Me-16 and H-2 (4, 12, and 16), Me-16 and H-9 (4), and Me-18 and H-10 (4 and 16) are fully consistent with those detected by Nakanishi.[17] The characteristic A-ring enone UV spectral λ_{max} (unusually high) and ϵ (unusually low) values for 4, 11, and 15 are compatible with available data[18] as well.

In conclusion, we note that the sequence leading to 4 proceeds with an economy of steps and functional group protection and concludes with a new annulation process, one whose generality we intend to explore. A conceptually similar tandem approach to the AB system of the more medicinally significant taxol might offer hope for its preparation with reasonable brevity.

Acknowledgment. Support by PHS Grant no. CA 41349 awarded by the National Cancer Institute, DHHS is gratefully acknowledged. The acquisition of a GC/MS system was made possible by grants from the Camille and Henry Dreyfus Foundation and the PQ Corporation, and of a high-field NMR spectrometer by grants from the W. M. Keck Foundation and Merck & Co., Inc.

Supplementary Material Available: Procedure for the transformation of 17 into 4, complete spectral and combustion analytical data for 4, 11, and 15, a chart of characteristic ^{1}H NMR chemical shifts and coupling constants for taxinine, 4, 12, and 16, and copies of ^{1}H NMR spectra and NOE difference spectra for 4, 12, and 16 (11 pages). Ordering information is given on any current masthead page.

(17) Woods, M. C.; Chiang, H.-C.; Nakadaira, Y.; Nakanishi, K. *J. Am. Chem. Soc.* **1968**, *90*, 522.

(18) For appropriate reference data, see that on compound VII (R = H) in: Kukes, M.; Eyre, D. H.; Harrison, J. W.; Scrowston, R. M.; Lythgoe, B. *J. Chem. Soc. C* **1967**, 448.

Aureolic Acid Antibiotics: A Simple Method for 2-Deoxy-β-glycosidation

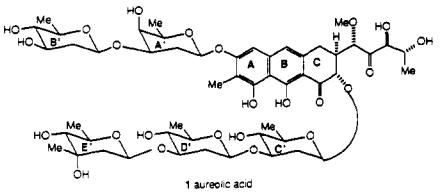
Subban Ramesh, Neelu Kaila, Gurmit Grewal, and Richard W. Franck*

Department of Chemistry and Institute for Biomolecular Structure and Function, Hunter College/The City University of New York, 695 Park Ave, New York, New York 10021

Received November 13, 1989

Summary: The phenylbis(phenylthio)sulfonium salt 8 electrophilically activates glycals for glycosyl transfer to form, in most cases, β-glycosides.

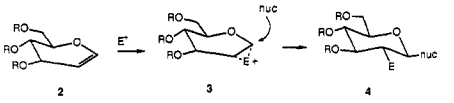
Sir: A problem of current interest to the organic chemistry community is the synthesis of 2-deoxy-β-glycosides, which are constituents of antibiotics such as the calicheamicins,[1] esperamicins,[2] benzanthrins,[3] and the aureolic acids 1 including its relatives, the chromomycins and the olivomycins, all of which are highly toxic antibiotics that also have antitumor properties.[4,5]



The specific requirements for an aureolic acid synthesis are that the procedure(s) work with phenols and acyloins under conditions where the acid- and base-sensitive aglycons can survive.[6,7] Of the 13 different methods recently reported,[8] we favored schemes where glycals 2 were ste-

Scheme I

(a) mechanism of electrophilic initiation of glycosyl transfer



(b) formation of E^+ in Ogawa's method

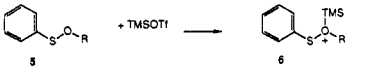


Table I. Glycosyl Transfers to Methanol

entry	glycal	reagent	β/α[a]	yield, %	$[\alpha]^{25}_D$ ($CHCl_3$) for β, deg
a	**9a**	8	3.7/1	83	
b	**9a**	7	1.3/1	75	
c	**9b**	8	2/1	62[b]	+5.4
d	**9c**	8	2/1	80	
e	**9d**	8	2/1	76[c]	-48.2
f	**9e**	8	2.7/1	86[d]	-31.2[e]
g	**9f**	8	1/10	80	
h	**9g**	8	12/1	92	

[a] Ratios determined by separation and isolation except for entries a-d. [b] In addition 2α-(phenylthio)-1α-isomer was obtained in 10% yield. [c] During workup, the 4,6-benzylidene of the glucal was partially cleaved. [d] During workup, the 4,6-isopropylidene of the glucal was completely cleaved. [e] Optical rotation for the 4,6-dihydroxyglucoside.

