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SYNTHETIC APPROACHES TOWARD NAPHTHYRIDINOMYCIN. I. STEREOSELECTIVE SYNTHESIS OF A TETRACYCLIC INTERMEDIATE.

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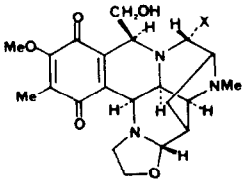
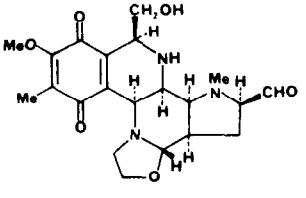
Abstract: A highly stereoselective synthesis of a tetracyclic intermediate 4 to the quinone antitumor antibiotic naphthyridinomycin 1 is described.

Naphthyridinomycin 1 is one of the most complex quinone antitumor antibiotics isolated to date.[1] It is a hexacyclic compound with eight chiral centers, containing such labile functional groups as aminal, oxazolidine, and quinone. In addition, the highly packed molecule has three contiguous chiral centers bearing basic nitrogen atoms. Although naphthyridinomycin is too toxic for medicinal use, it has been a target of vigorous synthetic studies in several laboratories because of its challenging structural features.[2] An elegant total synthesis of more stable cyanocycline (cyanonaphthyridinomycin) 2[3] has recently been reported by Evans and his co-workers.[4] In this communication we describe a stereoselective synthesis of the tetracyclic intermediate 4. We have succeeded in controlling the stereochemistry of six of the eight chiral centers of 1. The structure of the naphthyridinomycin equivalent 3 is provided for comparison. The stereochemistry of the remaining two chiral centers at aminal and at oxazolidine are expected to be thermodynamically controllable.



1: X = OH

2: X = CN



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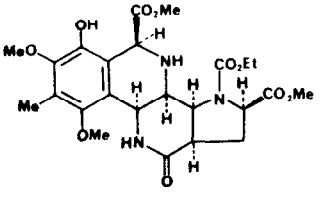

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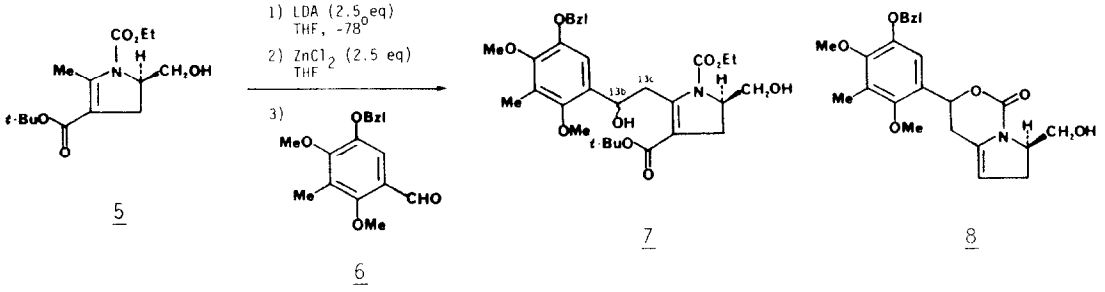
Our approach is featured by an efficient C(13b)-C(13c) bond formation as shown in Scheme I. Condensation of the zinc dienolate of the dihydropyrrole 5[5] with the highly substituted aromatic aldehyde 6[6] under the thermodynamic control conditions (0°, 25 min) afforded the desired, epimeric mixture of γ-alkylation product 7 in 59% yield. Use of the lithium dienolate of 5 gave predominantly the undesired cyclic urethane 8 even at -78°.

