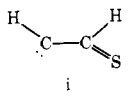
havior of a photofragmentable C_2H_2X species. On the other hand, the C_2H_2S fragment from **1a** appears to be generated and to remain intact at least during photoirradiation with Pyrex-filtered light.

(18) Further irradiation of the photolysate of **9** with the bare lamp results in the destruction of the thioketene and the appearance of bands at 1530 and 1485 cm^{-1}, perhaps due to carbon disulfide[19,20] or some other polysulfide. The course of this photodecomposition appears to be sensitive to traces of oxygen, and is concentration dependent.

(19) D. F. Smith, Jr., and J. Overend, *Spectrochim. Acta, Part A*, **26**, 2269 (1970).

(20) A. Krantz and J. Laureni, *J. Am. Chem. Soc.*, **97**, 6606 (1975).

(21) A mechanism involving the thiocarbene i could be responsible for the formation of a single isotopic thioketene species.[22]



i

(22) Dewar has predicted that the thiocarbene i would collapse without activation energy to thioketene: M. J. S. Dewar and C. A. Ramsden, *J. Chem. Soc., Chem Commun.*, 688 (1973).

(23) The ratio **3a/4a** appears to decrease in the series argon (highest value), nitrogen, carbon monoxide, and acetylene (lowest value) matrices. When methyl and dimethyl thiadiazoles are photolyzed, thioketenes are detectable. The formation of ethynyl sulfides and mercaptans may be suppressed by methyl substituents.

(24) All new infrared values reported for the thiadiazole system were recorded on a Perkin-Elmer Model 180 spectrometer.

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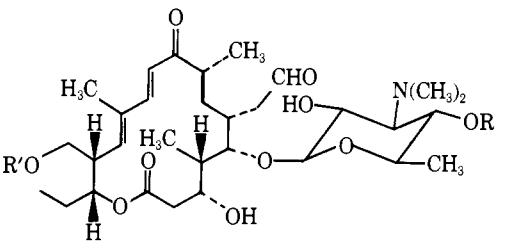
Tylonolide Hemiacetal, the Aglycone of Tylosin, and Its Partial Synthesis

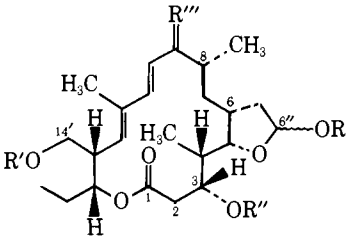
Sir:

Tylosin (**1**)[1] is one of the structurally most complex 16-membered macrolides[2] and has been widely used therapeutically as well as nutritionally.[3] We wish to describe herein (i) an efficient preparation of tylonolide hemiacetal (**2**) (the intact aglycone of **1**) which is demanded for biosynthetic modification of the macrolide,[4] and (ii) a partial synthesis of **2.** An adequate supply of **2** has permitted us to characterize **2** fully, accordingly to modify the structure previously proposed.[5b] Conversion of **2** into a seco-acid derivative (**3**) and subsequent cyclization to form the original ring system have also been achieved. This transformation represents the first successful lactonization of an authentic[6] 16-membered macrolide seco-acid. In addition, problems associated with the presence of the β-hydroxy group in **3** have led to the discovery of an efficient synthetic method for the preparation of β-lactones,[7] versatile intermediates often utilized for the introduction of other functional groups.