(1) Zein, N.; Sinha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198.

(2) Long, B. H.; Golik, J.; Forenza, S.; Ward, B.; Rehfuss, R.; Dabrowiak, J. C.; Catino, J. J.; Musial, S. T.; Brookshire, K. W.; Doyle, T. W. *Proc. Natl. Acad. Sci.* **1989**, *86*, 2.

(3) Rasmussen, R. R.; Nuss, M. E.; Scherr, M. H.; Mueller, S. I.; McAlpine, J. B.; Mitscher, L. A. *J. Antibiot.* **1986**, *39*, 1515.

(4) (a) A complete discussion of the isolation, structure proof, and biological activity of these materials to 1979, requiring several revisions in structure and stereochemistry: Remers, W. *The Chemistry of Antitumor Antibiotics*; Wiley: New York, 1979; Vol. 1, Ch. 3. (b) An update on isolations: Skarbeck, J. D.; Speedie, M. K. In "Antitumor Antibiotics of the Aureolic Acid Group Chromomycin A_3, Mithramycin A, and Olivomycin A"; Aszalos, A., Ed.; *Antitumor Compounds of Natural Origin: Chemistry and Biochemistry*; CRC Press: New York, 1981; Ch. 5. (c) Most recent isolations: Yoshimura, Y.; Koenuma, M.; Matsumoto, K.; Tori, K.; Terui, Y. *J. Antibiot.* **1988**, *41*, 53. (d) Definitive saccharide assignments: Thiem, J.; Meyer, B. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1331. Thiem, J.; Meyer, B. *Tetrahedron* **1981**, *37*, 551.

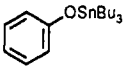
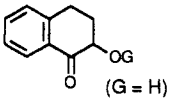
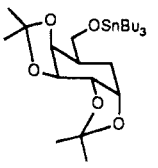
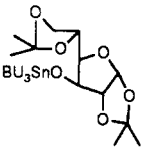
(5) A review of the synthetic chemistry in the field through 1987: Franck, R. W.; Weinreb, S. M. In *Studies in Natural Product Chemistry*; Rahman, A., Ed.; Elsevier: Amsterdam, 1989; pp 173-208.

(6) Recent papers: (a) Dodd, J. H.; Starrett, J. E., Jr.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 1811-1812. (b) Franck, R. W.; Bhat, V.; Subramaniam, C. S. *J. Am. Chem. Soc.* **1986**, *108*, 2455-2457. (c) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Chong, W. K. M. *J. Am. Chem. Soc.* **1987**, *109*, 7575-7577. (d) Roush, W. R.; Michaelides, M. R.; Tai, D. F.; Lesur, B. M.; Chong, W. K. M.; Harris, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 2984. (e) Thiem, J.; Schottmer, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 555-557. Reviews: (f) Reference 5 (g) Thiem, J. *Topics in Current Chemistry, Carbohydrate Chemistry*; Springer Verlag: New York, 1988.

(7) In an unpublished thesis from Professor Thiem's lab, there is described the Koenigs-Knorr coupling of a 2-deoxy-2α-bromosaccharide with an olivin derivative and a 21% yield of β-glycoside product was obtained. Schneider, G. *Untersuchung uber den Aufbau Modifizierter Aureolsauren*, dissertation der Universitat Hamburg, 1985.

0022-3263/90/1955-0005$02.50/0

Table II. Glycosyl Transfers to Nucleophiles Other Than Methanol

entry	glycal	reagent	aglycon ROH($SnBu_3$)	β/α[a]	yield, %	$[\alpha]^{25}_D$ ($CHCl_3$) for β, deg
a	**9a**	8		3.0/1	56	−19.6
b	**9a**	7	as a	1/1	60	
c	**9a**	8	 (G = H)	no α isolated	45	−17.6
d	**9a**	7	as c (G = $SnBu_3$)	2.9/1	40	
e	**9a**	8		5.3/1	70[b]	−58.4
f	**9a**	8		11.5/1	75[b]	−34.0
g	**9b**	8	as e	3.1/1	74	
h	**9e**	8	as e	5.7/1	79[c,d]	−56.1

[a] Ratios determined by separation and isolation except for entry g. [b] In addition, a small amount of the 2α-(phenylthio)-1α-isomer was obtained. [c] The 2α-(phenylthio)-1α-isomer was obtained in 10% yield. [d] During workup, the 4,6-isopropylidene of the glucal was partially cleaved.

