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A Convergent Synthetic Approach to the Nucleoside-Type Liposidomycin Antibiotics

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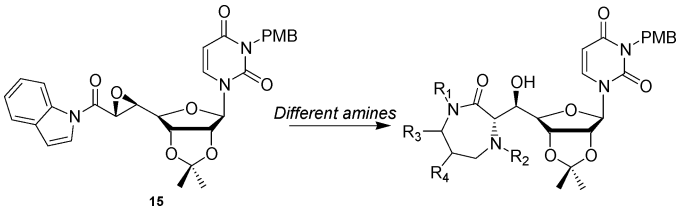
ABSTRACT



A synthetic approach toward the liposidomycins, a family of complex nucleoside-type antibiotics, is reported based on the synthesis of epoxy-amides derived from the reaction of sulfur ylides with the uridyl aldehyde derivative 6. To this end, the epoxy-amide derivative of indoline 14 was stereoselectively prepared and, after treatment with DDQ, transformed into the corresponding *N*-indole epoxyamide 15. The indole 15 provides ready access to a variety of structures related to the diazepanone core present in the liposidomycins by reaction with a variety of amines.

The growing emergence of drug resistance by specific bacterial strains to current antibiotics is becoming a problem of profound importance around the world, and has prompted the need for new antibiotics with novel mechanisms of action.[1] Of special concern have been the appearance of *Staphylococcus aureus* bacterial strains resistant to antibiotics such as the β-lactams and vancomycin, both inhibitors of the biosynthesis of the peptidoglycan cell wall in bacteria. In the meantime, new antibiotics, either from synthetic or natural sources, are continuously emerging.[2] Among them, the liposidomycins, isolated from *Streptomyces griseosporeus*,[3] constitute a new class of complex nucleoside-type antibiotics, which are structurally and biologically related to other uridyl peptide antibiotics such as the muraymycins, tunicamycins, mureidomycins, pacidamycins, napsamycins, and FR-900493.[4] Particularly, the liposidomycins comprise at least 12 active members whose major components are liposidomycin A (**1**), B (**2**), and C (**3**) (Figure 1).[5]

The antibiotic activity exhibited by the liposidomycins is due to their inhibition of the phospho-*N*-acetyl-muramoyl-pentapeptide-transferase (translocase I) enzyme, which is responsible for the first step of the lipid cycle involved in the biosynthesis of peptidoglycan in bacteria.[6] Other types of related antibiotics, such as the tunicamycins and moenomycin, display a similar mechanism of action; however, the liposidomycins have shown comparatively higher potency

† Deceased.

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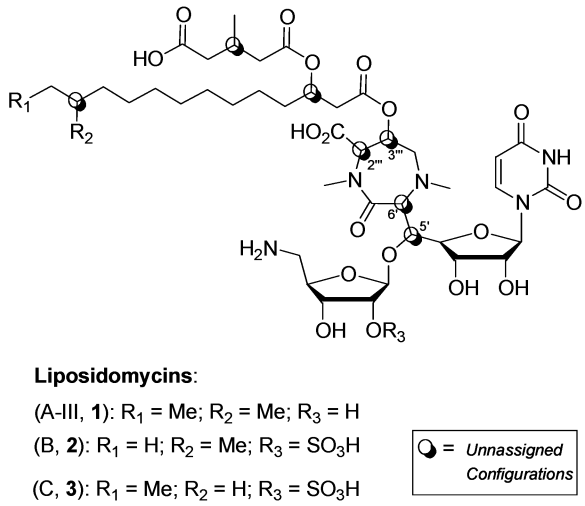
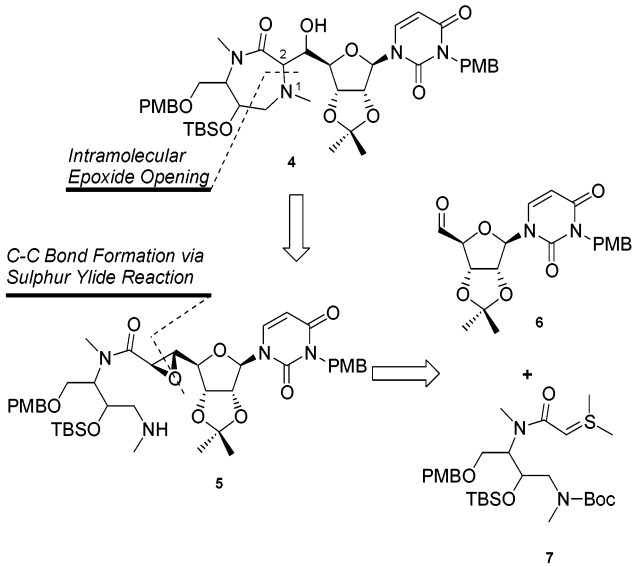


Figure 1. Molecular structures of liposidomycins.

