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Enantioselective Synthesis of (−)-LL-C10037α from Benzoquinone

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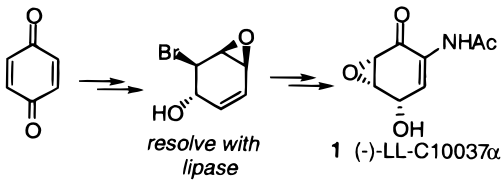
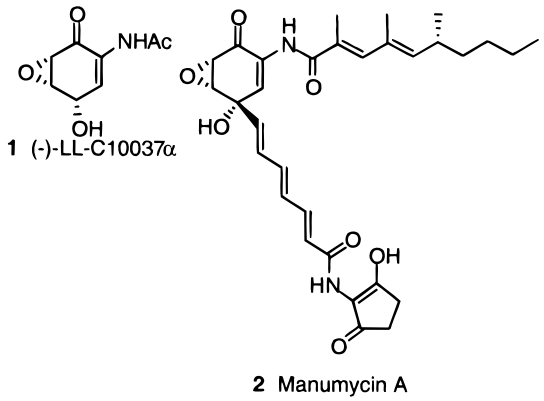
ABSTRACT



The enantioselective total synthesis of the *Streptomyces* metabolite (−)-LL-C10037α has been accomplished in 10 steps and 20% overall yield. An early chiral intermediate was resolved with *Candida rugosa* lipase to provide (+)-5 with an enantiomeric excess ≥98%. The synthesis is notable in that no protecting groups are required and that all carbons in the core structure of LL-C10037α are derived from the readily available *p*-benzoquinone.

LL-C10037α (**1**) is a metabolite of *Streptomyces LL-C10037* and shows antibacterial and antitumor activity.[1] After the initial report of the isolation,[1] the structure was revised and shown by an X-ray diffraction study to be the epoxyquinol **1**.[2] The absolute configuration was later confirmed by X-ray analysis of an ester derivative.[3] The epoxyquinol core of LL-C10037α is found in a number of other antibiotics including the manumycins,[4] such as manumycin A (**2**), alisamycin,[5] asukamycin,[6] and nisamycin.[7] The manumycins are noteworthy because they are also potent and selective inhibitors of Ras farnesyltransferase,[8] an enzyme linked to many human cancers.



Racemic syntheses of LL-C10037α have been published by the groups of both Wipf[9] and Taylor.[10] One enantiose-

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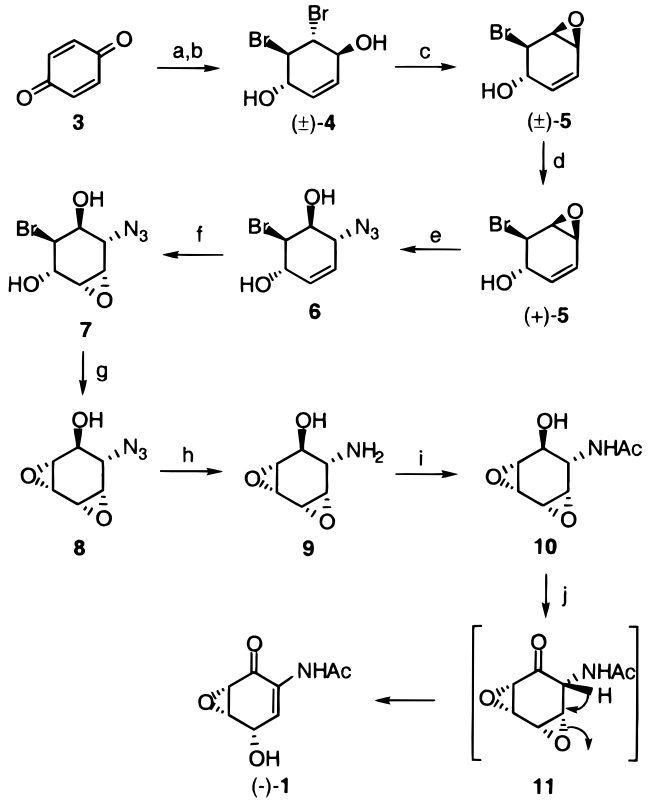
lective synthesis has also been accomplished, published by Wipf et al. in 1995.[9b] The synthesis relied on a chiral auxiliary to achieve enantioselectivity in an epoxidation reaction and was completed in an overall yield of ca. 1% from 2,5-dimethoxyaniline. Curiously, the enantiomer of (−)-LL-C10037α is also a natural product. The (+)-enantiomer, named (+)-MT 35214, has been efficiently synthesized by Taylor et al. using a phase-transfer catalyst to effect an enantioselective epoxidation. Unfortunately, a catalyst could not be found to produce the enantiomeric epoxide, thus precluding a synthesis of (−)-LL-C10037α.

