthesis of the Highly Potent Anti-HIV Natural Product Daurichromenic Acid along with Its Two Chromane Derivatives, Rhododaurichromenic Acids A and B

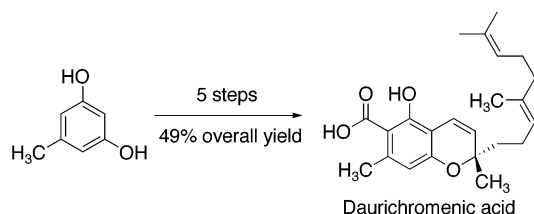
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ABSTRACT

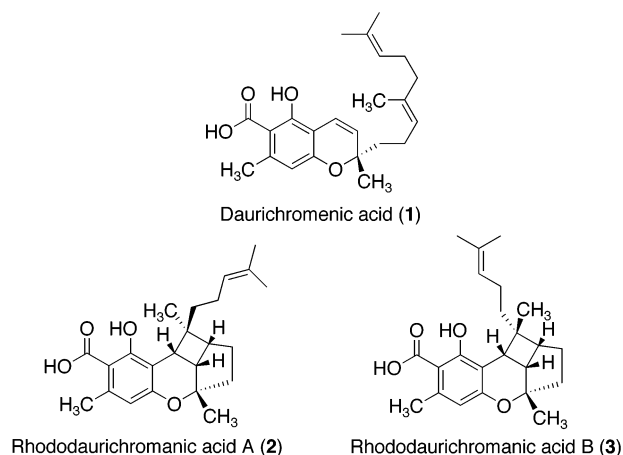


The highly potent anti-HIV natural product daurichromenic acid was successfully synthesized in only five steps with 49% overall yield. The key step in the synthetic strategy involves a microwave-assisted tandem condensation and intramolecular S_N2' -type cyclization to form the 2*H*-benzopyran core structure.

Two novel chromane derivatives rhododaurichromenic acids A (**2**) and B (**3**) were isolated from the leaves and twigs of *Rhododendron dauricum*, a plant that is distributed in the northern part of China, the eastern part of Siberia, and Hokkaido, Japan (Scheme 1).¹ A known natural product, daurichromenic acid (**1**), was also isolated from the same plant.² The absolute structures of these three compounds were determined on the basis of extensive spectroscopic examination and X-ray crystallographic analysis.¹ Daurichromenic acid (**1**) belongs to the family of chromene natural products and demonstrates highly potent anti-HIV activity in acutely infected H9 cells with an EC_{50} value of 5.67 ng/mL and therapeutic index (TI) of 3710. Rhododaurichromenic acids A (**2**) also showed relatively potent anti-HIV activity with an EC_{50} value of 0.37 mg/mL and a TI of 91.9. These two

compounds represent a new class of anti-HIV agents and are attractive synthetic targets.³

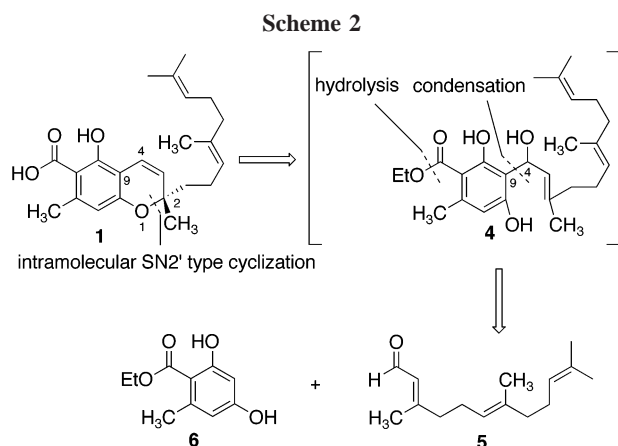
Scheme 1



(1) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamasishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559.

(2) Jpn. Kokai Tokko Koho, JP 82-28,080, 1982.

To supply sufficient quantities of the target material for pharmacological study, highly efficient syntheses of these complex molecules are required. Our careful analysis of the targets has led to a synthetic strategy that is characterized by the following important features: (1) convergency, (2) brevity, and (3) flexibility. Our retrosynthetic analysis of daurichromenic acid (**1**) is outlined in Scheme 2. Sequential



disconnection at O1–C2 and C4–C9 reveal fragments **5** and **6** as two starting materials, with tandem condensation and intramolecular S_N2' -type cyclization playing crucial roles in the synthetic strategy.

