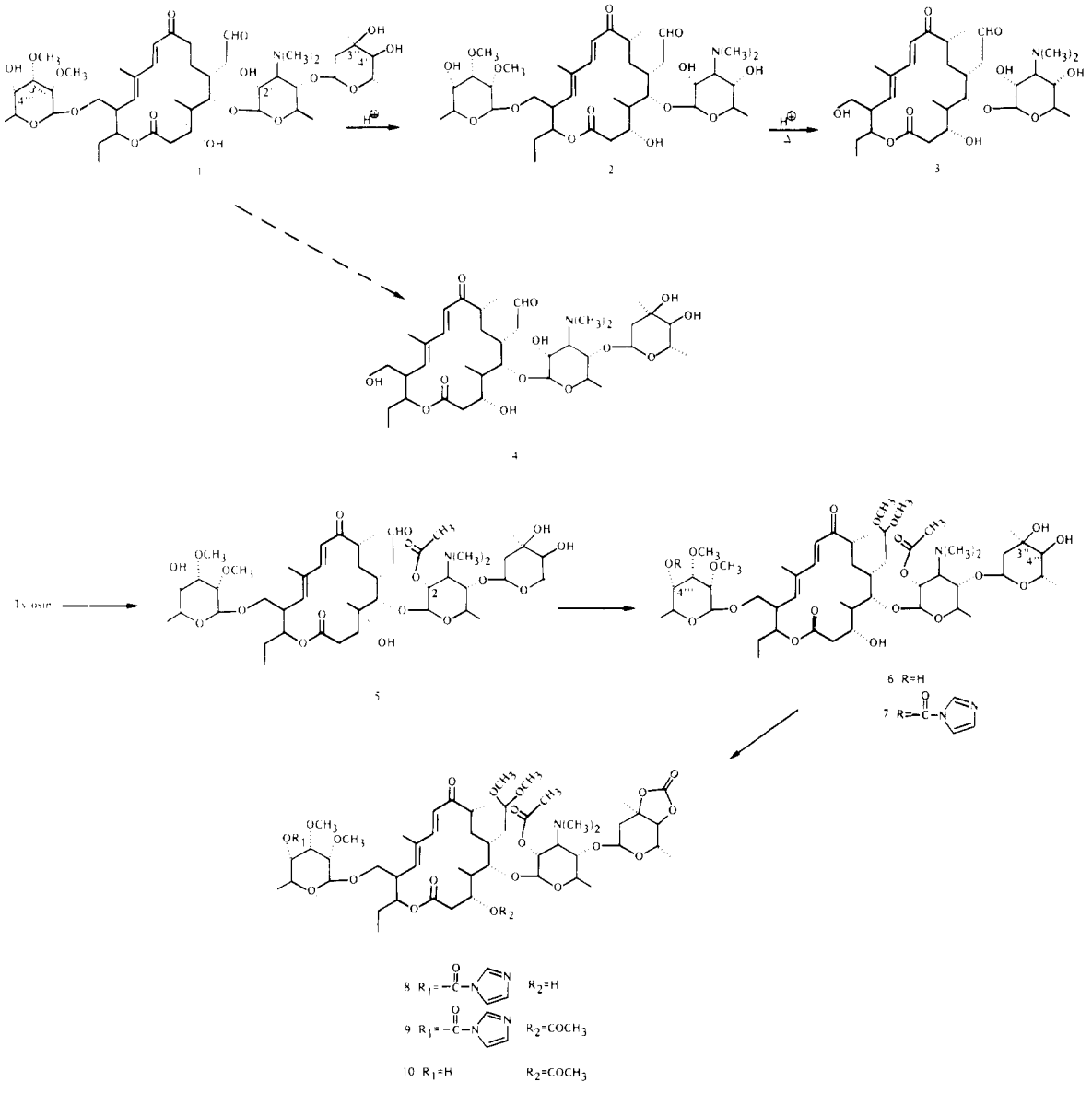
Selective Cleavage of the Mycinose Sugar from the Macrolide Antibiotic Tylosin: A Unique Glycosidic Scission

Summary: The selective scission of the mycinose glycosidic linkage in tylosin can be accomplished by treating the dehydromycinosyl tylonide derivative **11** with a primary amine hydrochloride, generating, in the process, the novel pyrrole rearrangement product **14.**

