Novel Synthesis and Structural Elucidation of Quinolone Antibiotics PC-3 (SF2420B) and YM-30059

Sir:

Previously, quinolone antibiotics PC-3 (SF2420B) (**1**) and YM-30059 (**2**) were independently isolated as microbial metabolites and shown to have a wide range of biological activities including antibacterial activities.[1~3]

PC-3 (**1**) has been deduced to have a 4-hydroxy-quinoline structure **1'** containing a 2-nonenyl side chain by spectral and synthetic means.[1,2] However, the ^{13}C-NMR spectrum of the analog PC-2 having a 2-heptenyl side chain was reported to show the presence of a C=O group (δ 177.8),[1] suggesting that PC-2 and PC-3 might be present in the 4-quinolone type such as **1**.[4]

The structure of YM-30059 was determined by the spectral studies to be the 1-hydroxy-4-quinolone **2**, which corresponds to the *N*-hydroxy analog of **1**. Both compounds **1** and **2** contain the C-8 de-conjugated side chain.

These structural and biological features attracted us to synthesize both compounds **1** and **2** by using our methodologies developed for the construction of the side chain.

The starting material **3** (Fig. 1) was prepared from aniline and ethyl 2-acetopropionate according to the reported procedures.[5,6] The structure was assigned as the quinolone **3**, but not as the 4-hydroxy-quinoline structure **3'**, by the ^{13}C-NMR studies (Table 1).[7]

Benzylation of **3** gave quantitatively the *O*-benzylated quinoline **6** (Scheme 1), the structure of which was determined by comparing the NMR spectra of the 4-quinolone **4** and 4-silyloxyquinoline **5**.

The quinoline **6** was oxidized to the *N*-oxide **7**, which was treated with tosyl chloride to give the chloride **9** through the intermediate **8**.[8]

The introduction of the C-8 side chain unit into **9** was examined under a variety of conditions.[9,10] The best result was obtained by our procedures using a vinyl aluminum in the presence of $Pd(PPh_3)_4$, while no reaction occurred without $Pd(PPh_3)_4$. The vinyl aluminum, which was prepared from 1-octyne and DIBAL in hexane at 60°C for 11 hours, was added to **9** with $Pd(PPh_3)_4$ to provide the desired *trans* olefin **10** without migration of the double bond.

On one hand, **10** was submitted to de-*O*-benzylation by using 1,4-cyclohexadiene on Pd-C to give PC-3 (**1**), which was identical with the natural product in all reported data.[1,2]

On the other hand, oxidation of **10** to give the *N*-oxide **11** was followed by the similar hydrogenolysis described above to produce the 1-hydroxy-4-quinolone **2**. This was identical in all respects with the authentic sample of YM-30059.

The ^{13}C-NMR spectra of both compounds **1** and **2** showed the signals due to the carbonyl carbons at δ 178.1 and 175.5, respectively, supporting that **1** and **2** predominantly exist in the 4-quinolone structures.

Fig. 1. Quinolone antibiotics PC-3 (SF2420B) and YM-30059, and the relating compounds with their characteristic chemical shifts in the ^{13}C-NMR spectra.

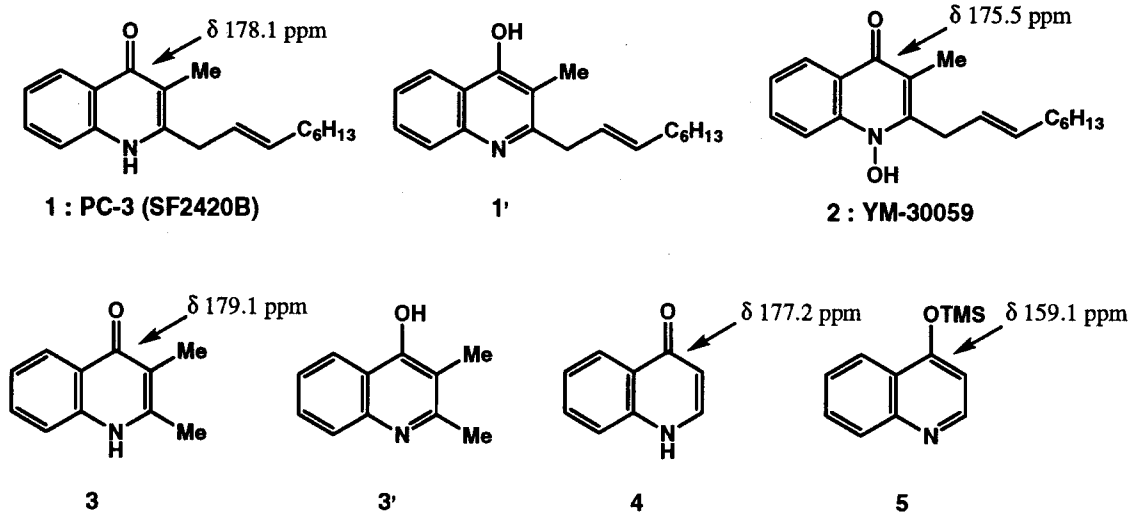

Table 1. Physico-chemical properties of compounds.

