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SYNTHESIS OF ANTI-RHEUMATIC AGENT EPOXYQUINOMICIN B

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Abstract: Anti-rheumatic agent (±)-epoxyquinomicin B was synthesized for a 22% overall yield in eight steps from commercially available 3-hydroxy-4-nitrobenzaldehyde *via* the intermediate quinone **6** prepared by selective phenol oxidation of **5** by use of Fremy's salt as the key step.

Anti-rheumatic drugs including nonsteroidal anti-inflammatory drugs (NSAIDs) or disease-modifying anti-rheumatic drugs (DMARDs) are used clinically[1], but they often cause a variety of harmful side effects such as gastrointestinal damage by NSAIDs[2] and hemocatharsis or lung injury by DMARDs[3]. Long-term administration of the drug for this disease compels the discovery of new anti-rheumatic drugs having less severe side effects.

Epoxyquinomicin B **1** is a member of the epoxyquinomicins, which were isolated by us from microbial sources as weak antibiotics[4]. Later, it was found to exhibit a potent inhibitory effect on type II collagen-induced arthritis *in vivo*. Epoxyquinomicin B showed low toxicity with an LD_{50} value of 50 mg/kg by intraperitoneal administration. The mode of action seemed to be different from that of NSAIDs[5] from the evidence that epoxyquinomicins did not inhibit the enzymatic activity of cyclooxygenase (unpublished data). To provide a sufficient quantity of this chemical for studying the mode of action and for establishing the structure-activity relationship by preparing its derivatives, we set about the total synthesis of **1**.

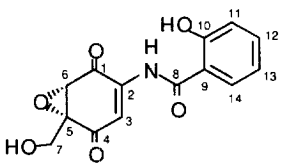

Figure 1. epoxyquinomicin B (**1**)

Total synthesis of (±)-alisamycin, (±)- and (-)-LL-C10037 α, which are structurally related to epoxyquinomicins, have been reported by Alcaraz *et al.* [6], and by Kapfer *et al.*[7] and Wipf *et al.*[8], respectively. Compared to these compounds, **1** possesses a hydroxymethyl group at the C-5 position on the 5,6-epoxy-2-cyclohexene-1,4-dione ring[9]. So we chose commercially available 3-hydroxy-4-nitrobenzaldehyde **2** as a starting material.

The synthetic route for (±)-**1** is outlined in Scheme 1. Compound **2** was reduced and then acetylated to the diacetate **3**. The ester **4** was obtained by selective deacetylation of the aryloxyacetyl group, followed by

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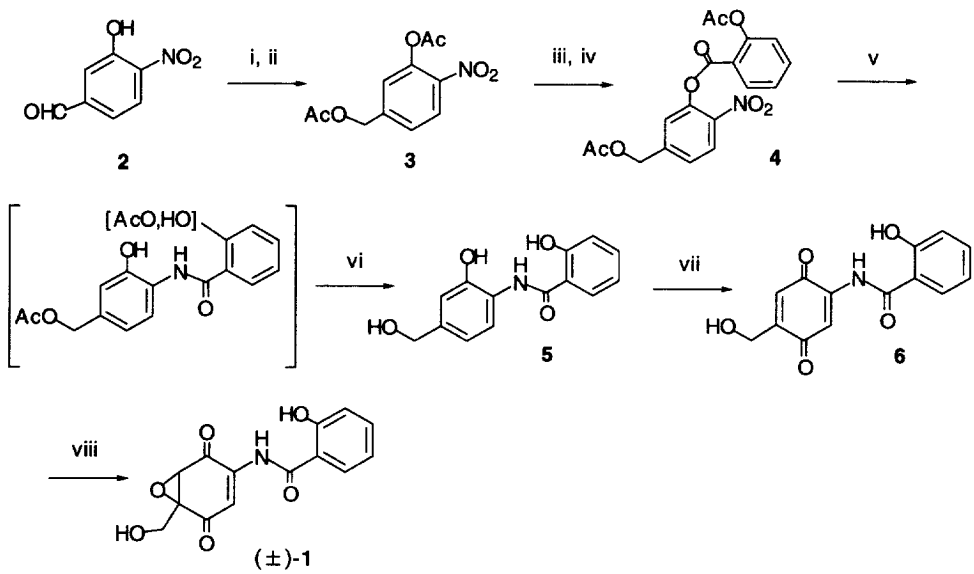
acylation with acetylsalicyloyl chloride. It was not neccesary to apply purifying procedures until after **4** had been purified by recrystallization from methanol. In the catalytic hydrogenation of **4**, the salicyloyl group migrated to the amino group to give an amide. Cleavage of the phenolic acetate on the salicyloyl group partially occurred during this reaction. The resultant mixture of the monoacetate and the diacetate was converted to the triol **5** as a sole product by hydrolysis in 1N NaOH. The triol **5** was selectively oxidized by potassium nitrosodisulfonate (Fremy's salt) in the two-phase system of AcOEt-water to the quinone **6** without affecting the phenolic alcohol on the salicyloyl moiety[10,11]. This selectivity is probably due to the low electron density on the salicyloyl group caused by a substituted carbonyl group[12]. Finally, the quinone **6** was epoxidated by hydrogen peroxide to give (±)-**1**[13]. Thus, (±)-**1** was successfully prepared for a 22% overall yield in 8 steps from 3-hydroxy-4-nitrobenzaldehyde. This synthetic route will enable us to prepare a large quantity of (±)-**1**. We also expect this route to be applicable for the synthesis of other epoxyquinomicins (A, C and D) and their derivatives.



