alkynes, unlike related unstrained amidometal complexes.[17] Further exploration of the reactions of these hydrazido complexes and their possible application to organic synthesis is under way.

Acknowledgment. We are grateful for financial support of this work from the National Institutes of Health (Grant No. GM25459) and for helpful discussions with Prof. Richard A. Andersen. We would also like to thank Michael J. Scott for his assistance in solving the crystal structure of compound **8**.

Supplementary Material Available: Spectroscopic and analytical data for complexes **1** and **3–11** and details of the structure determination for complexes **4** and **8**, including experimental description, ORTEP drawings showing full atomic numbering and packing in the crystal, and tables of crystal and data collection parameters, general temperature factor expressions (B's), positional parameters and their estimated standard deviations, and intramolecular distances and angles (44 pages); tables of observed and calculated structure factors for **4** and **8** (35 pages). Ordering information is given on any current masthead page.

(17) Three apparent exceptions: (a) See ref 9. (b) Casanuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738. (c) Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 4108.

Intramolecular α-Amidoyl to Aryl 1,5-Hydrogen Atom Transfer Reactions. Heteroannulation and α-Nitrogen Functionalization by Radical Translocation

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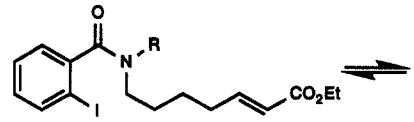
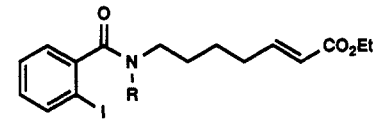
When the generation of oxygen-centered radicals at remote sites is followed by intramolecular hydrogen atom transfer, a powerful method to functionalize organic molecules results.[2] This strategy has recently been extended to the tin hydride method by generating carbon-centered radicals at remote sites (such as protecting groups) and translocating these radicals by 1,5-hydrogen atom transfer prior to cyclization.[3] In essence, this approach permits the indirect use of a C–H bond as a radical precursor in the tin hydride method. We now report that α-benzamidoyl radicals[4] generated from *o*-halobenzamides by a 1,5-hydrogen atom transfer undergo a variety of new radical addition and cyclization reactions. Our results indicate that the rotamer population of the starting *o*-halobenzamide often dictates the outcome of these reactions.

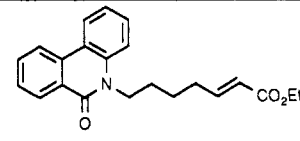
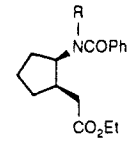
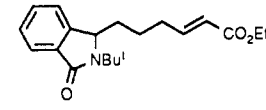
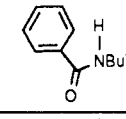
Table I. Tin Hydride Reduction of **6a–f**



6-anti



6-syn

R	anti/syn ratio	products from tin hydride reductn	
Ph (**6a**)	10/90		**7a**, 36%
C_6H_{11} (**6b**)	33/67		**7b**, 27%
C_4H_9 (**6c**)	50/50		**7c**, 43%
CH_2Ph (**6d**)	50/50		**7d**, 38%
$(CH_2)_4CH$=CHCO$_2$Et (**6e**)[a]			**7e**, 82%
Bu^t (**6f**)	>98/2		**8**, 38%
			**9**, 41%

[a] Rotamers **6**-anti and **6**-syn are identical in this symmetrically substituted amide.

