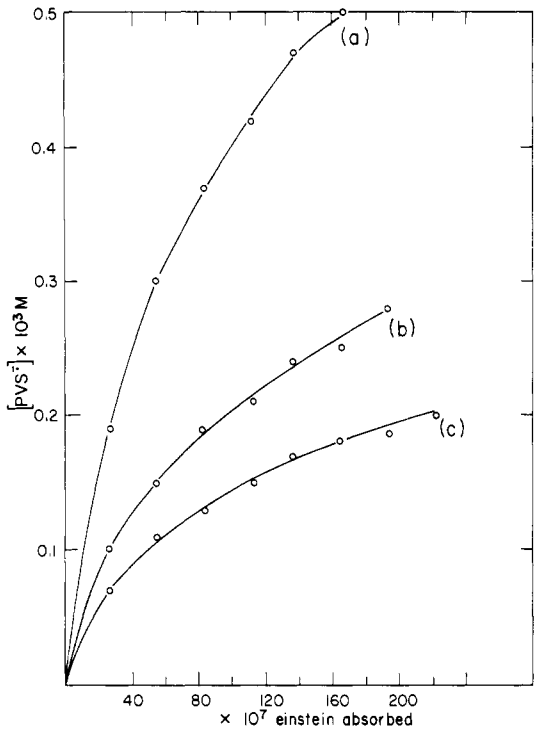

Figure 3. Propyl viologen radical ($PVS^{-}\cdot$) formation as a function of ionic strength of the system. Experiments at pH 9.8, $[PVS^0] = 1 \times 10^{-3}$ M, [TEA] = 1×10^{-3} M; sensitizer $Zn(TMPyP)^{4+}$ (4×10^{-6} M). (a) [NaCl] = 0.002 M; (b) [NaCl] = 0.1 M; (c) [NaCl] = 0.5 M.

strength of the reaction medium. Increasing the ionic strength is expected to decrease the surface potential of the particles[15,16] and shorten the range of effective electrostatic repulsions. Indeed, at an ionic strength of 0.5 M NaCl the quantum yield of $PVS^{-}\cdot$ production dropped to $\phi_{max} = 0.07$ (Figure 3).

The enhancing effect of the SiO_2 particles on the quantum yield is similar in a system that includes the positively charged $Ru(bpy)_3^{2+}$ instead of $Zn(TMPyP)^{4+}$ as sensitizer. A colloidal suspension of 0.1% SiO_2 particles containing $Ru(bpy)_3^{2+}$ (7.6×10^{-5} M), PVS^0 (1×10^{-3} M) and TEA (10^{-3} M) at pH 9.6 was deaerated and illuminated under the conditions previously described. The quantum yield for the photosensitized production of $PVS^{-}\cdot$ in the interfacial system ($\phi_{max} = 0.04$) was 13-fold that in the corresponding homogeneous system ($\phi_{max} = 0.003$). Again, as with the zinc sensitizer, flash photolysis experiments showed a large reduction in back-reaction rate (eq 2) in the presence of

$$Ru(bpy)_3^{2+} + PVS^0 \underset{k_b}{\overset{h\nu}{\rightleftharpoons}} Ru(bpy)_3^{3+} + PVS^{-}\cdot \qquad (2)$$

SiO_2: $k_b = 5.7 \times 10^7$ M^{-1} s^{-1} compared with $k_b = 7.9 \times 10^9$ M^{-1} s^{-1} in the homogeneous solution.

In conclusion, we have demonstrated that the introduction of the solid SiO_2 interface can affect strongly the efficiency of the photosensitized electron-transfer process. By proper charge functionalization of the electron acceptor and donor, electrostatic repulsive or attractive interactions can be established. The high charge density of the colloidal silica particles provides a driving force for charge separation and diminishes back reactions. The stabilized intermediary photoproducts might then be further coupled with efficient reactions that result in the decomposition of water. These aspects are currently being investigated.

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(16) Reference 14, Chapter 5, p 108.