Scheme 1. Retrosynthetic Analysis



in vitro with an ID_{50} of 0.03 μg/mL.[7] In addition to these prominent biological properties, the liposidomycins offer attractive structural features, characterized by a 3,6,7-trisubstituted-1,4-dimethyldiazepan-2-one system, which is linked to a uridine nucleoside moiety through a carbon bridge. Located at this carbon, we find a hydroxyl group, which is linked to a 5-deoxy-5-amino-ribofuranosyl residue by a glycosidic bond.[8] Despite the liposidomicins general structure having been previously elucidated, the absolute configurations of the indicated chiral centers in Figure 1, located in the diazepanone ring and in the *exo*-OH domains, remain unassigned.[9] Nevertheless, recent synthetic studies conducted by Knapp et al. have suggested that the configurations at C-5′ and C-6′ are (*S*).[10] Similarly, configurations at C-2‴ and C-3‴ have been tentatively established as 2‴*S* and 3‴*S* through further synthetic studies.[11] All these structural features, in conjunction with the biological properties of liposidomycins, compelled us to embark on a program aimed at the total synthesis of these natural nucleosides. In the present paper, we wish to report the first synthetic studies directed toward the synthesis of the diazepanone core structure of the liposidomycins, based on the chemistry of sulfur ylides, which is well suited to the preparation of not only the natural antibiotics but also of potentially bioactive analogues.[12]

Scheme 1 outlines briefly the retrosynthetic analysis of the liposidomycin core, using sulfur ylides to construct the diazepanone ring. According to this, the liposidomycins would initially be disconnected at the glycosydic site to obtain the corresponding donor derived from 5-deoxy-5-amino-D-ribose and the acceptor compound **4**. The second major retrosynthetic disconnection is at the N1−C2 bond of compound **4** to generate epoxyamide **5**, which would give rise to the corresponding diazepanone derivative **4** via an intramolecular 7-*exo-tet* cyclization reaction. Finally, epoxyamide **5** could be prepared from the corresponding aldehyde **6** by reaction with the sulfur ylide **7**, which would contain the suitable functionality present in the diazepanone ring.

Our initial synthetic studies were focused on a model compound to prove the efficiency of the designed strategy. Therefore, we commenced with the synthesis of the sulfonium salt **9** by conventional methods.[13] The reaction of aldehyde **6**[14] with the corresponding sulfur ylide derived from **9** was performed by two different procedures: (a) the one-phase method, in which the ylide was previously prepared, and (b) the two-phase method,[15] in which the ylide was generated in situ by treatment of **9** with an aqueous sodium hydroxide solution. In both cases, the epoxide **10** was obtained in 67% yield and high diastereoselectivity, approximately 90:10 according to the ^{1}H NMR spectra. The configurations for the new two chiral centers of the oxirane

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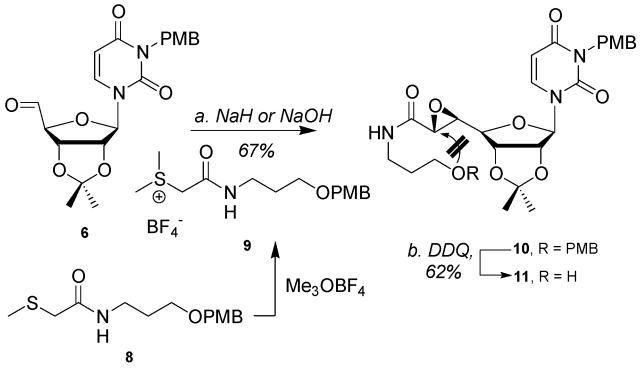
Scheme 2. First Synthetic Approach



ring were established based on synthetic and theoretical studies.[16] Unfortunately, this straightforward strategy presented two important drawbacks. One was the lack of reliability upon scale-up of the reaction sequence. In fact, the yields dropped considerably when the reactions were carried out on multigram scale. Also, attempts to produce the diazepanone ring by intramolecular cyclization from alcohol **11** to give the corresponding cyclic ether or by treatment of **11** with amines under Mitsunobu conditions to give the corresponding cyclic amines were unsuccessful (Scheme 2).

