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THE TOTAL SYNTHESIS OF (±)-NAPHTHYRIDINOMYCIN. II.[1] CONSTRUCTION OF THE PENTACYCLIC CARBON SKELETON.

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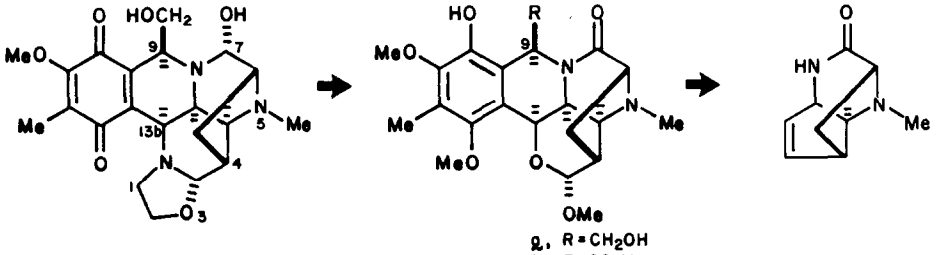
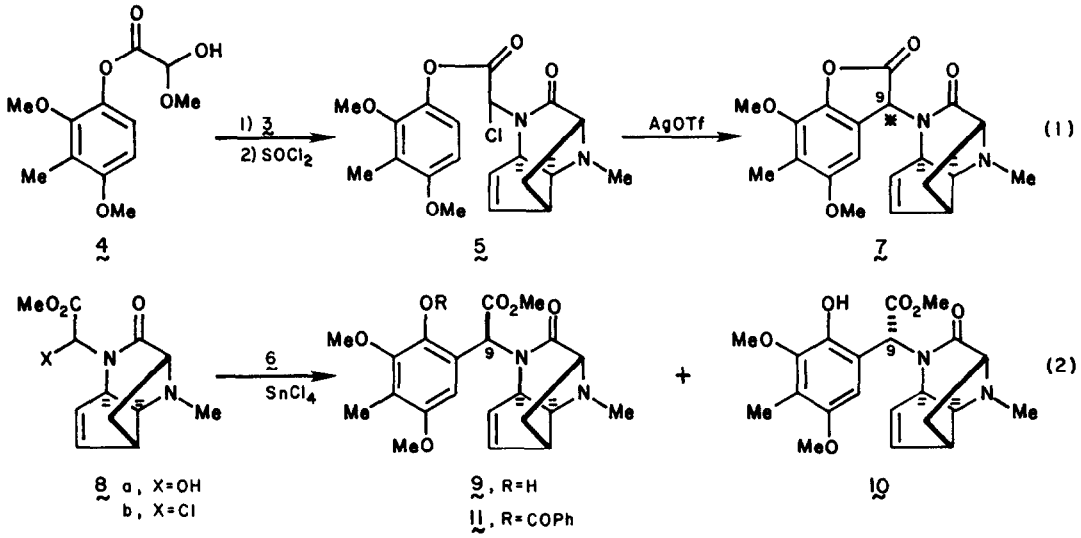
Abstract: A synthesis of an advanced pentacyclic intermediate to the quinone antibiotic naphthyridinomycin (1) is described. The stereoselective synthesis of **2b** from tricyclic lactam **3**[1] features a regio- and stereoselective, intermolecular amidoalkylation reaction and a Friedel-Crafts ring closure to annelate the aromatic nucleus.

Studies directed toward the stereoselective synthesis of the antitumor antibiotic naphthyridinomycin (1) have been the subject of considerable interest in several laboratories.[1,2] In the preceeding Communication,[1] we have described a strategy for the total synthesis of this challenging target, as well as an efficient route to the key intermediate **3**. In the present study we wish to describe the efforts that have led to the stereoselective synthesis of the advanced pentacyclic intermediate **2** which contains most of the architectural features required for naphthyridinomycin.