3-Acyltetramic Acid Antibiotics. 1. Synthesis of Tirandamycic Acid[1]

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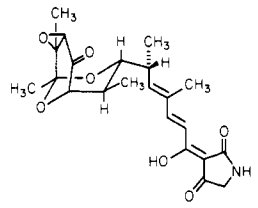
Received February 17, 1981

Tirandimycin (**1**)[2] is a member of a small group of 3-acyltetramic acid antibiotics[3] that have occasioned considerable interest[4] due to their potent inhibition of bacterial DNA-directed RNA polymerase[5] and the selective inhibition of terminal deoxynucleotidyltransferase from leukemic cells.[6] Together with the



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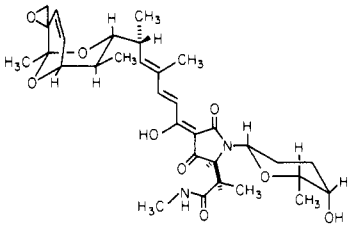

2

structurally similar streptolydigin[3a] (**2**), these antibiotics seem to exhibit contrasting activity to the simpler 3-acyltetramic acids known;[7] it is possible[4] that the differing activities is a result of the complex, 2,9-dioxabicyclo[3.3.1]nonane system common to both antibiotics. This very complexity as well as the opportunity to develop synthetic strategy for the construction of more diverse analogues of these interesting antibiotics prompted an investigation of their total synthesis. The successful conclusion of the first phase of this program—namely, the synthesis of tirandamycic acid (**23**)[2] in its optically active, natural form from D-glucose—is recorded here.[8]

The basic plan for this synthesis was the construction of a suitably substituted 2,9-dioxabicyclo[3.3.1]nonane system from the pyran form of the sugar and then modification of the rudimentary substitution to fit the complex pattern of the antibiotic. The first problem was the conversion of the sugar to an appropriate *C*-glycoside. This was efficiently accomplished through application of the ester enolate Claisen rearrangement[9] to the propionate **4** derived from the commercially available glycal **3**[10] (Scheme I),

† Postdoctoral Fellow of the National Institute of General Medical Sciences, 1978-1979.

(1) This investigation was supported by Grant CA-18191, awarded by the National Cancer Institute, DHEW, and the Hoffmann-La Roche Foundation.

(2) Duchamp, D. J.; Branfman, A. R.; Button, A. C.; Rinehart, K. L., Jr., *J. Am. Chem. Soc.* **1973**, *95*, 4077-4078. MacKellar, K. L.; Grostic, M. F.; Olson, E. C.; Wnuk, R. J.; Branfman, A. R.; Rinehart, K. L., Jr., *Ibid.* **1971**, *93*, 4943-4945.

(3) (a) Steptolydigin: Rinehart, K. L., Jr.; Beck, J. R.; Borders, D. B.; Kinstle, T. H.; Krauss, D. *J. Am. Chem. Soc.* **1963**, *85*, 4038-4039. (b) **Bu2313A** and B: Tsunakawa, M.; Toda, S.; Okita, T.; Hanada, M.; Nakagawa, S.; Tsukiura, H.; Naito, T.; Kawaguchi, H. *J. Antibiot.* **1980**, *33*, 166-172. (c) Nocamycin: Horvath, G.; Brazhnikova, M. G.; Konstantinova, N. V.; Tolstykh, IV.; Potapova, N. P. *Ibid.* **1979**, *32*, 555-558.

(4) See, for instance: Lee, V. J.; Branfman, A. R.; Herrin, T. R.; Rinehart, Jr., K. L., *J. Am. Chem. Soc.* **1978**, *100*, 4225-4236 and references cited therein.

(5) Reusser, F. *Infect. Immun.* **1970**, *2*, 77-81.

(6) DiCioccio, R. A.; Srivastava, B. I. S. *Biochem. Biophys. Res. Commun.* **1976**, *72*, 1343-1349.

(7) Gitterman, C. O., *J. Med. Chem.* **1965**, *8*, 483-486: Selmiciu, I.; Gruceanu, I.; Pal, B., *Pharm. Zentralhalle* **1965**, *104*, 480-488. Chernov, V. A.; Safonova, T. S. *Probl. Gematol. Pereliv. Krovi* **1965**, *10*, 3-13 (*Chem. Abstr.* **1966**, *64*, 8780f). Yuki, H.; Kitanaka, E.; Yamao, A.; Kariya, K.; Hashimoto, Y. *Gann* **1971**, *62*, 199-206.

(8) For other synthetic efforts restricted to the preparation of 3-dienoyltetramic acid analogues of these antibiotics, see, ref 4.

(9) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877.