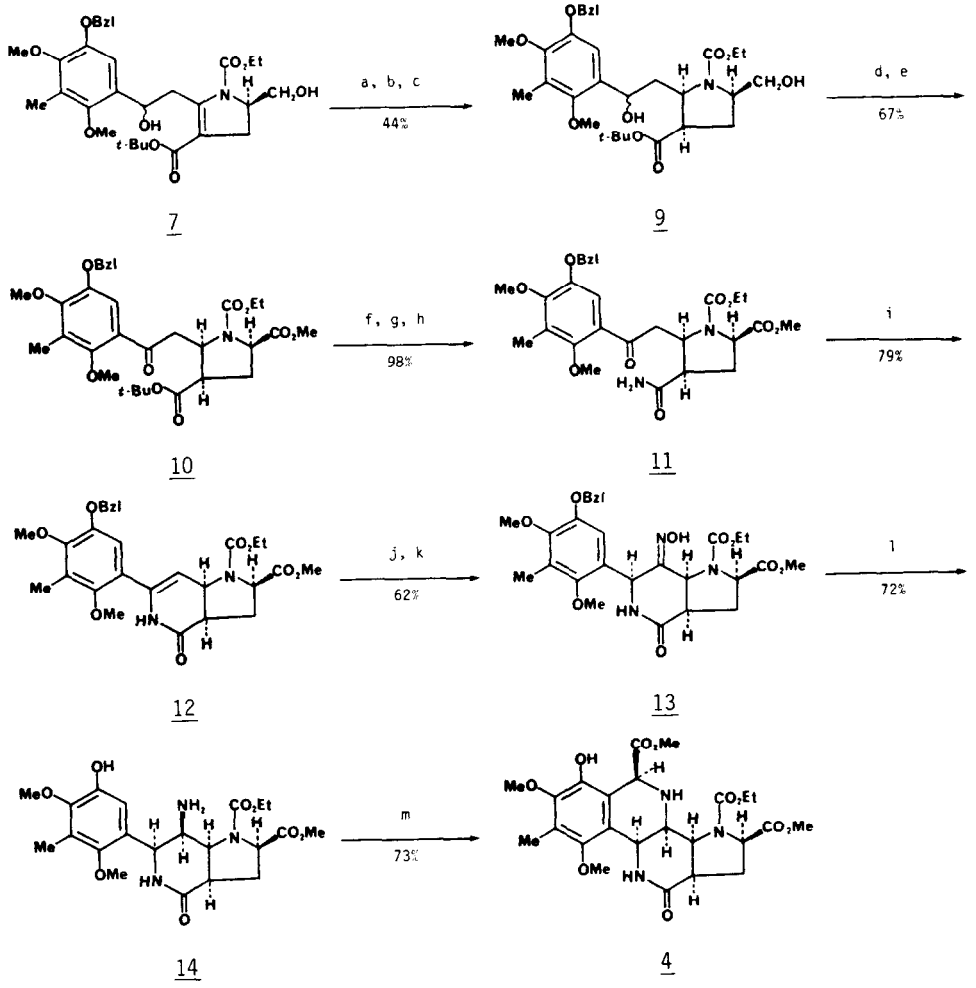
Scheme I



5 6 7 8

After hydrogenolytic removal of the benzyl ether of 7 (H_2 (1 atm), 10% Pd/C, EtOH) the dihydropyrrole ring was catalytically hydrogenated (H_2 (1500 psi), 5% Rh/C, EtOAc, 80°) to give, upon reprotection of the phenol ($PhCH_2Br$, K_2CO_3, DMF), the cis trisubstituted pyrrolidine 9 in 45% yield.[7] Since we had experienced some difficulties in selectively protecting the hindered primary alcohol, the diol 9 was then converted to the ketoester 10 (1. H_2CrO_4, acetone; 2. MeI, K_2CO_3) in 67% yield. At this stage the t-butyl ester 10 was transformed to the amide 11 in a conventional manner (1. TFA; 2. $ClCO_2Et$, Et_3N, CH_2Cl_2; 3. NH_3) in 98% yield. The critical cyclization of the ketoamide 11 was performed by treatment with CSA (0.4 eq) and quinoline (0.5 eq) in refluxing benzene to afford the desired enelactam 12 in 79% yield.[8] Manipulation of the reactive enamide system 12 was carried out by addition of nitrosyl chloride to a solution of 12 in CH_3CN-CH_2Cl_2 (2:1) at -30°. The resulting unstable α-chloroxime was reduced *in situ* with $NaBH_3CN$ in the presence of methanol to give highly crystalline oxime 13 (mp 220° dec.) in 62% yield. The reduction occurred from the less hindered, convex face of the molecule, and no isomeric oxime was detected in the reaction mixture. Judging from this high degree of stereoselectivity of the reduction, we could anticipate similar results for the reduction of the oxime 13. Indeed, catalytic hydrogenation of 13 (H_2 (1500 psi), Raney Ni (W-2), Et_3N, EtOH, 100°) gave exclusively the desired aminophenol 14 in 72% yield. To our great surprise, phenolic cyclization of the aminophenol 14 with methyl glyoxylate (MeOH, 120°, 1 hr) furnished the tetrahydroisoquinoline 4 as the predominant product in 73% yield.[9] The structure of 4 was confirmed by a single crystal X-ray analysis as shown in Fig 1.[10] Application of this highly promising route to the total syntheses of naphthyridinomycin 1 and cyanocycline 2 is currently under way in our laboratories.