Scheme 1. Reagents and conditions: i, $NaBH_4$, 5% $NaHCO_3$, 0 ℃, 30 min; ii, Ac_2O, pyridine, room temp., 30 min; iii, $KHCO_3$ (1.5 equiv.), MeOH, room temp., overnight; iv, acetylsalicyloyl chloride, 0 ℃, 30 min (50% from **2**); v, H_2 (1 bar), Raney Ni, AcOEt, AcOH, room temp., 8 h; vi, 1N NaOH, room temp., overnight (64%, 2 steps); vii, Fremy's salt, AcOEt, water, room temp., overnight (82%); viii, H_2O_2, 5% $NaHCO_3$, MeOH, room temp., 2 h, 85%

Selected Experimental Procedures and Analytical Data

4-(2-Hydroxybenzoylamino)-3-hydroxybenzylalchol (5). Compound **4** (4.67 g, 12.5 mmol) in a mixture of ethyl acetate (45 ml) and acetic acid (5 ml) was stirred with a catalytic amount of Raney-Ni under an atmosphere of hydrogen (1 atm) at room temperature for 8 hours. After filtration, 100 ml of ethyl acetate was added. The organic layer containing a mixture of monoacetate and diacetate was extracted with 1N NaOH (100 ml x 2). The aqueous layer of the extract was stirred overnight at room temperature to deprotect the acetyl group thoroughly. The mixture was adjusted to pH 2 with 1N HCl, and then extracted with ethyl acetate (200 ml). The organic layer was dried over Na_2SO_4 and evaporated to dryness to give a brown syrup (4.51 g), which was subjected to silica gel column chromatography with elution with toluene-ethyl acetate (2 : 1 then 3 : 2) to give **5** (2.06 g, 64% yield for 2 steps) as a pale yellow solid with the following properties.: mp 171-172 ℃; R_f=0.51 (toluene/acetone 1:1); MS (FAB) *m/z* 260 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 4.53 (2H, d, *J*=2.0 Hz), 6.84 (1H, dd, *J*=2.0 and 8.3 Hz), 6.93-7.00 (3H, m), 7.39 (1H, dt, *J*=2.0 and 8.3 Hz), 8.01 (1H, dd, *J*=1.5 and 7.8 Hz), 8.13 (1H, d, 8.3 Hz); IR ν_{max} (KBr) 3441, 3321, 1634, 1609, 1537, 1227 (cm^{-1}); UV λ_{max} (MeOH) nm (ε) 308 (16300)

2-(2-Hydroxybenzoylamino)-5-hydroxymethyl-2,5-cyclohexadiene-1,4-dione (6). Solution of **5** (5.62 g) in ethyl acetate (1000 ml) was cooled to 0 ℃, to which was added a cold aqueous solution (1000 ml) of Fremy's salt (24.9 g, purchased from WAKOPURE CHEMICAL INDUSTRIES, LTD.), then the mixture was stirred vigorously overnight under an atmosphere of argon at room temperature. The ethyl acetate layer was separated, and the aqueous layer was back-extracted with another 500 ml of ethyl acetate. The combined organic layer was washed with 10% aq NaCl (500 ml), dried over Na_2SO_4, evaporated under reduced pressure to dryness to afford crude **6** (5.78 g) as a brown yellow solid. After washing of the crude **6** with methanol (20 ml), pure **6** (4.87 g, 82% yield) was obtained as a yellow powder having the following properties.: mp 169-171 ℃; R_f=0.64 (toluene/acetone 1:1); MS (FAB) *m/z* 274 $(M+H)^+$; ^1H NMR (CD_3OD, 400 MHz) δ 4.46 (2H, d, *J*=2.0 Hz), 6.79 (1H, t, *J*=2.0 Hz), 6.96-7.03 (2H, m), 7.43 (1H, dt, *J*=2.0 and 8.3 Hz), 7.60 (1H, s), 8.01 (1H, dd, *J*=2.0 and 7.8 Hz); IR ν_{max} (KBr) 3515, 1651, 1609, 1528, 1339 (cm^{-1}); UV λ_{max} (MeOH) nm (ε) 267 (24100), 397 (3520)

(±)-epoxyquinomicin B. Compound **6** (200 mg, 0.73 mmol) suspended in a mixture of methanol (15 ml) and water (10 ml) was added 31% hydrogen peroxide (0.48 ml, 4.4 mmol) and 5% (w/v) aq $NaHCO_3$ (3.7 ml). After the reaction mixture had been stirred at room temperature for 2 hours, ethyl acetate (100 ml) was added to it. The ethyl acetate layer was washed with water, dried over Na_2SO_4, and evaporated to dryness to give crude racemic epoxyquinomicin B (195 mg) as a pale brown yellow solid. This crude material was washed with a small amount of methanol to produce pure **2** (180 mg, 85% yield) as a pale yellow powder. The ^1H NMR, IR, UV and MS spectra were in good accordance with those reported for natural (+)-epoxyquinomicin B[9].

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