In light of these discouraging results, we decided to modify the initial synthetic strategy by creating a new more convergent route. Accordingly, we decided to use the indoline epoxy-amide derivative **14** as a valuable key intermediate in the synthesis due to its facile oxidation[17] to the corresponding indole derivative **15**, which in turn can react with nucleophiles,[18] offering an excellent opportunity for the construction of the diazepanone ring via reaction with bidentate nucleophiles.

Thus, the reaction of **6** with the sulfonium salt **13**, prepared from sulfide **12** by treatment with the Meerwein salt, afforded epoxy-amide **14** in high yield and stereoselectivity. Furthermore, this reaction was achieved in multigram scale with no appreciable loss in yield. The oxidation of the indoline amide **14** with DDQ furnished the corresponding indole derivative **15** in 76% yield. To our delight, when indole **15** was treated with *N*,*N*′-dimethyl-1,3-propanediamine under mild conditions the corresponding diazepanone derivative **16** was smoothly obtained in good yield (Scheme 3).

(16) Chemically, Sharpless epoxidation of the allylic alcohol obtained by reaction of methyl 2,3-*O*-isopropylidene-*β*-D-*ribo*-pentonodialdo-1,4-furanoside with $Ph_3P{=}CHCO_2Me$, followed by reduction with DIBAL-H, with (+)-DET and (−)-DET, respectively, yielded the corresponding epoxides, which were compared with the one obtained from the epoxy alcohol obtained via the sulfur ylides. This result allowed one to conclude that the epoxide obtained via the sulfur ylides possessed a 2*R*,3*S* configuration at the oxirane ring. In addition, theoretical calculations executed on the starting aldehyde **6** revealed a conformational preference in which the *re* face of the aldehyde appeared to be the more accessible for the ylide attack, which is in agreement with the configuration found for the above epoxy amide obtained from methyl 2,3-*O*-isopropylidene-*β*-D-*ribo*-pentonodialdo-1,4-furanoside (see Supporting Information for details).

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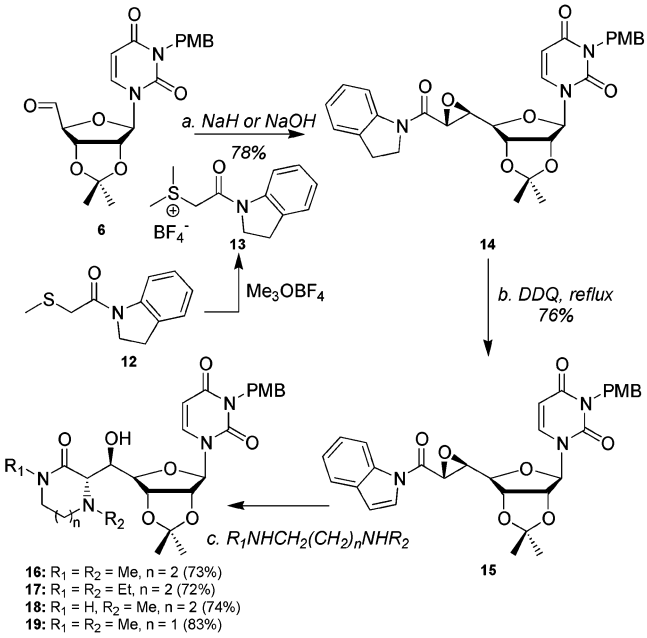
Scheme 3. Synthesis of the Diazepanone Ring



This encouraging result prompted us to extend the reaction to other nucleophiles to provide access to intermediates for the eventual incorporation into a synthetic scheme capable of reaching the target natural diazepanone moiety contained in the liposidomycins. Thus, simple diamines were reacted with indole **15**, to obtain cyclic compounds **17**−**19**. On the basis of these studies, it was concluded that an increase in the steric hindrance surrounding the nucleophilic nitrogens necessitated the use of forcing reaction conditions, with respect of the case of *N*,*N*′-dimethyl-1,3-propanediamine. It is interesting to note that for asymmetric diamines, the corresponding cyclic compound, **18**, was obtained in complete regioselectivity. On the other hand, the six-membered analogue of the diazepanone derivative was achieved in good yield when **15** was reacted with *N*,*N*′-dimethyl-1,2-ethanediamine.

