STUDIES ON THE TOTAL SYNTHESIS OF STREPTOGRAMIN ANTI-BIOTICS:
GRISEOVIRIDIN AND MADUMYCIN (A-2315A)

A. I. Meyers*, Jon Lawson, Richard A. Amos, Donald G. Walker and
Ronald F. Spohn
Department of Chemistry, Colorado State University,
Fort Collins, Colorado 80523

Abstract - A convergent synthesis of the macrocyclic anti-biotics
Madumycin II (A-2315A) and Griseoviridin is in progress. All of the
stereochemical centers and functional groups have been incorporated with
the former obtained as pure enantiomers. The routes, pitfalls, and
strategy leading to the main synthetic fragments are disclosed. All that
remains to complete the synthesis is the joining together of the two major
units (5, 6, and 7).

The streptogramin family of anti-biotics are broad spectrum acting and are comprised of
at least two active compounds; one being mainly peptidic in nature, the other consisting of
23-membered oxazole-containing ring, 1 or 2 (1). These are termed "Group A" while the
peptidic components 3, 4, are called "Group B." This class of anti-biotics was initially
discovered (2) in the culture of streptomyces graminofaciens in 1953 and extensive
structural elucidation studies have been performed since that time (3). Recently the struc-
ture of griseoviridin 2 was confirmed by x-ray studies (4). Since there are large

GROUP "A" FOR STREPTOGRAMINS

1 Madumycin II
   A-2315A

2 Griseoviridin

structural similarities between 1 and 2, it was felt that a synthetic effort, properly
planned, could be undertaken which will provide both macrocycles within the framework of the
projected strategy.
The retrosynthetic strategy to reach 1 is envisioned to arise out of the two fragments 5 and 6, both to be prepared in enantiomerically pure form with the absolute configurations as shown. Similarly, griseoviridin 2 is seen to be derived from the two fragments 7 and 8.

It is noteworthy that the oxazole moiety 5 and 8 are identical except for the methyl group at the diene position and slight modification in synthesis should provide both which could be used for madumycin and griseoviridin. For a synthetic approach to the 9-membered ring 7, present in griseoviridin, dissection leads one to propose the unsaturated ester 9 and a protected cysteine 10, which may be coupled to the desired product. The final product 7, however, contains a chiral center adjacent to the lactone linkage of the R-configuration whereas the unsaturated ester 9 is prepared containing an S-center at the corresponding position. Thus, an inversion of configuration will need to be accomplished in reaching the 9-membered ring.

The synthetic approach to S(+)−9 was carried out as shown in Scheme 1. Yeast reduction was found to be an excellent route to the (S)-hydroxyester (5) followed by protection of the hydroxyl group and reduction to the corresponding aldehyde. Oxidation via the Swern technique followed by Wadsworth-Horner-Emmons olefination gave enantiomerically pure unsaturated ester.

The cysteine derivative 10 was prepared smoothly by a four-step sequence shown in Scheme 2. Originating with D-cystine and protection of the carboxyl group as the t-butyl ester followed by benzylation, reduction, and chlorination with N-chlorosuccinimide, gave the requisite cysteine derivative in good overall yield. The latter was used immediately to
react with the unsaturated ester affording a 56% yield of sulfonyl chlorides as a 4:1 mixture. This mixture was transformed into a single regioisomer after heating at reflux in acetonitrile with epoxybutane as a proton scavenger. Thus, only a single, desired stereo-isomer was obtained (Scheme 3).

The sulfonyl chloride was subjected to elimination to the α-thio acryclic acid using triethyl amine in dichloromethane at 25° and was isolated as an E,Z mixture which was homogenized to a pure Z-isomer by reversible addition of phenylthiyl radical (PhSH 10%, AIBN, 2%, Scheme 4). Hydrolysis of the t-butyl and methoxymethyl groups were performed using HCl-DME (65°, 6h) thus setting the stage for the 9-membered ring closure. This was accomplished using triphenyl phosphine-diethylazodicarboxylate in benzene solvent at room temperature. The resulting lactone indicated that the ring closure had occurred with inversion to provide the R-configuration (Scheme 4) (6). Thus, the enantiomerically pure thiolactone 7 was reached without any separation of diastereomers or enantiomers.

For the unsaturated ester 6 required to reach madumycin 1, the presence of two chiral centers required an approach different than that for griseoviridin 2. The asymmetric aldol condensation described by Evans (7) provided the methodology required (Scheme 5). Thus the 2-methyl-3-hydroxy aldehyde, liberated in situ was homologated to the unsaturated ester which was virtually enantiomerically pure (~99.5%).