In 1968, a classic series of isotopic substitution experiments by Cohen et al.[5a] showed that 1,5-hydrogen transfer reactions of radicals **2** and **3**[5b] ($R^1 = R^2 = H/D$) were faster than rotation of amide C–N bonds (Scheme I). Modern knowledge of lifetimes of aryl radicals and rates of amide bond rotation supports the broader conclusion that the geometry of a typical amide C–N bond will be fixed during the entire lifetime of any aryl radical. Amide rotamers **1a** and **1b** interconvert in solution with typical lifetimes of 10^{-1}–10^{-2} s.[6] However, the maximum solution lifetime of radicals **2** and **3** probably cannot exceed 10^{-5} s,[7] precluding interconversion by C–N bond rotation. Assuming that rotamers **1a** and **1b** are equally reactive toward $Bu_3Sn^\bullet$, the relative amounts of **2** and **3** that are formed by halogen atom abstraction should be determined by the equilibrium concentrations of the starting

(1) (a) University of Waterloo. (b) University of Pittsburgh. (c) NATO Postdoctoral Fellow, 1987–1989. (d) Dreyfus Teacher-Scholar, 1985–1989; recipient of a National Institutes of Health Career Development Award, 1987–1992.

(2) Intramolecular hydrogen atom transfer is a fundamental organic free radical process. Reviews: Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in the Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, p 161. Wilt, J. W. In *Free Radicals*; Kochi, J. K., Ed.; Wiley-Interscience: New York, 1973; Vol 1, p 333. Recent examples: Petter, R. C.; Powers, D. G. *Tetrahedron Lett.* **1989**, *30*, 659. Baldwin, J. E.; Adlington, R. M.; Robertson, J. *Tetrahedron* **1989**, *45*, 909.

(3) (a) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900. (b) Cuevas, J.-C.; Snieckus, V. Presented at the 197th National Meeting of the American Chemical Society, Dallas, TX, April 1989; Abstract ORGN 190.

(4) For recent references to α-amidoyl radical generation, generally by the tin hydride method from functionalized precursors, see: (a) Martin, S. F.; Yang, C.-P.; Laswell, W. L.; Rüeger, H. *Tetrahedron Lett.* **1988**, *29*, 6685. (b) Choi, J.-K.; Ha, D.-C.; Hart, D. J.; Lee, C.-S.; Ramesh, S.; Wu, S. *J. Org. Chem.* **1989**, *54*, 279. For alternate methods of generation, see the following. Photochemical: (c) Aoyama, H.; Arata, Y. *J. Org. Chem.* **1987**, *52*, 4639 and references cited therein. (d) Azzouzi, A.; Dufour, M.; Gramain, J.-C.; Remuson, R. *Heterocycles* **1988**, *27*, 133. Ru(II) catalyzed: (e) Murahashi, S.-I.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* **1988**, *110*, 8256.

(5) (a) Cohen, T.; McMullen, C. H.; Smith, K. *J. Am. Chem. Soc.* **1968**, *90*, 6866. (b) For leading references to related 1,5-hydrogen atom transfer reactions, see: Beckwith, A. L. J.; Gara, W. B. *J. Chem. Soc., Perkin Trans. 2* **1975**, 593. Pines, S. H.; Purick, R. M.; Reamer, R. A.; Gal, G. *J. Org. Chem.* **1978**, *43*, 1337.

(6) (a) Review: Stewart, W. E.; Siddall, T. H., III *Chem. Rev.* **1970**, *70*, 517. (b) Rates of rotation of *N,N*-dimethylbenzamides: Jackman, L. M.; Kavanagh, T. E.; Haddon, R. C. *Org. Magn. Reson.* **1969**, *1*, 109. Spaargaren, K.; Korver, P. K.; van der Haak, P. J.; de Boer, Th. J. *Ibid.* **1971**, *3*, 605.

(7) The maximum lifetime of these aryl radicals is limited by their rate of reaction with benzene. Phenyl radical adds to benzene with a second-order rate constant, $k = 4.5 \times 10^5$ M^{-1} s^{-1} (Scaiano, J. C.; Stewart, L. C. *J. Am. Chem. Soc.* **1983**, *105*, 3609). Therefore, 1,5-hydrogen transfer must be faster than the pseudo-first-order rate constant $k > 10^6$ s^{-1}.