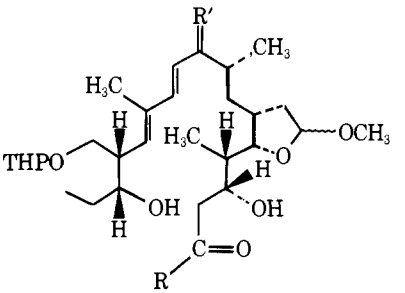
The glycoside linkage of an amino-sugar resists acid hydrolysis much more than that of a neutral sugar. Therefore, conditions normally required for the removal of an amino-sugar from a macrolide antibiotic induce extensive destruction of the aglycone.[8] Devices to secure the intact aglycone, therefore, involve conversion of the amino group into its *N*-oxide which is in turn eliminated from the sugar moiety (prior to or during the following milder acid hydrolysis) via a Cope elimination[9] or Polonovski reaction.[10] Thus conversion of *O*-mycaminosyl tylonolide (OMT)[5a,11] into its tetra(trifluoroacetate) and subsequent oxidation with *m*-chloroperoxybenzoic acid yielded the *N*-oxide which was again trifluoroacetylated. Refluxing a sodium acetate buffered aqueous tetrahydrofuran solution of this last compound effected hydrolysis of both the glycoside and trifluoroacetate groups. Column chromatography (Woelm Silica Gel) provided, in as high as 50% yield, tylonolide hemiacetal (**2**), mp 147–148 °C,



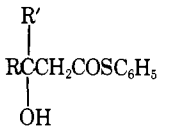
1, R = mycarosyl; R′ = mycinosyl
OMT, R = R′ = H



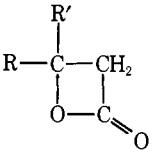
2, R = R′ = R″ = H; R‴ = O
4, R = R′ = R″ = $COCH_3$; R‴ = O
5, R = CH_3; R′ = R″ = H; R‴ = O
6, R = CH_3; R′ = THP; R″ = H; R‴ = H, OH



3, R = SC_6H_5; R′ = O
7, R = OH; R′ = H, OH



8, R, R′ = C_5H_{10}
9, R = n-C_8H_{17}; R′ = H



10, R, R′ = C_5H_{10}
11, R = n-C_8H_{17}; R′ = H

$C_{23}H_{36}O_7$ (elemental analysis and accurate mass).[12] The presence of a hemiacetal group rather than the previously reported acetal[5b] in **2** was shown by the formation of the triacetate (**4**) (rather than the monoacetate) and of a mixed acetal (**5**) with an alcohol (vide infra). All attempts to prepare the corresponding tylonolide acetal (with C(3)-O-) have failed. These results provide (synthetically important) information concerning the conformation of **2,** accepting the Celmer model[2b] for this aglycone. The C-3 OH group must be remotely located from the C-6″ OH in the actual conformer and its conversion into another conformational isomer in which the (intramolecular) acetal formation is likely to proceed must encounter a high energy barrier. Inspection of the CPK atomic model of **2** supports this supposition.

The methyl ether (acetal) (**5**) of **2** (trimethyl orthoformate), after the protection of its primary hydroxy group at the C-14′ position as a tetrahydropyranyl ether (dihydropyran, 5 min, room temperature), was reduced with $NaBH_4$ to afford the isomeric allylic alcohols **6.** The alkaline hydrolysis of **6** proceeded under reasonably mild conditions (1 N NaOH, 60 °C, 2 h) apparently due to the assistance of the C-3 hydroxy group.[13] The overall conversion of **2** into the β-hydroxycar-

boxylic acids (**7**) was effected nearly quantitatively, and all the possible isomers were separable on TLC. The isomeric mixture of **7** was converted into the imidazolides[6e,f,14] and then into the benzenethiol esters, and subsequent oxidation with MnO_2[15] provided the protected thiol esters (**3**) of the tylonolide seco-acid. Treatment of **3** with mercury (II) methanesulfonate[6d] in the presence of Na_2HPO_4, followed by acetic acid hydrolysis, afforded an approximately 17% yield of the product, identical in every respect with **2**. A yield of this magnitude is very gratifying in that, in addition to complicated conformational problems (vide supra), the lactonization did indeed compete favorably with the β-lactone formation. The latter reaction which proceeds in the absence of other hydroxy compounds in the reaction medium was fortuitously found during the course of model studies and represents a means of synthesizing β-lactones from ketones and aldehydes conveniently and in excellent yields. A brief summary of the synthesis is given below.