The basic plan for the elaboration of the tricyclic lactam **3** involved a sequential set of electrophilic aromatic substitution reactions consecutively on C(6) and C(5) of 3-methyl,2,4-dimethoxylphenol (**6**). Two independent variants of the first of these bond constructions are illustrated on the following page (eq 1,2). It is worth noting that the stereochemical outcome of both of these reactions was considered tenuous. There were also concerns associated with the regioselectivity of the intermolecular variant (eq 2). The illustrated intramolecular amidoalkylation was conveniently set up from the phenyl glyoxylate hemiacetal **4**[3]. Treatment of the tricyclic lactam **3** with **4** (4 equiv) in the presence of molecular sieves (25°C, CH_2Cl_2) afforded the expected hemiaminal which was subsequently chlorinated ($SOCl_2$) to provide the illustrated chlorolactam **5** (eq 1).



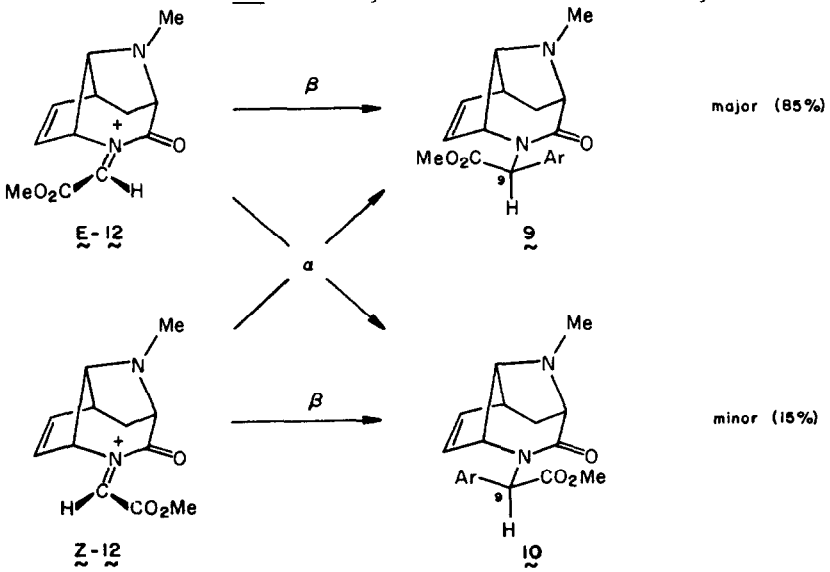
1 **2** a, R = CH_2OH; b, R = CO_2Me **3**



Cyclization of **5** with silver triflate (4 equiv, CH_2Cl_2, 25°C) afforded the lactone **7** in 58% yield. Unfortunately the C(9) diastereoselection was minimal (ratio, 1.5:1). Mild methanolysis (MeOH, heat) afforded equimolar quantities of the diastereomeric methyl esters **9** and **10**.

