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THE TOTAL SYNTHESIS OF (+)-NAPHTHYRIDINOMYCIN. I. PREPARATION OF A KEY TRICYCLIC LACTAM INTERMEDIATE.

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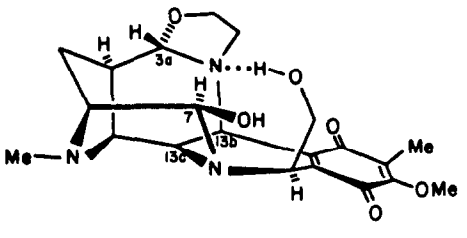
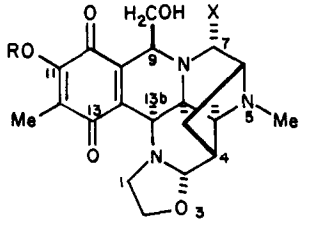
Abstract: A synthetic strategy for the preparation of the quinone antibiotic naphthyridinomycin is outlined. An efficient synthesis of key tricyclic intermediate **6** is described.

Naphthyridinomycin (**1**) is an architecturally interesting broad spectrum antibiotic produced by Streptomyces lusitanus.[1,2] The structure elucidation of **1** in 1974[1a,b] revealed its unique hexacyclic structure which shared a quinone nucleus common to both the mitomycins[3] and saframycins.[4] Over the last several years three additional naphthyridinomycin derivatives have been independently isolated and characterized by X-ray crystallography,[5] and one of these compounds, cyanocycline (cyanonaphthyridinomycin) (**2**), has been produced by cyanation of **1**.[6] In addition to their antibiotic activity, this family of natural products exhibits marked antitumor activity as well as acute toxicity. The architectural complexity of the naphthyridinomycins poses a number of interesting challenges from the standpoint of the development of a rational synthesis, and this objective is currently being pursued in several laboratories in addition to our own.[7] The purpose of this and the accompanying communication is to outline the general approach and progress that we have made toward the total synthesis of this family of quinone antibiotics.



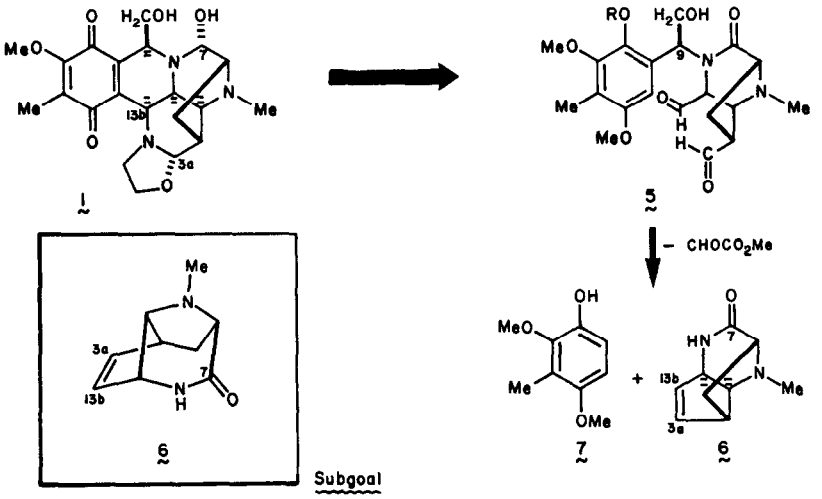
Naphthyridinomycin (**1**)



1, X = OH, R = Me
2, X = CN, R = Me
3, X = OH, R = H
4, X = CN, R = H

The general plan which we anticipate will accomodate the synthesis of both **1** and **2** is outlined in Scheme I. Several of the significant value judgments which have strongly influenced the evolution of the synthesis plan are worthy of some discussion.