The benzenethiol esters of β-hydroxycarboxylic acids (**8** and **9**), prepared from cyclohexanone (94%) and nonanal (80%) using the lithium salt of *S*-phenyl ethanethioate,[16] were reacted with 2 equiv of mercury (II) methanesulfonate (0.07 M in acetonitrile) in the presence of 8 equiv of Na_2HPO_4 at 25 °C for 10 min to provide the corresponding β-lactones (**10** and **11**) in 86 and 90% yields, respectively. Although we have not examined other substrates, the generality of this reaction is obvious. Quantitative conversion of β-lactones to alkenes has been well-documented.[7,17,18]

Supplementary Material Available: A listing of spectral data (3 pages). Ordering information is given on any current masthead page.

References and Notes

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(2) Recent reviews are: (a) W. Keller-Schierlein, *Fortschr. Chem. Org. Naturst.* **30**, 313–460 (1973); (b) W. D. Celmer, *Pure Appl. Chem.*, **28**, 413 (1971).
(3) J. M. McGuire, W. S. Bonieces, C. E. Higgins, M. M. Hoehn, W. M. Stark, J. Westhead, and R. N. Wolfe, *Antibiot. Chemother (Washington D.C.)*, **11**, 320 (1961), and several references quoted in ref 1 of this note.
(4) Work is underway in the laboratory of Dr. D. Perlman, Wisconsin.
(5) For degradative studies of **1**, see (a) R. B. Morin and M. Gorman, *Tetrahedron Lett.*, 2339 (1964). (b) R. B. Morin, M. Gorman, R. L. Hamill, and P. V. Demarco, *ibid.*, 4737 (1970). This report records the isolation of tylonolide acetal, $C_{23}H_{34}O_6$ "in very low yield". A compound believed to be this "acetal" has been obtained in 0.1–0.3% yield upon repetition of their work. It has been found to be identical with **2**. (c) H. Achenback, W. Regel, and W. Karl, *Chem. Ber.*, **108**, 2481 (1975).
(6) (a) R. B. Woodward, *Angew. Chem.*, **69**, 50 (1957). For our previous reports on syntheses of macrolide antibiotics, see (b) S. Masamune, C. U. Kim, K. E. Wilson, G. O. Spessard, P. E. Georghiou, and G. S. Bates, *J. Am. Chem. Soc.*, **97**, 3512 (1975); (c) S. Masamune, H. Yamamoto, S. Kamata, and A. Fukuzawa, *ibid.*, **97**, 3513 (1975); (d) S. Masamune, S. Kamata, and W. Schilling, *ibid.*, **97**, 3515 (1975); (e) S. Masamune, S. Kamata, J. Diakur, Y. Sugihara, and G. S. Bates, *Can. J. Chem.*, **53**, 3693 (1975); (f) G. S. Bates, J. Diakur, and S. Masamune, *Tetrahedron Lett.*, submitted; also see (g) E. J. Corey, K. C. Nicolaou, and L. S. Melvin, Jr., *J. Am. Chem. Soc.*, **97**, 654 (1975).
(7) For a brief summary of previous works, see W. Adam, J. Baeza, and J.-C. Liu, *J. Am. Chem. Soc.*, **94**, 2000 (1972).
(8) An exception is methymycin: C. Djerassi and J. A. Zderic, *J. Am. Chem. Soc.*, **78**, 6390 (1956).
(9) R. A. LeMahieu, M. Carson, R. W. Kierstead, L. M. Fern, and E. Grunberg, *J. Med. Chem.*, **17**, 953 (1974).
(10) S. Omura, A. Nakagawa, K. Suzuki, T. Hata, A. Jakuboski, and M. Tishler, *J. Antibiot.*, **27**, 147 (1974); N. N. Girotra and N. L. Wendler, *Tetrahedron Lett.*, 227 (1975).
(11) Desmycosin was supplied by Eli Lilly and Company through the courtesy of Dr. R. B. Morin. The purity of this material was estimated to be 60–70%.
(12) The stereochemistry of all structures shown in the note follows Celmer's suggestion[2b] and remains to be confirmed. An x-ray analysis of a derivative of **2** is in progress.
(13) When the C-3 hydroxy group was protected with the *tert*-butyldimethylsilyl group, the lactone opening required more drastic conditions and was accompanied by extensive dehydration to give α,β-unsaturated carboxylic acids.
(14) Direct use of the imidazolides for the ring closure met with little success. Cf. E. W. Colvin, T. A. Purcell, and R. A. Raphael, *J. Chem. Soc., Chem. Commun.*, 1031 (1972).
(15) A. J. Fatiadi, *Synthesis*, 133 (1976).
(16) J. Wemple, *Tetrahedron Lett.*, 3255 (1975).
(17) Spectral data of all the compounds described in this note appear in the microfilm edition of this journal and experimental details will be available upon request.