No.	Mp (°C)	NMR (270, 300, 400 or 600MHz; $CDCl_3$; δ ppm; *J* Hz)
1	199-201	^{1}H-NMR: δ 0.89(3H, t, *J*=7.0), 1.25-1.37(6H, m), 1.37-1.45(2H, m), 2.10(2H, dt, *J*=7.0&7.0), 2.16(3H, s), 3.47(2H, d, *J*=7.0), 5.55(1H, dt, *J*=15.0&7.0), 5.73(1H, dt, *J*=15.0&7.0), 7.28(1H, d, *J*=8.0), 7.29(1H, dd, *J*=8.0&8.0), 7.53(1H, ddd, *J*=8.0, 8.0&0.3), 8.37(1H, d, *J*=8.0) ^{13}C-NMR: δ 10.3, 14.1, 22.6, 28.9, 29.2, 31.7, 32.6, 35.3, 115.9, 116.7, 122.8, 123.1, 123.7, 126.4, 131.2, 137.4, 138.6, 145.9, 178.1
2	101-103	^{1}H-NMR(CD_3OD): δ 0.85(3H, t, *J*=7.0), 1.22-1.38(8H, m), 2.00-2.06(2H, m), 2.21(3H, s), 3.78(2H, br d, *J*=4.0), 5.58-5.61(2H, m), 7.43(1H, ddd, *J*=8.0, 7.0&1.0), 7.75 (1H, ddd, *J*=8.0, 7.0&1.0), 7.97(1H, br d, *J*=8.0), 8.29(1H, dd, *J*=8.0&1.0) ^{13}C-NMR(CD_3OD): δ 11.5, 14.3, 23.6, 29.8, 30.3, 32.6, 32.8, 33.5, 116.0, 116.3, 124.3, 124.6, 125.2, 126.2, 133.1, 135.1, 140.9, 152.1, 175.5(br)
3	>300	^{1}H–NMR(CD_3OD):δ2.14(3H, s), 2.50(3H, s), 7.34(1H, ddd, *J*=9.0, 9.0&1.0), 7.51(1H, br d *J*=9.0), 7.62(1H, ddd, *J*=9.0, 9.0&1.0), 8.23 (1H, dd, *J*=9.0&1.0) ^{13}C-NMR(CD_3OD): δ 10.8, 18.5, 116.6, 118.6, 124.5, 124.5, 126.1, 132.5, 140.5, 149.5, 179.1
6	116-118	^{1}H-NMR: δ 2.34(3H, s), 2.69(3H, s), 5.05(2H, s), 7.37-7.52(6H, m), 7.60(1H, ddd, *J*=7.0, 7.0& 1.0), 8.00-8.02(2H, m) ^{13}C-NMR: δ 12.5, 24.2, 76.1, 121.7, 121.8, 122.7, 125.5, 128.0, 128.4, 128.7, 128.7, 136.7, 147.8, 159.5, 160.8
7	149-150	^{1}H-NMR: δ 2.36(3H, s), 2.79(3H, s), 5.06(2H, s), 7.30-7.50(5H, m), 7.60(1H, dd,*J*=9.0&9.0), 7.75(1H, dd, *J*=9.0&9.0), 8.04(1H, d, *J*=9.0), 8.77(1H, d, *J*=9.0)
9	98-100	^{1}H-NMR: δ 2.51(3H, s), 4.87(2H, s), 5.09(2H, s), 7.40-7.60(6H, m), 7.68(1H, ddd, *J*=8.0, 8.0&1.0), 8.04(1H, d, *J*=8.0), 8.07(1H, d, *J*=8.0)
10	syrup	^{1}H-NMR: δ 0.86(3H, t, *J*=7.0), 1.20–1.40(8H, m), 2.02 (2H, dt, *J*=7.0 &7.0), 2.37(3H, s), 3.72(2H, dd, *J*=6.0&1.0), 5.06(2H, s), 5.48(1H, dtt, *J*= 15.0, 7.0&1.0), 5.67(1H, dtt, *J*=15.0, 6.0&1.0), 7.26-7.55(6H, m), 7.63(1H, ddd, *J*=8.0, 7.0&1.0), 8.02(1H, dd, *J*=8.0&1.0), 8.05(1H, d, *J*=7.0) ^{13}C-NMR: δ 11.9, 13.9, 22.6, 28.8, 29.3, 31.7, 32.6, 40.8, 76.1, 121.7, 122.7, 125.6, 126.2, 127.9, 128.4, 128.6, 128.6, 129.1, 132.8, 136.8, 148.1, 159.9, 162.3
11	syrup	^{1}H-NMR: δ 0.85(3H, t, *J*=7.0), 1.15-1.40(8H, m), 1.99(2H, dt, *J*=7.0&7.0), 2.36(3H, s), 3.95(2H, d, *J*=7.0), 5.04(3H, s), 5.55-5.75(2H, m), 7.35-7.60(6H, m), 7.71(1H, dd, *J*=7.0&7.0), 8.03(1H, d, *J*=7.0), 8.79(1H, d, *J*=7.0)

In summary, the efficient synthesis of quinolone antibiotics PC-3 (SF2420B) and YM-30059 has been achieved to confirm their structures.

