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The First Total Synthesis of a Member of the Manumycin Family of Antibiotics: Alisamycin

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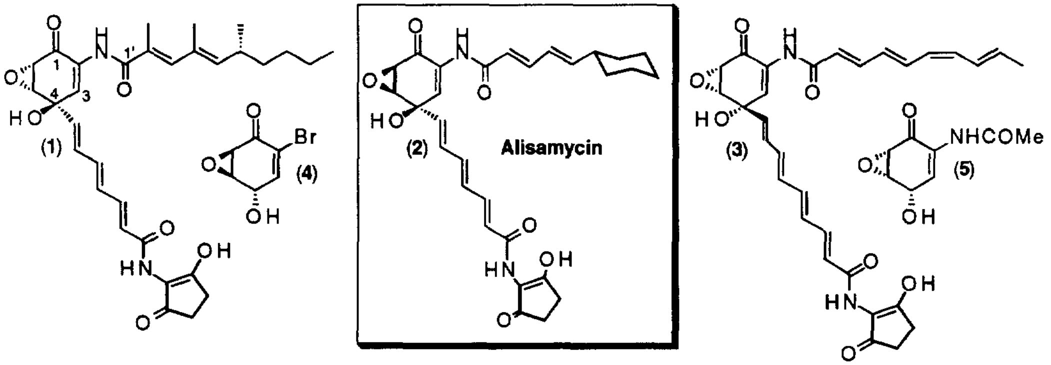
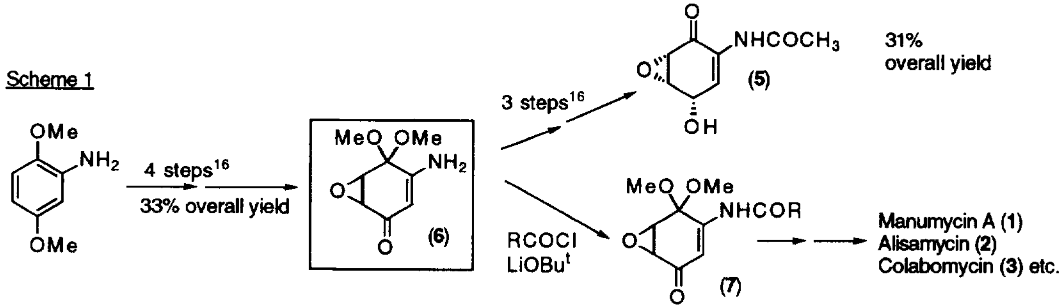
Abstract: The development of a general synthetic route to the manumycin family of antibiotics is described and exemplified by the first total synthesis of alisamycin in racemic form. Copyright © 1996 Elsevier Science Ltd

The isolation and purification of the antibiotic manumycin A (**1**) was first reported by Buzzetti *et al.* in 1963.[1] Further studies by Schröder and Zeeck confirmed the presence of the novel amino-epoxycyclohexenone structure[2] and subsequently a family of structurally-related natural products have been isolated from *Streptomyces* species. These include asukamycin,[3] U-62162,[4] U-56407,[5] nisamycin,[6] alisamycin (**2**),[7-9] colabomycin (**3**)[10] and manumycins B-G.[11] These compounds display a range of biological properties in addition to their antibacterial action including antifungal and enzyme inhibitory activity. The selective inhibition of *ras* farnesyltransferase is particularly exciting in view of its potential in cancer chemotherapy.[12] Alisamycin (**2**), the subject of this *Letter*, is a potent antibiotic (MIC 1.6 mg/ml against *Staphylococcus aureus*) which also possesses weak antifungal and cytotoxic activity.[7] Its structure was established by Chatterjee *et al.*[8] using a combination of mass spectrometry, IR, UV and NMR spectroscopy, and the absolute configuration was revealed as 4*R*, 5*S*, 6*R* using the exciton chirality method together with CD studies of degradation products.[9]