Sir: Tylosin (**1**) is a basic, structurally complex 16-membered ring macrolide antibiotic[1] that has enjoyed recent interest as an attractive subject for synthetic,[2] biosynthetic,[3] and conformational studies.[4] Previously, it has been shown that mild acid treatment of tylosin causes hydrolysis of the mycarose sugar to produce the antibiotic desmycosin (**2**).[5] Only under more vigorous hydrolytic conditions can the mycinose sugar be removed to yield *O*-mycaminosyl tylonide (**3**).[6,7] In the course of our research, we required technology to selectively remove the mycinose sugar from tylosin. To our knowledge, the cleavage of the mycinosyl glycosidic linkage, with retention of the mycarose sugar (to produce a tylosin derivative such as **4**), has not been reported. In this communication we describe a unique, nonhydrolytic mycinose scission which accomplishes this transformation. This method involves an interesting rearrangement which ultimately leads to the isolation of the heretofore unknown 2-acetyl-3-methoxypyrroles **14A** and **14B.**

Our plan of attack was to chemically manipulate the C_4''' alcohol in the mycinose sugar to render the mycinose glycosidic linkage more labile. As a primary goal, we decided that the C_4''' ketone **11** would be a useful intermediate.[8] It was obvious from the beginning that our success would hinge on being able to protect the other functionality in tylosin so that oxidation could be specifically carried out at C_4'''. Therefore, the following sequence of reactions was performed.

Tylosin (**1**) was treated with 1.2 equiv of acetic anhydride in CH_2Cl_2, in the absence of an external base,[9] to give 2′-acetyltylosin (**5**)[10] in quantitative yield. Carefully controlled acidic methanol conditions allow the formation of acetal **6**[10] in 85% yield.[11] Reaction of **6** with 2 equiv of 1,1′-carbonyldiimidazole (CH_2Cl_2, room temperature 20 h) produces carbonate derivative **8.**[10] It is apparent from the study of this reaction that the C_4''' carbamate **7** forms quantitatively with the first equivalent of carbonyldiimidazole; the second equivalent forms the $C_3''C_4''$ carbonate **8.** The carbonate **8** can be successively acylated, (acetic anhydride, 4-(dimethylamino)pyridine, TEA, CH_2Cl_2, room temperature, 20 h) at the C_3 position (85% yield; compound **9**) and the C_4''' carbamate removed (THF, H_2O, Na_2CO_3, room temperature, 12 h) to yield the C_4''' hydroxytylosin derivative **10.**[10] The overall yield from **1** to **10** is approximately 50%.



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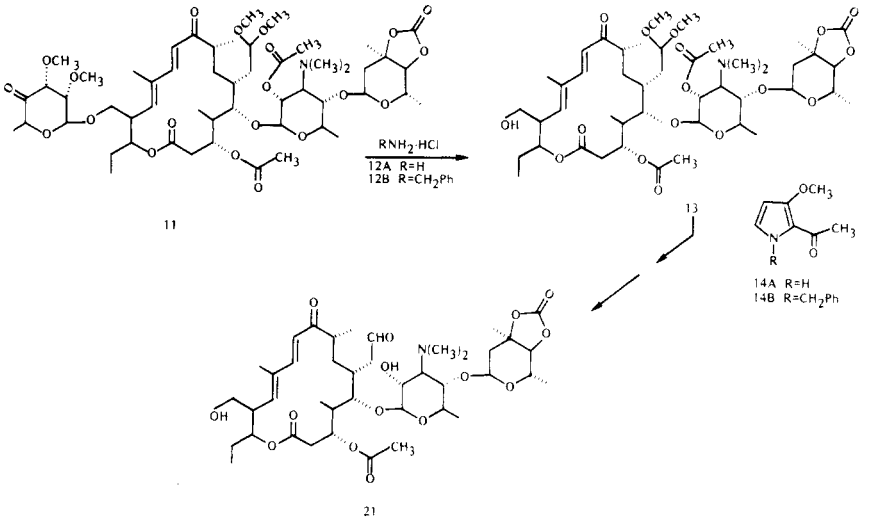
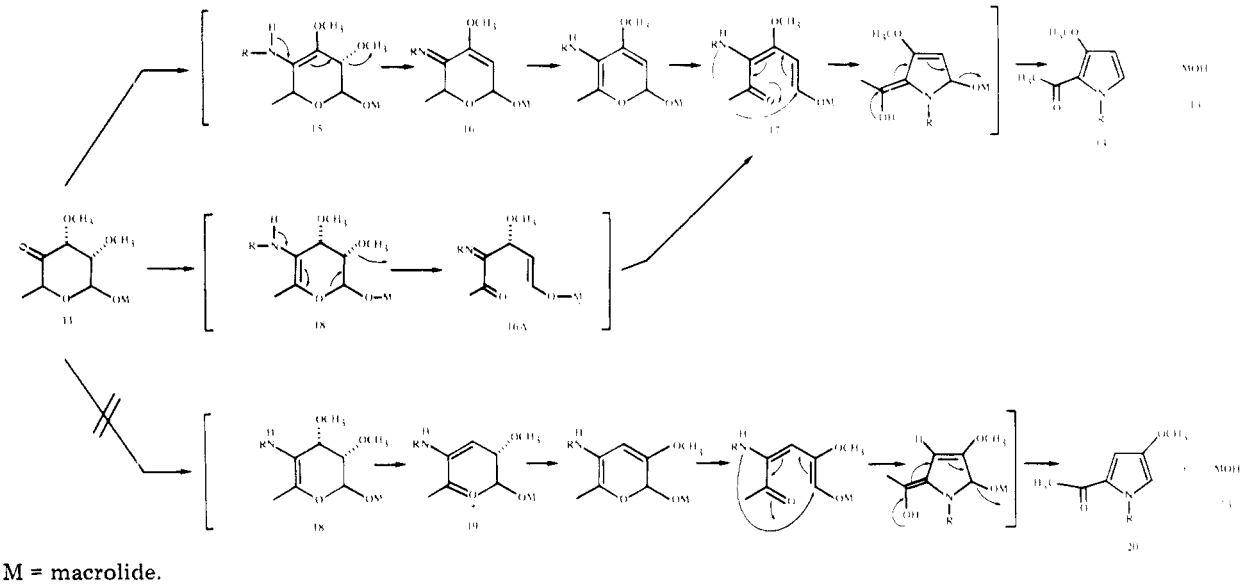