Continuing our program of using enzymes in the enantioselective synthesis of highly functionalized, biologically active molecules,[11] we now report the synthesis of LL-C10037α starting from readily available benzoquinone (Scheme 1). The first part of the synthesis follows previous

Scheme 1[a]



[a] Reagents: (a) Br_2, 0 °C; (b) $NaBH_4$, 0 °C, 81% over two steps (ref 13); (c) KOH, 0 °C, 92%; (d) (±)-**5** (6.8 g), *Candida rugosa* lipase (Sigma) (200 wt %), 4:1 toluene/isopropenyl acetate (125 mL), 6 d, 47%, ≥98% ee; (e) NaN_3, $ZnSO_4$, 95%; (f) MCPBA, 94%; (g) KOH, 0 °C, 86%; (h) Pd/S, H_2; (i) Ac_2O, Et_3N, 84% over two steps; (j) Dess−Martin periodinane, 87%.

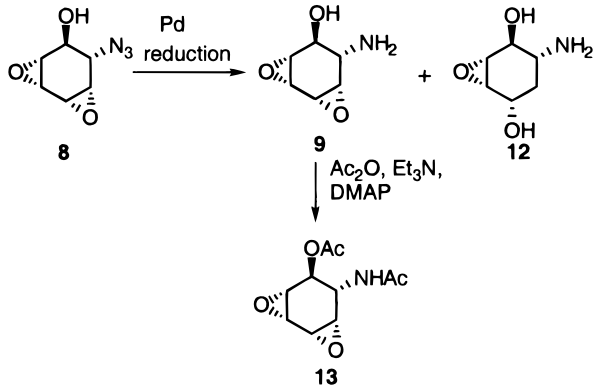
work by our group in which epoxide **5** was enzymatically resolved and shown to react with various nucleophiles by opening the epoxide at the allylic position.[12] Following the literature procedure from Altenbach, Stegelmeier, and Vogel,[13] *p*-benzoquinone was sequentially trans-brominated and stereoselectively reduced with sodium borohydride to give the diol **4**. By treating the C_2-symmetrical diol **4** with base and maintaining the temperature at 0 °C, only one of the hydroxyl groups closes to form the monoepoxide (±)-**5** in excellent yield (92%). Maintaining the temperature at 0 °C is crucial during this step, since permitting the reaction to warm to room temperature allows for formation of the corresponding diepoxide.[13]

Racemic epoxide **5** was exposed to *Candida rugosa* lipase in toluene/isopropenyl acetate; only (−)-**5** was acetylated, leaving (+)-**5** untouched. Separation from the acetylated product by flash chromatography produced (+)-**5** in 47% yield and ≥98% ee [$[\alpha]^{25}_D$ +170 (*c* 1.0, $CHCl_3$) (lit.[12] $[\alpha]^{25}_D$ +174 (*c* 1.0, $CHCl_3$); lit.[14] $[\alpha]^{25}_D$ +170.6 (*c* 0.812, $CHCl_3$))]. Recrystallization did not result in increased optical rotation.