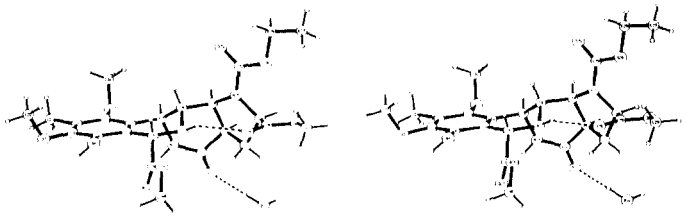
Scheme II



7 9 10 11 12 13 14 4

(a) H_2 (1 atm), 10% Pd/C, EtOH; (b) H_2 (1500 psi), 5% Rh/C, EtOAc, 80°; (c) $PhCH_2Br$, K_2CO_3, DMF, 80°; (d) Jones oxid., RT; (e) MeI, K_2CO_3, acetone, reflux; (f) TFA, RT; (g) $ClCO_2Et$, Et_3N, CH_2Cl_2, 0°; (h) NH_3, CH_2Cl_2, 0°; (i) CSA, quinoline, benzene, reflux; (j) NOCl, CH_3CN-CH_2Cl_2 (2:1), -30°; (k) $NaBH_3CN$, MeOH, -30° to 0°; (l) H_2 (1500 psi), Ra-Ni (W-2), Et_3N, EtOH, 100°; (m) $OHCCO_2Me$, MeOH, 120°.

Fig I



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4. Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2478.

5. Prepared from ethyl α-carbethoxyaminoacrylate in a three-step sequence in 73% yield: (1) ethyl α-carbethoxyaminoacrylate, t-butyl acetoacetate (1.5 eq), NaOEt (0.2 eq), EtOH, 70°, 15 min; (2) p-TsOH (0.2 eq), quinoline (0.24 eq), Dean-Stark trap, toluene, reflux, 20 min; (3) $LiEt_3BH$ (2.2 eq), THF, 0°.

6. Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957.

7. Substantial amount of the cyclohexylmethyl compound was obtained when Rh/C hydrogenation was performed on the benzyl ether 7.

8. Prolonged heating caused slow aromatization to give the pyridone derivative.

9. When heated at 130° in xylene, the kinetic product 4 gradually underwent isomerization to give the thermodynamically more favorable epimer. Since no appreciable epimerization was observed on the corresponding acetate, 4 might epimerize through retro-Michael and Michael additions mechanism.

10. We are indebted to Drs. L. J. Todaro, A.-M. Chiu, and J. J. Partridge of Hoffmann-La Roche Inc. for an X-ray structure determination of 4.

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