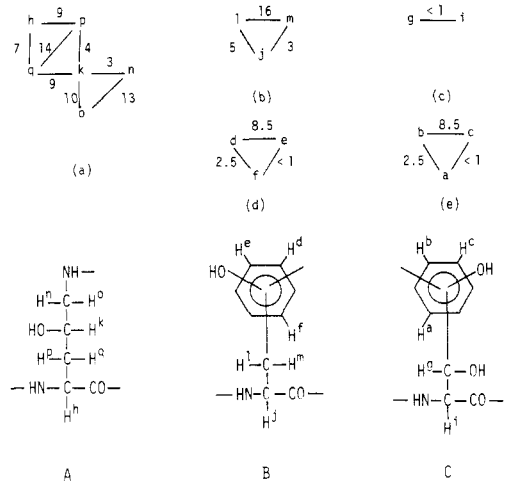


Figure 1. Partial structures A–C and the ^1H–^1H relationships a–e. The ^1H–^1H relationships a, b, and c were obtained by decoupling experiments on 1, while d and e were derived by those on 2. The very small vicinal coupling constant of the H^g–H^i is presumably due to a dihedral angle close to 90° caused by a restricted conformation of WS-43708A.

Table I. ^1H NMR (400 MHz) Chemical Shifts, Multiplicities, and Coupling Constants (J, Hz) for WS-43708A (1), 2, and 4

	1[a]	2[b]	4[c]
H^a	7.40, m (3 H)	7.39, d (2.5)	7.78, br d (2)
H^b	and	7.17, dd (2.5, 8.5)	7.61, dd (2, 8.5)
H^c	6.93, m (2 H)	6.83, d (8.5)	7.62, br d (8.5)
H^d		7.11, dd (2.5, 8.5)	7.48, dd (2.5, 8.5)
H^e		6.78, d (8.5)	6.96, d (8.5)
H^f	6.87, br s	6.88, d (2.5)	7.33, d (2.5)
H^g	5.84, br s	5.70, br s	7.57, s
H^h	5.02, dd (7, 9)	5.09, dt (8.8, 7.5)	
H^i	4.91, br s	4.63, br d (9.5)	
H^j	4.47, dd (3, 5)	4.56, dt (7.5, 3.3)	4.80, dt (7.5, 7.5)
H^k	4.09, dddd (3, 4, 9, 10)	3.64, m	
H^l	3.55, dd (5, 16)	3.16[d]	3.22, d (7.5)
H^m	3.03, dd (3, 16)	2.77, dd (3.3, 15)	
H^n	3.17, dd (3, 13)	3.16[d]	
H^o	2.97, dd (10, 13)	3.07, m	
H^p	2.11, ddd (4, 9, 14)	1.79, m	
H^q	1.95, ddd (7, 9, 17)	1.50, m	
H^r		7.62, d (7.5)	6.23, d (7.5)
H^s		8.50, d (8.8)	
H^t		8.53, d (9.5)	
H^u		7.88, t (5.5)	
H^v		1.84, s (6 H)	1.95, s (3 H)
H^w			
H^x		3.71, s (3 H)	4.10, s (3 H)
H^y			3.73, s (3 H)
H^z			3.91, s (3 H)

[a] D_2O–DCl. [b] Me_2SO-d_6. [c] $CDCl_3$. [d] Overlapping signals of H^l and H^n prevented the examination of their multiplicities.

with the phenolic hydroxy group to the benzofuran structure 3. These chemical evidence thus leads to the partial structure B + C.

The problem remaining is to link A and B + C for the full structure of WS-43708A. Since a molecular model study indicated that an intramolecular cyclization of B + C itself is practically impossible, insertion of fragment A was proposed. This was corroborated by the ^1H NMR spectrum of 1 in D_2O–NaOD, in which, in contrast to upfield shifts of 0.36 and 0.67 ppm, respectively, for H^i and H^j (δ 4.90 and 4.47 in D_2O–DCl), no shift was observed on

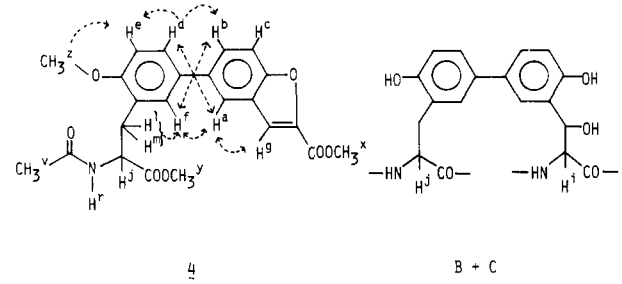


Figure 2. Structure of 4 and the partial structure B + C. The observed NOEs in 4 are shown by dotted line arrows.