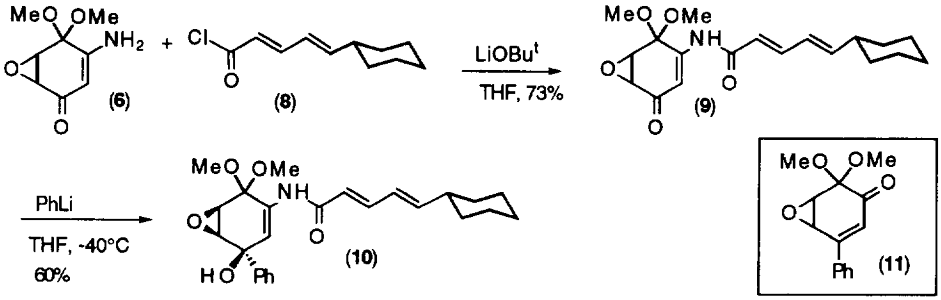
Biosynthetic studies have been carried out in this area,[3b,13] but to our knowledge, none of the manumycin family have succumbed to total synthesis. However, we, and others, have developed synthetic routes to the related compounds bromoxone (**4**),[14] and LL-C10037α (**5**),[15,16] which lack the polyene side chains. Our initial aim was to utilise the key epoxide (**7**),[16] employed in our synthesis of LLC10037α, as the cornerstone of a general route to the manumycin family of antibiotics (Scheme 1). This *Letter* describes the successful implementation of this strategy resulting in the first synthesis of racemic alisamycin (**2**).

Scheme 1



In earlier studies, we have shown that amine (**6**) could be acylated with a range of acid chlorides using lithium *tert*-butoxide in THF to give amides (**7**).[16] In principle, organometallic addition to C-4 (manumycin numbering) of (**7**) would provide a direct entry into the natural products but this approach appeared to be fraught with potential problems, particularly concerning the regio and stereoselectivity of the addition reaction. We were especially concerned about the likely low reactivity of the C-4 carbonyl group, which is a vinylogous imide, and which would be further deactivated by deprotonation of the amide substituent. Model studies were therefore carried out as shown in Scheme 2.

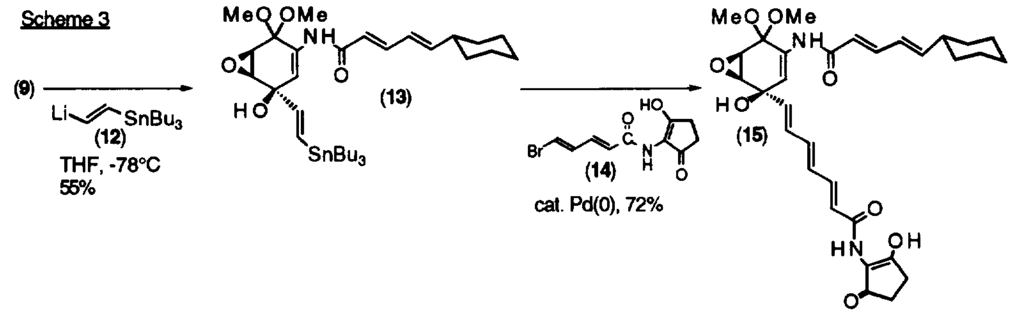
Scheme 2



Thus, acylation of amine (**6**) with acid chloride (**8**) gave amide (**9**).[16] Remarkably, reaction of amide (**9**) with phenyllithium in THF, gave a good yield of adduct (**10**)[17] as a single diastereoisomer and no other byproducts were observed. The *syn*-stereochemistry of compound (**10**) was assigned on steric grounds and by analogy with related reduction reactions.[16]