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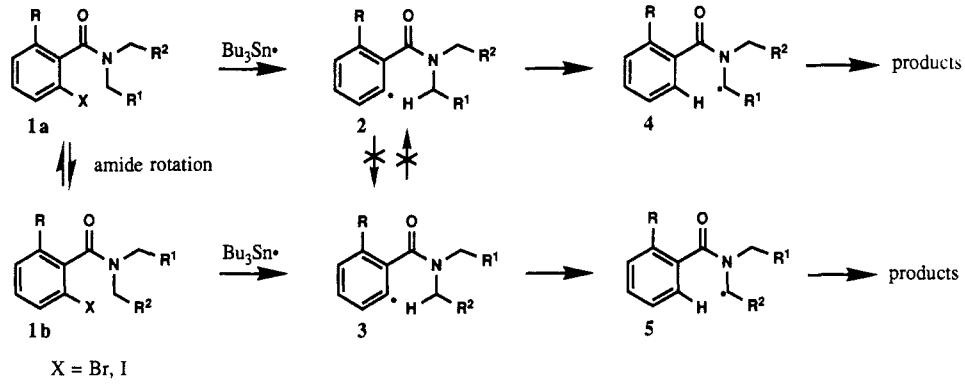
Scheme I

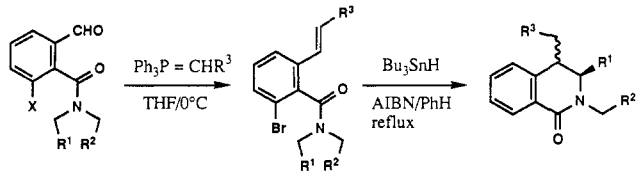


1a 2 4

1b 3 5

X = Br, I

Scheme II

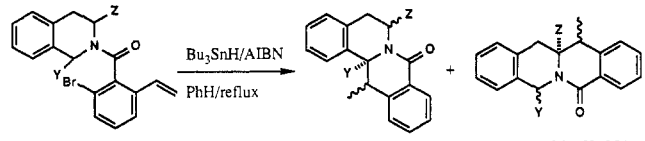


10 11

9a: $R^1 = R^2$ = Me, X= TMS
9b: $R^1 + R^2 = (CH_2)_3$, X = TMS
9c: $R^1 = R^2$ = Me, X = Br
9d: $R^1 + R^2 = (CH_2)_3$, X = Br
9e: $R^1 + R^2 = (CH_2)_2$, X = Br
9f: $R^1 = R^2$ = H, X = Br

a: $R^1 = R^2$ = Me, R^3 = H
b: $R^1 = R^2$ = Me, R^3 = Ph
c: $R^1 = R^2$ = Me, $R^3 = CO_2Et$
d: $R^1 + R^2 = (CH_2)_2$, R^3 = H
e: $R^1 + R^2 = (CH_2)_3$, R^3 = H
f: $R^1 = R^2 = R^3$ = H

Scheme III



12a: Y = Z = H
12b: Y = TMS, Z = H
12c: Y = H, Z = CO_2Et

13a (*cis* Me, H, 21%) 14a (*trans* Me, H, 35%)
13b (0%) 14b (54%)
13c (36%) 14c (36%)

rotamers **1a/b**. Because **2** can only produce **4** by 1,5-hydrogen transfer, and **3** can only produce **5**, the final products should ultimately relate back to the amide rotamer population of the starting material **1**.