H^h (δ 5.02 in both D_2O–DCl and D_2O–NaOD), indicating that the α-amino acid group of A is incorporated in a cyclic peptide structure.[6,7] Reduction of 2 with $NaBH_4$ in MeOH gave alcohol 5 (FABMS, m/z 559 (M^+ + 1)), in the ^1H NMR spectrum (CD_3OD) of which a singlet-like signal (δ 4.89, CD_3OD) corresponding to H^i in 2 was changed to a triplet (δ 4.20, J = 7.5 Hz) coupled to the newly formed methylene group (δ 3.65 (dd, J = 7.5, 11 Hz) and 3.78 (dd, J = 7.5, 11 Hz)). This indicates that the carboxylic acid function in 1 is bonded to C-8 bearing H^i. Consequently, peptide bonds between N-9/C-10 and N-12/C-13 are postulated to give the full structure of 1, without stereochemistry, for WS-43708A.[8]

The biphenyl group incorporated in the 15-membered cyclic peptide portion of WS-43708A is unique and such compounds are rarely found in nature.[9] The exceptional activity of WS-43708A against gram-positive bacteria will be reported separately.

Registry No. 1, 95485-50-0; 2, 95485-51-1; 3, 95485-52-2; 4, 95485-53-3; 5, 95485-54-4; *erythro*-γ-hydroxy-L-ornithine hydrochloride, 95485-55-5.

(6) For the pH-dependent chemical shifts of the α-methine protons of peptides, see: Sheinblatt, M. *J. Am. Chem. Soc.* **1966**, *88*, 2845.
(7) The ^1H NMR spectrum (Me_2SO-d_6) of 2 showed a triplet (J = 5.5 Hz) corresponding to the amido H originated from the δ-amino group of A at δ 7.88 coupled to H^n and H^o (δ 3.07 (m) and 3.16 (m)), thus supporting that the δ-amino group of A in 1 is unsubstituted.
(8) Stereochemical deductions aside from that of the ornithine portion are the subject of future publications.
(9) As far as we are aware, the only antibiotics that contain a biphenyl group as part of a cyclic peptide system are those that belong to the vancomycin group of antibiotics, see: Barna, J. C. J.; Williams, D. H. *Annu. Rev. Microbiol.* **1984**, *38*, 339.

Itsuo Uchida, Masami Ezaki
Nobuharu Shigematsu, Masashi Hashimoto*

Exploratory Research Laboratories
Fujisawa Pharmaceutical Co., Ltd.
2-1-6, Kashima, Yodogawa-ku
Osaka 532, Japan

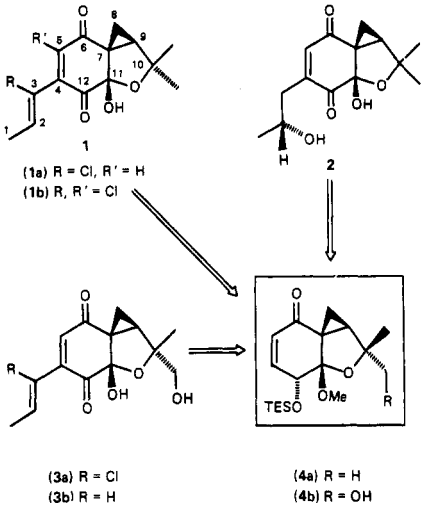
Received December 18, 1984

Total Synthesis of (–)-Gilmicolin

Summary: The total synthesis of (–)-gilmicolin is disclosed; assignment of absolute stereochemistry is thereby secured.

