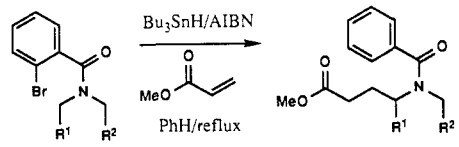
Scheme IV



15 16

a: $R^1 = R^2 = H$; b: $R^1 = R^2 = Me$; c: $R^1 + R^2 = (CH_2)_2$;
d: $R^1 + R^2 = (CH_2)_3$; e: $R^1 = H$, $R^2 = Ph$; f: $R^1 = TMS$, $R^2 = H$

conditions, styryl (**10b**) and ethyl acrylate (**10c**) substituted systems led to corresponding products **11b** and **11c** in 60–70% yields and 1:1 diastereomeric ratios. Extension to the pyrrolidino (**10d**) and piperidino (**10e**) amides provided access to the benzoindolizidinone (**11d**) and benzoquinolizidinone (**11e**) derivatives (45–60% yields). Dimethylamide **10f** gave dihydroisoquinolone **11f** in lower yield (36%) together with debrominated uncyclized material (11%).

In order to evaluate the 1,5-hydrogen atom transfer process in more complex systems, we prepared the tetrahydroisoquinoline derivatives **12a–c**[18] and subjected them to the standard tin hydride conditions. Compounds **12a** and **12c** led to approximately 1:1 diastereomeric mixtures of angular (**13a**, **13c**)[19] and linear (**14a**, **14c**) dibenzoquinolizidinones respectively in yields shown in Scheme III. Surprisingly, silylated derivative **12b** gave only the linear tetracycle **14b**.

A series of simple *o*-bromobenzamides **15a–f** were prepared in order to probe the efficacy of intermolecular interception of the nucleophilic α-amidoyl radical by electron-deficient alkenes (Scheme IV).[20] When subjected to the standard tin hydride conditions in the presence of methyl acrylate (5 equiv), the symmetrical substrates **15a–d** afforded α-substituted products **16a–d** (68–91% yields).[21] Unsymmetrical amides **15e,f** similarly led to esters **16e,f** in lower yields together with considerable amounts (>30%) of reduced products. The exclusive formation of **16e** does not coincide with the rotamer population of the starting amide (55% Me anti to C=O). We speculate that 1,5-hydrogen transfer from the benzyl group may occur, but that the resulting radical is too stabilized to add rapidly enough to methyl acrylate. The selective formation of **16f** (55%) was not anticipated, and the unusual results of the silicon systems warrant further investigation. Compound **16c** was hydrolyzed and converted into 2-pyrrolizidinone,[22] thus revealing the "protective group" nature of the 1,5-hydrogen atom transfer strategy.

These preliminary results demonstrate that radical translocation to form α-amidoyl radicals at normally unreactive sites has useful synthetic consequences for intra- and intermolecular modes of carbon–carbon bond formation. They also suggest synthetic strategies for selective generation of α-amidoyl radicals in unsymmetrical tertiary amides based on control of amide rotamer populations.[23]

Acknowledgment. The group at Waterloo is indebted to Dr. K. U. Ingold for the initial mechanistic insight, to Professor R. Funk for encouraging the pursuit of the original idea, and to NSERC and Merck Frosst Canada for financial support. The group at Pittsburgh thanks Professor T. Cohen for helpful discussions and the National Institutes of Health for support.

(18) Compounds **12a** (90%) and **12c** (33%) were prepared by treatment of 3-hydroxy-7-bromophthalide with tetrahydroisoquinoline and 3-carbomethoxytetrahydroisoquinoline (Dean, R. T.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 2115), followed by Wittig reaction as described for the preparation of **10**; **12b** was obtained (23%) from **12a** by reaction with LiTMP/TMSCl (Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155) followed by Wittig reaction.

(19) Represent skeleta of the 13-methylprotoberberine class of alkaloids: Shamma, M.; Moniot, J. L. *Isoquinoline Alkaloids Research 1972–1977*; Plenum Press: New York, 1978; p 209. Bhakuni, D. S.; Jain, S. In *The Alkaloids*; Brossi, A., Ed.; Academic: Orlando, 1986; Vol. 28, p 95.

(20) Although observed under photochemical radical-generating conditions (Sinnreich, J.; Elad, D. *Tetrahedron* **1968**, *24*, 4509), bimolecular addition reactions of α-amidoyl radicals are not well documented.

(21) Use of the Stork method[17] on **15a** gave **16a** in somewhat lower yield (78%).

(22) Edwards, O. E.; Paton, J. M.; Benn, M. H.; Mitchell, R. E.; Watanatada, C.; Vohra, K. N. *Can. J. Chem.* **1971**, *49*, 1648.

(23) Hydrogen atom transfer reactions may be more widespread in tin hydride chemistry than is generally recognized. Tin deuteride experiments[16] may be appropriate to detect such "invisible" rearrangements.