To test this model, we prepared the series of amides **6a–f** shown in Table I. One amide substituent was chosen such that rapid cyclization might follow radical translocation while the other was selected to alter the rotamer population of the starting amide. The rotamer populations of **6a–d** and **6f** were determined by ^1H NMR, and rotamer geometries were assigned by standard methods.[8] Table I illustrates the products that were isolated when each of the amides was reduced by standard syringe pump addition of 2 equiv of tributyltin hydride in benzene (80 °C). A correlation between the types of products formed and the starting rotamer population is evident. Amide **6a** is unfavorably disposed for radical translocation, but favorably disposed for cyclization to form **7a**.[9] For **6b–d**, the yields of products **7b–d** resulting from translocation/cyclization[10] roughly correspond to the percent of the requisite rotamer precursor. Symmetrical amide **6e**, which contains acceptors in both side chains, gives an excellent yield of **7e**. We believe that compound **6f** gives efficient radical translocation, but for reasons that we do not yet understand, the ultimate products **8** and **9** do not derive from subsequent cyclization to the unsaturated ester.[11]

Symmetrical amides like **6e** provide high yields of cyclic products, but waste one acceptor group. In contrast, locating the acceptor group on the aryl ring of the benzamide is not wasteful. A series of substrates **9** was prepared by directed orthometalation methods (Scheme II).[12] Thus, one-pot metalation (*sec*-BuLi/TMEDA/THF/−78 °C), silylation (TMSCl), metalation, formylation (DMF) sequences led to 2-formyl-6-(trimethylsilyl)-benzamides **9a** and **9b** in 50–60% yields. Ipso bromodesilylation (Br_2/CH_2Cl_2/reflux/24 h)[13] afforded the corresponding bromobenzamides **9c** and **9d** (60–66%).[14] Conventional Wittig chemistry furnished the 2-vinyl-6-bromobenzamides **10a–f** in 80–85% yields.

Upon treatment under the standard tin hydride conditions [Bu_3SnH (2 equiv), AIBN (5 mol %) in refluxing benzene solution (0.02 M)],[15] compound **10a** cleanly afforded the dihydroisoquinolone **11a** in 67% yield as a 1:1 mixture of separable diastereomers.[16] Use of the iodo derivative corresponding to **10a** yielded **11a** in similar yield and stereoselectivity. Application of the catalytic tin hydride method of Stork [Bu_3SnCl (0.1 equiv), AIBN (0.1 equiv), $NaCNBH_3$ (2 equiv), *t*-BuOH; 0.05 M, reflux, 6 h][17] on **10a** led to **11a** in lower yield (40%). Under the standard

(8) (a) Lewin, A. H.; Frucht, M. *Org. Magn. Reson.* **1975**, *7*, 206. (b) Lewin, A. H.; Frucht, M.; Chen, K. V. J.; Benedetti, E.; Di Blasio, B. *Tetrahedron* **1975**, *31*, 207. (c) In addition to restricted rotation about the amide C–N bond, **6a–f** exhibited restricted rotation about the Ar–CO bond.[8a] This rotation is analogous to biaryl rotation, and we do not believe it is important in this analysis (Scheme I) because it serves only to interconvert enantiomers.

(9) (a) Related cyclizations have been conducted electrochemically, and yields of cyclization have been correlated with amide rotamer populations. Grimshaw, J.; Haslett, R. J.; Trocha-Grimshaw, J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2448. Grimshaw, J.; Haslett, R. J. *Ibid.* **1980**, 657. (b) A similar mechanistic picture probably also applies to cyclizations of *N*-(*o*-halophenyl)benzamides and acylamides; see: Bowman, R.; Heaney, H.; Jordan, B. M. *Tetrahedron Lett.* **1988**, *29*, 6657. Togo, H.; Kikuchi, O. *Heterocycles* **1989**, *28*, 373. Tertiary amides give cyclic products because the rotamer with Ar anti to C=O is favored, but secondary amides fail to cyclize because Ar is syn to C=O.

(10) Interestingly, the cyclization products are predominantly or exclusively cis.

(11) Compounds like **8** are formed only with *N*-*tert*-butyl amides. Compound **9** is formed in small amounts in some other cyclizations, and we suspect that it may result from oxidation (oxidant unknown) of the α-amidoyl radical to an acyl iminium ion and subsequent hydrolysis.[5]

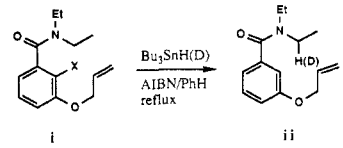
(12) Snieckus, V. *Chem. Rev.* **1990**, In press. Snieckus, V. *Bull. Soc. Chim. Fr.* **1988**, 67. Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306.