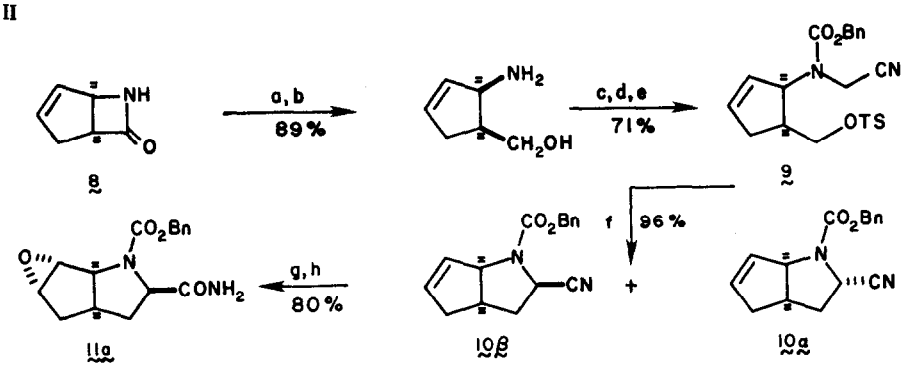
Scheme I



First, it has been assumed that thermodynamic considerations will prevail in the construction of the aminal centers at C(3a) and C(7). Second, it has been presumed that the dialdehyde **5**, as its equivalent synthon **6**, might serve as a versatile intermediate that might be elaborated to the target structure. Finally, it should be stated that we had no preconceived bias as to the stereochemical course of the proposed amidoalkylation reaction[8] between **6**, 7[9], and methyl glyoxylate. In the following paragraphs are described an efficient synthesis of the important tricyclic intermediate **6** from the bicyclic β-lactam **8**.

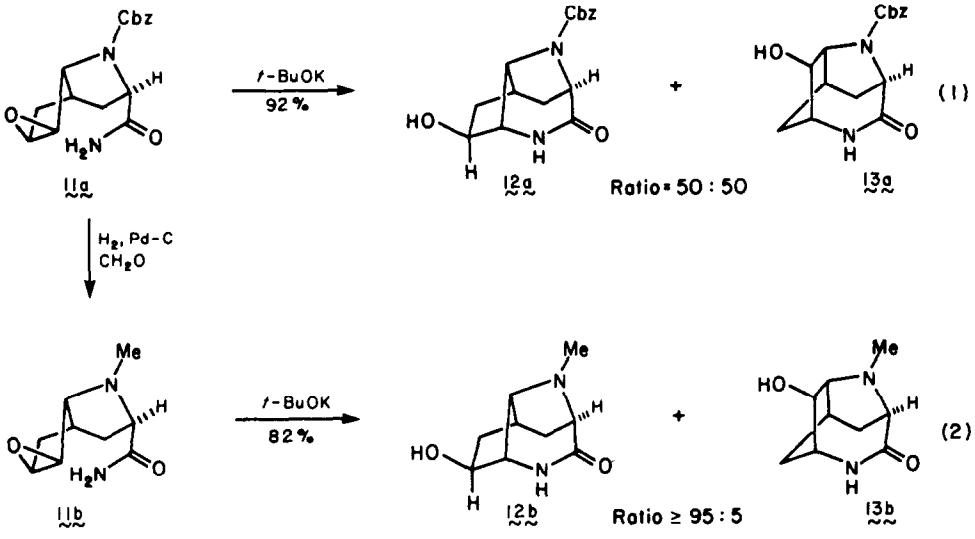
Bicyclic β-lactam **8**[10] was prepared in 50-65% yield from cyclopentadiene and chlorosulfonyl isocyanate by an improved procedure.[11] This stereospecific cycloaddition serves to establish the required relative stereochemistry at C(4) and C(4a) in the target structure **1**. The conversion of β-lactam **8** to nitrile tosylate **9** was accomplished in high overall yield as outlined in Scheme II. Upon treatment with potassium t-butoxide (t-BuOH, THF, RT), **9** underwent cyclization to afford a mixture of stereoisomeric bicyclic nitriles **10α** and **10β** (1.5:1) suggesting that the stereochemical outcome of the cyclization was a result of thermodynamic control. Preparatively, the undesired isomer **10α** was subjected to potassium t-butoxide catalyzed equilibration and separation to provide a 58% yield of **10β** after a single recycle.