Synthesis of 2*H*-benzopyrans (chrom-3-enes) has been the subject of many investigations.⁴ The reaction developed by Shigemasa appeared to be quite promising for the synthesis of this class of natural products.⁵ Unfortunately, we found that the reaction between **6** and **5**⁶ was extremely slow under Shigemasa's conditions. The mixture gave only 15% yield of the desired product **7** after being heated at reflux for 4 days (Table 1, entry 1). The yield was improved to 32% when the mixture was heated at 90 °C in a sealed tube for 1 day (entry 2). However, the reaction stopped, and the yield could not be improved even with the addition of excess aldehyde **5** and longer heating time.

Because the intramolecular S_N2' -type cyclization is a fast reaction, the overall slow reaction is presumably due to the high activation energy in the condensation reaction. It is

(3) For the synthesis of rhododaurichromenic acids A and B and methyl daurichromenic ester, see: Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935.

(4) (a) Dotz, K. H. *Pure Appl. Chem.* **1983**, *55*, 1689 and references therein. (b) Henry, G. E.; Jacobs, H. *Tetrahedron* **2001**, *57*, 5335. (c) Chang, S.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 864. (d) Saimoto, H.; Yoshida, K.; Murakami, T.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem.* **1996**, *61*, 6768. (e) North, J. T.; Kronenthal, D. R.; Pullockaran, A. J.; Real, S. D.; Chen, H. Y. *J. Org. Chem.* **1995**, *60*, 3397. (f) Gabbutt, C. D.; Hartley, D. J.; Hepworth, J. D.; Heron, B. M.; Kanjia, M.; Rahman, M. M. *Tetrahedron* **1994**, *50*, 2507. (g) Cruz-Almanza, R.; Perez-Flores, F.; Lemini, C. *Heterocycles* **1994**, *37*, 759. (h) Rao, U.; Balasubramanian, K. K. *Tetrahedron Lett.* **1983**, *24*, 5023. (i) Sartori, G.; Casiraghi, G.; Bolzoni, L.; Casnati, G. *J. Org. Chem.* **1979**, *44*, 803.

(5) Saimoto, H.; Yoshida, K.; Murakami, T.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem.* **1996**, *61*, 6768.

(6) Compound **5** was readily prepared via MnO_2 -mediated oxidation of *trans,trans*-Farnesol (70%).

Table 1. Various Conditions for the Formation of 2*H*-Benzopyran, the Core Structure of Daurichromenic Acid

entry	conditions	yield
1	5 (1.2 equiv), $Ca(OH)_2$ (0.83 equiv), MeOH, reflux, 4 days	15%
2	5 (1.2 equiv), $Ca(OH)_2$ (0.83 equiv), MeOH, sealed tube, 90 °C, 1 day	32%
3	5 (1.2 equiv), $Ca(OH)_2$ (0.83 equiv), MeOH, microwave irradiation, 3 × 1 min	23%
4	5 (1.2 equiv), $CaCl_2 \cdot 2H_2O$ (0.83 equiv), NEt_3 (3.32 equiv), EtOH, microwave irradiation, 20 × 1 min	50%
5	5 (1.2 equiv), $CaCl_2 \cdot 2H_2O$ (0.83 equiv), NEt_3 (3.32 equiv), EtOH, reflux, 2 days	<5%
6	(i) 5 (2.0 equiv), $CaCl_2 \cdot 2H_2O$ (0.83 equiv), NEt_3 (3.32 equiv), EtOH, microwave irradiation, 20 × 1 min; (ii) 5 (1.0 equiv), microwave irradiation, 20 × 1 min	70%
7	5 (2.0 equiv), pyridine, microwave irradiation, 25 min	<5%

known that microwave irradiation can accelerate many reactions.⁷ Thus, we decided to investigate the possibility of applying microwave irradiation to accelerate our tandem condensation and intramolecular S_N2' -type cyclization.