0022-3263/85/1950-1342$01.50/0

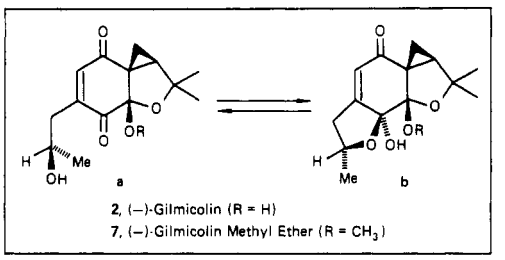
Sir: In 1982 we recorded the total synthesis of mycorrhizin A (**1a**),[2,3] simplest member of a small, albeit architecturally novel, class of fungal metabolites, which now includes chloromycorrhizin A (**1b**),[3] gilmicolin (**2**),[4] mikrolin (**3a**),[5] and dechloromikrolin (**3b**).[5] Central to this venture was the development of a unified synthetic strategy wherein enone **4a** (or its hydroxyl derivative **4b**) was proposed to be an ideal, common advanced intermediate, which could service all members of the class.

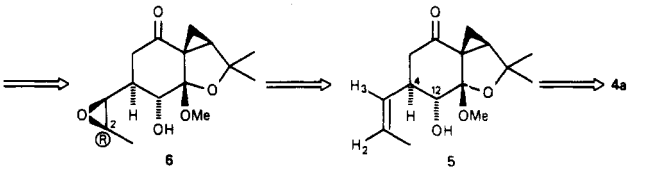


Our interest in these metabolites stems not only from their unique structural features (i.e., spirocyclopropane and hemiketal functionalities) but also from their potent antifungal activity.[6] In this communication we report the first total synthesis of (−)-gilmicolin (**2**) which further exploits our unified synthetic strategy.

Gilmicolin (**2**), a minor fungal metabolite of *Gilmaniella humicola* Barron, was isolated and characterized by Tamm and co-workers in 1979 in connection with their biosynthetic work on mikrolin and dechloromikrolin.[4] Structural elucidation, initially derived via spectral and chemical studies, was subsequently confirmed via single-crystal X-ray analysis.[4] The absolute stereochemistry was based on analogy to that found in mycorrhizin A (**1a**) and mikrolin (**3a**). Interestingly, gilmicolin exists in solution as a 3:1 mixture of **2b** and **2a**, respectively. In diethyl ether their solubility properties were found to be quite different; this observation permitted the isolation and X-ray analysis of **2b**.

From the retrosynthetic perspective, we envisioned construction of the gilmicolin framework via conjugate addition of a propenyl unit to enone **4a**. Epoxidation of **5** followed by oxidation of the resultant alcohol **6** under conditions that would lead to epoxide opening (i.e., β-elimination) and isomerization of the resultant exocyclic olefin would then afford gilmicolin methyl ether (**7**).





Pivotal in this analysis was the stereochemical outcome of the proposed homoallylic, hydroxyl-directed epoxidation. Here, careful examination of the possible transition states for a metal ion catalyzed epoxidation,[7] assuming a trans relationship between the C(12)-secondary hydroxyl and the C(4)-propenyl unit in **5**,[8] suggested that the cis olefin would afford epoxy alcohol **6** with the requisite *R* configuration at C(2).

With this overview, we began the synthesis of (−)-gilmicolin via treatment of enone **4a** (available in 60% ee from our mycorrhizin A synthetic venture[4,9]) with lithium dipropenylcuprate[10] generated from 1-bromo-1-propene (85:15, cis–trans mixture) at 0 °C. The result was an 85:15 mixture (GC, NMR) of olefins **5**[11] and **8**,[11] respectively, after removal of the silyl ether [$(n\text{-Bu})_4$NF, THF, 0 °C, 10 min]. The combined yield after separation via flash chromatography[12] was 55%. Stereochemical assignments were based on careful analysis of the high-field ^{1}H NMR (500 MHz);[13] first, the cis isomer **5** displayed a $J_{2,3}$ coupling

(1) Camille and Henry Dreyfus Teacher Scholar, 1978–1983; National Institutes of Health (National Cancer Institute) Career Development Award, 1980–1985.