Scheme I[a]



[a] M = macrolide.

With the rest of the functionality suitably protected, we were now ready to chemically manipulate the mycinose C_4''' alcohol. Oxidation of **10** (Me_2SO, DCC, pyridinium trifluoroacetate, room temperature, 2 h) smoothly converts the C_4''' alcohol to the ketone derivative **11**[10] (75% yield). It was then discovered that the mycinose glycosidic linkage could be selectively cleaved by treating **11** with a primary amine hydrochloride **12** (R = H or benzyl) in warm 2-propanol. The exclusive products formed in this reaction are the tylonide derivative **13**[10] and the respective 2-acetyl-3-methoxypyrrole derivative **14A** (R = H)[12] or **14B** (R = benzyl).[13] Pyrroles **14A** or **14B** can easily be separated from macrolide **13** by simple hexane trituration of the reaction mixture. This sequence represents the first reported cleavage of the mycinose sugar from tylosin in which the mycaminose–mycarose glycosidic linkage remains intact.

While the mechanism of this unique, nonhydrolytic glycosidic cleavage has not been studied in detail, we speculate that the reaction proceeds as outlined in Scheme I. After initial imine formation, isomerization to either the $C_3'''C_4'''$ enamine (macrolide numbering; intermediate **15**) or the $C_4'''C_5'''$ enamine (intermediate **18**) occurs. Elimination of the C_2''' methoxy group through nitrogen participation (structure **16** and/or **16A**) followed by electrocyclic ring opening produces intermediate **17**. Michael addition followed by aromatization via elimination of the macrolide nucleus yields the final compounds **13** and **14** (R = H or benzyl). It is interesting to note that elimination of the C_3''' methoxy group through oxygen participation in structure **18** would produce intermediate **19**. Isomerization of intermediate **19** followed by electrocyclic ring opening and Michael addition would produce the 2,4-disubstituted pyrrole **20**. That structure **20** is *not* present is easily confirmed by analyzing the coupling constants of the $C_{2,3}$ pyrrole hydrogens in **14A** and **14B** (J = 3.1 Hz).[14]

Macrolide **13** can be successively deacylated (methanol, room temperature, 24 h) followed by removal of the acetal (difluoroacetic acid, acetonitrile, H_2O)[4a] to produce the demycinosyltylonide derivative **21**.[10] The antibacterial activity of **21**, and the overall contribution of the mycinose sugar to the antibacterial activity of tylosin, will be discussed in future publications.

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References and Notes

(1) Tylosin tartrate is sold commercially under the registered trademark Tylan by Elanco Products company, a division of Eli Lilly. For pertinent biological information see: J. M. McGuire, W. S. Bonieces, C. E. Higgins, M. M. Hoehn, W. M. Stark, J. Westhead, and R. N. Wolfe, *Antibiot. Chemother.*, **11**, 320 (1961).