(13) Mills, R. J.; Snieckus, V. *Tetrahedron Lett.* **1984**, *25*, 483. Mills, R. J.; Horvath, R. F.; Sibi, M. P.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 1145.

(14) Tertiary amides not accessible by direct orthometalation methods were prepared by a general route from 3-hydroxy-7-bromophthalide, obtained from **9d** (6 N HCl/reflux, 95% yield). For example, treatment of the phthalide with $SOCl_2$ followed by pyrrolidine or dimethylamine gave benzamides **9e** or **9f** respectively, in 60% overall yield. See: Sloan, K. B.; Koch, S. A. M. *J. Org. Chem.* **1983**, *48*, 635.

(15) (a) Shankaran, K.; Sloan, C. P.; Snieckus, V. *Tetrahedron Lett.* **1985**, *26*, 6001. (b) Sloan, C. P.; Cuevas, J.-C.; Quesnelle, C.; Snieckus, V. *Ibid.* **1988**, *29*, 4685.

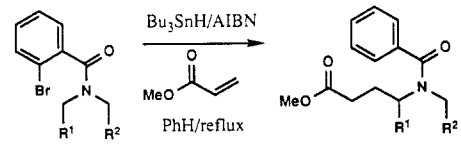
(16) That a 1,5-hydrogen atom transfer intervenes in the reduction of i to ii was first recognized by a tin deuteride experiment (Sloan, C. P. M.Sc. Thesis, University of Waterloo, 1987).



i ii

(17) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303.

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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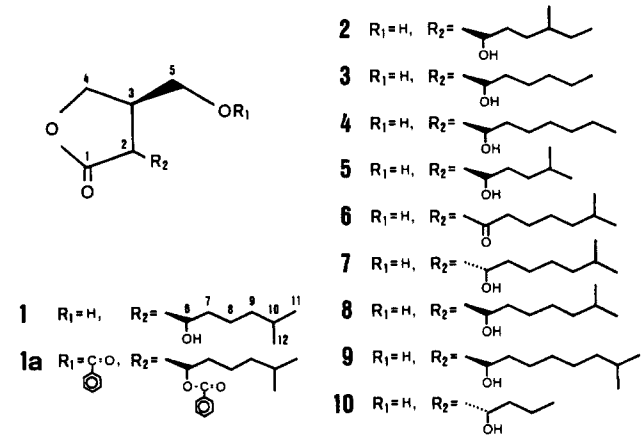
In *Streptomyces*, some signal molecules which control cytodifferentiation and secondary metabolites production are known. We have recently isolated five virginiamycin inducing factors, virginiae butanolide (VB) A–E (**1–5**), from the culture broth of *S. virginiae* and found that they have a 2,3-disubstituted 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 1 **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.

(2) Kondo, K.; Higuchi, Y.; Sakuda, S.; Nihira, T.; Yamada, Y. *J. Antibiot.* **1989** In press.

(3) Kleiner, E. M.; Pliner, S. A.; Soifer, V. S.; Onoprienko, V. V.; Balashova, T. A.; Rosynov, B. V.; Khokhlov, A. S. *Bioorg. Khim.* **1976**, *2*, 1142–1147.

(4) Gräfe, U.; Schade, W.; Eritt, I.; Fleck, W. F.; Radics, L. *J. Antibiot.* **1982**, *35*, 1722–1723.

(5) Gräfe, U.; Reinhardt, G.; Schade, W.; Eritt, I.; Fleck, W. F.; Radics, L. *Biotechnol. Lett.* **1983**, *5*, 591–596.

(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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