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The Synthesis of Novel Analogues of the Manumycin Family of Antibiotics and the Antitumour Antibiotic LL-C10037α

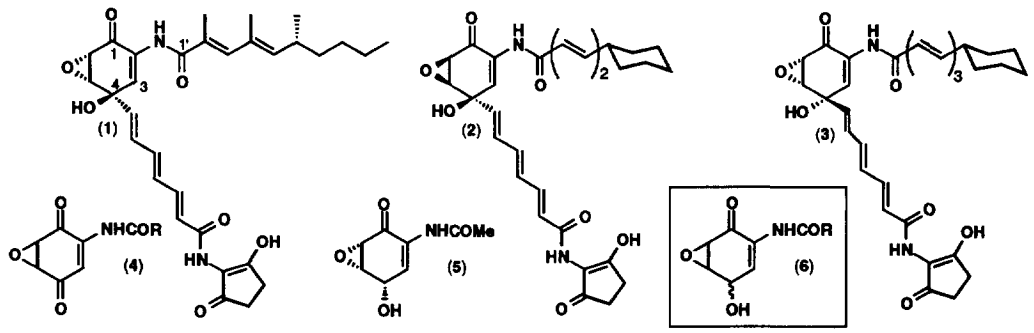
Isabelle Kapfer,[a] Norman J. Lewis,[b] Gregor Macdonald[a] and Richard J. K. Taylor[a,*]

[a]Department of Chemistry, University of York, Heslington, York YO1 5DD, UK

[b]SmithKline Beecham Pharmaceuticals, Leigh, Tonbridge, Kent TN11 9AN, UK

Abstract: Efficient approaches to the central amino-epoxycyclohexenone core of the manumycin family of antibiotics are described. The use of this methodology to prepare the antitumour antibiotic LL-C10037α and its epimer, both in racemic form, and a number of analogues of manumycin, alisamycin and asukamycin, lacking the C-4 substituent, are then outlined.

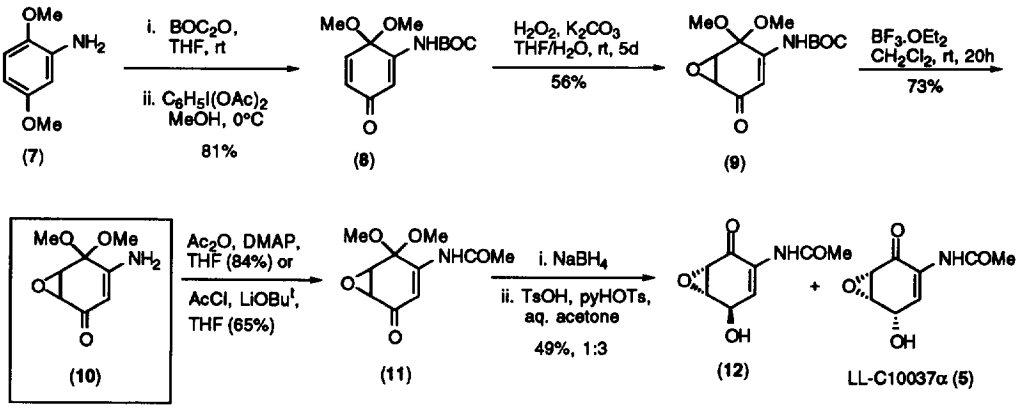
Manumycin A (**1**) was first isolated from *Streptomyces parvulus* (strain Tü 64) by Buzzetti and collaborators in 1963[1,2] and since then a family of structurally-related antibiotics have been isolated from *Streptomyces* species. These include alisamycin (**2**)[3] and asukamycin (**3**),[4] in addition to others.[5] All of these compounds are based on a central amino-epoxycyclohexenone core with "Southern" and "Eastern" polyunsaturated side chains linked to C-4 and to the amine substituent, respectively. Most of the manumycin family exhibit a range of biological effects including antibiotic, antifungal, cytotoxic and elastase inhibibitory activities. In addition, manumycins have recently been identified as potent and selective inhibitors of Ras farnesyltransferase[6] and thus are potential anticancer agents.[7] The complex structures, and metabolic instability, of the natural products would seem to limit their potential as drugs. However, it has been established that the oxidised degradation products (**4**) of the manumycins also act as Ras farnesyltransferase inhibitors:[6] in addition, the natural product LL-C10037α (**5**)[8] has been shown to possess antitumour properties. These observations indicate that it might be possible to design and synthesise simplified manumycin analogues (**6**) lacking the C-4 "Southern" polyene chain but retaining useful biological activity.



To date, there have been no reported syntheses of any of the manumycin antibiotics although some of the less complex, structurally-related analogues have recently been prepared by total synthesis. We devised[9] a short route to bromoxone[10] and Wipf *et al.* prepared LL-C10037α (**5**)[11] and recently utilised this chemistry to prepare compounds of type (**6**).[12] This latter publication prompts us to describe our own, more convenient,

synthesis of (±)-LL-C10037α (Scheme 1) and the application of this chemistry to the preparation of compounds of general structure (**6**). We identified enamine (**10**) as an extremely useful pivotal intermediate and set out to investigate its synthesis and stability.