(2) S. Masamune, Y. Hayase, W. K. Chan, and R. L. Sobczak, *J. Am. Chem. Soc.*, **98**, 7874 (1976).

(3) E. T. Seno, R. L. Pieper, and F. M. Huber, *Antimicrob. Agents Chemother.* **11**, 455 (1977); S. Ōmura, A. Nakagawa, H. Takeshima, J. Miyazawa, C. Kitao, F. Piriou, and G. Lukacs, *Tetrahedron Lett.*, 4503 (1975).

(4) (a) S. Ōmura, A. Nakagawa, M. Machida, and H. Imai, *Tetrahedron Lett.*, 1045 (1977); (b) H. Achenback, W. Regel, W. Karl, *Chem. Ber.*, **108**, 2481 (1975).

(5) R. L. Hamill, M. E. Haney, Jr., M. Stamper, and P. F. Wiley, *Antibiot. Chemother.*, **11**, 328 (1961).

(6) R. B. Morin and M. Gorman, *Tetrahedron Lett.*, 2339 (1964).

(7) The basic mycaminose sugar is stable to the hydrolysis conditions used to remove the neutral mycarose and mycinose sugars. More vigorous acid hydrolysis leads to aglycone degradation. Conditions have been previously reported which allow efficient scission of mycaminose from the aglycone. All of the methods involve conversion of the *N,N*-dimethylamine to the corresponding *N*-oxide. Glycosidic cleavage then proceeds using modified Polonovski conditions (A. Nakagawa, K. Suzuki, K. Iwasaki, K. Kaji, S. Ōmura, A. Jakubowski, and M. Tishler, *Chem. Pharm. Bull.*, **24**, 1749 (1976); N. N. Girotra and N. L. Wendler, *Tetrahedron Lett.*, 227 (1975), or trifluoroacylation followed by mild acid hydrolysis.[3] In the 14-membered ring macrolide series, a Cope elimination of the *N*-oxide of desosamine followed by elimination of the resulting neutral sugar has been reported: R. A. LeMahieu, M. Carson, R. W. Kierstead, L. M. Fern, and E. Grunberg, *J. Med. Chem.*, **17**, 953 (1974). This concept was first demonstrated by Celmer in his elegant studies defining the absolute configuration of the 14-membered ring macrolides: W. D. Celmer, *J. Am. Chem. Soc.*, **87**, 1797 (1965).

(8) It was felt that cleavage of the mycinose linkage via the C_4''' ketone could possibly be carried out using a Reformatsky type reaction analogous to the reported elimination of bromine from α-bromo ketones. See: T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Am. Chem. Soc.*, **89**, 5727 (1967). However, due to the ease of glycosidic scission using the conditions reported in this communication, the above approach was not investigated.

(9) W. D. Celmer, "Antibiotics Annual 1958–1959", Medical Encyclopedia, Inc., New York, 1959, pp. 277.

(10) All compounds have IR, UV, NMR, and ^{13}C NMR spectra consistent with their structures. High-resolution mass spectral data were obtained for all compounds, the results of which supported their structures.

(11) S. Rakhit and K. Singh, *J. Antibiot.*, **27**, 221 (1974).

(12) Compound **14A:** mp 113–114 °C (from ether); NMR ($CDCl_3$) δ 9.4–10 (br s, 1 H, NH), 6.88 (dd, 1 H, C_2H), 5.88 (dd, 1 H, C_3H), 3.90 (s, 3 H, OCH_3), 2.40 (s, 3 H, acetate methyl). Upon irradiation of the NH (δ 9.7) both the C_2 (δ 6.88) and C_3 (δ 5.88) protons collapse to doublets with J = 3 Hz. The high-resolution mass spectrum gives a parent *m/e* 139.0631 indicating $C_7H_9O_2N$ (±0.3 ppm).

(13) Compound **14B:** NMR ($CDCl_3$) δ 7.26 (m, 5 H, aromatics), 6.78 (d, J = 3 Hz, 1 H, C_2H), 5.90 (d, J = 3 Hz, 1 H, C_3H), 5.56 (s, 2 H, benzyl CH_2), 3.90 (s, 3 H, OCH_3), 2.43 (s, 3 H, acetate methyl). The high resolution mass spectrum gives a parent *m/e* 229.1091 indicating $C_{14}H_{15}O_2N$ (±1.2 ppm).

(14) Coupling constants for 2,4-disubstituted pyrroles, J = 1.1 Hz: L. M. Jackman, and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, New York, p 306.