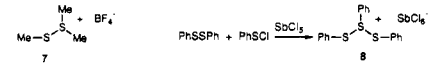
reoselectively activated by below-plane electrophilic attack (*lk* at C-1 relative to C-5 with *R* configuration) to form onium species **3** followed by nucleophilic ring opening to form **4** (Scheme I).[9]

We first examined the Ogawa approach where an aryl sulfenate ester of the aglycon is preformed and then apparently activated to a thiooxonium species by trimethylsilylation.[8c] Although our model acyloin sulfenate was extremely sensitive, we were able to synthesize the first 2-deoxy-β-glycoside of an acyloin.[10]

However, when we tried to extend the sulfenate method to phenols, problems developed because the precursor sulfenate esters of phenol could not be prepared. We believe that the mechanism of the Ogawa method involves an intermediate thiooxonium salt **6**, which is formed when TMS triflate reacts with the oxygen of the sulfenate ester **5**. The thiooxonium salt **6** is then attacked by the glucal to form the episulfonium salt[11] as in Scheme I, which is then opened by sulfenate ester to form product and a regenerated thiooxonium species. Thus, we reasoned that other reactive thioonium salts might serve to activate glucals for glycosylation.

We chose the commercially available (methylthio)-sulfonium salt **7** and the easily prepared (phenylthio)-sulfonium salt **8** for further study.[12] Although both

thiosulfonium initiators of glycosylation



thiosulfonium species had been shown to activate simple alkenes for the addition of nucleophiles, their use in sugar

(8) (a) Nicolaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466; a method using 1-fluoro-2-phenylthio sugars as precursors to episulfonium intermediates. (b) Wiesner, K.; Tsai, T. Y. R.; Jin, H. *Helv. Chim. Acta* **1985**, *68*, 300; bridging participation via a 3α-carbamate. (c) Ito, Y.; Ogawa, T. *Tetrahedron Lett.* **1987**, *28*, 2723; sulfenate esters plus glucals. (d) Michalska, M.; Borowiecka, M. *J. Carbohydr. Chem.* **1983**, *2*, 99; addition of *O,O*-dimethylphosphorodithioic acid to glucals followed by reaction with sodium alcoholates. (e) Thiem, J.; Gerken, M. *J. Org. Chem.* **1985**, *50*, 954; participation of a 2α-bromine in a Koenigs–Knorr reaction. (f) Kaye, A.; Neidle, S.; Reese, C. B. *Tetrahedron Lett.* **1988**, *29*, 2711; a correction of Jaurand, G.; Beau, J.-M.; Sinay, P. *Chem. Commun.* **1981**, 572. Perez, M.; Beau, J.-M. *Tetrahedron Lett.* **1989**, *30*, 75; formation of episelenium species by addition to glucals. (g) Preuss, R.; Schmidt, R. R. *Synthesis* **1988**, 694. Application of the Schmidt glycosyl imidate method to 2-(phenylthio)pyranoses, which, in turn, arise from addition of phenylsulfenyl chloride to glucals, 4 steps overall. (h) Trumtel, M.; Veyrieres, A.; Sinay, P. *Tetrahedron Lett.* **1989**, *30*, 2529. Tavecchia, P.; Trumtel, M.; Veyrieres, A.; Sinay, P. *Ibid.* **1989**, *30*, 2533; deoxygenation of 2-acetates or deamination of 2-formylamino sugars via their isonitriles. (i) Crich, D.; Ritchie, T. J. *Chem. Commun.* **1988**, 1461. Crich, D.; Ritchie, T. J. *Carbohydr. Res.* **1989**, *190*, C5; reductive decarboxylation of a carboxylic acid at C-1 with the anomeric effect directing axial hydrogen introduction. A multistep precursor synthesis is required. To the best of our knowledge, this is the only prior report of a synthetic phenyl 2-deoxy-β-glycoside, obtained in 18% overall yield for the two key steps. (j) Kahne, D.; Lim, J. J.; Miller, R.; Paguaga, E. *J. Am. Chem. Soc.* **1988**, *110*, 8716. A radical method, based on the principles of ref 8i, which requires a thio orthoester precursor to be synthesized. (k) Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1982**, 683; cyclization of acyclic sugar precursor prepared via Wittig chemistry. (l) Barrett, A. G. M.; Bezuidenhoudt, B. C. B.; Howell, A. R.; Lee, A. C.; Russell, M. A. *J. Org. Chem.* **1989**, *54*, 2275; redox cyclization of thionoesters. (m) Binkley, R. W.; Koholic, D. J. *J. Org. Chem.* **1989**, *54*, 3577; insoluble silver silicate catalysis in Koenigs–Knorr requiring no participation by group at C-2.