The extension of these studies to more complex amines, to construct the diazepanone ring contained in the natural liposidomycins, was similarly screened. Toward such a goal, a set of complex secondary amines **20**−**23**[19,20] were prepared and reacted with the epoxy indole **15** to obtain epoxy-amides **24**−**27**, respectively. Thus, it was observed that the reaction showed a high sensitivity toward steric effects, as was demonstrated for bulky amines in which no reaction or decomposition products were formed (see Supporting Information for details). With respect to the electron-withdrawing effects introduced in amines with an amide group (amine **23**), the reaction does not seem to be affected, given the reasonable yield obtained for the desired product, amide **27** (68%).

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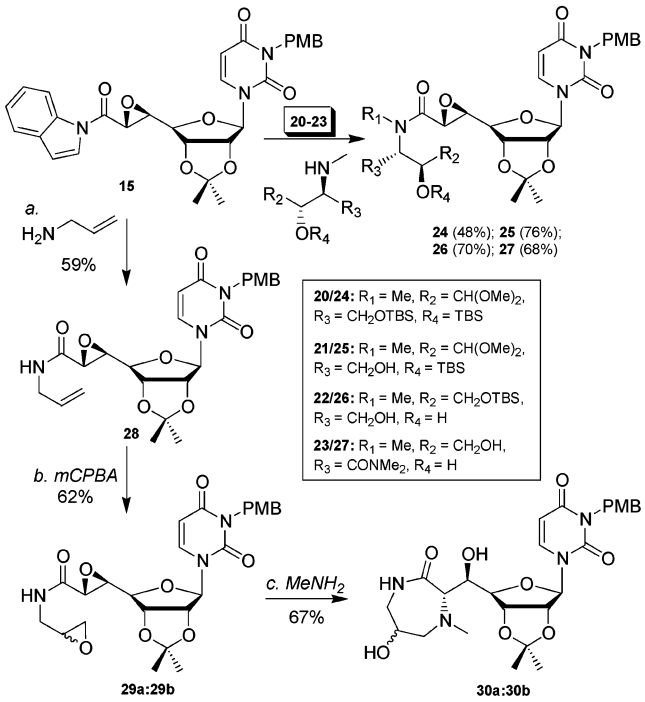
Scheme 4. Construction of Functionalized Diazepanone Rings



It is worthy to mention that compounds **24**−**27** possess suitable functionality amenable to the introduction of the required groups to complete the diazepanone ring. Initial attempts to accomplish the synthesis of the diazepanone system contained in the natural product were performed beginning from the acyclic precursors **24**−**27**. However, none of the numerous attempted methods proved to be effective in the construction of such a diazepanone ring.

According to Scheme 4, a second possible strategy toward a functionalized diazepanone ring was pursued. In this new route, the allyl amide precursor **28**, prepared from indole **15** by reaction with allylamine, was subjected to an epoxidation reaction with *m*-CPBA to obtain epoxides **29a/29b** in a 1:1 mixture of inseparable stereisomers in a reasonable yield. The mixture of diepoxides **29** was then treated with an aqueous solution of methylamine to obtain the corresponding cyclic derivatives **30a/30b** by a double oxirane opening process, probably initiated by an intermolecular opening reaction of methylamine with the terminal epoxide, followed by a second intramolecular opening of the epoxy-amide by the resulting secondary amine in a regioselective manner.

In conclusion, we report a new approach to the liposidomycins aimed at delivering not only the natural compounds but also analogues thereof. Initial results have proved the feasibility and efficiency of our synthetic approach toward the diazepanone ring system present in this class of complex nucleoside antibiotics. Our future synthetic endeavors include the construction of the real system contained in liposidomycins based on the reported strategy, followed by the linkage of the 5-deoxy-5-aminoribose unit via a glycosylation reaction. Both synthetic transformations are currently being investigated.

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Supporting Information Available: Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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