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AN APPROACH TO THE SYNTHESIS OF THE NAPHTHYRIDINOMYCIN ALKALOIDS: THE SYNTHESIS OF TWO SUBUNITS

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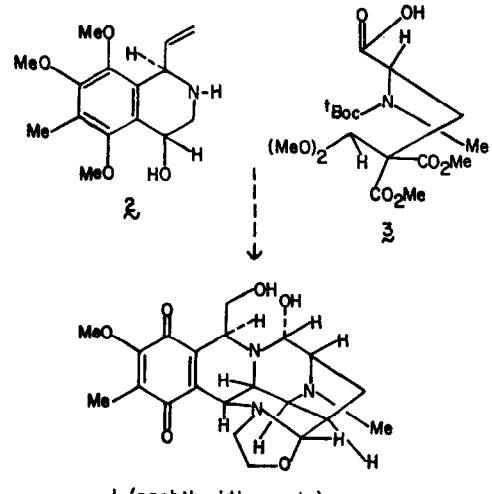
Summary: The preparations of the tetrahydroisoquinolinol (**2**) and the γ-carboxy-γ-formylglutamate (**3**) subunits, required for a proposed synthesis of naphthyridinomycin, are described.

The isolation and structure determination of the antibiotic, naphthyridinomycin (**1**), was described by an Ayerst group in collaboration with Hanessian.[1,2] The clinical significance, if any, of this substance, remains to be demonstrated. However, naphthyridinomycin already merits interest at the biological level because it is the most striking member of a rather large collection of structurally related alkaloids, **all of which** are reputed to possess antitumor or antibiotic properties.[3] Moreover, from the perspective of pure chemistry, a total synthesis of compound **1** would require solutions to a number of substantial problems.[4] Accordingly, we have undertaken synthetic studies in this area. The goal would be a strategy of sufficient versatility to embrace naphthyridinomycin and other members of this series.[5]

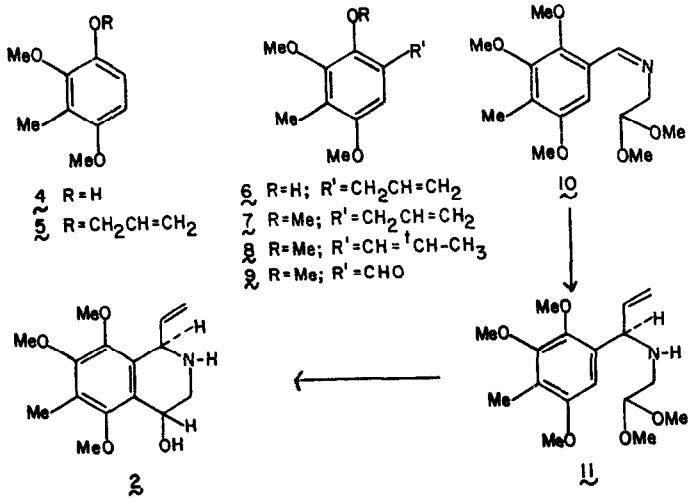
The basic plan involves merger of the tetrahydroisoquinolinol, **2**, with the amino acid derivative, **3**, through an amide bond. In this Letter we describe the synthesis of these two compounds. In the following Letter[6] we describe the chemistry of the amide which is obtained by coupling of these subunits.



1 (naphthyridinomycin)

The synthesis of the tetrahydroisoquinolinol started with the well-known phenol **4**. Following chemistry worked out concurrently in our laboratory,[7] and that of Kishi,[8] compound **4** was converted (NaH/allyl bromide; DMF) to **5** (90%, crude yield). Upon Claisen rearrangement (N,N-dimethylaniline; 190°; 5 hours) of **5**, compound **6** was obtained (quantitative crude yield). Methylation (NaH/MeI; DMF) of the phenol provided **7** (90% from **4**). Migration of the double bond was achieved quantitatively through reaction of **7** with palladium dichloride·bis acetonitrile.[9] Ozonolysis of **7** (O_3, MeOH, -78°, sudan red-7B indicator[10] till disappearance of the color, followed by 3 minutes of ozone) and reductive workup with zinc dust in acetic acid provided an 86% yield of aldehyde **9**.[11] Although five steps were employed in going from **4** to **9**, the high (77%) overall yield, and the absence of need for chromatographic separation, rendered this route more conducive to large scale operations than several shorter paths.

