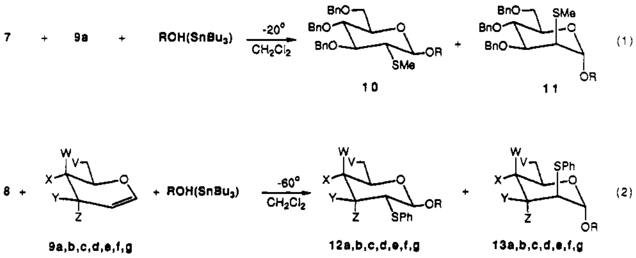
chemistry had not previously been reported. The thiosulfonium salts have in fact proven to be exceptionally useful reagents for glycosyl transfer of glucal derivatives **9a–g** to a variety of hydroxyl donors (aglycons) as summarized in eqs 1–2. Table I documents the variety of glycal types tested with 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 $\beta$-selective reagent. It is worthy of note that 3-deoxyglucals **9b** and **9c** (Table I, entries c and d; Table II, entry g), afford $\beta$-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 $\beta/\alpha$ 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.

reactions and products



a W = Z = H; V = X = Y = OBn (glucal)
b W = Y = Z = H; V = X = OBn (3-deoxy-glucal)
c W = X = Y = Z = H; V = OBn (3,4-dideoxy-glucal)
d W = Z = H; V,X = $\mathrm{O_2{>}CHPh}$ ; Y = OBn (glucal)
e W = Z = H; V,X = $\mathrm{O_2{>}CMe_2}$ ; Y = OBn (glucal)
f W = Y = H; V = X = Z = OBn (allal)
g X = Z = H; V = W = Y = OBn (galactal)

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-$\beta$-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-

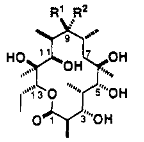
---

[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.

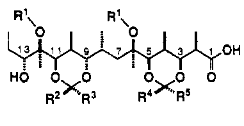
[2] (a) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131. (b) Woodward, R. B.; et al. *J. Am. Chem. Soc.* **1981**, *103*, 3213. (c) Kinoshita, M.; Arai, M.; Tomooka, K.; Nakata, M. *Tetrahedron Lett.* **1986**, *27*, 1815. (d) Stork, 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 © 1990 American Chemical Society

fective for the cyclization of unsuitably protected seco-acid derivatives.[3] Recently, Stork and Rychnovsky reported that the 9,11-cyclic methyl acetal (5) with a favorable conformation of the C8–C11 portion readily cyclized to the corresponding 14-membered lactone, whereas the isomeric methyl acetal (4) and the dimethyl acetal (3) failed to cyclize.[2d] We recently synthesized 6 and tried to cyclize to the corresponding lactone, but attempts using the Corey[2b,4] and Yamaguchi methods[5] were unsuccessful. Only the Yamaguchi method augmented by a high concentration of DMAP produced the lactone, and only in poor yield (27%).[2e,f] From these results, it was judged that both a proper conformation and strong activation are crucial requirements for achieving an efficient cyclization of seco-acid derivatives. Accordingly, we decided to synthesize 7, anticipating that it would be a promising cyclization substrate.



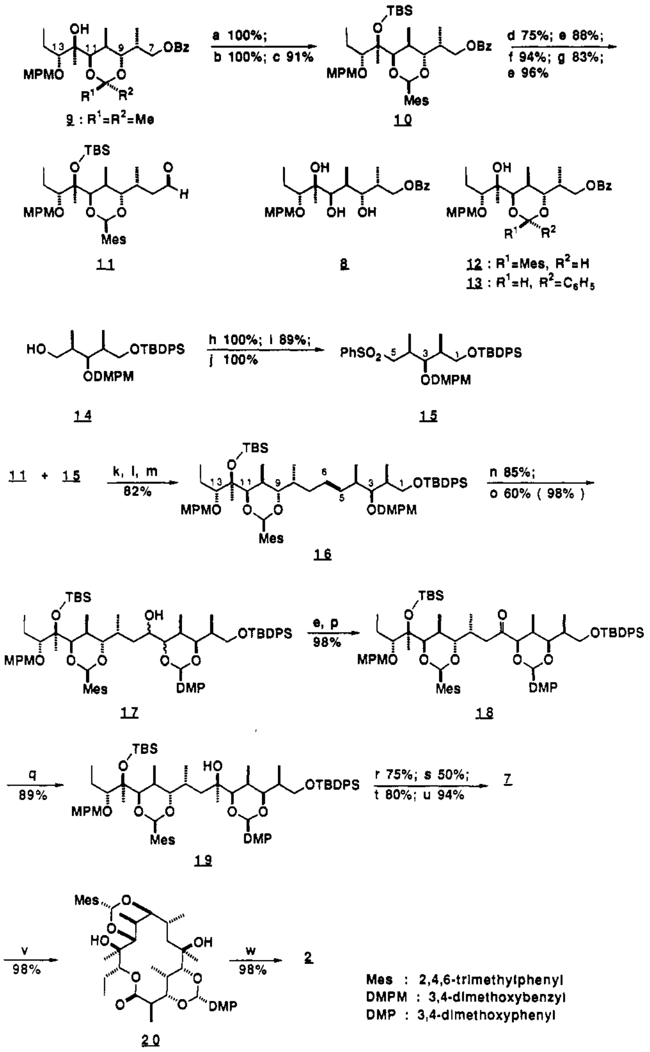
1 : $R^1$, $R^2$=O
2 : $R^1$=OH, $R^2$=H