Biosynthesis of Virginiae Butanolide A

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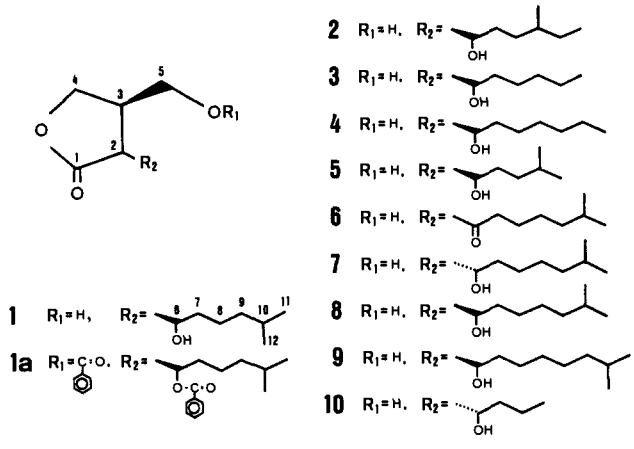
In *Streptomyces*, some signal molecules which control cytodifferentiation and secondary metabolites production are known. We have recently isolated five virginiamycin inducing factors, virginiae butanolide (VB) A–E (**1–5**), from the culture broth of *S. virginiae* and found that they have a 2,3-disubstituted butanolide skeleton,[1,2] which is common to other known signal molecules produced by a variety of *Streptomyces* species, such as A-factor **6**,[3] factor I **7**,[4] Gräfe's factors **1**, **8**, and **9**,[5] and IM-2 **10**.[6] There



is no information concerning the biosynthesis of this unique butanolide skeleton usually because the amount of a signal molecule produced by a microbe is extremely small.[7] In this paper, we report the preliminary elucidation of the origin of the carbon skeleton of **1** by using a strain of *S. antibioticus* which is a high producer of **1**.[8]

Cultures of *S. antibioticus* were performed in a 500-mL Sakaguchi flask containing 100 mL of medium.[8,9] Sodium acetate

(1) Yamada, Y.; Sugamura, K.; Kondo, K.; Yanagimoto, M.; Okada, H. *J. Antibiot.* **1987**, *40*, 496–504.

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(6) Sato, K.; Nihira, T.; Sakuda, S.; Yanagimoto, M.; Yamada, Y. *J. Ferment. Bioeng.* **1989**, *68*, 170–173.

(7) A few μg of **1** was obtained from 1 L of the broth of *S. virginiae*.

(8) Ohashi, H.; Zheng, Y.-H.; Nihira, T.; Yamada, Y. *J. Antibiot.* **1989**, *42*, 1191–1195.

(9) Production medium consists of 0.75% Bacto-casitone, 0.75% yeast extract, 1.5% glycerol, and 0.25% NaCl (pH 6.5). In a feeding experiment of glycerol, potato starch was used instead of glycerol.

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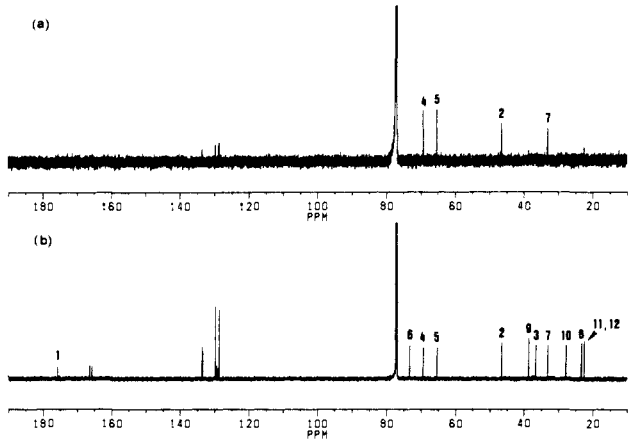

Figure 1. ^{13}C NMR spectra of **1a**: (a) derived from [1,3-^{13}C]glycerol (0.062 mg in 0.6 mL of $CDCl_3$, 18211 transients) and (b) natural abundance (3.0 mg in $CDCl_3$, 1515 transients).

(100 mg) was added to the culture twice at 24 and 48 h since the addition of it increased the yield of **1**. After a total of 96 h of incubation, the broth (10 × 100 mL) was treated with charcoal and SEP-PAK C_{18} cartridge to obtain the crude **1**. Benzoylation of crude **1** and further purification by HPLC gave 1 mg of **1a**.

Next, instead of sodium acetate, a mixture of sodium acetate (50 mg) and sodium [1-^{13}C]acetate (99 atom % ^{13}C, 50 mg) was administered to the culture (15 × 100 mL broth), and workup yielded 1.87 mg of **1a**. The 150.9-MHz ^{13}C NMR spectrum[10] of this sample showed enrichment at C-1 (6.6%) and C-6 (5.8%). Sodium [2-^{13}C]acetate (99 atom % ^{13}C, 50 mg) was fed next (15 × 100 mL broth), and the ^{13}C NMR spectrum of the obtained **1a** (1.88 mg) revealed enrichment at C-2 (10.7%) and C-7 (9.3%). In the next experiment, sodium [1-^{13}C]isovalerate[11] (2.5 mg) was fed (5 × 100 mL broths) eight times, so as to avoid the growth inhibition by too much addition of it at one time. The ^{13}C NMR spectrum of the obtained **1a** (0.33 mg) showed enrichment only at C-8 (7.3%), revealing that isovaleric acid was incorporated into the five carbons of **1** from C-8 to C-12.