The condensation of aldehyde **9** with aminoacetaldehyde dimethylacetal (benzene reflux; Dean Stark trap) furnished a quantitative (crude) yield of **10**, which reacts with vinyl magnesium bromide to give a quantitative (crude) yield of **11**. Dissolution of the latter in 6N HCl[12] for ca. 24 hours, followed by basification first to pH=3 then to pH=11, afforded a 70% yield (from **9**) of the tetrahydroisoquinolinol **2** as a single stereoisomer (stereochemistry unassigned).

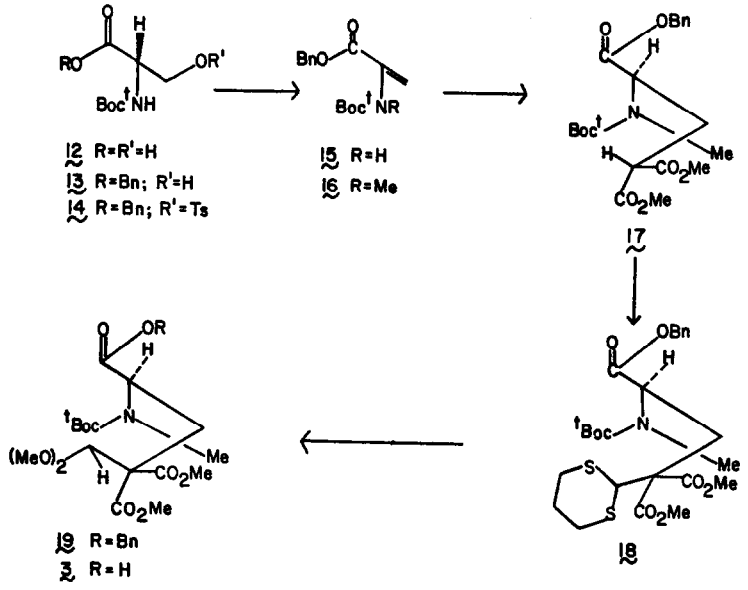


The synthesis of the interesting glutamate derivative **3** started with the commercially available ^{t}Boc-serine (**12**) and proceeded (benzyl bromide, triethylamine, acetone, reflux) through its benzyl ester **13** and thence (pyridine, TsCl, -5°→rt) to the tosylate **14** (78% crude yield from **12**). Elimination of tosylic acid was smoothly accomplished with diethylamine in 1:1 ether-ethyl acetate at room

temperature. The dehydroalanine derivative, **15**, thus generated, was methylated (KH; MeI ether) to afford **16**.[13] Reaction of sodiodimethyl malonate (THF 0°; rt) with compound **16**,[14] led to the substituted γ-carboxyglutamate **17** in 96% yield.

The critical "C_1" unit was introduced through the reaction of 2-chloro-1,3-dithiane[15] on the lithium salt generated by the action of lithium di-isopropylamide on **17** (THF; 0°). Compound **18**, thus obtained in 81% yield, was converted in 83% yield to **19** through the agency of N-bromosuccinimide and silver nitrate in methanol. The desired differentiated acid **4** was now available by hydrogenolysis (H_2-Pd/C-ethyl acetate) of the benzyl group of **19**. The overall yield of **3** from **12** was ca. 40-45%.

In summary, the two subunits **2** and **3**, which could be useful for a variety of target systems related to **1**, are now available through straightforward, high-yielding chemistry.



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