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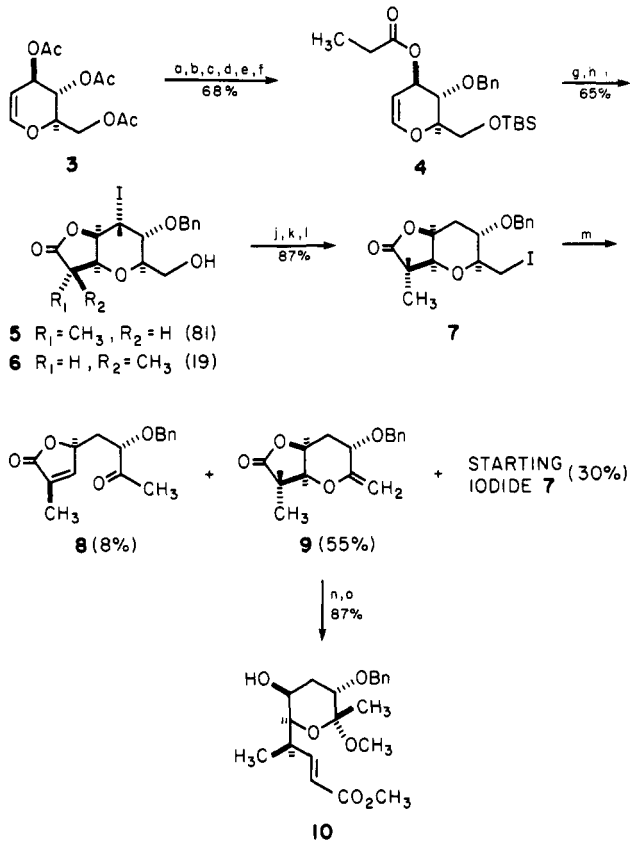
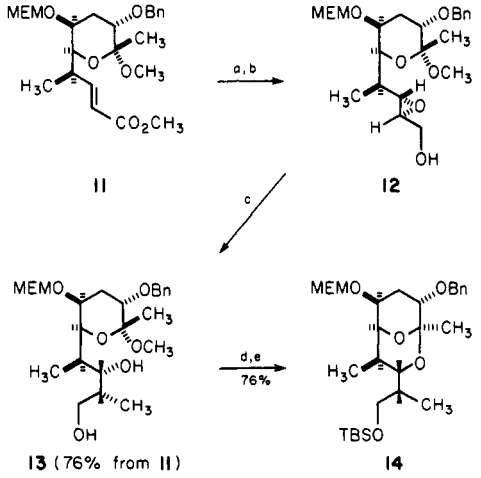
Scheme I. Construction of *C*-Glycoside **10**[a]



[a] (a) NaOMe, MeOH; (b) TBSCl, pyr; (c) BzCl, pyr, −35–0 °C; (d) BnBr, KH, THF, 0 °C; (e) alcoholic, NaOH; (f) C_2H_5COCl, pyr, room temperature, 12 h; (g) $(TMS)_2NH$, BuLi, THF, −78 °C; TBSCl, HMPA; C_6H_6, reflux, 1 h; (h) aq HCl, THF; (i) KI, I_2, $NaHCO_3$; (j) *n*-Bu_3SnH, EtOH, room temperature, 12 h; (k) TsCl, pyr, 0 °C, 20 h; (l) NaI, MEK, reflux, 18 h; (m) 2 equiv of AgF, 8 equiv pyr, CH_3CN, room temperature, 15 h; (n) CH_3OH, *p*-TsOH (catalytic), reflux, 15 h; (o) DIBAL, $CH_3C_6H_5$, −78 °C, 2 h; $(C_6H_5)_3P{=}CHCO_2CH_3$, THF, 12 h.

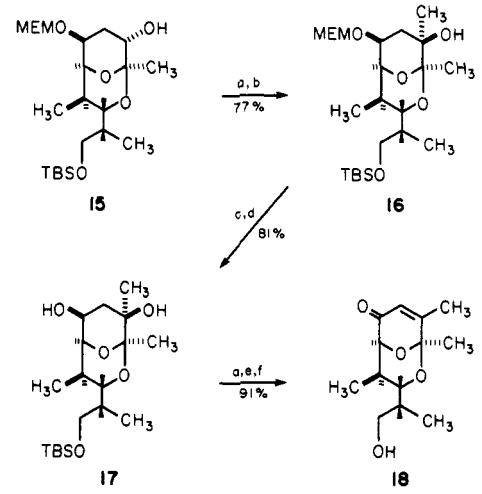
Scheme II. Formation of 2,9-Dioxabicyclo[3.3.1]nonane **14**[a]



[a] (a) DIBAL, THF, −78 °C, 3.5 h; (b) MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 10 h; (c) CuBr, Me_2S, CH_3Li, Et_2O, 11 h; (d) 0.05 equiv of *p*-TsOH, $HCCl_3$, 60 °C, 1 h; (e) TBSCl, pyr, 0 °C, 2 h.