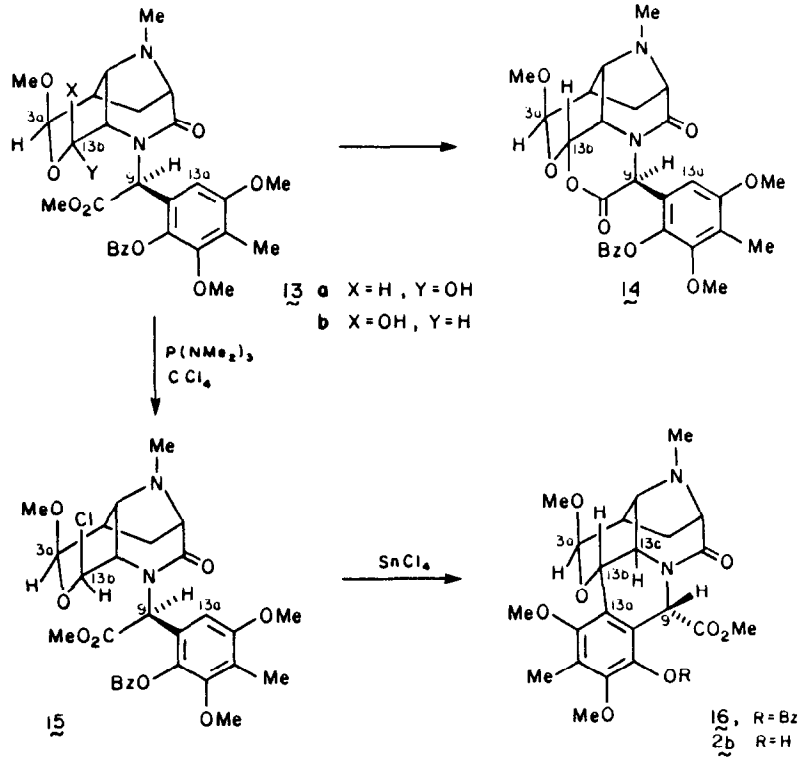
The surprising lack of stereocontrol and disappointing overall yield (33%) observed for the intramolecular sequence, encouraged us to examine the corresponding intermolecular reaction (eq 2). Accordingly the tricyclic lactam **3** was condensed with monomeric methyl glyoxylate[4,5] (CH_2Cl_2, 25°C) to form adduct **8a**, which was then treated with thionyl chloride (CH_2Cl_2, 25°C) to provide **8b** (96% overall) isolated as the free base. In the crucial step, the reaction of chloride **8b** with phenol **6** (1.3 equiv) promoted by tin tetrachloride (2.6 equiv, CH_2Cl_2, 0°C to 25°C) gave a mixture of several amidoalkylation products. Separation of this mixture by MPLC on silica gel afforded the desired isomer **9** in 56% yield and the associated C(9) epimer **10** in 10% yield (naphthyridinomycin numbering). More conveniently, the desired C(9) diastereomer could be obtained via direct crystallization in a 48% overall yield from the tricyclic lactam **3**.

Scheme I



The regiochemical assignments for structures **9** and **10** are based upon solid chemical evidence: (1) Treatment of **9** with base (excess NaOMe, MeOH, 0°C) gave a 1:1.6 mixture of **9** and **10**, indicating that these two substances are epimeric at C(9), and; (2), adducts **9** and **10** are identical to the two methyl esters formed upon the cleavage of lactone **7** in refluxing methanol. The assignment of the relative stereochemistry indicated as in **9** to the major adduct was based upon structural studies on later intermediates (vide supra). A rationale for the stereochemical course of this amidoalkylation is obscured by two ambiguous structural features of the acylimmonium ion **12** (see Scheme I). First, it is not obvious which of the illustrated acylimmonium ions, **E-12** or **Z-12**, is the putative intermediate in the reaction. More significantly, it is also not immediately apparent which is the more accessible prochiral electrophile diastereoface (α or β). Since Lewis acid complexation with the basic nitrogen should further encumber the β-face, we view this reaction as proceeding via amidoalkylation of **Z-12** predominately from the α-face.

Having coupled lactam **3** with the aromatic nucleus in a stereoselective manner, our attention then turned to the construction of the C(13a)-C(13b) bond. The hydrochloride salt of benzoate **11** was subjected to ozone in methanol at -78°C in the presence of Sudan III,[6] followed by reductive workup of the peroxidic intermediates (H_2, 5% Pd-C, -78°C to 25°C). This procedure resulted in a mixture of tetrahydropyranols from which the major isomers **13a** and **13b** were isolated in 70% yield by silica gel chromatography (**13a:13b** = 1:1). In addition, a minor component (approx. 18%) could be isolated as a mixture of stereoisomers, and was found to be regioisomeric with regards to substitution at C(3a) and C(13b). Structural assignment of the major product diastereomer was conveniently secured by lactonization to **14**.



Typically, this crude ozonolysis product was used for the subsequent reactions without purification. The mixture of pyranols was treated with $(Me_2N)_3P$ (1.3 equiv) and CCl_4 (33 equiv)[7,8] in CH_2Cl_2 (-78°C to 25°C) to afford chloride **15**[9] as the major component, along with HMPA. This solution was treated directly with $SnCl_4$ (2.5 equiv, -78°C to 0°C) to provide pentacycle **16** in 42% yield, overall from **11**. Hydrolysis of the benzoate ester gave phenol **2b** in a straightforward manner (NaOH, H_2O, THF, MeOH, 84%).