(2) Koft, E. R.; Smith, A. B., III. *J. Am. Chem. Soc.* **1982**, *104*, 2659. For other work in this area, see: Brown, R. F. C.; Matthews, B. R.; Rae, I. D. *Tetrahedron Lett.* **1981**, *22*, 215. Brown, R. F. C.; Fallon, G. D.; Gatehouse, B. M.; Jones, C. M.; Rae, I. D. *Aust. J. Chem.* **1982**, *35*, 1665. Brown, R. F. C.; Edwards, G. L.; Jones, C. M.; Rae, I. D.; Teo, P. Y. T. *Aust. J. Chem.* **1983**, *36*, 1263.

(3) Trofast, J.; Wickberg, B. *Tetrahedron* **1977**, *33*, 875. Stalhandske, C.; Svensson, C.; Sarnstrand, C. *Acta Crystallogr., Sect. B* **1977**, *33*, 870.

(4) Chexal, K.; Tamm, C.; Clardy, J.; Hirotsu, K. *Helv. Chim. Acta* **1979**, *62*, 1129.

(5) Bollinger, P.; Zardin-Tartaglia, T. *Helv. Chim. Acta* **1976**, *59*, 1809. Weber, H. P.; Petcher, T. J. *Helv. Chim. Acta* **1976**, *59*, 1821.

(6) J. Trofast, Ph.D. Thesis, Lund Institute of Technology, Lund, Sweden, 1978.

(7) Mihelich, E.; Daniels, K.; Eickhoff, D. *J. Am. Chem. Soc.* **1981**, *103*, 7690.

(8) Precedent for the proposed stereochemical outcome of the cuprate addition derived from the mycorrhizin A synthesis; see ref 2.

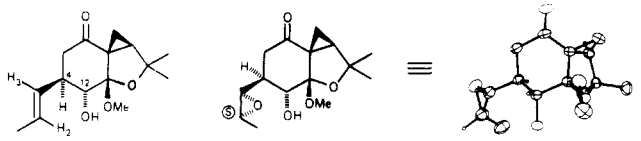
(9) Recently, we have completed an enantioselective synthesis of (+)-mycorrhizin A from **4a**; unpublished results of D. Huryn.

(10) Linstrumelle G.; Krieger, J. K.; Whitesides, G. M. *Org. Synth.* **1976**, *55*, 103.

(11) All new compounds gave 250-MHz ^{1}H NMR, IR, high-resolution mass spectra, and/or satisfactory C, H combustion analysis in accord with the structure given. All yields recorded are based upon isolated material which was >97% pure. The NMR and IR spectra of representative intermediates are given below. **5**: IR ($CHCl_3$) 3530 (br, m), 3020 (s), 2980 (s), 2950 (s), 1700 (s), 1395 (m), 1380 (m), 1075 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.32 (s, 3 H), 1.45 (s, 3 H), 1.67 (dd, J = 1.65 Hz, 7.5 Hz, 3 H), 1.74–1.82 (m, 2 H), 2.23 (dd, J = 5.0 Hz, 10.0 Hz, 1 H), 2.25 (dd, J = 11.3 Hz, 18.8 Hz, 1 H), 2.66 (dd, J = 5.0 Hz, 18.8 Hz, 1 H), 2.73 (d, J = 5.0 Hz, 1 H), 3.10 (dddd, J = 5.0 Hz, 10.0 Hz, 11.3 Hz, 11.3 Hz, 1 H), 3.28 (s, 3 H), 3.85 (dd, J = 5.0 Hz, 10.0 Hz, 1 H), 5.36 (qdd, J = 1.65 Hz, 11.3 Hz, 11.3 Hz, 1 H), 5.64 (qd, J = 7.5 Hz, 11.3 Hz, 1 H). **6**: IR ($CHCl_3$) 3600–3400 (br, m), 2990 (s), 2940 (s), 1700 (s), 1395 (m), 1380 (m), 1220 (s), 1100 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.32 (d, J = 7.5 Hz, 3 H), 1.34 (s, 3 H), 1.44 (s, 3 H), 1.77 (dd, J = 5.0 Hz, 10.0 Hz, 1 H), 1.88 (dd, J = 5.0 Hz, 7.5 Hz, 1 H), 2.15–2.34 (m, 3 H), 2.54 (d, J = 1.5 Hz, 1 H), 2.88 (dd, J = 7.5 Hz, 20.0 Hz, 1 H), 3.04–3.17 (m, 2 H), 3.38 (s, 3 H), 4.22 (dd, J = 1.5 Hz, 6.3 Hz, 1 H). **7**: IR ($CHCl_3$) 3600 (m), 3500 (br, m), 3010 (s), 2980 (s), 2940 (s), 1700 (m), 1675 (s), 1610 (w), 1390 (s), 1380 (s), 1100 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.22 (s, 3 H), 1.28 (d, J = 7.5 Hz, 3 H), 1.34 (s, 3 H), 1.55–1.74 (m, 2 H), 1.90 (dd, J = 4.7 Hz, 8.4 Hz, 1 H), 2.18 (dd, J = 5.6 Hz, 8.4 Hz, 1 H), 2.56 (dd, J = 4.6 Hz, 13.4 Hz, 1 H), 2.75 (dd, J = 7.5 Hz, 13.4 Hz, 1 H), 3.28 (s, 3 H), 3.96–4.14 (m, 1 H), 6.75 (s, 1 H). **2**: IR ($CHCl_3$) 3540 (m), 3020 (s), 2990 (m), 2940 (m), 1685 (s), 1310 (s), 1230 (s), 1210 (s), 1095 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.40 (s, 3 H), 1.46 (s, 3 H), 1.52 (d, J = 6.6 Hz, 3 H), 1.65 (dd, J = 5.0 Hz, 10.0 Hz, 1 H), 1.80 (dd, J = 5.0 Hz, 7.5 Hz, 1 H), 2.35 (dd, J = 7.5 Hz, 10.0 Hz, 1 H), 2.80 (ddd, J = 2.5 Hz, 8.8 Hz, 16.9 Hz, 1 H), 3.00 (dd, J = 6.6 Hz, 16.9 Hz, 1 H), 3.80 (s, exchangeable, 1 H), 4.08 (s, exchangeable, 1 H), 4.46 (qdd, J = 6.6 Hz, 6.6 Hz, 8.8 Hz, 1 H), 6.06 (br s, 1 H).