To introduce the nitrogen present in the natural product, (+)-**5** was treated with sodium azide in the presence of zinc sulfate to form azide (−)-**6** in 95% yield. As expected, the epoxide was attacked at the more labile allylic position (confirmed by X-ray analysis of (±)-**6**). Next, the oxygen that was to become the hydroxyl group in the final product was introduced stereoselectively by hydroxyl-directed *m*-CPBA epoxidation[15] to give (−)-**7** (94%). The relative stereochemistry of the epoxidation was confirmed by X-ray analysis on (±)-**7**. The epoxide (−)-**7** was transformed into the diepoxide (−)-**8** with potassium hydroxide in methanol at 0 °C (86%).

We anticipated a tandem oxidation/β-elimination reaction on amide **10** would lead directly to the final product **1**. To arrive at **10**, we required chemoselective reduction of the azide function in (−)-**8**, leading to **9**. Our initial attempts to reduce the azide by hydrogenation[16] produced the desired amine **9** along with an epoxide-reduced product tentatively assigned structure **12** (Scheme 2). A variety of catalysts were

Scheme 2



examined, including palladium on carbon, palladium hydroxide on carbon (Pearlman's catalyst), and palladium, sulfided, 5 wt % on carbon (Aldrich) as well as a number of

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solvents (EtOH, MeOH, EtOAc); all produced mixtures. In examining other methods of azide reduction, we found that reduction with triphenylphosphine[17] proceeded smoothly to give the desired product **9**. Unfortunately, the triphenylphosphine oxide produced in the reaction made purification of **9** or the diacetylated product **13** extremely difficult. Finally, in examining the Pd hydrogenation conditions further, we found that the sulfided palladium on carbon catalyst when run in THF gave the amine **9** as the only detectable product by TLC and NMR. Due to the extreme polarity of the amine **9**, the crude material was acetylated directly with acetic anhydride and triethylamine to provide the penultimate acetamide **10** (84% over two steps).

A potential complication in the strategy of an oxidation/elimination sequence for conversion of **10** to **1** is that the elimination reveals a new alcohol in the desired product **1** that could be further oxidized to an epoxyquinone. To our delight, the Dess−Martin periodinane[18] reacted quickly with **10** in acetonitrile to provide (−)-LL-C10037α in a very good yield of 87%. The reaction appeared to be complete within 20 min, and no signs of the ketone **11** were seen by TLC. To account for the selective formation of **1**, we propose that the periodinane reacts quickly with the hydroxyl functionality, thus forming a complex and thereby sequestering all of the reagent so that as the product **1** forms no reagent is available for over-oxidation to an epoxyquinone. The proton and carbon NMR spectra of the synthesized (−)-**1** matched perfectly those of the natural product.[1,2] After one recrystallization, the optical rotation and melting point were in excellent agreement with the naturally obtained material: mp 149−151 °C; $[\alpha]^{22}_{D}$ −201 (*c* 0.34, MeOH) [lit.[1] mp 153 °C; lit.[3] $[\alpha]^{20}_{D}$ −202 (*c* 0.334, MeOH)].

In summary, we have synthesized (−)-LL-C10037α using an enzymatic resolution on an early intermediate. Starting from benzoquinone, the title compound was synthesized in 10 steps and 20% overall yield.[19] Notable reactions include a chemoselective azide reduction with sulfided palladium on carbon and a tandem oxidation/β-elimination reaction. Although LL-C10037α is a densely functionalized small molecule, no protecting groups were needed during the synthesis, which contributed to the high efficiency achieved.

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Supporting Information Available: Experimental procedures and full characterization for the optically active compounds **6**−**10** and (−)-**1**, ^{1}H NMR spectra for these compounds, and X-ray structures for (±)-**6** and (±)-**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The overall yield includes the resolution step, which has a maximum yield of only 50%.