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Rearrangements Encountered in the Attempted Syntheses of Pyridoazepinone Carboxylic Acids

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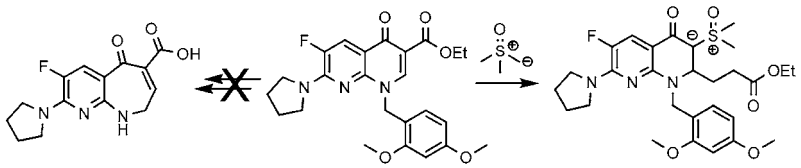
ABSTRACT



Attempts to synthesize pyridoazepinone carboxylic acids such as 33 by standard methodologies resulted exclusively in unusual and unexpected rearrangement products. Seven-membered ring formation was attempted by ring expansion of a six-membered ring and by aldol ring closure. In each case, the major product resulted from rearrangement of the starting material without detection of the desired product. Ultimately, an isomeric pyridoazepinone ethyl ester was prepared; however, attempted saponification resulted in another unusual rearrangement.

Naphthyridones with the general structure **1** (Figure 1), where R_1 = alkyl, cycloalkyl, or aryl and R_7 = cycloalkylamino, are well-known antibacterial agents belonging to the quinolone class of gyrase inhibitors.[1,2] Recently, it was shown that similar compounds such as **2**, where R_1 = H, are antibacterial agents that inhibit protein synthesis in a wide variety of bacterial species.[3] The discovery that naphthyridones without a carbon substituent on N-1 have antibacterial activity without concomitant gyrase inhibition activity launched an extensive search for structural modifications of **2** that would improve inhibitory activity against bacterial protein synthesis. We believed that the identification of **2** as a lead compound was solely a result of structural bias in the screening library and further optimization by structural modification would prove fruitful. In the course of optimization, we proposed preparation of seven-membered ring analogues of generic structure **3** (Figure 1); however, attempts at the synthesis of several variations of **3** resulted in unexpected rearrangements without detection of any of the predicted products.

Seven-membered rings have a long and storied history both in synthetic chemistry and in drug discovery. Many methodologies have been developed or adapted for the production of seven-membered rings.[4,5] Included among these are the acyloin condensation and intramolecular aldol reaction and ring-expansion reactions, including the Beckman rearrangement and numerous fused aziridine- and cyclopropane-opening reactions.[6] More recently, ring-closing metathesis

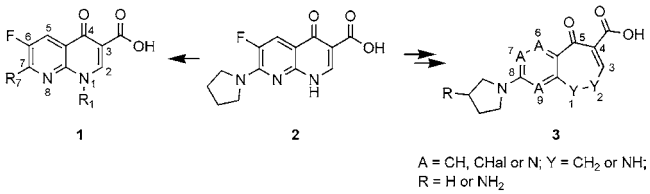


Figure 1. General structure of naphthyridone antibiotics (**1**), antibacterial lead compound (**2**), and proposed seven-membered ring analogues (**3**).

(1) Andersson, M. I.; MacGowan, A. P. *J. Antimicrob. Chemother*. **2003**, *51* (Suppl. S1), 1−11.
(2) *The Quinolones*, 2nd ed.; Andriole, V. T., Ed.; Academic Press: San Diego, CA, 1998.
(3) Dandliker, P. J.; Pratt, S. D. et al. *Antimicrob. Agents Chemother*. **2003**, *47*, 3831−3839.

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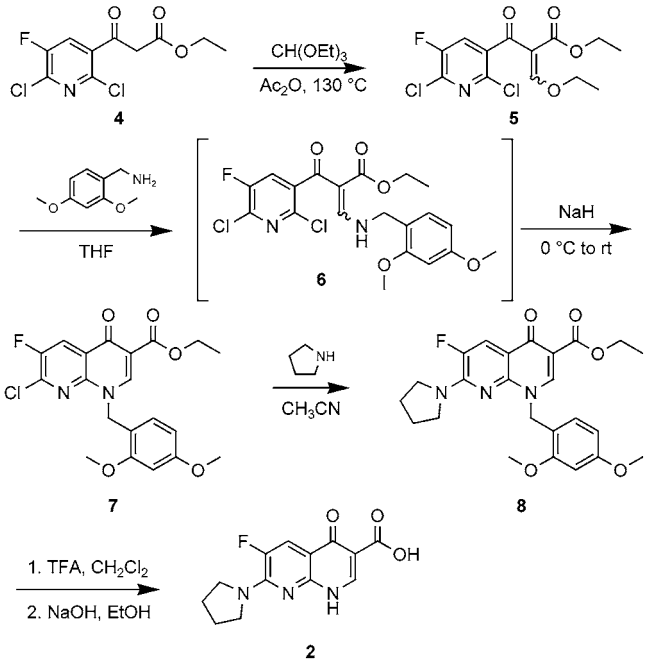
Scheme 1