Labeled glycerol was fed in a medium without glycerol in spite of a drastic decrease in the yield to avoid the high dilution of labeled glycerol. [1,3-^{13}C]Glycerol[12] (50 mg) was administered to the culture (5 × 100 mL broth) twice at 24 and 48 h, and 0.062 mg of **1a** was obtained. The ^{13}C NMR spectrum of **1a** (Figure 1) clearly showed enrichment at C-4 (6.2%) and C-5 (6.1%) and also C-2 (4.5%) and C-7 (3.7%) due to offshoot [2-^{13}C]acetate. Unfortunately, an expected two-bond coupling between C-4 and C-5 could not be observed under the measurement condition[10] because of its small value.[13] But its CI-MS spectrum revealed that non-, mono-, and di-^{13}C-labeled molecular species were present in it with the ratio of their relative abundances of 100:8.5:6.1.[14] Since the majority of dilabeled molecules must be the molecule labeled at C-4 and -5, and the mol % of a dilabeled one (5.3%) calibrated from the ratio was approximately consistent with the incorporation % estimated by NMR of C-4 (4.5%)[15] or C-5 (4.4%),[15] it was concluded that C-4 and C-5 resulted from an intact glycerol molecule.

(10) Spectra were taken on a Brucker AM 600 spectrometer with power gated broad band proton decoupling (sweep width = 38462 Hz, 128 K data points, pulse width = 43°, acquisition time = 1.704 s). Each signal was unambiguously assigned by DEPT, COSY, and C-H COSY experiments.

(11) [1-^{13}C]Isovaleric acid was synthesized from K^{13}CN (99 atom % ^{13}C) and isobutyl bromide.

(12) [1,3-^{13}C]Glycerol (77 atom % ^{13}C at C-1, 99 atom % ^{13}C at C-3) was synthesized from K^{13}CN and sodium [1-^{13}C]acetate (99.4 atom % ^{13}C) as described in the following: Chen, T. S. S.; Chang, C.; Floss, H. G. *J. Am. Chem. Soc.* **1981**, *103*, 4565-4568.

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(15) These values were deduced from the enrichment % of peaks and the contamination % of [1-^{13}C]glycerol.

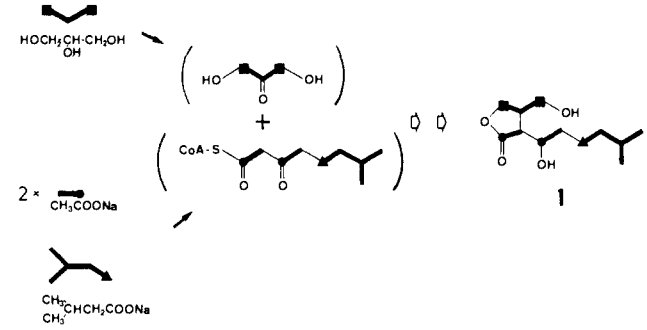

Figure 2. Biosynthetic origin of **1**.

The origin of the skeleton of **1** is summarized in Figure 2, and we believe that these subunits except for isovaleric acid moiety are common in all signal molecules of 2-(1′-hydroxyalkyl)-3-(hydroxymethyl)butanolides produced by *Streptomyces*. A probable route for its formation is a reductive coupling between the β-ketoacid started from isovaleryl-CoA and the C_3 unit from glycerol, such as dihydroxyacetone or its derivatives (Figure 2). Work to prove this hypothesis is now in progress.

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Registry No. 1, 109215-47-6; $HOCH_2CH(OH)CH_2OH$, 56-81-5; acetic acid, 64-19-7; isovaleric acid, 503-74-2.

A Water-Stable Manganese(V)–Oxo Complex: Definitive Assignment of a $\nu_{Mn^V=O}$ Infrared Vibration

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Although there are over 120000 entries in the *Chemical Abstracts Formula Index* for manganese, fewer than ten unique fully characterized species of manganese(V), -(VI), and -(VII) are stable under normal conditions.[2,3] The preponderance of lower oxidation state compounds is typical of the middle and later transition metals, yet the rareness of higher oxidation state complexes does not imply lack of importance. These compounds provide the major source of prima facie metallooxidants,[3] and in manganese chemistry, permanganate is a classic example. Manganese(V)–oxo complexes are the subject of considerable current interest as reactive intermediates in oxidation reactions with porphyrin[4a-c] and salen[4d] systems, and manganese–oxo complexes of a number of lower oxidation states have a probable role in the oxygen-evolving complex in photosynthesis.[5] Man-

(1) (a) Dreyfus Teacher-Scholar, 1986-1990; Alfred P. Sloan Research Fellow, 1986-1989. (b) California Institute of Technology; current address, Department of Chemistry, Carnegie Mellon University.

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