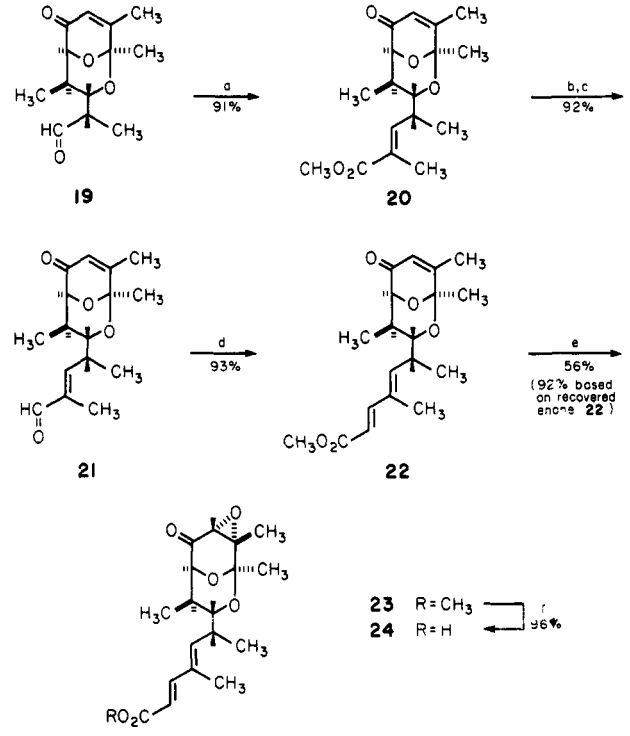
itself readily prepared[11] in two steps from D-glucose. The mixture of side-chain epimers formed in an 81:19 ratio from this rearrangement was best separated by direct crystallization of the

Scheme III. Construction of the Enone **18**[a]



[a] (a) PDC, CH_2Cl_2; (b) CH_3MgBr, Et_2O, −15 °C; (c) *n*-BuLi, *n*-C_6H_{14}, room temperature, 8 h; (d) $Hg(OAc)_2$, 1:1 THF-H_2O; (e) 1.1 equiv of pyr-*p*-TsOH, 5 equiv of Me_2SO, C_6H_6, reflux, 12 h; (f) CH_3OH, CSA, 12 h.

Scheme IV. Completion of the Synthesis of Tirandamycic Acid (**24**)[a]



[a] (a) $(C_6H_5)_3P{=}C(CH_3)CO_2C_2H_5$, C_6H_6, reflux, 12 h; (b) DIBAL, Et_2O, 0 °C, 3 h; (c) $(COCl)_2$, Me_2SO, −60 °C; (d) $(C_6H_5)_3P{=}CHCO_2CH_3$, C_6H_6, reflux, 16 h; (e) *t*-BuOOH, Triton B, C_6H_6, reflux, 12 h; (f) KOH, CH_3OH–H_2O, 48 h.

iodolactones **5** and **6**. Firm proof of the stereochemical assignments made here was obtained from the single-crystal X-ray structural analysis[12] of the deiodolactone available after tin hydride reduction of the minor iodolactone **6**.

With the Cl side chain in place, it was next necessary to alter the oxidation state at C5 in preparation for ring closure to the bicyclic ketal. For this the major iodolactone **5** was converted to the alternate iodolactone **7** from which the elimination of the

(10) Pfanstiel Laboratories, Inc., Waukegan, IL 60085.
(11) Roth, W.; Pigman, W. *Methods Carbohyd. Chem.* **1963**, *2*, 405–408.
(12) Carroll D. J.; Mandel, G. S.; Mandel, N. S. *Acta Crystallogr.*, in press.

elements of HI led to the enol ether **9**. While several procedures[13] were explored for this process, only a modification of the AgF/pyridine conditions to include CH_3CN as solvent gave reasonable results, and even then small amounts of the unstable butenolide **8** were unavoidably formed.[14] A satisfactory conversion to the enol ether **9** was, however, possible, and subsequent transformation of this material to the hydroxy ester **10** in excellent yield followed standard procedures.