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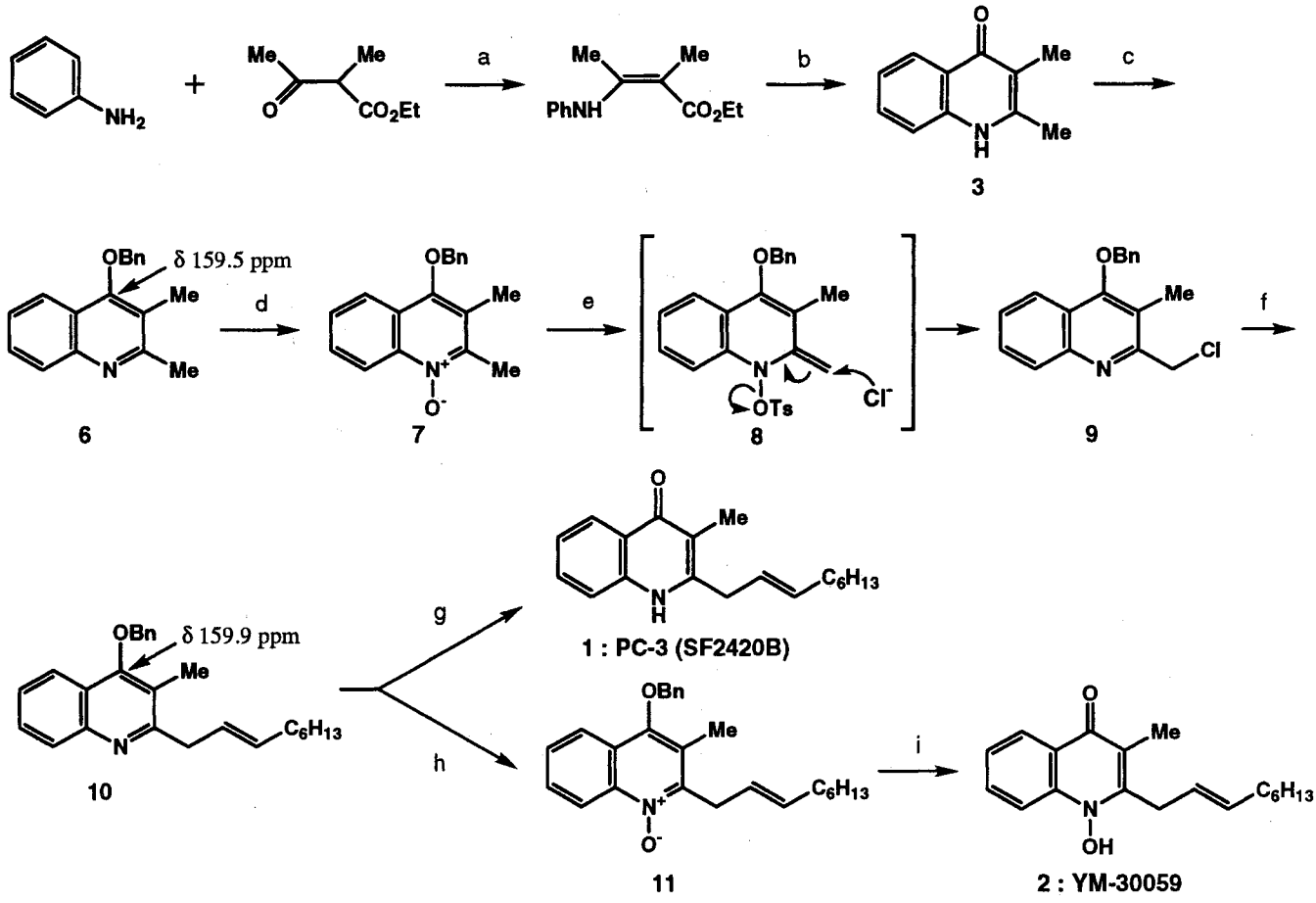
Scheme 1.



Conditions; (a) AcOH/ PhH, reflux; quant. (b) Ph_2O, 250°C; 64% (c) BnCl, K_2CO_3/ DMF, 60°C; 99% (d) MCPBA/ $CHCl_3$, rt; 85% (e) TsCl, K_2CO_3/CH_3CN, rt; 75% (f) 1)1-octyne, DIBAL/ *n*-hexane, 60°C 2) $Pd(PPh_3)_4$, THF, rt; 60% (g) 10% Pd-C, 1,4-cyclohexadiene, rt; 80% (h) MCPBA/ $CHCl_3$, 0°C; 74% (i)10% Pd-C, 1,4-cyclohexadiene, rt; quant.

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