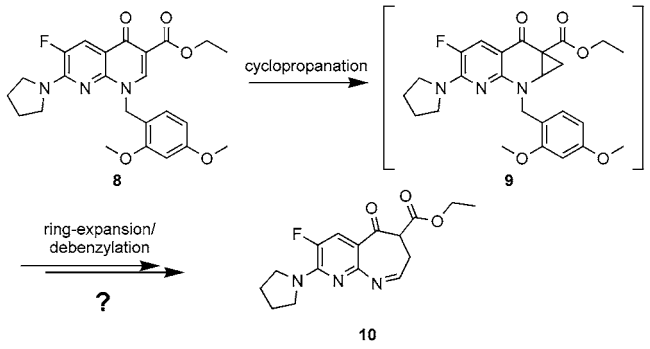
has become the method of choice for the synthesis of many different ring systems.[7,8] In the pharmaceutical industry, discovery of azepine and diazepine peptidomimetics with wide-ranging biological activities inspired many syntheses of new seven-membered heterocycles. On the basis of the wealth of published information, we anticipated that a method or methods for the preparation of compounds of generic structure **3** would be revealed.

Synthesis of the naphthyridone ring system is generally accomplished by intramolecular nucleophilic aromatic substitution on a 2-chloropyridine as shown in Scheme 1.[9]

In a one-pot procedure, β-ketoester **4** is converted first to vinyl ether **5** by reaction with triethyl orthoformate in acetic anhydride. Removal of solvent followed by treatment of **5** with 2,4-dimethoxybenzylamine affords vinylogous imide **6**, which cyclizes upon addition of sodium hydride to provide naphthyridone **7**. Subsequent substitution at C-7 with pyrrolidine and sequential deprotection affords the N-1 unsubstituted naphthyridone **2** of the lead series. [10]

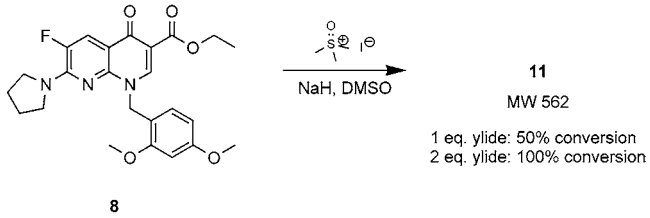
Scheme 2 illustrates an approach to analogues of lead compound **2** via ring expansion of naphthyridone **8**. In the proposed sequence, simple access to compound **10** was envisioned via cyclopropanation/ring expansion of naphthyridone **8**. Oxidation or isomerization of **10** would then provide the desired α,β-unsaturated system. We had previously observed that naphthyridones such as compound **8** underwent selective 1,4-reduction with various borohydride

Scheme 2



reducing agents without significant reduction of either carbonyl group. This observed electrophilicity at C-2 led us to choose sulfur ylides as cyclopropanating agents for the desired transformation. To this end, naphthyridone **8** was treated with trimethylsulfoxonium iodide/sodium hydride in DMSO (Scheme 3). Upon treatment with 1 equiv of the ylide,

Scheme 3



50% conversion to a single product occurred, with 50% starting material remaining unreacted. Addition of a second equivalent of ylide resulted in quantitative conversion to a single product that was inconsistent with either a cyclopropane or the corresponding ring-expansion product. Mass spectrometry indicated a molecular weight of 562, consistent with addition of one methylene group plus 1 equiv of the sulfur ylide. Analysis of the product by multidimensional NMR techniques, including COSY, ROESY, HSQC, and HMBC, led to the identification of sulfur ylide **11** (Scheme 4) as the sole product of the reaction.[11]

A proposed mechanism for the formation of **11** is illustrated in Scheme 4. Apparently, the desired cyclopropanation reaction occurs to provide intermediate **9**. However, addition of a second equivalent of the sulfur ylide to the keto group is more facile than ring expansion, and tetrahedral intermediate **12** is formed. Under normal circumstances, **12** would be expected to form an epoxide by elimination of dimethyl sulfoxide;[12] however, in the proposed mechanism