Before completion of the construction of the desired 2,9-dioxabicyclo[3.3.1]nonane system, it remained to introduce the elements of CH_3OH in place of the side-chain double bond of the hydroxy ester **10**. This transformation is an example of a currently topical synthetic problem,[15] namely, the stereoselective formation of 2,4-dimethyl-1,3-alkadiols. After exploration of these alternate procedures,[15] it was found (Scheme II) that the steric bulk of the pyran system in which the hydroxyl group was blocked as an ether (not an acetate!) was sufficient to direct epoxidation and subsequent lithium dimethylcuprate cleavage in the desired fashion. Thus, the ester **11**, obtained from the alcohol **10** in 93% yield with β-methoxyethyl chloromethyl ether and Hunig's base,[16] was first reduced to the corresponding allylic alcohol which was then epoxidized. The oxide with the structure **12** was the major [10:1 (NMR)] component of an epimeric mixture. Subsequent dimethylcuprate cleavage led to the diol **13** in excellent yield, and ring closure, effected by mild acid treatment, established the desired 2,9-dioxabicyclo[3.3.1]nonane **14**.

With the completion of the bicyclic nucleus of the antibiotic, the synthesis devolves to the alteration of the substitution pattern and the attachment of the dienoic acid side chain. Neither of these operations proved to be trivial. Removal of the benzyl blocking group [H_2, 10% Pd/C, EtOH (85%)] afforded the alcohol **15** (Scheme III), and subsequent oxidation and then methylmagnesium bromide addition produced the tertiary alcohol **16**. The (β-methoxyethoxy)methyl ether blocking group, however, could not be cleaved by the common conditions.[17] Fortunately, it was found that treatment of this tertiary alcohol **16** with butyllithium led to a mixture of the diol **17** and the corresponding vinyl ether. Treatment of this mixture with $Hg(OAc)_2$ in 1:1 $THF-H_2O$ served to cleave the vinyl ether, and a good overall yield of the diol **17** was realized. Conversion of this diol **17** to the enone **18** by oxidation and then dehydration completed the modification of the top portion of the ring system.

Surprisingly, the aldehyde function of the keto aldehyde **19**[18] that results from oxalyl chloride–Me_2SO oxidation (>98% yield by NMR, TLC analysis) of the enone alcohol **18** is quite hindered and sluggish toward carbonyl addition reagents. Several approaches[19] for the direct addition of the dienoic acid side chain were explored and abandoned when predominant fragmentation of the bicyclic ring system was observed. Finally, prolonged (12–24 h) treatment of the keto aldehyde with *base-free* (α-carbethoxyethylidene)triphenylphosphorane[20] at reflux in benzene led stereoselectivity[20] to the unsaturated ester **20** (Scheme IV). Conversion of this unsaturated keto ester **20** to the keto aldehyde **21** required first reduction to the diol and then reoxidation, but Wittig-type condensation to form the new keto ester **22** was very efficient.

The final epoxy ketone formation was again nontrivial as standard basic hydrogen peroxide conditions led to extensive degradation of the system. The transformation was reproducibly accomplished with the *t*-BuOOH–Triton B procedure after extensive experimentation, and methyl tirandamycate (**23**), indistinguishable (IR, NMR, TLC, $[\alpha]_D$) from natural material,[22] was obtained. Hydrolysis of this ester affords tirandamycic acid (**24**) (~5% overall yield in 34 steps; average yield per step 92%). Further refinement and modification of this synthetic approach is currently under investigation. Utilization of this synthetic scheme for the incorporation[24] of the tetramic acid portion of tirandamycin (**1**) itself and the preparation of 3-acyltetramic acid analogues that bear similar 2,9-dioxabicyclo[3.3.1]nonane ring systems [for example, streptolydigin (**2**)] is being actively pursued.[26]

Supplementary Material Available: Infrared and proton magnetic resonance spectra, optical rotations, physical constants, thin-layer chromatographic mobility, and elemental combustion analyses of all previously unknown isolated intermediates (13 pages). Ordering information is given on any current masthead page.

(13) AgF/pyridine alone (Helferich, B.; Himmen, E. *Chem. Ber.*, **1928**, *61*, 1825–1935) led to virtually a 1:1 mixture of the butenolide **8** and the enol ether **10**, while DBU/DMF led only to extensive decomposition. Attempted elimination through the corresponding 6-(3-nitrophenyl)selenoxide was thwarted when selenide could not be oxidized (Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947–949).

(14) Due to the acidity of the hydrogen adjacent to the lactone carbonyl and the basicity of the medium needed to effect the elimination of HI, the fragmentation of the desired lactone enol ether **9** to form the butenolide **8** was unavoidable. On AgF/pyridine treatment the lactone enol ether **9** is readily transformed into the butenolide **8**. Modification of this scheme by preliminary reduction of the iodolactone **7** and protection of the resulting iodohemiacetal and then HI elimination is being explored.