As expected, a much faster reaction was indeed observed when the reaction was irradiated in a microwave oven.⁸ After only 3 min of irradiation, compound **7** was isolated in 23% yield (entry 3).⁹ However, we were not able to improve the yield with longer irradiation time or with the addition of more aldehyde **5**. After screening a few different reaction conditions, we found that the reaction between **5** and **6** in the presence of $CaCl_2 \cdot 2H_2O$, NEt_3 , and EtOH provided 50% yield of the desired product **7** and required only 20 min of microwave irradiation (entry 4). Without microwave irradiation, the yield of compound **7** was only 5% (entry 5). The optimized conditions were listed in entry 6 in which the mixture of compound **5** (2.0 equiv) and compound **6** (1.0 equiv) was irradiated for 20 min. Then, an additional 1.0 equiv of compound **5** was added and the mixture was irradiated again for 20 min. Using these optimized conditions allowed compound **7** to be isolated in 70% yield. It should be noted that in the absence of $CaCl_2 \cdot 2H_2O$, NEt_3 , and EtOH, only a trace amount of compound **7** was isolated when the reaction was run in pyridine (entry 7).¹⁰

Unfortunately, the hydrolysis of the ester functionality of compound **7** to daurichromenic acid (**1**) proved to be extremely difficult. After examining many procedures,¹¹ we

(7) For a recent review on microwave-assisted reactions, see: (a) Caddick, S. *Tetrahedron* **1995**, *51*, 10403. (b) Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 233.

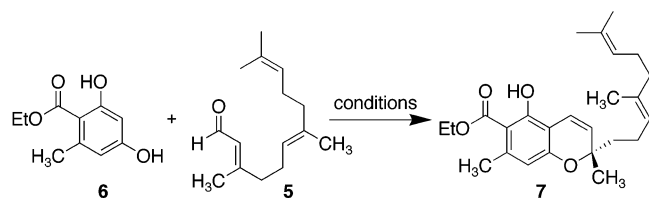
(8) We simply use a commercial household microwave to run the reaction. It is a Panasonic model NNS740 (1200 W).

(9) Reaction was carried out in a sealed 60 mL Teflon pressure vessel (purchased from Savillex Corp) filled with Argon.

(10) Subburaj, K.; Trivedi, G. K. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 259.

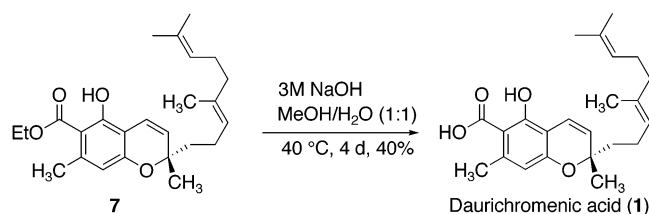
(11) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley: New York, 1999.

Scheme 3



found that the best conditions (3 M NaOH in MeOH/H₂O at 40 °C for 4 days) provided daurichromenic acid (**1**) in only 40% yield. Although this two-step total synthesis is highly concise, the low yield in the hydrolysis step coupled with the expensive starting material **6** led us to investigate the possibility of conducting microwave-assisted reaction using carboxylic acid as the substrate.