(4) Bremner, J. B. *Prog. Heterocycl. Chem.* **2003**, *15*, 385−430.
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(8) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4450.
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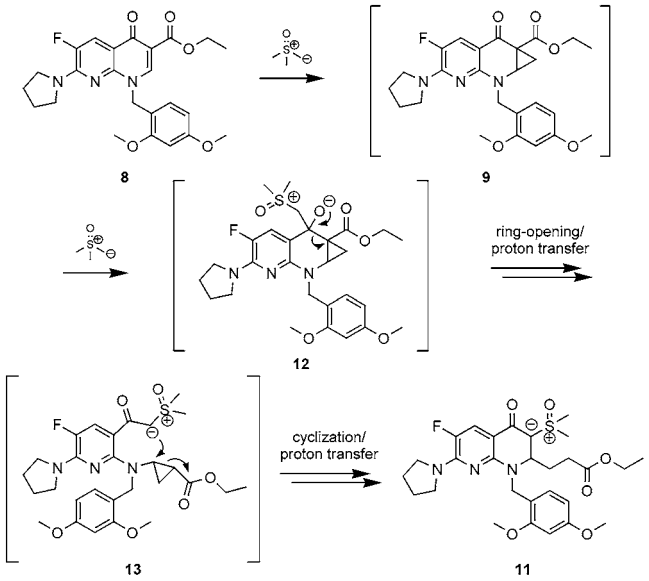
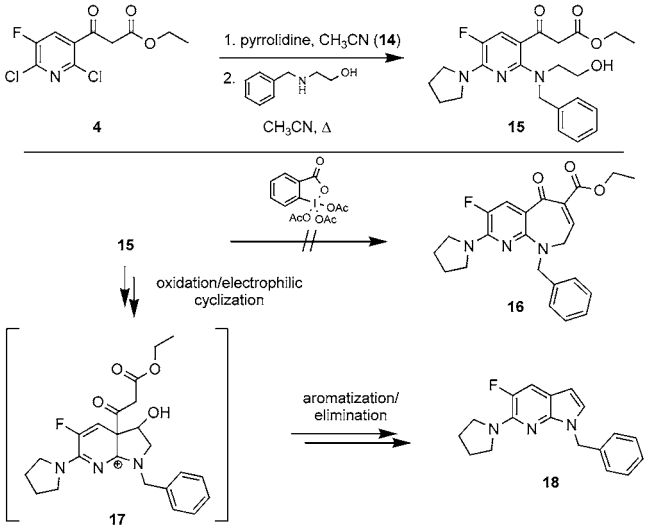
(11) For references to a similar stable ylide, see: Beautement, K.; Clough, J. M. *Tetrahedron Lett.* **1984**, *25*, 3025−3028.
(12) Trost, B. M.; Melvin, L. S. *Sulfur Ylides: Emerging Synthetic Intermediates*; Academic Press: New York, 1975.

Scheme 4



Scheme 5



the tetrahedral intermediate breaks down with concomitant ring-opening to provide a cyclopropyl ester enolate that, after proton transfer, affords sulfur ylide **13**. It is possible that intermediate **12** eliminates DMSO to form an epoxide as expected, but in the presence of DMSO solvent, the elimination is reversible. In this case, irreversible formation of **13** drives the reaction in the observed direction. Intermediate **13** is a very electrophilic "push−pull" cyclopropane[13] that reacts accordingly via ring-opening/proton transfer to afford the observed product **11**. In this sequence, an apparently straightforward route to a seven-membered ring is circumvented by a highly unusual, counterintuitive reaction pathway. We did not anticipate that 1,2-addition of a sulfur ylide to the keto group of **9** would compete with 1,4-addition to naphthyridone **8**. Even more remarkable is the elimination of a cyclopropane ester enolate from intermediate **12** over the well-precedented epoxidation pathway.

A second synthetic approach to a pyrido[2,3-*b*]azepinone **16** (Scheme 5) was proposed via one-pot oxidation/intramolecular aldol reaction sequence starting with alcohol **15**. *β*-Ketoester **4** reacts with 1 equiv of pyrrolidine very selectively para to the ketoester functionality, providing the monosubstituted derivative (**14**) in high yield. Subsequent displacement of the second chloride was accomplished with *N*-benzyl ethanolamine in refluxing acetonitrile to provide the desired alcohol. Treatment of **15** with the Dess−Martin periodinane was then expected to result in oxidation of the primary alcohol to an aldehyde followed by spontaneous intramolecular aldol cyclization.[14] Whether or not the aldol product would eliminate to provide the desired α,*β*-unsaturated system was difficult to predict; however, under the acidic reaction conditions we considered elimination likely. In fact, when **15** was treated with 1 equiv of the periodinane, a single product formed that was unstable to prolonged exposure to silica gel and to air and was not spectroscopically consistent with the desired product or with any of the obvious intermediates in its predicted formation. Careful analysis of the ^{1}H NMR spectrum combined with the observed molecular weight of the product as determined by mass spectrometry resulted in identification of azaindole **18** as the sole product of the reaction. This identification was confirmed by two-dimensional NMR analysis.