Arthur A. Nagel,* Lawrence A. Vincent

Pfizer Central Research
Groton, Connecticut 06340

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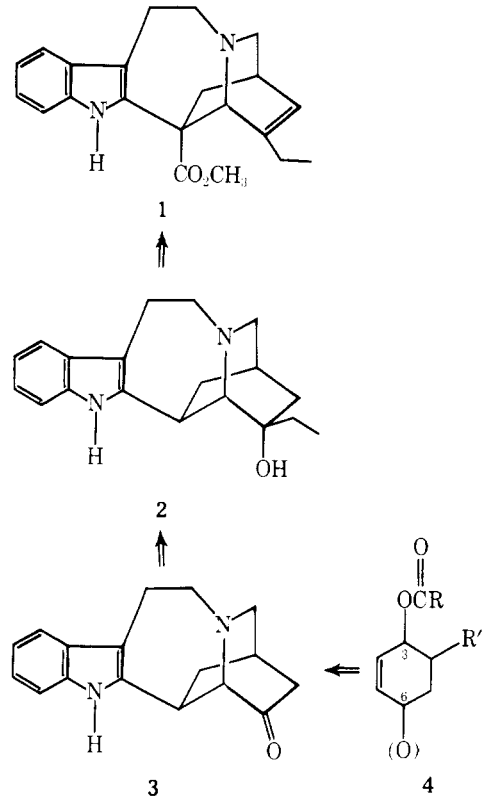
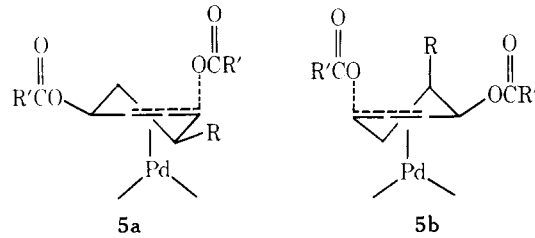
Synthesis of (±)-Catharanthine via Organopalladium Chemistry

Summary: A synthesis of 16-decarbomethoxy-20(S^*)-hydroxydihydrocatharanthine, an intermediate that has been converted to catharanthine in two stages, is available in seven steps from acrolein and (*E,E*)-1,4-dipivaloxy-1,3-butadiene.

Sir: The partial synthesis of vinblastine and vincristine, clinically important antitumor agents, from catharanthine and vindoline makes the synthesis of these latter alkaloids of prime importance.[1,2] The development of a convenient route into the iboga alkaloids immediately led us to focus on the most important member of this family, catharanthine (1).[3] We chose as our target the alcohol **2** since Büchi, in an elegant



procedure, was able in two stages to introduce the carbomethoxy group[4] and effect dehydration.[3a] A synthesis of the alcohol **2** is most easily envisioned from the ketone **3**. For our approach based upon palladium-catalyzed reactions,[5,6] the synthesis requires a cyclohexene **4** that bears oxygen substituents at the 3 and 6 positions. In the simplest approach, these substituents would both be acyloxy groups (i.e., **5**) in which selective ionization of the 3 substituent induced by palladium(0) would be required. Because of lower steric re-



pulsions, the transition state resembling **5a** might be thought to be of lower energy than that resembling **5b** and thus produce the correct product. Scheme I outlines our synthesis.

1,4-Dipivaloxy-1,3-butadiene,[7,8] mp 113–115 °C, gave a single Diels–Alder adduct **6**[8] with acrolein in the presence of boron trifluoride etherate. The NMR spectrum (H_A, δ 5.60, t, J = 4 Hz; H_C, 5.24, dd, J = 10, 6 Hz; H_B, 3.76, ddd, J = 11, 4, 3 Hz) confirms the stereochemistry as shown. Reductive amination by first forming the imine and then quenching with sodium borohydride gave the first cyclization substrate **7**,[8] mp 119–121 °C, in addition to the alcohol corresponding to **6** which results from incomplete imine formation. The aminobis(pivalate) **7** was added to a preheated solution of the palladium catalyst in acetonitrile containing triethylamine with TLC monitoring to determine when reaction was complete (~20 min) to give isoquinuclidine **8**.[8] Comparison of the spectral data to related isoquinuclidines as well as the successful completion of the project confirms the assignment. A single isomeric byproduct, tentatively assigned structure **11**[8] on the basis of spectral comparison to **12** and interpretation of the 270-MHz proton [H_A, δ 5.00, s; H_B, 3.5, d, J = 6 Hz; H_C, 3.29, ddd, J = 10, 6.5, 2 Hz; H_D, 2.59, d, J = 10 Hz; H_E, 2.43,

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