Scheme 1

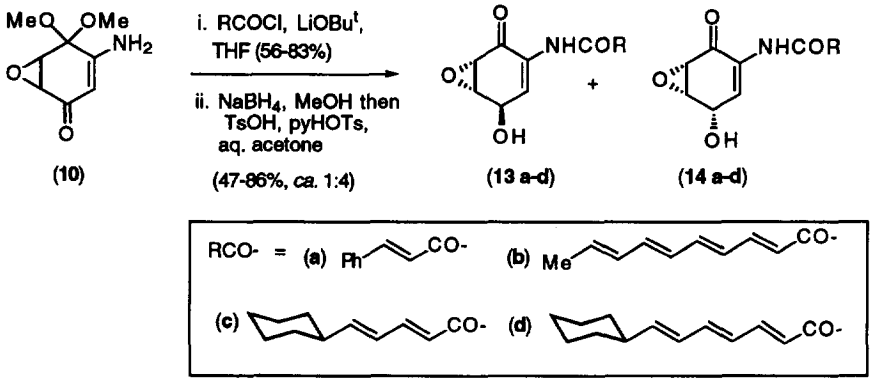


The early steps (Scheme 1) were based on our recent synthesis of (-)-aranorosin[13] and are similar to those employed by Wipf and Kim[11,12] although we opted to utilise *tert*-butoxycarbonyl (BOC) as the *N*-protecting group.[14] Thus, protection of 2,5-dimethoxyaniline (**7**) with BOC_2O and oxidation of the product using $PhI(OAc)_2$[15] gave monoacetal (**8**) in 81% overall yield (Scheme 1). Several epoxidation methods were investigated for the conversion of (**8**) into monoepoxide (**9**). On a small scale (0.4 mmol) sodium perborate[16] gave the best results (39% + 47% recovery of starting material) but the efficiency diminished as the reaction was scaled up. On a larger scale the preferred procedure involved the use of H_2O_2/K_2CO_3 in aq. THF (methoxy conjugate addition adducts were observed when methanol was employed as solvent). In order to obtain the key amine intermediate (**10**) selective removal of BOC in the presence of the methyl acetal was required. This was efficiently achieved using boron trifluoride etherate and activated molecular sieves in dichloromethane at room temperature. This novel procedure[17] is potentially useful in other systems and we are currently exploring its scope and limitations. To our delight, amine (**10**) proved to be a stable, crystalline solid (m.p. 156-157°C) which could be stored at -20°C for several weeks without noticeable decomposition. Intermediate (**10**) is a vinylogous amide and therefore rather unreactive to standard acylation conditions. Acetylation was achieved in good yield (84%) with an excess of acetic anhydride (but not acetyl chloride) and DMAP in THF. The requirement for an excess of an acid anhydride seemed to limit the value of this route for the preparation of manumycin analogues and therefore other acylating conditions were explored. It was eventually found that acetylation could be carried out using 1.2 equivalents of acetyl chloride providing lithium *tert*-butoxide[18] was employed as base. Reduction of (**11**) using sodium borohydride followed by acetal hydrolysis using Wipf's conditions[11,12] gave a separable 3:1 mixture of (±)-LL-C10037α (**5**) and its *anti*-isomer (**12**). The NMR characteristics of (**5**) and (**12**) were entirely consistent with published data.[8,11,12] The route to (±)-LL-C10037α is only 7 steps and, although unoptimised proceeds in >10% overall yield. It

also reduces the number of protection-deprotection steps compared to the published procedure[11,12] and avoids the need for *N*-(allyloxy)carbonyl deprotection [Bu_3SnH, $PdCl_2(PPh_3)_2$, AcOH].

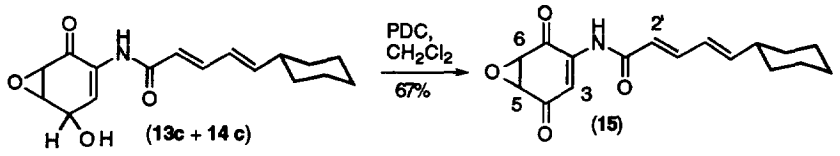
The main value of the chemistry shown in Scheme 1, however, is in making available amine (**10**), a versatile and stable intermediate for the synthesis of manumycin analogues. The coupling of (**10**) to a range of acid chlorides[19] was explored next (Scheme 2). The lithium *tert*-butoxide procedure proceeded efficiently although the yields diminished slightly with highly conjugated systems. Reduction and deacetalisation as before gave *anti/syn* mixtures (**13/14**) which (with the exception of **13b/14b**) were separated by chromatography on silica gel or by preparative TLC. In related systems we have shown[9] that the stereoselectivity of the reduction process can be controlled by variation of reducing agent and solvent; in this study we wanted to obtain both *syn* and *anti*-isomers for biological screening and so an optimisation study was not carried out. Amides (**13a,b**) and (**14a,b**) represent novel manumycin/colabomycin analogues whereas amides (**14c**) and (**14d**) are the (±)-4-unsubstituted analogues of alisamycin (**2**) and asukamycin (**3**), respectively.

Scheme 2



We also extended this chemistry to produce oxidised degradation products of type (**4**) lacking the C-4 polyene chain (Scheme 3). Thus PDC oxidation of the mixture of alcohols (**13c/14c**) produced the known degradation product (**15**) of alisamycin (**2**) {key ^{1}H-NMR data [7.62 (1H, d, J 2.2 Hz, H-3), 5.91 (1H, d, J 15, H-2'), 3.93 (1H, d, J 3.6, H-6), 3.84 (1H, dd, J 3.6, 2.2, H-5)] and ^{13}C-NMR data [191.0, 188.2, 165.0, 152.4, 146.1, 139.0, 125.3, 120.0, 115.2, 53.8, 52.5, 41.2, 32.1, 25.9, 25.8] compare extremely well to literature[3] values}.

Scheme 3



The simple and efficient synthetic route to the central core of the manumycin antibiotics, and the procedure for the attachment of the "Eastern" side chain, described above should be of great value for the preparation of a range of analogues (**4**) and (**6**) for structure-activity studies. We are currently carrying out such a

programme as well as exploring extensions of the chemistry described above to allow a synthetic entry into 4-substituted analogues and hence to the manumycin family of natural products.

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