Carbohydrates in Organic Synthesis. Synthesis of 16-Membered-Ring Macrolide Antibiotics. 6.[1] Total Synthesis of *O*-Mycinosyltylonolide: Coupling of Key Intermediates and Macrocyclization

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Received October 20, 1981

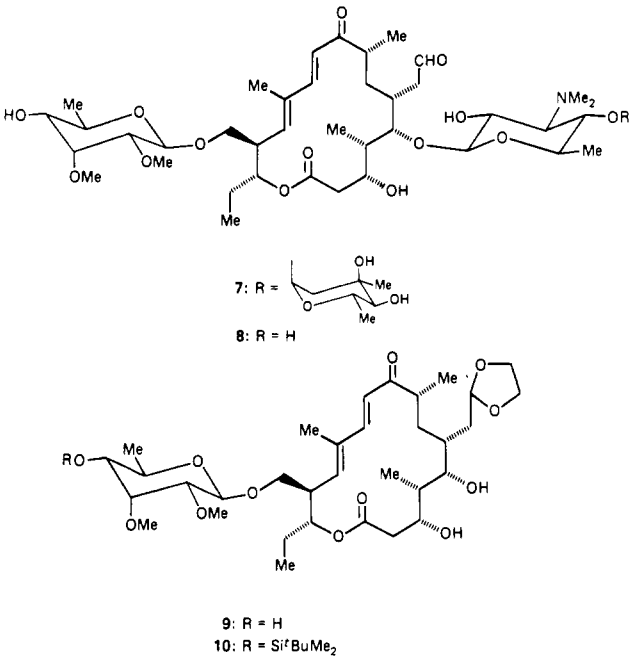
In the preceding communication[1] we detailed the enantioselective synthesis of the three segments **4**–**6** (Scheme I, ref 1) required for the total synthesis of *O*-mycinosyltylonolide (**1**) (Scheme I). In the present communication we describe the efficient coupling of these fragments and a highly efficient macrocyclization reaction culminating in the first successful total synthesis of *O*-mycinosyltylonolide (**1**) in its naturally occurring form with a high degree of stereocontrol.

The strategy chosen for the final assembly of *O*-mycinosyltylonolide (**1**) was based on the assumptions that (a) an open-chain precursor resembling the final natural product as much as possible in its substituents would be entropically favored for final macroring closure and (b) an internal keto phosphonate condensation with a carbonyl group would be a most advantageous means to construct the 16-membered macrocycle. Scheme I outlines how this strategy was executed.

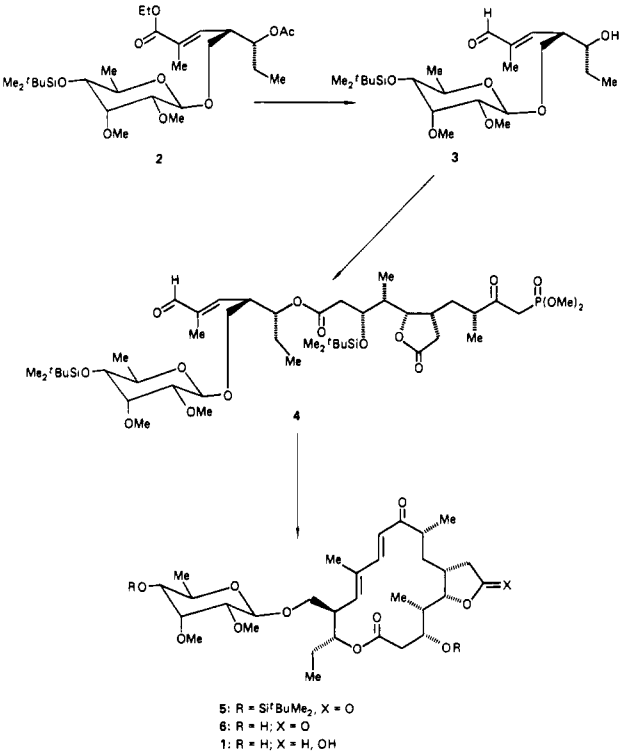
Activation of the phenyl thio sugar derivative **4** (Scheme I, ref 1, ca. 1:1 mixture of anomers) with NBS (1.1 equiv, CH_2Cl_2, 25 °C) in the presence of the hydroxy compound **5** (Scheme I, ref 1) resulted in efficient coupling[2] producing the β-glycoside **2**[3,4] (Scheme I) and its α-anomer in 85% total yield, with the undesired α-anomer, however, predominanting under these conditions (α:β ratio ca. 9:1 by ^1H NMR spectrometry and isolation, flash column chromatography, silica, ether–petroleum ether; 1:1 R_f (α) 0.19, R_f(β) 0.48). A more acceptable stereoselectivity was, however, observed simply by changing the reaction medium from CH_2Cl_2 to CH_3CN[5] (α:β ratio ca. 2:3) leading to satisfactory yields of **2** (ca. 50% after purification). Reaction of **2** with excess Dibal (5 equiv, CH_2Cl_2, −78 °C, reduction of ethyl ester, and removal of acetate) followed by MnO_2 oxidation (CH_2Cl_2, 25 °C) afforded the hydroxy aldehyde **3**[6] in 92% overall yield.