constant of 11.7 Hz, while the corresponding value for the trans isomer was 15.9 Hz.[14] Second, $J_{4,12}$ in both isomers (ca. 13 Hz) was consistent with a C(4)–C(12) trans relationship (vide infra).[8] Interestingly, when the cuprate reagent was allowed to warm to 25 °C followed by addition of enone **4a**, the isomer ratio shifted to 96:4 in favor of the cis isomer. To accommodate this improvement in stereoselectivity, in conjunction with a somewhat diminished yield, we suggest that the higher temperature promotes a more facile bimolecular coupling of the trans cuprate vs. the cis isomer.[15] Fortunately, utilization of an excess of cuprate reagent (ca. 2.5 equiv) precludes starting material recovery.

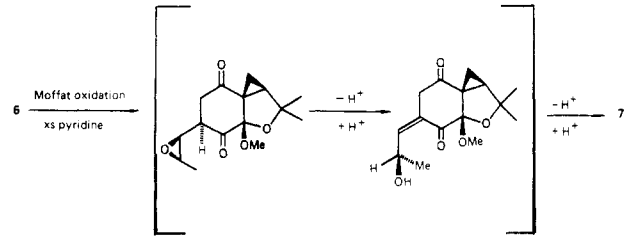
Turning next to the key epoxidation, treatment of olefin **5**[11] with *tert*-butyl hydroperoxide, $Mo(CO)_6$, and Na_2HPO_4 (1.5:0.03:0.05 equiv, respectively in benzene)[16] provided a single epoxy alcohol (**6**)[11] in 84% yield. The stereochemical outcome in this case was assigned initially by default, that is, via preparation and rigorous structural assignment of the alternative isomer (i.e., **9**); confirmation came with



8 9

completion of the gilmicolin venture (vide infra). Toward this end, epoxidation of olefin **5** with *m*-CPBA, as expected, afforded a 1:1 mixture of epoxy alcohols **6** and **9**.[11] The latter was a crystalline solid (mp 116–117 °C). Single-crystal X-ray analysis (see ORTEP) established not only the configuration at C(2) as *S* but also confirmed the stereochemical outcome of the conjugate addition [i.e., the substituents at C(4) and C(12) disposed trans].[17]

