An Efficient Regioselective and Diastereoselective Synthesis of the Epoxy-quinol Functionality as Building Block for the Manumycin Antibiotics by the Sequence of Photooxygenation, Reduction and Weitz–Scheffer Epoxidation

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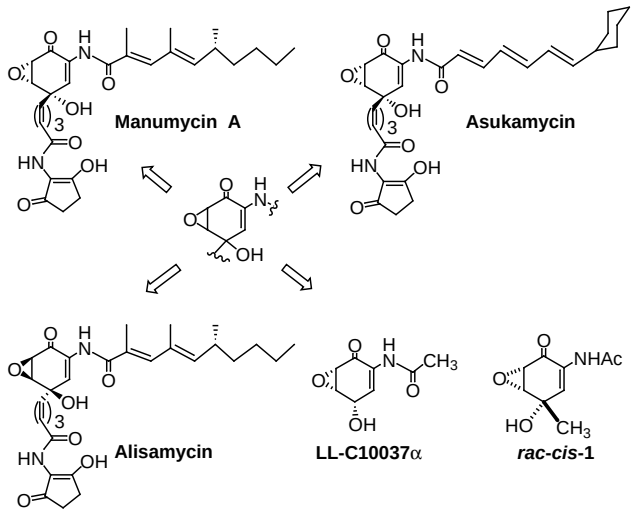
Abstract: The photooxygenation of the acetanilide **2** affords the hydroperoxide **3**, which by titanium-tetraisopropoxide-catalyzed reduction with dimethyl sulfide gives the corresponding quinol **4**. Regioselective and diastereoselective Weitz–Scheffer epoxidation of the latter by *tert*-butyl hydroperoxide (TBHP) and DBU as base catalyst leads to the *cis*-epoxy quinol **1**, the essential functionality in *Manumycin* antibiotics.

Key words: photooxygenation, quinol, Weitz–Scheffer epoxidation, diastereoselectivity, regioselectivity

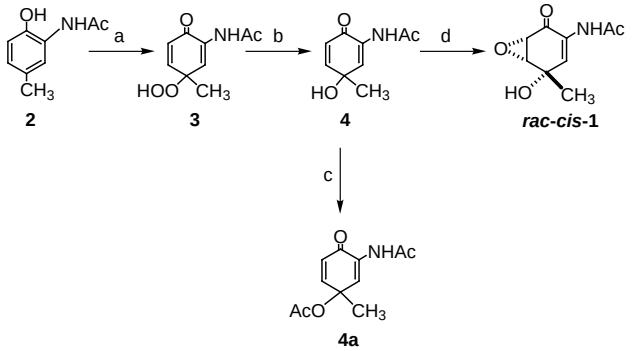
The antibacterial manumycin **A** (Scheme 1) was first isolated from *Streptomyces parvulus* in 1963 and since then a family of structurally related antibiotics has been obtained from the *Streptomyces* species.[1,2] More recently, alisamycin[3] and asukamycin[4] and others[5] have been characterized. The manumycin natural products possess a wide range of bioactivity, in addition to their established antibacterial properties.[6]



Scheme 1

The significant discovery is that manumycins act as selective inhibitors of ras farnesyl transferase and might be of use in cancer chemotherapy.[7] However, in view of the metabolic instability of these natural products, it would seem that their potential as drugs should be limited; nonetheless, it has been established that the structurally related product LL-C10037α[8,9] without side chains possesses potent antitumor properties. The latter observation suggests that the complex side chains are not essential and, consequently, it should be worthwhile to prepare such simplified manumycin analogues, which might display useful biological activity. For the purpose of structure-activity studies, an efficient and versatile synthesis of manumycin derivatives was desirable.