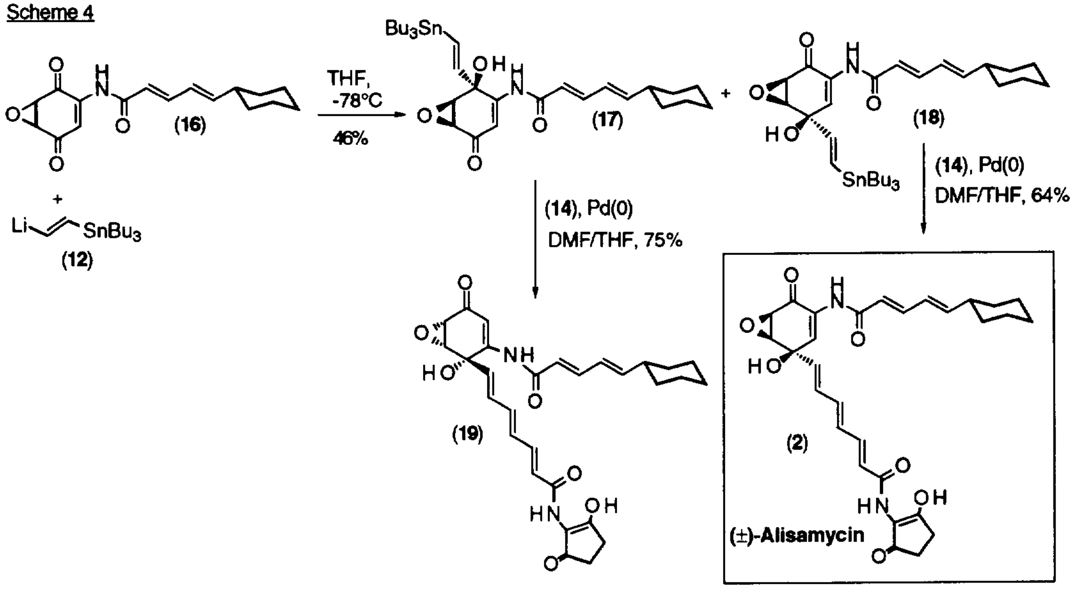
With this success we proceeded to devise a method for the introduction of the Southern side chain. This was achieved as shown in Scheme 3. Treatment of (**9**) with *E*-2-tributylstannylethenyllithium (**12**), generated from the corresponding bis-stannane,[18] introduced an embryonic C-4 side chain giving (**13**) in 55% yield (79% based on recovered starting material). Stille-type coupling[19] of vinyltin reagent (**13**) with vinyl bromide (**14**)[20] proceeded efficiently using $PdCl_2(PPh_3)_2$/DIBAL-H in DMF/THF at room temperature to give (**15**) in 72% yield. All that was required to complete the synthesis of alisamycin was to deprotect the acetal functionality of (**15**). Unfortunately, using a number of procedures,[21] either little reaction occurred or, under more forcing conditions, decomposition was observed. Similar problems were encountered when attempting to deprotect the phenyl analogue (**10**): the only product that could be isolated was ketone (**11**) resulting from enamide hydrolysis (with lithium perchlorate in MeCN[21b] (**11**) was formed in almost quantitative yield).

Scheme 3



We therefore turned to a more direct (and even more speculative) synthetic approach (Scheme 4). In this procedure, organometallic addition was carried out using the unprotected "dione" (**16**).[16] Treatment with *E*-2-tributylstannylethenyllithium (**12**) gave two major products (**17**) and (**18**) (46%, 1:1.3), resulting from attack at each of the ring carbonyl groups. The stereochemical assignments were again made on the basis of steric considerations and, in the case of (**18**), this was confirmed by conversion into alisamycin.

Scheme 4



Adducts (**17**) and (**18**) were separated by chromatography and individually coupled to vinyl bromide (**14**) using $PdCl_2(PPh_3)_2$/DIBAL-H as before. This produced racemic alisamycin (**2**) in 64% yield, the structure being confirmed by comparison of IR, MS, ^1H- and ^{13}C-NMR data with authentic spectra.[22] The NMR data for the epoxycyclohexenone nucleus was particularly informative [Found δ_H: H-3, 7.41 (d, 2.5 Hz), H-5, 3.72 (dd, 3.5, 2.5 Hz), H-6, 3.67 (d, 3.5 Hz); δ_C: C-3, 126.0, C-5, 57.4, C-6, 53.0. Authentic[8] δ_H: H-3, 7.40 (d, 2.6 Hz), H-5, 3.70 (dd, 3.6, 2.6 Hz), H-6, 3.65 (d, 3.6 Hz); δ_C: C-3, 126.3, C-5, 57.4, C-6, 52.9]. In addition, the novel regioisomer (**19**) of alisamycin was prepared by homologation of (**17**) in 75% yield.

The methodology for Southern side chain introduction and elaboration is applicable to all of the manumycin family. We are currently optimising the synthetic route to the nucleus in enantiomerically pure form and will then apply this methodology to other members of this group of natural products.

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