Attention was now turned to the oxazole portion of the streptogramins, 5 and 8, and its acquisition was evaluated via the retrosynthetic sequence shown (Scheme 6). The sequence called for stepwise disconnection of the C11-C12 bond, then of the C15-C16 bond. This would allow homologation, with reasonably accessible synthons to reach the target 5 or 8.
The first goal was to prepare the requisite 2-methyl-5-carboxyoxazole and this was done using the Cornforth synthesis (8) (Scheme 7). Next, according to retrosynthetic Scheme 6, the carbanion derived from the 2-methyl group was to be formed. However, all attempts to lithiate the 2-methyl group failed giving only metalation at the 5-position. It was found that both kinetic and thermodynamic conditions gave only metalation at the 5-position (9) (Scheme 8) despite reports in the literature that 2-methyl oxazoles may be metalated as desired. The presence of the 4-carboxy substituent undoubtedly perturbs the electronics and directs metalation adjacent to itself. The anomalous behavior of the 2-methyl-5-carboxyoxazole towards metalation forced us to revise our plan to reach the elaborated oxazoles 5 and 8 necessary for the macrolide synthesis. The approach which ultimately bore fruit was to return to the Cornforth oxazole synthesis and metalate the methyl group while
still in the open-chain form prior to cyclization to the oxazole. This tactic was indeed successful (9) and allowed the elaboration of the requisite oxazole by many different electrophiles (Scheme 9, E = alkyl halides, aldehydes, ketones). Thus it can be reported that the oxazole anion $\text{11}$ finds as its synthetic equivalent, the carbanion, $\text{12}$.

With the oxazole elaboration in hand, the next task was to prepare the appropriate chiral aldehyde shown in Scheme 6. This was prepared from L-malic Acid through the sequence depicted in Scheme 10 (10). It was found, however, that the acetonide alcohol was comprised of a 9:1 mixture of 5- and 6-membered acetonides and the latter was removed by recrystallization of their respective p-nitrobenzoates. Reaction of the enantiomerically pure aldehyde with the imidate after LDA treatment to generate the carbanion, gave the adduct which was cyclized smoothly using ZnCl$_2$ as the Lewis Acid. The product (Scheme 11) was a 1:1 mixture of diastereomeric alcohols which were not easily separated. The retrosynthetic scheme 6 required that the two oxygen functions be syn at C15 and C13. It was indeed fortunate to find that in the process of transposing the acetonide from a sec-alcohol to a primary alcohol, necessary to continue elaboration (Scheme 6), a diastereoselective resolution occurred providing pure primary alcohol and recovered secondary alcohol. Thus upon treatment of the mixture of alcohols (Scheme 12) with the acetal of mesityl aldehyde, enantiomerically pure acetal was formed containing the proper stereochemistry. Furthermore, the epimeric alcohol, containing the opposite stereochemistry was recovered and could be recycled to the desired acetal, after oxidation to the ketone followed by reduction. Structural proof for the proper enantiomer, wherein both oxygen substituents were syn was readily
achieved by pmr studies. The stereochemistry of the primary alcohol could not be properly elucidated, however, the corresponding aldehyde (Scheme 13) readily responded to pmr analysis and showed that the three substituents were all equatorial. Since the product was prepared from (S)-malic acid (Scheme 10) this fixed the stereochemistry and configuration of the other center as (R) - exactly what was required for the natural anti-biotics 1 and 2.

The synthetic route to 5 and 8 continued by homologation of the acetal aldehyde to the unsaturated aldehyde using the imine phosphonate as a modified Horner-Wadsworth-Emmons reagent (11) (Scheme 14). The ene-al was formed, as expected, as the pure trans product. This was not the case, however, when the propylimine phosphonate was employed, to provide the methyl analog necessary to reach 5 (R=Me). Due to the poor elimination of the phosphonic ester, the yield of olefin never exceeded 20%. The use of the trimethylsilyl imine, however, proceeded smoothly to furnish the unsaturated aldehyde (Scheme 15) albeit as a 3:1 mixture of E,Z isomers. Heating with pyridine hydrochloride converted this mixture to a 15:1 ratio of the correct E-isomer.
Elaboration of the ene-als to the diene amine was accomplished via a novel route which gave pure E,E-diene (Scheme 16) (12). The use of vinyl tri(n-butyl) phosphonium bromide, sodio-phthalimide, and the aldehyde gave good yields of pure E-allyl amines. When vinyl triphenylphosphonium bromide was employed, the products formed mixtures of E and Z allyl amines. A number of examples demonstrated the generality of this technique.

Thus, the unsaturated aldehyde was transformed into the protected diene-amine which was enantiomerically pure and now ready to couple to the other fragments to reach griseoviridin and madumycin (Scheme 17).
At this writing, no attempts have been made to converge the synthesized fragments into the final macrocyclic targets since efforts are currently focused on obtaining sufficient material to carry out the cyclizations. Nevertheless, we have shown that the key fragments for the streptogramin "Group A" components are accessible via synthesis in enantiomerically pure form. Further work is in progress.

Acknowledgement - This work was supported by the National Institutes of Health.

REFERENCES
t Chemother., 3, 1283 (1953).