These natural products possess a central epoxy-quinol functionality, with polyunsaturated side chains linked to the C-5 position and the amino substituent. This unit is thought to originate from 3-amino-4-hydroxybenzoic acid through a biosynthetic pathway with a building block from the TCA cycle.[10a,b] A consequence of this synthetic pathway is the *syn* orientation of the epoxide (relative to the hydroxy group), a feature that is common to most manumycins. In the present work, we describe a convenient diastereoselective synthesis of the racemic epoxy-quinol *cis*-**1**, in which we have employed an effective sequence of photooxygenation, reduction, and Weitz–Scheffer epoxidation (Scheme 2).



Scheme 2 Reagents: (a) O_2, TPP, hν, acetone/CH_2Cl_2, –25 °C, 2 d, 62% yield; (b) Me_2S (1.2 equiv), $Ti(O\text{-}i\text{-}Pr)_4$ (5 mol%), CH_2Cl_2, 20 °C, 1 h, 4 Å molecular sieves, 83% yield; (c) Ac_2O, pyridine, CH_2Cl_2, 20 °C, 5 d, 67% yield (relative to converted material, conversion ca. 60%); (d) TBHP (1.2 equiv), DBU, CH_2Cl_2, 20 °C, 3 d, 78% yield.

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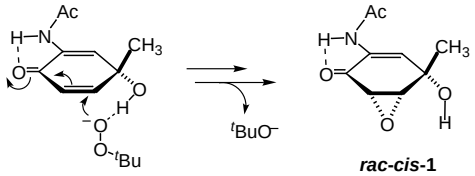
For the synthesis of the epoxy-quinol *cis*-**1,** we selected as starting material the known acetanilide **2** with the hydroxy functionality and methyl substituent.[11] TPP-sensitized photooxygenation of the acetanilide **2** at –25 °C resulted in the hydroperoxide **3** (Scheme 1, step a). After column chromatography on silica gel, the hydroperoxide **3** was isolated in 62% yield.[12] The use of the tetra-*n*-butyl ammonium fluoride, claimed as catalyst for the photooxygenation of phenolic substrates,[13] is unnecessary; in fact, it caused a low yield of impure hydroperoxide **3**. The IR, ^{1}H NMR and ^{13}C NMR spectral data substantiate the structure assignment. The IR exhibited the characteristic hydroperoxide band at 3340 cm^{-1} and a strong, highly conjugated carbonyl absorption at 1654 cm^{-1}. In the ^{1}H NMR spectrum, the olefinic protons display an AB pattern at δ = 7.08–6.27 ppm, as required by the α,β-unsaturated enone functionality, of which the olefinic proton proximate to the methyl group is further split into a doublet by the vinylic proton next to the acetamide group through *W* coupling. The ^{13}C NMR spectrum possesses the two expected carbonyl resonances at δ = 180.2 and 163.4 ppm, which confirm the presence of the conjugated enone and amide functionalities.

The reduction of the hydroperoxide **3** with dimethyl sulfide,[14] catalyzed by titanium tetraisopropoxide, gave the desired quinol **4** (Scheme 1, step b) in high yield.[15] The proposed structure for the quinol **4** is based on spectral and analytic data. For further structural proof, quinol **4** was converted to the corresponding acetate **4a,** whose assignment is consistent with its spectral and analytic data (Scheme 1, step c). Thus, in an efficient two-step sequence, the hydroxyl and enone functionalities were conveniently introduced in the acetanilide **2**.

The Weitz–Scheffer epoxidation of the quinol **4** with *t*-butyl hydroperoxide (TBHP) and catalytic amounts of DBU as base afforded the racemic epoxide *cis*-**1** (relative to the hydroxy group) in 78% yield (Scheme 1, step d).[16] Fortunately, the Weitz–Scheffer epoxidation of the quinol **4** gave only a single diastereomer, namely *cis*-**1** and no other products. In contrast, the use of hydrogen peroxide instead of *t*-butyl hydroperoxide as oxygen source resulted in a low yield of the quinol **4**.