Coupling of key intermediate **3** (Scheme I) with the carboxylic acid **6** (Scheme I, ref 1) proceeded smoothly in concentrated CH_2Cl_2 solution (1.0 M) in the presence of dicyclohexylcarbodiimide (DCC, 1.1 equiv) and (dimethylamino)pyridine (DMAP, 0.1 equiv)[7] at 25 °C leading to the required open-chain precursor keto phosphonate aldehyde **4**[6] in 88% yield. We were now ready to attempt the crucial cyclization to the 16-membered tylosin skeleton.

Scheme I



Scheme II



When the acylic precursor **4** was exposed to powdered anhydrous K_2CO_3 (6 equiv) and 18-crown-6 (12 equiv) in dilute toluene solution (0.001 M) at 70 °C (5 h)[8], the expected cyclic product **5** was produced smoothly. *This reaction not only proceeded in excellent yield (80%) but, furthermore, produced the desired macrocycle with the C-8 methyl group in its natural configuration, as shown in structure* **5**.[6,9] The identity of this substance was confirmed from its spectral data and by desilylation (excess HF·pyridine, THF, 25 °C) to afford the advanced intermediate **6**,[6] identical in all respects with a product derived from

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(1) Part 5: Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 0000.

(2) This is an exceptionally mild and efficient glycosidation. For a related example of glycoside bond formation using a 2-pyridinethiol glycoside and NBS see: Hanessian, S.; Bacquet, C.; Lehong, N. *Carbohydr. Res.* **1980**, *80*, C17. A systematic study at this new methodology will be forthcoming.

(3) All new compounds were fully characterized by spectroscopic (^1H NMR, IR, MS, $[\alpha]_D$) means and exhibited satisfactory analytical and/or high-resolution data. Yields refer to isolated chromatographically and spectroscopically homogeneous materials.

(4) The stereochemistry of the glycoside bond in **2** and **3** was determined by ^1H and ^{13}C spectroscopic data: C-1 for **2** (β-anomer, δ 100.84; α-anomer δ 96.57); H-1 for **2** (β-anomer, δ 4.58, $J_{1,2}$ = 7.8 Hz; α-anomer, δ 4.79, $J_{1,2}$ = 4.0 Hz; corresponding proton in tylosin has $J_{1,2}$ = 8.0 Hz). See: (a) Bock, K.; Lundt, I.; Peterson, C. *Tetrahedron Lett.* **1973**, 1037. (b) Omura, S.; Nakagawa, A.; Neszmelyi, A.; Gero, S. D.; Sepulchre, A.-M.; Piriou, F.; Lukacs, G. *J. Am. Chem. Soc.* **1975**, *97*, 4001.