Scheme 5 illustrates a proposed mechanism for azaindole formation. Apparently, oxidation of the primary alcohol proceeds as expected. However, the resultant aldehyde reacts not with the enol of the *β*-ketoester but instead undergoes a Friedel−Crafts-type cyclization to afford intermediate **17**. Rearomatization via intermolecular transfer of malonate to a reaction byproduct affords a 3-hydroxy-azaindoline that leads to **18** upon dehydration. While electrophilic aromatic substitution would not generally be expected to compete with aldol cyclization, in retrospect the nature of the substrate in this situation may especially favor Friedel−Crafts cyclization. To begin with, five-membered ring formation is kinetically much faster than seven-membered ring formation. Normally, one would not expect this kinetic advantage to overcome the thermodynamic barrier of breaking aromaticity necessary for Friedel−Crafts-type cyclization. However, proposed cationic intermediate **17** is exceptionally resonance-stabilized by three nitrogen atoms, and this thermodynamic stabilization combined with the kinetic advantage of five-membered ring formation could explain the outcome of the reaction. Additionally, loss of carbon dioxide through decomposition of ethyl malonate may provide an added driving force.

Scheme 6 illustrates the successful preparation of a pyridoazepinone ethyl ester. Pyrido[4,3-*c*]azepinone **28** was isolated as a minor byproduct in the synthesis of 5-chloromethylnaphthyridone **27**. Cyclization of the vinylogous imide intermediate formed by reaction of **26** with 2,4-dimethoxybenzylamine proceeds via competing six- and seven-membered ring-forming pathways favoring **27** by a

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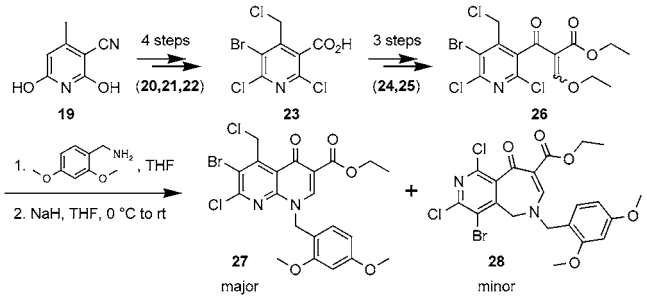
(14) Fleming, F. F.; Huang, A.; Sharief, V. A.; Pu, Y. *J. Org. Chem.* **1999**, *64*, 2830−2834.

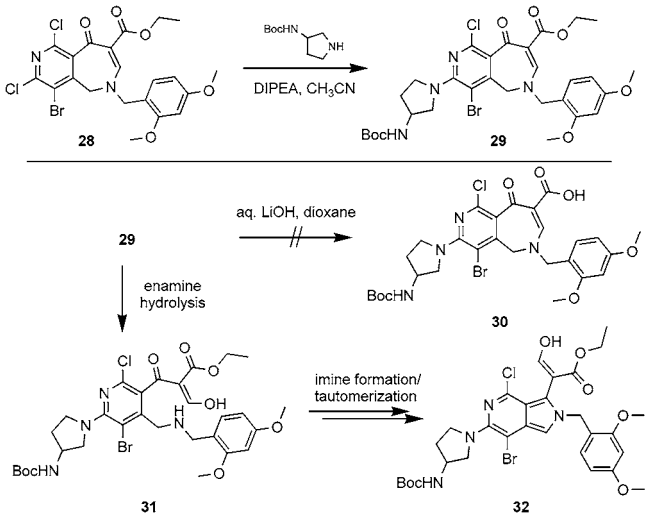
Scheme 6



ratio of approximately 9:1 as determined by LC-MS. Although the synthetic route to **28** was not optimal, this represented the first instance in which a seven-membered ring analogue of lead compound **2** was isolated. Addition of Boc-protected 3-aminopyrrolidine to **28** afforded compound **29** (Scheme 7) with only trace amounts of the regioisomeric addition product. Preparation of the first compound of generic structure **3** required only saponification and acid-catalyzed deprotection of **29**. Ethyl ester **29** was subjected to standard saponification conditions (aqueous lithium hydroxide in dioxane), affording a single product. However, ^{1}H NMR showed the presence of an ethyl group in the product and mass spectrometry indicated identical molecular weights for starting material and product. Multidimensional NMR analysis of the isolated material led to identification of azaisoindole **32** as the sole reaction product. As illustrated in Scheme 7, hydroxide apparently undergoes 1,4-addition to the vinylogous imide instead of the expected attack on the ester carbonyl, resulting in overall hydrolysis of the enamine functionality. Amine intermediate **31** then undergoes intramolecular imine formation and tautomerization to provide the observed product **32**.

In summary, we have described the attempted synthesis of compounds of generic structure **3** using three standard synthetic methodologies. In each case, unusual reactions

Scheme 7



occurred providing unexpected rearrangement products. The reactions described above exemplify the difficulties often encountered in seven-membered ring synthesis. Although not typical, these examples demonstrate seemingly extraordinary and circuitous reaction pathways taken to avoid seven-membered ring formation.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds and complete ^{1}H and ^{13}C NMR assignments and two-dimensional spectra for compounds **11**, **14**, **18**, **29**, and **32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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