3 : $R^1$=H, $R^2$=$R^3$=$R^4$=$R^5$=Me
4 : $R^1$=$R^2$=H, $R^3$=$R^4$=$R^5$=Me
5 : $R^1$=$R^3$=H, $R^2$=$R^4$=$R^5$=Me
6 : $R^1$=MOM, $R^2$=$R^3$=$R^4$=$R^5$=Me
7 : $R^1$=$R^3$=$R^5$=H, $R^2$=Mes, $R^4$=DMP

The 9,11-dimethyl acetal (9),[2e,6] readily prepared from the triol (8), was first converted to the 9,11-mesityl acetal (10) (Scheme I) with the desired configuration and conformation.[7] In a series of conventional reactions 10 was readily converted to the aldehyde (11),[8] which was condensed in the usual way with the sulfone (15) derived from 14,[6] and then desulfonated[10] to give the 5,6-*E*-olefin (16) in high yield. Highly stereoselective construction of the C5 and C6 chiral centers was achieved by taking advantage of the MPM (4-methoxybenzyl) type protecting groups.[9,11] Thus oxidation of 16 with $OsO_4$ gave a mixture of diols, which was treated with DDQ to give the acetal (17).[11] A diastereoisomeric mixture of 6-ketones obtained by Swern oxidation of 17 was treated with $K_2CO_3$ to give mainly the thermodynamically more stable isomer (18) with the desired C5 configuration (40:1). The final chiral center at C6 was readily constructed by the Cram addition (nonchelation) of MeLi at −78 °C to give 19 with 21:1 selectivity. Finally, 19 was readily converted to the seco-acid (7).

**Scheme I**[a]



[a] (a) TBSOTf, 2,6-(t-Bu)$_2$$C_5H_3N$, $CH_2Cl_2$, room temperature, 24 h; (b) 2 N HCl, MeOH, room temperature, 10 min; (c) MesCH(OMe)$_2$, CSA, $CH_2Cl_2$, room temperature, 2 h; (d) 3 N NaOH, EtOH, room temp, 4 h; (e) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −78 °C; (f) $Ph_3P^+CH_2OBnCl^-$, *n*-BuLi, THF, −78 °C to room temperature; (g) Raney Ni (W2) $H_2$, EtOH, room temperature; (h) MsCl, $Et_3N$, DMAP, $CH_2Cl_2$, 8 h; (i) PhSNa, THF-DMF (1:2), room temperature, 30 min; (j) MCPBA, $CH_2Cl_2$, 0 °C, 45 min; (k) 15, *n*-BuLi, then 11, $Et_2O$, −60 °C, 1 h; (l) $Ac_2O$, $Et_3N$, DMAP, $CH_2Cl_2$, room temperature, 8 h; (m) 5.2% Na-Hg, MeOH-AcOEt (2:1), −30 to 0 °C, 5 h; (n) $OsO_4$ (cat.), NMO-$H_2O$, MeCOMe, room temperature, 20 h; (o) DDQ, toluene, 0 °C, 3 h; (p) $K_2CO_3$, MeOH, room temperature (q) 1.4 M MeLi, THF, −78 °C, 10 min; (r) TBAF, HMPA, 60 °C, 48 h; (s) $CrO_3$, $H_2SO_4$, $H_2O$, MeCOMe, −15 °C, 30 min, then $CH_2N_2$, $Et_2O$; (t) 10% Pd–C, $H_2$, EtOH, room temperature, (u), 3 N NaOH, MeOH, 18 h; (v) 2,4,6-$Cl_3C_6H_2COCl$, $Et_3N$, xylene, 48 h, then DMAP (2 equiv, 20 mM), room temperature, 10 min; (w) $Pd(OH)_2$–C, $H_2$, EtOH, room temperature 12 h.