(5) (a) Lemieux, R. V.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2205. (b) West, A. C.; Schuerch, C. *J. Am. Chem. Soc.* **1973**, *95*, 1333.

(6) All physical properties are recorded in the Supplementary Material.

(7) (a) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522. (b) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1979**, 4475. (c) Ziegler, F. E.; Berger, G. D. *Synth. Commun.* **1979**, *9*, 539.

(8) Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954.

(9) The C-8 epimer of **5** was similarly produced starting from the minor isomer of the hydroboration of olefin **21** (Scheme IV, ref 1).

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natural tylosin (vide infra). To complete the synthesis, **6** was selectively reduced (4.0 equiv of Dibal, CH_2Cl_2, −78 °C, reduction of dienone and γ-lactone) and oxidized (1.3 equiv of DDQ, benzene, 25 °C) to produce *O*-mycinosyltylonolide (**1**) in 76% overall yield. Synthetic **1** was identical in all respects with an authentic sample obtained by degradation of tylosin as described below.

Mild acid hydrolysis of tylosin (**7**) (Scheme I) (dilute HCl, THF, 25 °C or AcOH–THF–H_2O, 25 °C) detaches only mycarose from the molecule producing *O*-mycinosyl-*O*-mycaminosyltylonolide (**8**) in 90% yield.[10] Both the highly methoxylated mycinose and the basic, N-containing mycaminose are resistant to acid hydrolysis under normal conditions that will allow survival of the rest of the molecule. A Polonovski type degradation of **8** [(a) 1.1 equiv of *m*-CPBA, CH_2Cl_2, 0 °C, 0.5 h followed by 8.0 equiv of $(CF_3CO)_2O$ and 8.0 equiv of pyridine, 0 °C, 0.5 h and then aqueous $KHCO_3$ workup and 1.0 equiv of anhydrous K_2CO_3, MeOH, O °C, 1 h)], however, furnished *O*-mycinosyltylonolide (**1**) in 76% yield after chromatographic purification. The same compound (**1**) was also produced by direct degradation of tylosin (**7**) under the above conditions (65% yield).[11] MnO_2 (excess, CH_2Cl_2, 48 h) oxidation of *O*-mycinosyltylonolide (**1**) led to compound **6** in high yield (87%).

So that the potential of *O*-mycinosyltylonolide (**1**) as a precursor to tylosin (**7**) could be demonstrated, a number of final chemical maneuvers were performed. Thus, reaction of (**1**) with ethylene glycol in the presence of camphorsulfonic acid as catalyst yielded the acetal **9** as a major product (65%),[12] liberating the C-5 hydroxyl for selective glycosidation. Although molecular models as well as chemical evidence indicate that no protection of the C-3 hydroxyl group should be needed, protection of the mycinose-bound hydroxyl might be necessary for steric-reactivity reasons for such glycoside formation attempts. Selective blockade of this hydroxyl was, therefore, sought and achieved by treating **9** sequentially with (a) phenylboronic acid (1.2 equiv, benzene, azeotropic removal of water at reflux to form a cyclic boronate ester at C-3 and C-5), (b) *tert*-butyldimethylsilyl chloride (excess imidazole, DMF, 25 °C), and (c) acetone–H_2O (3:1, 25 °C, 1 h) to remove the boronate furnishing compound **10** in 72% overall yield.

This highly efficient and stereocontrolled total synthesis of *O*-mycinosyltylonolide (**1**) clearly demonstrates the advantageous utilization of carbohydrates in the construction of the 16-membered ring macrolide antibiotics.[13–15] At present, no practical methodology exists for completing the remaining disaccharide, mycaminose-containing unit, due to the well-recognized problems of glycosidation of N-containing sugars.[16] New strategies directed toward this goal are currently under way in these laboratories.

Acknowledgment. We express our many thanks to Drs. George T. Furst and Tom Terwilliger of the Department of Chemistry, University of Pennsylvania, for their spectroscopic assistance and helpful discussions. Our thanks are also due to Dr. J. F. Downing of Lilly Research Laboratories, Eli Lilly and Co., Greenfield, IN, for a generous gift of tylosin. This work was financially supported by the National Institutes of Health (Grant GM 26879), Merck Sharp & Dohme, the A. P. Sloan Foundation, and the Camille and Henry Dreyfus Foundation.