With epoxy alcohol **6** in hand, there remained only the conversion to gilmicolin methyl ether (**7**) and hydrolysis of the mixed ketal to complete the synthesis. We selected the Moffat oxidation[18] anticipating that use of excess pyridine would, after initial oxidation, effect both epoxide opening and isomerization of the resultant exo olefinic bond. In the event, treatment of **6** with 6 equiv of dicyclohexylcarbodiimide/Me_2SO and 2 equiv of pyridine afforded gilmicolin methyl ether (**7**) in 51% yield. Final



hydrolysis of the mixed methyl ketal via the Trofast–Wickberg protocol (50% HBF_4, dioxane, H_2O)[3] led to (–)-gilmicolin [$[\alpha]^{24}_D$ –25.1° (*c* 0.49, methanol); lit.[4] $[\alpha]^{24}_D$ –48 ± 2° (*c* 0.143, methanol)] in 44% yield.[19] That in fact gilmicolin was in hand was established via careful comparison of the physical and spectral properties with those derived from natural (–)-gilmicolin (**2**).[20]

In summary, the first total synthesis of (–)-gilmicolin has been achieved. The synthesis proved short (i.e., five steps from our common advanced intermediate), efficient, highly stereocontrolled, and secured for the *first* time the absolute stereochemistry of (–)-gilmicolin. Studies directed toward the synthesis of other members of this class will be reported in due course.

Acknowledgment. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (Institute of General Medical Sciences) through Grant No. GM-24680. In addition, we thank Drs. George Furst and Patrick Carroll of the University of Pennsylvania Spectroscopic Facilities for aid in obtaining the high-field NMR and X-ray spectral data, respectively.

(12) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(13) We thank Professor Stanley Opella and the Smith Kline Research Laboratories for obtaining the 500-MHz NMR spectra of **6** and **8**.
(14) Jackman, L. M.; Sternnell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed; Pergamon Press: Oxford, 1969; p 301.
(15) Whitesides, G. M.; Casey, C. P. *J. Am. Chem. Soc.* **1966**, 88, 4541.
(16) Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *J. Am. Chem. Soc.* **1974**, *96*, 5254.
(17) Unpublished results of P. Carroll of this laboratory.
(18) Pfitzner, K. E.; Moffat, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5670.
(19) The observed optical purity of synthetic (–)-gilmicolin is consistent with the optical purity (ca. 60% ee) of **4a** obtained via asymmetric hydroboration.
(20) We thank Professor C. Tamm, University of Zurich, for providing spectral data of natural (–)-gilmicolin.

Amos B. Smith, III,*[1] Donna M. Huryn

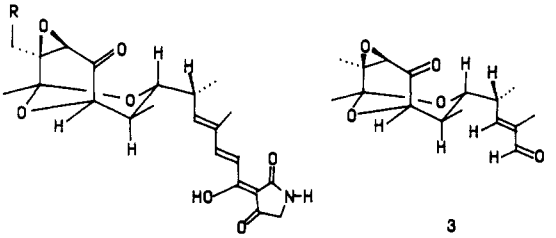
The Department of Chemistry, The Monell Chemical Senses Center, and The Laboratory for Research on the Structure of Matter The University of Pennsylvania Philadelphia, Pennsylvania 19104

Received November 29, 1984

A Versatile 3-Acyltetramic Acid Reagent

Summary: The 3-acyltetramic acid derived Emmons reagent **6** undergoes smooth reaction with saturated and unsaturated aldehydes to afford easily characterized adducts which are readily debenzylated under acidic conditions.

Sir: In conjunction with synthetic efforts aimed at the construction of the natural products tirandamycin A (**1**) and tirandamycin B (**2**),[1] we became mired in the tactical problem of coupling aldehyde **3** onto a 3-acyltetramic acid residue. At the time we had reached this juncture, others,



tirandamycin-A(1); R=H
tirandamycin-B(2); R=OH

3

namely, Rinehart,[2] Boeckman,[3] and DeShong,[4] had addressed this situation. Unfortunately, the methodology described by these authors proved inappropriate for our

(1) Reusser, F. In "Antibiotics: Mechanism of Action of Antibacterial Agents"; Hahn, F. E., Ed.; Springer-Verlag: New York, 1979; Vol. V, Part I, p 361, and references cited therein.

0022-3263/85/1950-1344$01.50/0