The first synthesis of the *Streptomyces* derived antibiotic U-62162

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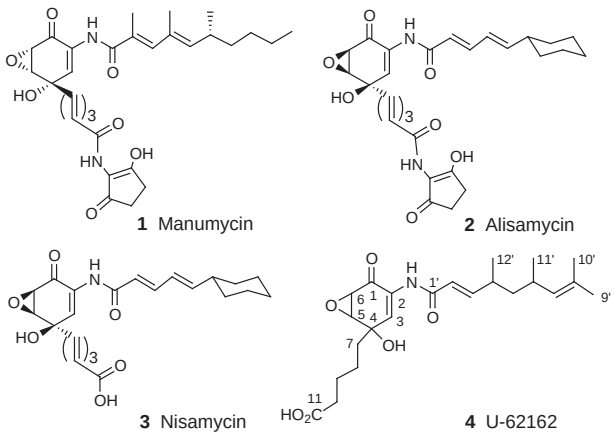
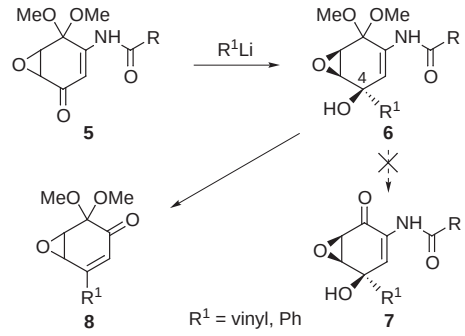
U-62162, a member of the manumycin family of antibiotics, has been prepared as a mixture of diastereoisomers and shown to contain a *syn*-hydroxy epoxide nucleus and a 1,3-*syn*-disposed dimethyl unit in the upper side chain; the cornerstone of the synthetic route utilises organometallic addition to a monoprotected quinone epoxide—the first time this approach has been successfully employed to prepare a manumycin antibiotic.

The manumycin group of natural products, which includes manumycin A **1**[1] and alisamycin **2**,[2] have attracted a great deal of attention due to their antibiotic, antitumour and enzyme inhibitory properties.[1–4] With two exceptions, all members of this family have a 2-amino-3-hydroxycyclopentenone polyenamide lower side chain. The exceptions are nisamycin **3**,[3] which is the carboxylic acid corresponding to alisamycin, and U-62162 **4**.[4] U-62162, an antibiotic isolated from *Streptomyces verdensis* (UC-8157), was reported by researchers from the Upjohn Company in 1982, and has a unique five-carbon saturated lower side chain terminating in a carboxylic acid. Extensive NMR experiments were carried out to assign structure **4**, but the only stereochemical information revealed was the *E*-orientation of the alkene in the top side chain.



We recently reported[5] the first total synthesis of alisamycin **2** and nisamycin **3**. The initial synthetic approach investigated for these compounds involved organometallic elaboration of the monoprotected quinone epoxide **5**, as summarised in Scheme 1.



Scheme 1

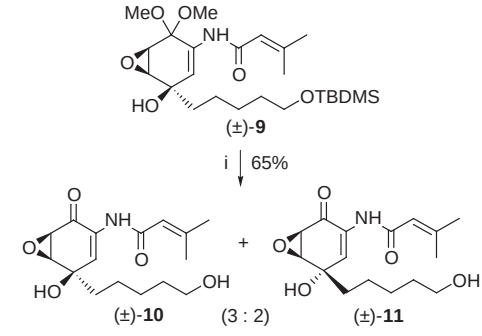
This approach was ultimately unsuccessful because of the lability of the C-4 hydroxy group, which is tertiary and doubly allylic in adduct **6** when R^1 is an unsaturated lower side chain; attempted hydrolysis of the acetal moiety to give **7** resulted, under a wide range of conditions, in the formation of degradation products, one of which was tentatively identified as enone **8**. A successful alternative approach to alisamycin and nisamycin was eventually designed,[5] but we were intrigued by the possibility that the original methodology, shown in Scheme 1, might be applicable to the synthesis of related compounds in which the hydroxy group is less labile, *i.e.* where R^1 is not alkenyl. Here we describe the successful implementation of this approach for the synthesis of U-62162.‡