Registry No. 1, 80879-01-2; **2**, 80879-02-3; **2**, α isomer, 80924-99-8; **3**, 80879-03-4; **4**, 80879-04-5; **5**, 80879-05-6; **6**, 80879-06-7; **7**, 1401-69-0; **8**, 11032-98-7; **9**, 80879-07-8; **10**, 80879-08-9.

Supplementary Material Available: A listing of the physical properties of key intermediates (2 pages). Ordering information is given on any current masthead page.

(10) Hamill, R. L.; Haney, M. E., Jr., Stamper, M.; Wiley, P. F. *Antibiot. Chemother. (Washington, D.C.)* **1961**, *11*, 328.

(11) Similar conditions were used by Masamune in the degradation of *O*-mycaminosyltylonolide in his elegant preparation of tylonolide, the aglycon of tylosin: Masamune, S.; Hayase, Y.; Chan, W. K.; Sobczak, R. L. *J. Am. Chem. Soc.* **1976**, *98*, 7874.

(12) Concomitantly, the isomeric hydroxyethyl furanoside was also formed as a minor product and separated from **9** chromatographically.

(13) For an elegant carbohydrate approach to the erythromycins see: Hanessian S. *Pure Appl. Chem.* **1977**, 49, 1201.

(14) (a) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Tetrahedron Lett.* **1979**, 2327. (b) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981**, *103*, 1224. (c) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1224.

(15) For independent work in this area see: (a) Ziegler, F. E.; Gilligan, P. J.; Chakraborty, U. R. *Tetrahedron Lett.* **1979**, 3371. (b) Ziegler, F. E.; Gilligan, P. J. *J. Org. Chem.* **1981**, *46*, 3874. (c) Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, 2837. (d) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *Tetrahedron Lett.* **1981**, *22*, 3997.

(16) Although Tatsuta et al. have succeeded in attaching the similar disaccharide unit on carbomycin B, the reported glycosidation yields are rather low: Tatsuta, K.; Tanaka, A.; Fujimoto, K.; Kinoshita, M.; Umezawa, S. *J. Am. Chem. Soc.* **1977**, *99*, 5826.

Synthesis and Characterization of a New Surface Derivatizing Reagent To Promote the Adhesion of Polypyrrole Films to n-Type Silicon Photoanodes: *N*-(3-(Trimethoxysilyl)propyl)pyrrole

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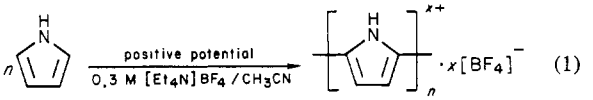
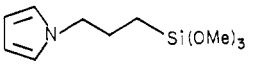
Received December 21, 1981

Four research groups have suggested that "polypyrrole"[1] formed by anodic polymerization of pyrrole, eq 1, can be used to protect



(1)

n-type semiconductors from photoanodic decomposition.[2–5] A problem encountered in the use of the polypyrrole is that it is not persistently attached to the surface,[2] though it does appear that adhesion to n-type Si is improved by metallization of the surface prior to anodic polymerization of the pyrrole.[4,5] Generally, polypyrrole can be peeled from the substrate to give free standing films.[1] Work in this laboratory has established that $(RO)_3Si$ groups can be used to anchor redox-active polymers to surfaces to protect against photocorrosion.[6] We now report the synthesis, characterization, and application of *N*-(3-(trimethoxysilyl)-propyl)pyrrole, I, as a photoanode derivatizing reagent that can



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be covalently anchored to the electrode via reaction of surface OH groups (eq 2).[7] The pendant pyrrole functionality can then be used as the initiation site for polymerization of pyrrole, thereby serving to covalently anchor the polypyrrole (eq 3). This sort

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