We previously reported that the efficiency of Yamaguchi's lactonization[5] was highly dependent on the concentration of DMAP.[2e,f,12] When DMAP (2 equiv) was added to a 10 mM xylene solution of the mixed anhydride of 7

---

(3) Woodward et al. reported that only one among 17 variously protected seco-acid derivatives having correct chiral centers cyclized to give a 9-dihydroerythronolide A derivative in reasonable yield.[2b]

(4) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.

(5) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(6) Tone, H.; Nishi, T.; Oikawa, Y.; Hikota, M.; Yonemitsu, O. *Chem. Pharm. Bull.* **1989**, *37*, 1160.

(7) Although the yield was unsatisfactory, 10 was also synthesized from the triol (8)[2e,6] via the 9,11-mesityl acetalization into 12 (42%) followed by TBS protection (76%). The 6-membered acetal ring of 12 is present in a chair conformation with axial C8 and equatorial C12 substituents ($J_{10,11}$ = 2.0 Hz, $J_{9,10}$ = 0 Hz, $J_{8,9}$ = 11.0 Hz). This conformation is the same as those of the seco-acid (7) and its lactonization product (20) (see ref 17). In analogy with the 9,11-methyl acetalization,[2d] the phenyl acetalization of 8 gave the undesired acetal (13) with a twist-boat conformation, in which both C8 and C12 substituents are pseudoequatorial based on *J* values ($J_{10,11}$ = 3.0 Hz, $J_{9,10}$ = 4.5 or 4.0 Hz, $J_{8,9}$ = 4.0 or 4.5 Hz) and NOE data.

(8) It is worth noting that the fourth step (debenzylation with Raney Ni) proceeded without any detectable loss of the 13-MPM group.[9]

(9) (a) Oikawa, Y.; Tanaka, T.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1984**, *25*, 5397. (b) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

(10) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833. (b) Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829, 834.

(11) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889.

(12) The role of DMAP was also confirmed by the Corey method.[2b,4] Under the usual conditions (high dilution in refluxing toluene, 72 h), the yield of 20 was only 6%, whereas in the presence of DMAP (25 mM) 20 was obtained in 60% yield. A better result was obtained at room temperature without using the high dilution technique, i.e., a 10 mM benzene solution of 2-pyridyl thiol ester of 7 in the presence of DMAP (20 mM) was stirred for 10 days to give 20 in 74% yield. Under the same conditions in the presence of $Et_3N$ instead of DMAP, no 20 was obtained.

and 2,4,6-trichlorobenzoic acid at room temperature, the lactonization proceeded quite rapidly and was completed within 8 min to give the lactone (**20**) in almost quantitative yield.[13,15] This excellent lactonization can be explained in terms of reflection of both the suitable conformation of **7**[17] and the efficient formation of the highly reactive acylpyridinium salt.[13]

Finally, removal of the protecting groups gave 9-dihydroerythronolide A (**2**), which was readily converted to the title compound (**1**).[2c]

**Acknowledgment.** We thank Dr. A. Kinumaki, Tanabe Seiyaku Co., Ltd., for cooperation in obtaining NMR (NOESY) spectra.

**Supplementary Material Available:** Physical data for compounds **7**, **10**, **11**, **14**, **15**, **16**, **18**, **19**, and **20** (4 pages). Ordering information is given on any current masthead page.

---

(13) The activation effect of DMAP may be explained in terms of formation of a more reactive acyl pyridinium salt as already proposed by Steglich et al.[14] Although attempts to detect the acylpyridinium salt by NMR spectroscopy were unsuccessful, an indirect proof was obtained by the silica gel TLC analysis of the reaction mixture at regular time intervals, i.e., after 1 min, the seco-acid (**7**) and the mixed anhydride were mainly detected probably because the acylpyridinium salt was too labile to exist under the TLC conditions. However, the two compounds disappeared with time, and after 8 min the lactone (**20**) was detected as a single spot. The difference in reactivity between the Yamaguchi mixed anhydride and the Corey active ester is presumably due to the difference in rate and efficiency of the formation of the acylpyridinium salt.

(14) Höfle, G.; Steglich, W.; Vorbruggen, H. *Ang. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(15) DCC was also effective for the lactonization as reported by Keck et al.,[2d,16] but a longer time was required [**7** (17 mM), DCC (50 mM), DMAP (31 mM), CSA (17 mM), in $CH_2Cl_2$, room temperature, 8 h, 85%].