Model studies (Scheme 2) were carried out to assess the viability of this approach. Compound **9**, prepared using similar procedures to those described later, was treated with TsOH in aqueous acetone, giving a reasonable yield of the required alcohols **10** and **11**. The fact that the two epimers were formed during the reaction indicates that some carbocation formation is still occurring, but as the enamide unit remained intact, and hydrolysis products of type **8** were not observed, this route was thus adopted for the synthesis of U-62162.

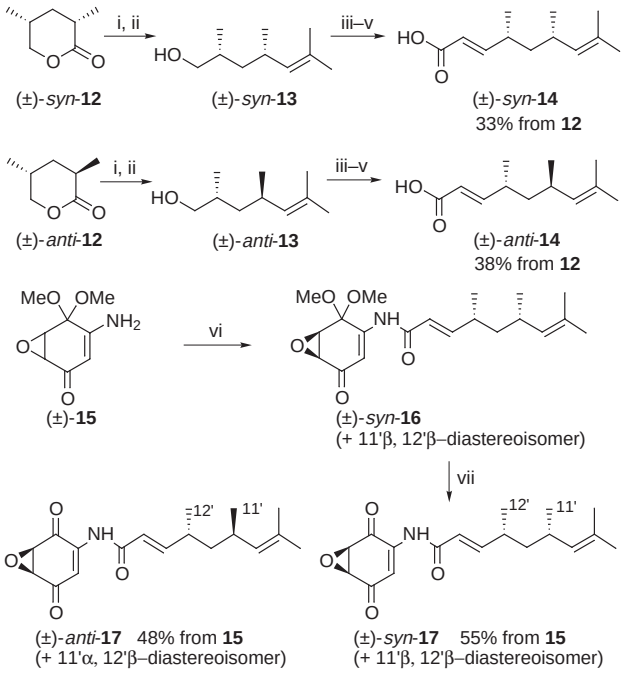
The first objective in the natural product synthesis was to elucidate the relative stereochemistry of the side chain methyl substituents in the upper side chain (Scheme 3). The readily available[7] *syn*- and *anti*-dimethylvalerolactones **12** were therefore converted into the isomeric alcohols **13** and on to the acids **14** using the straightforward sequence illustrated. Treatment of acids **14** with oxalyl chloride in CH_2Cl_2 gave the corresponding acid chlorides which were used to acylate amine **15**.[5] The resulting adducts **16**, as diastereomeric mixtures, were then converted into quinone epoxides **17** *via* the three-step sequence shown.

The high-field NMR spectra of the *syn*- and *anti*-diastereomers of **16**, **17** and the other acylated intermediates, were compared to the data published for U-62162.[4] Significant differences were observed, which indicated that the natural product contained the *syn*-dimethyl arrangement [*e.g. syn*-**17**: δ_H 0.91 (3 H, d, *J* 6.5, H-11′); *anti*-**17**: δ_H 0.89 (3 H, d, *J* 6.5, H-11′); U-62162:[4] δ_H 0.91 (3 H, d, *J* 6.6, H-11′). We therefore set out to convert *syn*-**16** into U-62162 (Scheme 4).

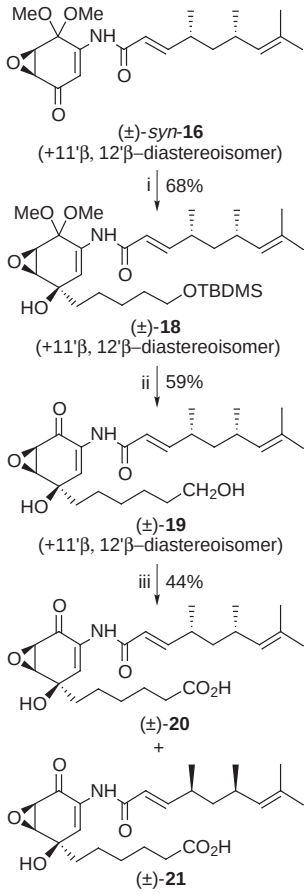
5-*tert*-Butyldimethylsilyloxy-1-iodopentane[8] was transmetallated (Bu^tLi, Et_2O) and then treated with *syn*-**16**; as