Scheme 4



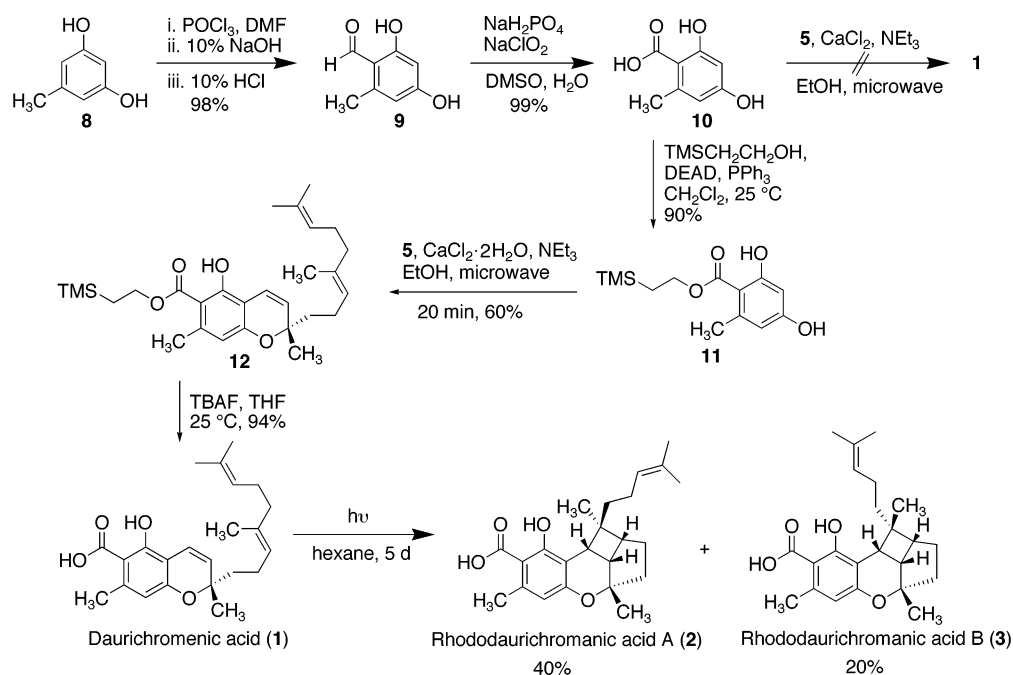
The revised approach is outlined in Scheme 5. Formylation of orcinol **8** with POCl₃ and DMF gave aldehyde **9** (98%),¹² which was oxidized to the corresponding carboxylic acid **10**

(NaClO₂, 99%).¹³ However, microwave irradiation of the mixture of compounds **10** and **5** failed to provide any desired product **1**. Therefore, we decided to synthesize β -trimethylsilyl ethyl ester **11** that can be easily converted to carboxylic acid in the end. Reaction of **10** with 2-(trimethylsilyl)ethanol under Mitsunobu conditions afforded ester **11** in 90% yield.¹⁴ A mixture of compound **11**, aldehyde **5** (2 equiv), CaCl₂·H₂O, NEt₃, and EtOH was sealed in a Teflon pressure vessel and irradiated in a microwave oven 20 times for 1 min intervals. The desired product **12** was isolated in 60% yield.¹⁵ Treatment of compound **12** with TBAF gave daurichromenic acid in 95% yield.¹⁶ Compound **1** was irradiated with a low-pressure mercury lamp for about 5 days to afford a mixture of rhododaurichromenic acids A (40%) and B (20%).¹⁷ The physical data of synthetic daurichromenic acid are identical to those reported by Kashiwada,¹ whereas the physical data of rhododaurichromenic acids A and B are identical to those reported by Hsung et al.¹⁸

In conclusion, we have successfully developed highly efficient total syntheses of daurichromenic acid and rhododaurichromenic acids A and B. We have demonstrated the versatility of microwave technology in the synthesis of 2*H*-benzo[*b*]pyrans (chrom-3-enes). The synthetic application of microwave technology in the synthesis of designed analogues and in the solid-phase combinatorial synthesis is currently underway in our laboratories and will be reported in due course. Furthermore, the highly potent anti-HIV activity of these molecules suggests an exciting adventure into the realms of investigations of molecular design, chemical synthesis, and biological activity.

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Scheme 5



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(12) Xie, L.; Takeuchi, Y.; Cosentino, L. M.; McPhail, A. T.; Lee, K.-H. *J. Med. Chem.* **2001**, *44*, 664.

(13) Nicolaou, K. C.; Rodríguez, R. M.; Mitchell, H. J.; Suzuki, H.; Fylaktakidou, K. C.; Baudoin, O.; van Delft, F. L. *Chem. Eur. J.* **2000**, *6*, 3095.

(14) Roush, W. R.; Coffey, D. S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11331.

Supporting Information Available: Complete spectroscopic data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) Control reactions (heating in either reflux or in a sealed tube) appeared to be extremely slow without microwave irradiation.

(16) All compounds have been fully characterized.

(17) Based on recovered starting material.

(18) Hsung noted that there were three critical typos in the ^{13}C NMR of rhodaurichromanic acids A and B reported by Kashiwada. See Supporting Information of Hsung's paper: Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3938.