Synthesis of the Antitumor Antibiotic LL-C10037α

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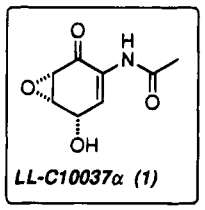
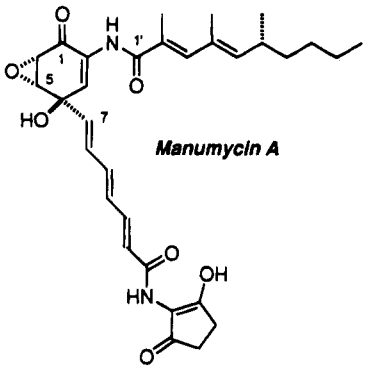
Summary: (±)-LL-C10037α and its C(4)-epimer were prepared in nine steps from 2,5-dimethoxyaniline. The concise synthetic route represents the first synthesis of this highly functionalized antitumor antibiotic and is useful for the preparation of analogs of the putative pharmacophore of the Ras farnesyltransferase inhibitor manumycin.

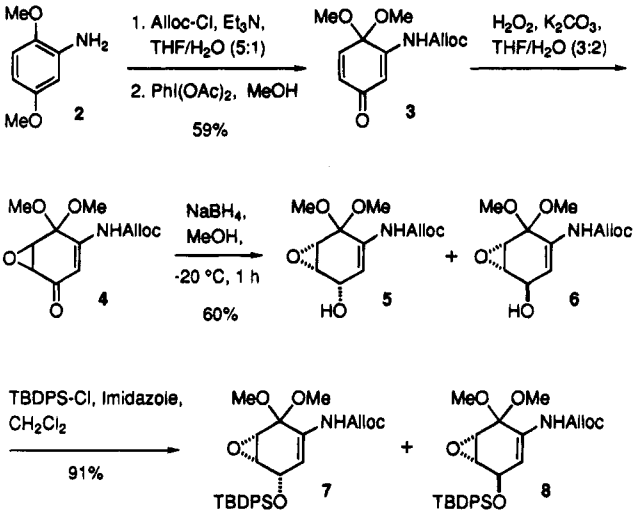
The *Streptomyces* metabolite LL-C10037α was isolated in 1984 by Lee and co-workers from Lederle laboratories.[2] Its structure was subsequently revised to the epoxyquinol **1** on the basis of an X-ray diffraction analysis and exciton circular dichroism studies.[3] Gould and co-workers also established the biosynthesis of the antibiotic from 3-hydroxyanthranilic acid via the shikimic acid pathway.[4] MT35214, obtained by acetylation of the *Streptomyces* sp. NCIB 11813 metabolite MM14201,[5] forms an enantiomeric pair with **1**.[3] LL-C10037α shows close structural resemblance with the core mC_7N unit of the manumycin group of antibiotics.[6]





Manumycins have recently been identified as potent and selective inhibitors of Ras farnesyltransferase,[7] and the epoxyquinol core and its aminoacyl side chain resembling a farnesyl group were proposed as pharmacophores.[8] The fact that the *ras* oncogene may contribute to as many 30% of all human cancers has triggered an intensive search for specific inhibitors of Ras p21 processing.[9,10] A synthetic route to the manumycin core will considerably facilitate structure–activity studies with Ras farnesyltransferase. In this paper, we present an efficient approach toward LL-C10037α.

Scheme 1



Similar to our recently demonstrated strategy toward the diepoxy ketone natural product aranorosin,[11] we selected a hypervalent iodine oxidation of an electron-rich arene for the preparation of the key synthetic intermediate. Quinone **3** was obtained as a monoacetal in 59% yield from commercially readily available 2,5-dimethoxyaniline (**2**) (Scheme 1). Subsequent epoxidation with basic hydrogen peroxide in aqueous THF and reduction with $NaBH_4$ in methanol at −20 °C provided a 5.3:1 ratio of *syn*- and *anti*-epoxy alcohols **5** and **6** in 60% yield. In the presence of 3 equiv of $CeCl_3$,[12] a 2:1 mixture of **5** and **6** was formed.

After silylation of the secondary allylic alcohol function with *tert*-butyldiphenylsilyl chloride, *syn*- and *anti*-isomers were separated by chromatography on silica gel. The major isomer, *syn*-epoxy ether **7**, was deprotected with a mixture of *p*-toluenesulfonic acid and PPTs in aqueous acetone at a carefully controlled pH of 3–4 to give 81% of epoxyenone **9** (Scheme 2). Due to the considerable

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(1) Eli Lilly Grantee, 1993–1994; Alfred P. Sloan Research Fellow, 1994–1995; recipient of an American Cyanamid Faculty Award, 1994.