Scheme 2 *Reagents and conditions*: i, TsOH, aq. acetone



Scheme 3 *Reagents and conditions*: i, DIBAL-H, THF, −78 °C (ref. 7); ii, $Ph_3P{=}CMe_2$, THF, 0 °C; iii, DMSO, $(COCl)_2$, −60 °C, then Et_3N, CH_2Cl_2, room temp.; iv, $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, room temp.; v, LiOH, aq. MeOH–THF; vi, acid chloride from **14**, LiOBu^t, THF, 0 °C; vii, $LiHBEt_3$, THF, −78 °C, then K10, CH_2Cl_2, room temp., then PDC, CH_2Cl_2, room temp.



Scheme 4 *Reagents and conditions*: i, $Li(CH_2)_5OTBDMS$, Et_2O, −78 °C; ii, TBAF, THF, room temp., then TsOH, aq. acetone; iii, PCC, NaOAc, CH_2Cl_2, room temp., then $NaClO_2$, KH_2PO_4, 2-methylbutene, aq. Bu^{t}OH, room temp.

expected,[5] addition occurred with total stereoselectivity from the face opposite the epoxide. The deprotection of adduct **18** could be carried out directly using TsOH in aqueous acetone but the process was rather slow and inefficient. The preferred method involved fluoride-induced desilylation followed by acetal hydrolysis using TsOH. This sequence gave diol **19** (accompanied by a small amount of the *anti*-hydroxy epoxide§ which was easily removed by chromatography). Oxidation of **19** to an inseparable mixture of the corresponding acids **20**/**21** was achieved by a two-step procedure (PCC, then sodium chlorite). Compounds **20**/**21,** although a diastereomeric mixture, showed data consistent with that published for U-62162 [*e.g.* δ_H (synthetic) 7.42 (d, *J* 2.5, H-3) 3.68 (dd, *J* 4.0, 2.5, H-5), 3.55 (d, *J* 4.0, H-6); δ_H (published[4]) 7.43 (d, *J* 2.7, H-3) 3.69 (dd, *J* 4.0, 2.7, H-5), 3.56 (d, *J* 4.0, H-6); δ_C (synthetic) 190.2 (C-1), 130.6 (C-2), 130.3 (C-3), 71.2 (C-4), 58.6 (C-5), 53.7, C-6); δ_C (published[4]) 189.6 (C-1), 130.0 (C-2), 129.8 (C-3), 70.6 (C-4), 57.9 (C-5), 53.0, C-6)].§ The *syn*-hydroxy epoxide arrangement, now confirmed for U-62162, is in accord with the biosynthetic rationale recently proposed by Gould and Floss.[9]

This research establishes an efficient route to the antibiotic U-62162 and also provides further stereochemical information. We are now working to assign U-62162 as **20** or **21** and to complete an enantioselective synthesis.

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Notes and References

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‡All new compounds were fully characterised by high field ^1H and ^{13}C NMR spectroscopy and by high resolution mass spectrometry, with the exception of those in Scheme 2 (NMR characterisation only). All compounds are racemic and **16**–**19** are mixtures of diastereoisomers.

§ The *anti*-hydroxy epoxide isomer of **19** was also converted into the corresponding diastereomeric U-62162 analogues. The NMR spectrum of this mixture showed significant differences to **20**/**21** [*e.g.* δ_H 7.55 (d, *J* 3.0, H-3); δ_C 128.9 (C-3), 60.2 (C-5)], providing further evidence that the natural product possesses the *syn*-hydroxy epoxide stereochemistry.

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