(15) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343–4346. Johnson, M. R.; Kishi, Y. *Ibid.* **1979**, 4347–4350. Hasan, I.; Kishi, Y., *Ibid.* **1980**, 4229–4232. Still, W. C.; Darst, K. P. *J. Am. Chem. Soc.* **1980**, *102*, 7385–7387.

(16) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809–812.

(17) Cleavage of the β-(methoxyethoxy)methyl ether with (a) $ZnBr_2$ and $TiCl_4$;[16] (b) $TrBF_4$ (Barton, D. H. R.; Magnus, P. D.; Smith, G.; Streckert, G.; Zurr, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 542–552. (c) Aqueous HCl/THF afforded, beside traces of the corresponding alcohol, predominately degradation products. A similar experience was recently reported by: Anderson, R. J.; Adams, K. G.; Chinn, H. R.; Hendrick, C. A. *J. Org. Chem.* **1980**, *45*, 2229. He used *n*-BuLi and then aqueous mineral acid to remove the blocking group.

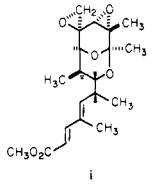
(18) The keto aldehyde **19** was clearly formed in this reaction but was unstable toward chromatography and/or distillation as well as storage. It was therefore used in its initially isolated crude form.

(19) (a) (4-Carbomethoxy-but-3-en-2-ylidene)triphenylphosphorane, THF, reflux. (For preparation of the Wittig reagent, see: Auwers, K. V. *Liebigs Ann. Chem.* **1923**, *432*, 46–99. Buchta, E.; Burger, K. *Ibid.* **1952**, *576*, 155–168. Buchta, E.; Andree, F. *Chem. Ber.* **1959**, *92*, 3111–3116.) (b) Methyl 4-(diethylphosphono)crotanate, NaH or KH, DME, 0 °C. (For the preparation of the phosphonate by application of the Michaelis–Arbuzov reaction, see: Kosolapoff, G. M. "Organophosphorus Compounds", 1st ed.; Wiley: New York, 1950, Chapter 7.) (c) Isopropenylmagnesium bromide, ether or THF, −78 °C.

(20) For preparation of the reagent, see: Isler, O.; Gutmann, H.; Montavan, M.; Rüegg, R.; Ryser, G.; Zeller, P., *Helv. Chim. Acta* **1957**, *40*, 1242–1249. Oppolzer (Oppolzer, W.; Grayson, J. I., *Ibid.* **1980**, *63*, 1706–1710) recently reported the isolation of only the *E* ester. In the present system the *E* and the *Z* ester were isolated in a ratio of 50:1.

(21) Yang, N. C.; Finnegan, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 5845–5848.

(22) Methyl tirandamycate (**23**) was obtained by treatment of an authentic sample of tirandamycin[23] in ether solution at 0 °C with diazomethane. This reaction is unique in that the ketone carbonyl appears to be virtually equal in its reactivity toward diazomethane as the carboxyl group and the diepoxide ester **i** was invariably also formed.



i

(23) We are grateful to Dr. B. J. Magerlein (Upjohn Co., Kalamazoo, MI) for providing such a generous sample of authentic (+)-tirandamycic acid so that these ancillary experiments were possible.

(24) The direct acylation of tetramic acid and its derivatives has been the subject of numerous inquiries,[25] but, to date, no efficient general procedure is available. Alternate approaches that are compatible with the current synthesis of the dioxabicyclic ring system are being explored.

(25) Bhat, S. V.; Kohl, H.; Ganguli, B. N.; deSouza, N. J. *Eur. J. Med. Chem.* **1977**, *12*, 53–57. van der Baan, J. L.; Barnick, W. F. K.; Bickehaupt, F. *Tetrahedron* **1978**, *34*, 223–231. Lee, V. J.; Branfman, R.; Herrin, T. R.; Rinehart, K. L., Jr., *J. Am. Chem. Soc.* **1978**, *100*, 4225–4236. Toda, S.; Nakagawa, S.; Naito, T.; Kawaguchi, H. *J. Antibiot.* **1980**, *33*, 173–181.

(26) All new compounds isolated during this work have been characterized by satisfactory combustion and spectral (NMR, IR) analyses and optical rotation, and these data are recorded under supplementary material.