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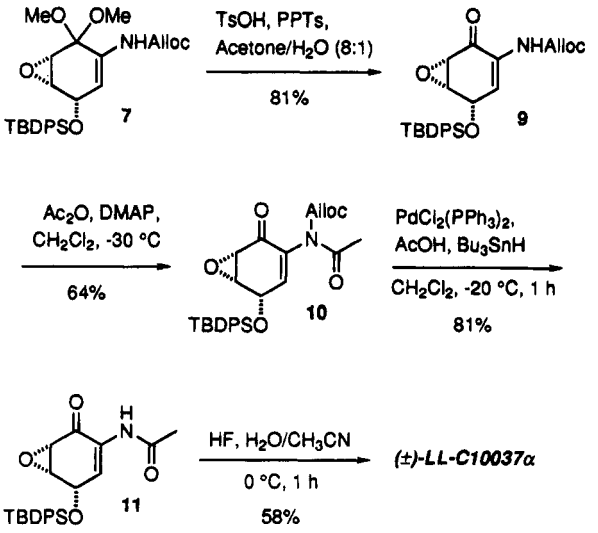
Scheme 2



chemical instability of the *N*-unprotected derivative of **9**,[4] removal[13] of the (allyloxy)carbonyl group was performed on imide **10**, obtained by low-temperature *N*-acetylation of enone **9** with acetic anhydride in the presence of 0.5 equiv of DMAP. Palladium-catalyzed deallylation of **10** occurred readily in the presence of 3 equiv of AcOH and 2 equiv of Bu_3SnH at −20 °C and gave amide **11** in 52% yield from **9**. Final deprotection of this compound required an extensive optimization of the desilylation conditions. In basic and in aprotic acidic media, epoxy alcohol **1** decomposed rapidly. Addition of a concentrated solution of **11** in acetonitrile to an excess of aqueous HF at 0 °C led to a more controllable cleavage of the BDPS ether and allowed the isolation of the desired (±)-LL-C10037α in 58% yield.

An analogous sequence of reactions provided the C(4)-epimer of LL-C10037α (**12**) in 25% overall yield from **8** (Scheme 3). The *anti*-relationship between the secondary alcohol and the epoxy function in the unnatural **12** matches the manumycin mC_7N-core even more closely than LL-C10037α.[14]

The regulation of the oncogene product Ras p21 by inhibition of farnesyltransferase (FTase) is an attractive approach for developing a new class of anticancer drugs.[15]

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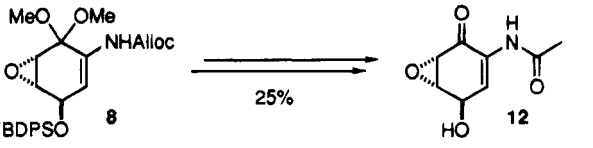
Scheme 3



(4-Epi)-LL-C10037α

Whereas the preparation of mimetics of the CAAX tetrapeptide sequence at the Ras carboxy terminus is actively pursued in several industrial and academic laboratories,[16] the use of farnesyl diphosphate (FPP) analogs represents an interesting alternative. Manumycin acts as a competitive inhibitor (IC_{50}: 5μM) of FTase with respect to FPP, but as a noncompetitive inhibitor vs Ras p21.[10] Our synthesis of LL-C10037α in nine steps and 8% overall yield from dimethoxyaniline represents the first preparation of the manumycin core. A slight modification of this route provides an access to the C(4)-epimer **12**. Since the acyl side chains in **1** and **12** are introduced in the very last steps of the syntheses, this methodology provides a general entry toward aminoacyl epoxyquinols and SAR studies of Ras farnesyltransferase inhibitors.

Supplementary Material Available: Experimental procedures and compound characterization data (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) The spectroscopic data for synthetic LL-C10037α are identical with the natural product and differ considerably from its C(4)-epimer **12**. LL-C10037α (**1**): ^1H NMR ($CDCl_3$) δ 7.56 (bs, 1 H), 7.44 (dd, 1 H, *J* = 3.1, 2.1 Hz), 4.85 (ddd, 1 H, *J* = 10.7, 3.2, 3.1 Hz), 3.89 (ddd, 1 H, *J* = 3.9, 3.2, 2.1 Hz), 3.61 (d, 1 H, *J* = 3.9 Hz), 2.27 (d, 1 H, *J* = 10.7 Hz), 2.13 (s, 3 H); ^1H NMR (DMSO-d_6) δ 9.04 (bs, 1 H), 7.05 (dd, 1 H, *J* = 2.7, 2.3 Hz), 5.78 (d, 1 H, *J* = 4.6 Hz), 4.78 (ddd, 1 H, *J* = 4.6, 2.7, 2.5 Hz), 3.77 (ddd, 1 H, *J* = 4.3, 2.5, 2.3 Hz), 3.54 (d, 1 H, *J* = 4.3 Hz), 1.99 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 189.7, 169.5, 128.3, 63.3, 53.7, 52.2, 23.7. (*4-epi*)-LL-C10037α (**12**): ^1H NMR ($CDCl_3$) δ 7.69 (bs, 1 H), 7.60 (dd, 1 H, *J* = 5.3, 2.4 Hz), 4.89 (dddd, 1 H, *J* = 7.4, 6.8, 5.3, 1.1 Hz), 3.85 (dddd, 1 H, *J* = 6.8, 3.7, 2.4, 1.1 Hz), 3.61 (dd, 1 H, *J* = 3.7, 1.1 Hz), 2.64 (dd, 1 H, *J* = 7.4, 1.1 Hz), 2.14 (s, 3 H); ^1H NMR (DMSO-d_6) δ 9.08 (bs, 1 H), 7.27 (dd, 1 H, *J* = 5.4, 2.3 Hz), 5.73 (dd, 1 H, *J* = 5.5, 1.2 Hz), 4.63 (dddd, 1 H, *J* = 6.0, 5.5, 5.4, 0.9 Hz), 3.76 (dddd, 1 H, *J* = 6.0, 3.8, 2.3, 1.2 Hz), 3.64 (dd, 1 H, *J* = 3.8, 0.9 Hz), 2.01 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 189.6, 169.7, 130.4, 125.6, 61.8, 57.4, 52.7, 23.8.

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