The structural assignment of the *cis*-**1** epoxide rests mainly on its ^{1}H and ^{13}C NMR spectra. The olefinic proton occurs as a doublet at δ = 7.38 (*J* = 2.7 Hz) ppm, the epoxide protons display an AB pattern at δ = 3.68–3.53 ppm, in which the low-field portion is further coupled to the olefinic proton proximate to the acetamide group.[17] NOE experiments confirmed the *cis* configuration. The ^{13}C NMR spectrum consists of four sp^2 carbon and five sp^3 carbon signals, in support of the assigned structure for the epoxy-quinol *cis*-**1**. Evidently, the hydroxy-directing effect[18] operates efficiently in the Weitz–Scheffer epoxidation to afford exclusively the *cis*-configured epoxide **1**. A hydrogen bond between the quinol hydroxy group and the *tert*-butyl hydroperoxide anion directs the delivery of the oxygen atom to the dienone face towards which the hydroxy group points, as shown in the transition structure of Scheme 3. The more electrophilic, unfunctionalized enone C=C double bond is attacked regioselectively.



Scheme 3

The present synthetic strategy is concise, convenient and of well defined regioselectivity as well as diastereoselectivity. Moreover, the reported for the preparation of manumycin-type epoxy quinols employs readily available phenolic starting materials. The efficiency of this protocol should provide a variety of epoxy quinol derivatives for the structure-activity studies with ras farnesyl transferase of such manumycin analogues.

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(12) **Procedure for the Preparation of *N*-(3-Hydroperoxy-3-methyl-6-oxocyclohexa-1,4-dienyl)-acetamide(3)**: A sample of the acetanilide **2** (1.0 g, 6.0 mmol) and *meso*-tetraphenylporphine (TPP, 50 mg) in acetone:methylene chloride (7:3; 80 mL) was irradiated for 2 d at –25 °C with a 400-W sodium lamp, while a gentle stream of dry oxygen gas was allowed to pass through the solution. After removal of the solvent (ca. 10 °C, 15 Torr), the mixture was

chromatographed on silica gel (100 g) with EtOAc:petroleum ether (40–50 °C) (1:1) as eluent to remove TPP as the first fraction. Further elution gave the title compound (0.74 g, 62%) as a white solid. Recrystallization from EtOAc:CH_2Cl_2 gave colorless plates, mp 125–126 °C(dec); ^{1}H NMR (250 MHz, CD_3COCD_3): δ = 11.05 (br s, 1 H), 8.45 (br s, 1 H), 7.67 (d, *J* = 3.0 Hz, 1 H), 7.08 (dd, *J* = 10.0, 3.0 Hz, 1 H), 6.27 (d, *J* = 10 Hz, 1 H), 2.16 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR (63 MHz, CD_3COCD_3): δ = 180.2, 163.4, 153.3, 133.0, 128.8, 127.3, 78.9, 23.8, 23.3; IR (KBr): 3340, 3164, 2846, 1654, 1646, 1532, 1396, 1343, 1242, 1136, 1060 cm^{-1}. Anal. Calcd for $C_9H_{11}NO_4$ (197.1): C, 54.82; H, 5.62; N, 7.10. Found: C, 55.16; H, 5.77; N, 7.11.