Scheme II



Legend. a) MeOH, HCl. b) Na_2CO_3, H_2O; LAH, Et_2O. c) NaCN, $CH_2O{\cdot}NaHSO_3$, MeOH, H_2O. d) CbzCl, $Et(i\text{-}Pr)_2N$, CH_2Cl_2, 0°C. e) TsCl, pyr, +5°C. f) t-BuOK, t-BuOH, THF, 25°C. g) MCPBA, CH_2Cl_2. h) H_2O_2, Na_2CO_3, acetone, H_2O, reflux.

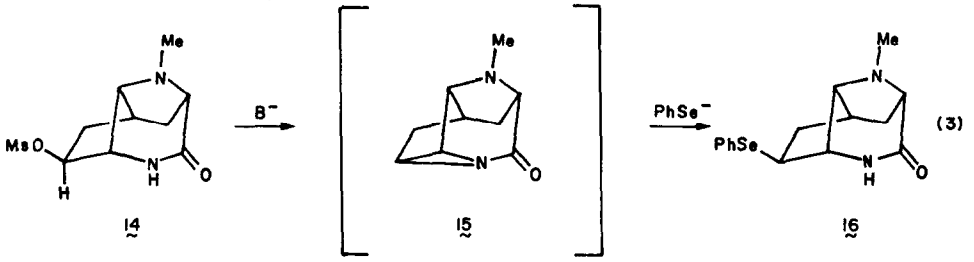
Selective epoxidation of **10** β from the convex face[12] followed by hydrolysis of the nitrile function gave epoxyamide **11a**. We anticipated that **11a** would undergo base-promoted ring closure to the six-membered lactam **12a**, thereby forming the desired tricyclic skeleton (eq 1). Unfortunately, the reaction of **11a** with potassium t-butoxide in t-butanol gave a 1:1 mixture of **12a** and isomeric lactam **13a** in 92% yield. In an attempt to improve the regioselectivity of this cyclization, the corresponding N-methyl epoxide **11b** was prepared from **11a** via hydrogenolysis in the presence of formaldehyde (1 atm H_2, 5% Pd-C, MeOH, 95%). When **11b** was subjected to the above cyclization conditions, the desired lactam **12b** was obtained in 82% yield (eq 2). It was a pleasant surprise to find that no more than trace quantities (less than 5%) of the undesired tricyclic lactam accompanied this cyclization. The structure of **12b** was confirmed by X-ray crystallography.[13] This dramatic change in regioselectivity suggests that C-O bond breaking is more advanced than N-C bond making in the transition state, such that a partial positive charge resides on the epoxide carbon undergoing displacement. The greater electron withdrawing capability of the Cbz-N function of **11a** apparently disfavors epoxide cleavage at the desired, proximal carbon.



(1)

(2)

With tricyclic alcohol **12b** in hand, it remained only to eliminate the elements of water to arrive at key intermediate **6**. Alcohol **12b** was converted to the corresponding phenyl selenide, via the mesylate **14** ($MeSO_2Cl$, Et_3N, CH_2Cl_2, 95%; PhSeSePh, $NaBH_4$, EtOH, 80°C, 97%). Analysis of the coupling patterns in the 500 MHz ^1H NMR spectrum of the phenyl selenide **16** indicated that the mesylate displacement had occurred with retention of configuration (eq 3).



(3)

This observation indicates that neighboring group participation of the lactam nitrogen is occurring, and strongly implicates the intermediacy of acylaziridine **15**.[14] Finally, oxidative elimination of selenide **16** as its trifluoroacetate salt (3 equiv. t-BuOOH, $CHCl_3$) gave tricyclic olefin **6** in 88% yield.