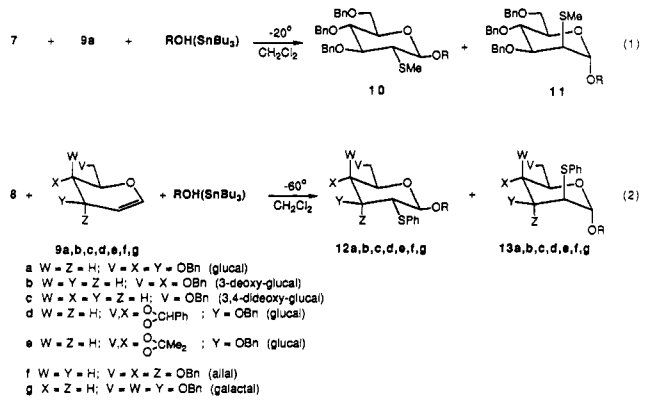
(9) For leading references to glucal-based glycosidations via 1,2-onium intermediates, other than for the 2-deoxy-β-series discussed in this report. (a) Iodonium glucals: (i) Thiem, J.; Klaffke, W.; Springer, D. *Carbohydr. Res.* **1988**, *174*, 201, and more than 30 earlier papers by the Thiem group. (ii) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6656. (b) Brigl's anhydride (epoxidized glucals): (i) Lemieux, R. U.; Huber, G. *J. Am. Chem. Soc.* **1953**, *75*, 4118. (ii) Lemieux, R. U. *Can. J. Chem.* **1953**, *31*, 949. (iii) Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661.

(10) Ramesh, S.; Franck, R. W. *Chem. Commun.* **1989**, 960.

(11) Smit, W. A.; Zefirov, N. S.; Bodrikov, I. V.; Krimer, M. Z. *Acc. Chem. Res.* **1979**, *12*, 282; a critical discussion of episulfonium ions.

(12) (a) For a review of reactive sulfonium salts, see: Capozzi, G.; Modena, G. *Organic Sulfur Chemistry: Theoretical and Experimental Advances*; Bernardi, F., Csizmadia, I. G., Mangini, A., Eds.; Elsevier: Amsterdam, 1985. (b) For the use of methylsulfonium species for intramolecular etherification, see: (i) O'Malley, G. J.; Cava, M. P. *Tetrahedron Lett.* **1985**, *26*, 6159. (ii) Capozzi, G.; Lucchini, V.; Marcuzzi, V.; Modena, G. *J. Chem. Soc. Perkin Trans. I* **1981**, 3106. (c) For the preparation of the arylbis(arylthio)sulfonium salts: Gybin, A. S.; Smit, W. A.; Bogdanov, V. S.; Krimer, M. Z.; Kalyan, J. B. *Tetrahedron Lett.* **1979**, *19*, 383.

chemistry had not previously been reported. The thiosulfonium salts have in fact proven to be exceptionally useful reagents for glycosyl transfer of glucal derivatives **9a–g** to a variety of hydroxyl donors (aglycons) as summarized in eqs 1–2. Table I documents the variety of reactions and products



glycal types tested with methanol as nucleophile, whereas Table II illustrates the range of nucleophiles examined. In some cases, the nucleophilicity of the aglycon hydroxyl group must be enhanced by prior stannyl ether formation.[13] It should be noted that our method works for *both phenols and acyloins* as well as the more common primary and secondary sugar alcohols. The (phentylthio)sulfonium salt 8 was found to be the more β-selective reagent. It is worthy of note that 3-deoxyglucals **9b** and **9c** (Table I, entries c and d; Table II, entry g), afford β-glycoside as major product. Thus, a steric effect of the pseudoequatorial allylic 3-substituent is only partially accountable for the face selectivity observed with glucal **9a**. On the other hand, the pseudoaxial and axial groups in allal derivative **9f** and galactal species **9g** are very effective directors, with a complete switch of face selectivity to *ul* in the allal case, and the highest *lk* preference with galactal (Table I, entries g and h). Since the rather rigid bicyclic glucals **9d,e** (Table I, entries e and f; Table II, entry h), also yield major products, which must be accounted for by below-plane attack of the sulfur reagent, we cannot invoke flipped chair forms to account for the *lk* outcome.[14] Interestingly, the β/α ratio depends on the nature of the nucleophile, with methanol affording low selectivity compared to sugar nucleophiles. Thus the simple mechanism outlined in Scheme I will have to be modified to include the nucleophile in the step that controls face selectivity. However, we wish to defer a discussion of these aspects of the mechanism until a more comprehensive set of data is available.