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(15) **Procedure for the Preparation of *N*-(3-Hydroxy-3-methyl-6-oxocyclohexa-1,4-dienyl)-acetamide(4)**: To a magnetically stirred solution of the hydroperoxide **3** (0.50 g, 2.53 mmol) and 4 Å molecular sieves (2 g) in methylene chloride (75 mL) at 10 °C were added dimethyl sulfide (0.19 g, 3.0 mmol) and titanium tetraisopropoxide (36.0 mg, 0.12 mmol). After 1 h of stirring, the reaction was stopped by the addition of water (50 μL), and the solids were removed by filtration. The solvent was evaporated (ca. 15 °C, 15 Torr), the residue was loaded on a short silica gel column (30 g), and eluted with a 4:1 mixture of EtOAc:petroleum ether (40–50 °C) to afford the title compound (0.38 g, 83%) as a colorless oil. Crystallization from a mixture of EtOAc:petroleum ether gave colorless needles, mp 104–105 °C; ^{1}H NMR (250 MHz, CD_3COCD_3): δ = 8.58 (br s, 1 H,), 7.95 (d, *J* = 3.0 Hz, 1 H), 7.27 (dd, *J* = 10.0, 3.0 Hz, 1 H), 6.33 (d, *J* = 10 Hz, 1 H), 4.87 (br s, 1 H), 2.36 (s, 3 H), 1.68 (s, 3 H); ^{13}C NMR (63 MHz, CD_3COCD_3): δ = 180.2, 169.3, 155.7, 132.1, 130.5, 124.3, 67.5, 27.9, 23.8; IR (KBr): 3277, 2966, 1655, 1611, 1533, 1383, 1234, 1092, 1054 cm^{-1}. Anal. Calcd for $C_9H_{11}NO_3$ (181.1): C, 59.66; H, 6.12; N, 7.73. Found: C, 59.25; H, 6.14; N, 7.67. **Selected data for 4a**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.00 (br s, 1 H), 7.68 (d, *J* = 3.0 Hz, 1 H), 6.95 (dd, *J* = 10.0, 3.0 Hz, 1 H), 6.26 (d, *J* = 10 Hz, 1 H), 2.10 (s, 3 H), 2.00 (s, 3 H), 1.54 (s, 3 H); ^{13}C NMR (63 MHz, $CDCl_3$): δ = 179.6, 169.5, 169.1, 152.1, 131.2, 128.2, 125.3, 74.7, 26.9, 24.6, 21.3; IR (KBr): 3352, 2980, 1734, 1695, 1657, 1516, 1400, 1368, 1341, 1240, 1099 cm^{-1}. Anal. Calcd for $C_{11}H_{13}NO_4$ (223.1): C, 59.19; H, 5.87; N, 6.27. Found: C, 59.14; H, 5.78; N, 6.16.

(16) **Procedure for the Preparation of cis-*N*-(5-Hydroxy-5-methyl-2-oxo-7-oxabicyclo[4.1.0]hept-3-en-3-yl)-acetamide (cis-1)**: To a magnetically stirred solution of the quinol **4** (0.34 g, 1.87 mmol) in CH_2Cl_2 (30 mL) at r.t. (ca. 20 °C) were added anhyd *tert*-butylhydroperoxide (TBHP) (2.24 mmol; 0.56 mL, ca. 4.0 M in dichloroethane) and one drop of DBU. The resulting mixture was stirred at r.t. (ca. 20 °C) for 3 d, the solvent was removed (10 °C, 10 Torr), and the mixture was chromatographed on silica gel (40 g), by eluting with a 4:1 mixture of EtOAc:petroleum ether (40–50 °C). The first fraction consisted of unreacted TBHP; further elution gave the quinol epoxide *cis*-**1** (0.29 g, 78%) as a white solid. On recrystallization from CH_2Cl_2:EtOAc (1:1) colorless needless were obtained, mp 185–186 °C. ^{1}H NMR (250 MHz, CD_3COCD_3): δ = 8.19 (br s, 1 H), 7.38 (d, *J* = 2.7 Hz, 1 H), 4.71 (br s, 1 H), 3.68 (dd, *J* = 4.0, 2.7 Hz, 1 H), 3.53 (d, *J* = 4.0 Hz, 1 H), 2.09 (s, 3 H), 1.46 (s, 3 H); ^{13}C NMR (63 MHz, CD_3COCD_3): δ = 189.5, 169.5, 130.7, 128.0, 68.2, 58.6, 53.0, 27.4, 23.7; IR (KBr): 3361, 3268, 3002, 1698, 1650, 1542, 1373, 1260, 1125, 1097, 1032, 931 cm^{-1}. Anal. Calcd for $C_9H_{11}NO_4$ (197.1): C, 54.82; H, 5.62; N, 7.10. Found: C, 54.73; H, 5.55; N, 7.03.

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