The following communication describes important subsequent transformations of this intermediate to analogs closely related to naphthyridinomycin (1).[15,16]

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References and Notes.

1. (a) Sygusch, J.; Brisse, F.; Hannessian, S.; Kluepfel, D. Tetrahedron Lett. **1974**, 4021-4023; erratta: Tetrahedron Lett. **1975**, 170. (b) Sygusch, J.; Brisse, F.; Hanessian, S. Acta. Cryst. **1976**, B32, 1139-1142. (c) Kluepfel, D.; Baker, H.A.; Piattoni, G.; Sehgal, S.N.; Sidorowicz, A.; Kartar, S.; Vezina, C., J. Antibiotics **1975**, 28, 497-502.
2. Biosynthesis: Zmijewski, M.J., Jr.; Mikolajczak, M.; Viswanatha, V.; Hruby, V.J. J. Am. Chem. Soc. **1982**, 104, 4969-4971.
3. For a review, see: Franck, R.W. Fortschr. Chem. Org. Naturst. **1979**, 38, 1-45.
4. Total synthesis: Fukuyama, T.; Sachleben, R.A. J. Am. Chem. Soc. **1982**, 104, 4957-4958.
5. (a) Itoh, J.; Omoto, S.; Inouye, S.; Kodama, Y.; Hisamatsu, T.; Niida, T.; Ogawa, Y. J. Antibiotics **1982**, 35, 642-644. (b) Hayashi, T.; Noto, T.; Nawata, Y.; Okazuki, H.; Sawada, M.; Ando, K. ibid. **1982**, 35, 771-777.
6. Zmijewski, M.J., Jr.; Goebel, M.J. J. Antibiotics **1982** 35, 524-526.
7. For an alternative approach see: Danishefsky, S.; O'Neill, B.T.; Taniyama, E.; Vaughn, K. Tetrahedron Lett. **1984**, 25, 4199-4202. Danishefsky, S.; O'Neill, B.T.; Springer, J.P. ibid. **1984**, 25, 4203-4206.
8. Review: Zaugg, H.E. Synthesis **1970**, 49-73. Preparation of α-substituted α-amino acids: Ben-Ishai, D.; Peled, N.; Sataty, I. Tetrahedron Lett. **1980**, 21, 569-572; and earlier papers in this series. Ozaki, Y.; Iwasaki, T.; Horikawa, H.; Miyoshi, M.; Matsumoto, K. J. Org. Chem. **1979**, 44, 391-395; and references cited therein.
9. Nakatsubo, F.; Cocuzza, A.J.; Keeley, D.E.; Kishi, Y. J. Am. Chem. Soc. **1977**, 99, 4835-4836.
10. Malpass, J.R.; Tweedle, N.J. J. Chem. Soc., Perkin Trans. I **1977**, 874-884.
11. The reaction between chlorosulfonyl isocyanate and cyclopentadiene was carried out in ether between -16 and -24°C, followed by reductive hydrolysis of the N-chlorosulfonyl β-lactam (Na_2SO_3, K_2HPO_4, 0°C). Careful attention must be paid to reaction temperature.
12. An 8.7% yield of the isomeric epoxide was isolated. The unfractionated isomer ratio was 91:9 by glc.
13. The X-ray study was carried out by N.S. Mandel and G.S. Mandel at the Medical College of Wisconsin.
14. The failure of direct base-promoted elimination of the mesylate (DBU, toluene, reflux or t-BuOK, DMSO) may have resulted from partitioning of this highly strained and reactive intermediate **15** into undesired pathways.
15. Evans, D.A.; Biller, S.A. Tetrahedron Letters, accompanying communication.
16. This and the following Letter were taken from the Ph.D. thesis of S.A. Biller, California Institute of Technology, 1982.

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