(18) The authors thank Dr. P. E. Georghiou for his preliminary work on this project and the National Research Council of Canada for financial support.

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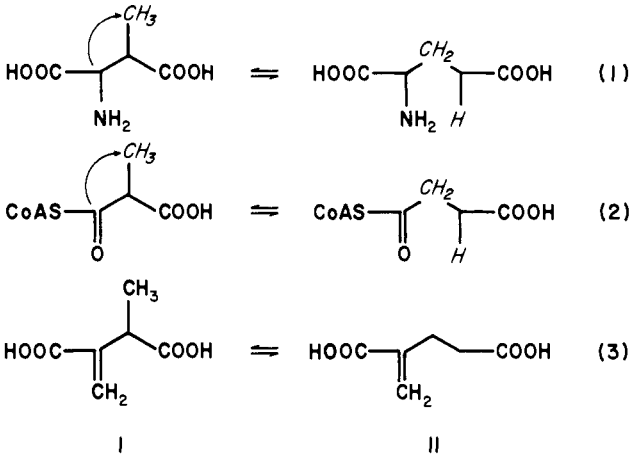
Vitamin B_{12} Model Studies. Migration of the Acrylate Fragment in the Carbon-Skeleton Rearrangement Leading to α-Methyleneglutaric Acid

Sir:

Coenzyme B_{12} is an essential cofactor in the three known enzyme-catalyzed carbon-skeleton rearrangements.[1] They are the reversible interconversions: β-methylaspartate $\rightleftarrows$ glutamate[2] (eq 1), methylmalonyl-SCoA $\rightleftarrows$ succinyl-SCoA[3] (eq 2), and methylitaconate $\rightleftarrows$ α-methyleneglutarate[4] (eq 3). It has been established by carbon labeling that the glycyl fragment migrates in the β-methylaspartate rearrangement[5] and that the carbonyl-SCoA group migrates in the methylmalonyl-SCoA rearrangement.[6] It has also been established that exchange with solvent water does not occur in the course of the rearrangements.[7] The latter observation was made understandable by the discovery[8] that the 5′-methylene of the deoxyadenosine of the coenzyme is the instrument of hydrogen transfer in all the coenzyme B_{12} dependent carbon-skeleton rearrangement reactions.



A nonenzymatic model intermediate (IV) for the methylitaconate $\rightleftarrows$ α-methyleneglutarate transformation (eq 3) has recently been introduced.[9] The model intermediate IV was synthesized by the reaction of vitamin B_{12s} with bis(tetrahydropyranyl) bromomethylitaconate (III). On standing in aqueous solution the model IV yields rearranged α-methyleneglutaric acid (II) together with unrearranged methylitaconic acid (I) and butadiene-2,3-dicarboxylic acid (VII).[9] Thus, I and II are the products of a reduction reaction. Since, the model reaction provides no role for deoxyadenosine, it was important to learn the source of the hydrogen introduced into the products I and II.

When the crude dry alkyl cobalamin IV was dissolved in D_2O and allowed to stand at 25 °C, in the dark, under nitrogen, for 200–300 h, at pH 5–9,[10] deuterium was incorporated into the products (V and VI).

The butadiene-2,3-dicarboxylic acid (VII) contained no deuterium as shown by its NMR and mass spectra. By con-