In order to determine the relative stereochemistry at C(9) and C(3a), a nuclear Overhauser enhancement study [11,12] was performed on phenol **2b** using the NOE difference technique at 500 MHz.[12] Irradiation of the C(9) proton resulted in an enhancement of the C(13c) proton and vice versa. This establishes a syn relationship between these protons and secures the C(9) stereochemical assignment of **2b** and its precursors. Related enhancement experiments secured the stereochemistry of the incorporated methoxyl-bearing stereocenter at C(3a) (naphthyridinomycin numbering) as illustrated in structures **16** and **2b**. A subsequent X-ray analysis of **16** confirmed all stereochemical assignments.[13]

During the course of the synthesis of pentacyclic lactam **2b**, reasonable precedent has been established for dealing with many of the stereochemical and redox issues inherent in a projected synthesis of naphthyridinomycin. For example, we have employed this advanced intermediate to evaluate two important redox issues to be faced at later stages in the synthesis. One of our first observations pertained to the reduction of the C(9) carbomethoxyl moiety in pentacyclic lactam **2b**. Due to the "double peri-interaction" of this substituent with the resident oxygen functions at C(7) and C(10), this function has been found to be inert to a host of hydride reagents. On the other hand, this reduction is readily accomplished at earlier points in the synthesis prior to pentacycle construction. We have also encountered similar problems in the establishment of the quinone ring via the oxidation of either **2a** or **2b**. We have thus concluded that the potential pitfalls associated with the advanced redox transformations leading to the target structure should not be underestimated. A successful solution to this final set of problems will be reported shortly.

Acknowledgments. This research was supported by the National Institutes of Health (GM33328-02).

References and Notes.

1. Part I: Evans, D.A.; Biller, S.A. Tetrahedron Lett. **1985**, preceeding communication.
2. See references 1,2, and 5 in Part I.[1]
3. Adduct **4** was prepared via ozonolysis of the E crotonate ester of phenol **6** (O_3, CH_3OH, -78°C; CH_3SCH_3, -78°C to 25°C).
4. Polymeric methyl glyoxylate was prepared by the method of Kelly,[5] and was converted to the monomer by redistilling from P_2O_5 and collecting the distillate at -78°C. Material thus obtained was 90-95% monomer as estimated by ^1H NMR.
5. Kelly, T.R.; Schmidt, T.E.; Haggerty, J.G. Synthesis **1972**, 544-545.
6. Veysoglu, T.; Mitscher, L.A.; Swayzee, J.K. Synthesis **1980**, 807-810.
7. Downie, I.M.; Lee, J.B.; Matough, M.F.S. J. Chem. Soc., Chem. Commun. **1968**, 1350-1351.
8. Ireland, R.E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C.S. J. Org. Chem. **1980**, 45, 48-61.
9. The stereochemistry depicted in **15** is based upon the large anomeric effect (approx. 2.7 kcal/mol) which is characteristic of pyranosyl chlorides.[10] The ^1H NMR spectrum indicated that the chloride derived from **13a** and **13b** was greater than 90% a single isomer.
10. Stoddart, J.F. "Stereochemistry of Carbohydrates"; Wiley: New York, 1971; Chapter 3, pp. 67-87; and references cited therein.
11. a) Anet, F.A.L.; Bourn, A.J.R. J. Am. Chem. Soc. **1965**, 87, 5250-5251. b) Noggel, J.H.; Schirmer, R.E. "The Nuclear Overhauser Effect"; Academic Press: New York, 1971.
12. Hall, L.D.; Sanders, J.K.M. J. Am. Chem. Soc. **1980**, 102, 5703-5711. J. Org. Chem. **1981**, 46, 1132-1138.
13. The X-ray study was carried out by N.S. Mandel and G.S. Mandel at the Medical College of Wisconsin.

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