(16) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

(17) Comparison of $J$ values ($^1$H NMR) of the seco-acid (**7**) ($J_{10,11}$ = 2.0 Hz, $J_{9,10}$ = 0 Hz, $J_{8,9}$ = 11.5 Hz, $J_{7,8}$ = 0, 7.0 Hz, $J_{4,5}$ = 1.5 Hz, $J_{3,4}$ = 1.5 Hz, $J_{2,3}$ = 10.0 Hz) with those of the lactone (**20**) ($J_{10,11}$ = 1.5 Hz, $J_{9,10}$ = 0 Hz, $J_{8,9}$ = 11.0 Hz, $J_{7,8}$ = 0, 11.5 Hz, $J_{4,5}$ = 1.0 Hz, $J_{3,4}$ = 1.0 Hz, $J_{2,3}$ = 11.0 Hz) revealed that rotation of only the C7–C8 bond (the least substituted bond) was presumably required for the lactonization of **7** into **20**, although accurate NOE and NOESY measurements are required for unequivocal determination of the C5–C7 conformation of **7**.

---

# *Articles*

## Computer-Assisted Mechanistic Evaluation of Organic Reactions. 17. Free Radical Chain Reactions

Ellen R. Laird and William L. Jorgensen*

*Department of Chemistry, Purdue University, West Lafayette, Indiana 47907*

*Received June 20, 1989*

A mechanistic model for free radical chain reactions has been developed for the computer program CAMEO. The controlling algorithm treats all reactions as a series of fundamental radical processes, i.e., abstractions, additions, and fragmentations. Chain-propagating steps are mimicked by automatic resubmission of selected intermediates. This paper provides an overview of radical chain processes and descriptions of the rules implemented for the logical prediction of chain reaction sequences. Several prominent examples that demonstrate the synthetic utility of free radical reactions and the success of the CAMEO program in predicting complex sequences are presented. An appendix which describes the algorithm for estimating homolytic bond dissociation energies is included.

### I. Introduction

CAMEO is an interactive computer program for the logical prediction of organic reaction products. Given graphical input of starting materials and conditions, the program arrives at its conclusions by application of mechanistic rules. The approach is unique in that large databases and topological simplifications are avoided; reaction modules correspond to and are designed for the evaluation of reactions by the type of intermediate involved. The program is presently capable of analyzing base-catalyzed and nucleophilic,[1] acid-catalyzed and electrophilic,[2,3] electrophilic aromatic,[4] pericylic,[5] oxidative,[6] and reductive[7] reactions.

The program has now been expanded to include analysis of organic free radical chain reaction sequences. Mechanistically, the program treats the intermediates of chain reactions by iterative consideration of three fundamental processes, i.e., abstractions, additions, and fragmentations. This paper opens with an overview of these fundamental processes and their controlling physical aspects, which provide a basis for the organization and implementation of the chemistry in the CAMEO program. The competitions between the fundamental processes and the rules implemented for their treatment are then specifically considered in Section III. The paper concludes with several chain reaction sequences for illustration of the program's capabilities as well as the emerging recognition of free radical

---

(1) (a) Salatin, T. D.; Jorgensen, W. L. *J. Org. Chem.* **1980**, *45*, 2043. (b) Salatin, T. D.; McLaughlin, D.; Jorgensen, W. L. *J. Org. Chem.* **1981**, *46*, 5284. (c) Peishoff, C. E.; Jorgensen, W. L. *J. Org. Chem.* **1985**, *50*, 1056. (d) Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1986**, *51*, 3513. (e) Metivier, P.; Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1987**, *52*, 3724. (f) Gushurst, A. J.; Jorgensen, W. L. *J. Org. Chem.* **1988**, *53*, 3397.

(2) McLaughlin, D. R. Ph.D. Thesis, 1983, Purdue University.

(3) Bures, M. G.; Jorgensen, W. L. *J. Org. Chem.* **1988**, *53*, 2504.

(4) Bures, M. G.; Roos-Kozel, B. L.; Jorgensen, W. L. *J. Org. Chem.* **1985**, *50*, 4490.

(5) (a) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 3923. (b) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1984**, *49*, 3001.

(6) Paderes, G. D.; Jorgensen, W. L. *J. Org. Chem.* **1989**, *54*, 2058.

(7) Metivier, P.; Paderes, G. D.; Jorgensen, W. L., manuscript in preparation.

0022-3263/90/1955-0009$02.50/0 © 1990 American Chemical Society