The simplicity of our method should be highlighted: *to the glycal and the alcohol, or its tributyltin ether, in solution at −60 °C is added, by syringe technique, the required amount of a solution of sulfonium salt. The salt is prepared by adding a solution of PhSCl and PhSSPh to a commercially available solution of $SbCl_5$ also maintained at −60 °C. When the reaction is complete, aqueous bicarbonate is added and the reaction mixture is warmed to room temperature and worked up.* Raney nickel desulfurization is more facile in the phenyl thioether series than the methyl thioether family. For example, W-2 RaNi in THF converts the product from entry a, Table II, into the phenyl 2-deoxy-β-glycoside at room temperature in 70% yield.

It remains to be seen whether the unsubstituted phenyl reagent will give the highest yields and the best face selectivities. Also, application of our method to glucals with ester blocking groups awaits experimentation. Although there are published methods that do, in some cases, give better selectivity and do, in some cases, work with electron-withdrawing blocking groups, we believe that the class of (phenylthio)sulfonium species, illustrated by reagent 8, will be generally useful in the field of 2-deoxyglycoside chemistry. They will play an important role in the eventual synthesis of the aureolic acid antibiotics.

Acknowledgment. We are indebted to the National Cancer Institute for grant CA 37359 and to CUNY for PSC research awards that supported this work. NMR instruments used were obtained through grants NSF-PCM 111745 and NIH RR 03214. Our work has benefitted from several exchanges with Prof. J. Thiem under the auspices of grant INT 8712570 awarded by the US–FRG Cooperative Research Program of NSF.

(13) Thiem, J.; Klaffke, W. *J. Org. Chem.* **1989**, *54*, 2006. We are indebted to Prof. Thiem for the access to his results prior to publication.

(14) Thiem, J.; Ossowski, P. *J. Carbohydr. Chem.* **1984**, *3*, 287; a thorough analysis of the possibilities that flipped chair forms of glucals are the basis for below-plane attack.

Stereoselective Synthesis of Erythronolide A via an Extremely Efficient Macrolactonization by the Modified Yamaguchi Method[1]

Masataka Hikota, Hitoshi Tone, Kiyoshi Horita, and Osamu Yonemitsu*

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

Received October 3, 1989

Summary: The seco-acid derivative **7**, which has the 9,11- and 3,5-diols protected as the mesityl- and 3,4-dimethoxyphenyl (DMP) acetals, respectively, was stereoselectively synthesized from D-glucose and converted to Yamaguchi's mixed anhydride, which was treated with a high concentration of DMAP at room temperature to rapidly give the 14-membered lactone in 98% yield. Removal of the protecting groups gave 9-dihydroerythronolide A.

Sir: A high dilution technique is usually essential for the cyclization of activated seco-acid derivatives into complex macrolactones such as 9-dihydroerythronolide A derivatives.[2] However, even this technique is sometimes inef-

(1) Chiral synthesis of polyketide derived natural products. 27. For part 26, see: Horita, K.; Nagato, S.; Oikawa, Y.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1726.

(2) (a) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131. (b) Woodward, R. B.; et al. *J. Am. Chem. Soc.* **1981**, *103*, 3213. (c) Kinoshita, M.; Arai, M.; Tomooka, K.; Nakata, M. *Tetrahedron Lett.* **1986**, *27*, 1815. (d) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565. (e) Tone, H.; Nishi, T.; Oikawa, Y.; Hikota, M.; Yonemitsu, O. *Tetrahedron Lett.* **1987**, *28*, 4569. (f) Tone, H.; Nishi, T.; Oikawa, Y.; Hikota, M.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1167.

0022-3263/90/1955-0007$02.50/0