Biomimetic Total Synthesis of Quinolactacin B, TNF Production Inhibitor, and Its Analogs

Sir:

A novel quinolone antibiotic, quinolactacin B (**1**) was isolated by NAKAGAWA's group from the fermentation broth of *Penicillium* sp. EPF-6,[1,2] as one of new inhibitors including quinolactacins A and C (**5** and **6**) active against tumor necrosis factor production and the structure was determined by spectral analyses.

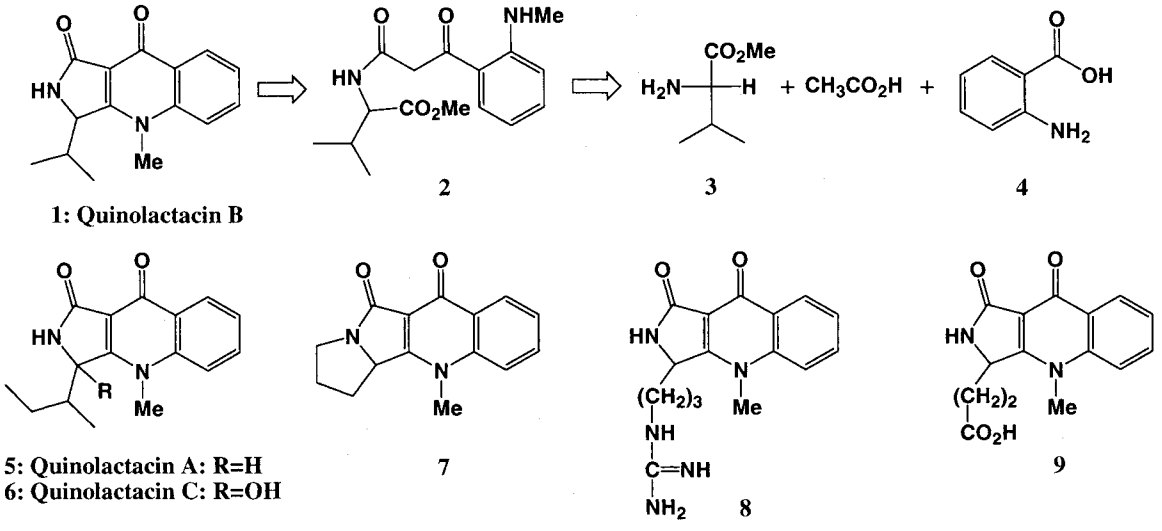
From the retrosynthetic perspective, quinolactacin B (**1**) is expected to be synthesized through the precursor **2** from three components, valine (**3**), anthranilic acid (**4**) and acetic acid as depicted in Fig. 1, suggesting that **1** might be also biologically synthesized from the same starting materials. Cyclization of **2** can be envisioned as involving *via* a Dieckmann reaction.

The natural analogs **5** and **6** could be produced from another amino acid, isoleucine.

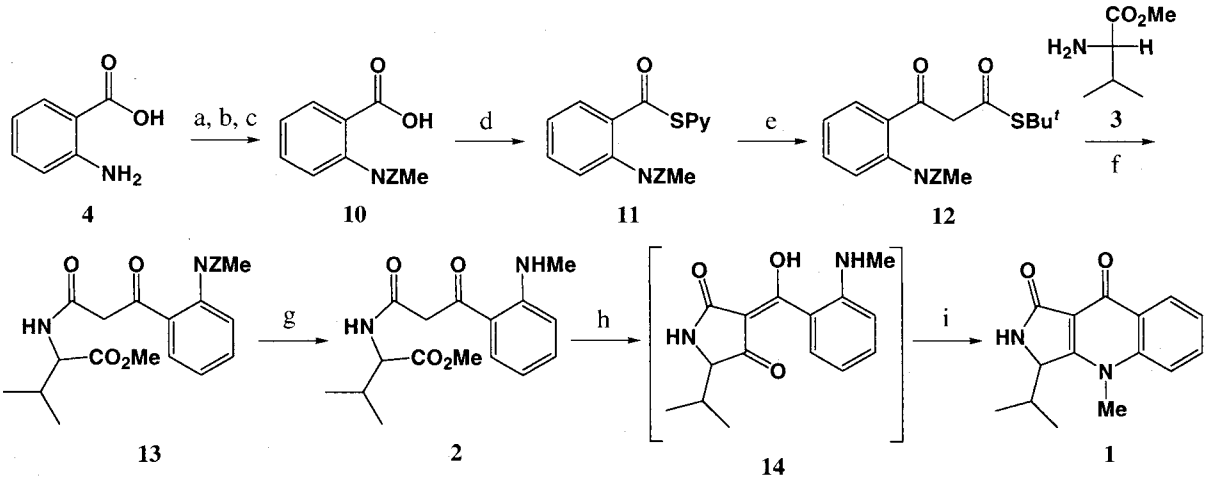
Herein we describe the biomimetic synthesis of **1** and its analogs **7**~**9**.

The starting anthranilic acid (**4**) was converted into the

Fig. 1.



Scheme 1.



Conditions; (a) ZCl, Na_2CO_3/THF-H_2O, rt, 3 hours; 98% (b) MeI, NaH/DMF, rt, 15 minutes; 79%
(c) KOH/MeOH-H_2O, 65°C, 10 hours; 75% (d) 2,2'-dipyridyl disulfide, PPh_3/THF, rt, 5 hours; 84%
(e) CH_3COSBu^t, $LiN(TMS)_2$/THF, -78°C to rt, 1 hour; 68% (f) Et_3N, CuI/THF, rt, 30 minutes; 75%
(g) H_2, Pd-C/EtOH, rt, 1 hour; 93% (h) NaOMe/MeOH, reflux, 12 hours (i) Silica gel; 65% in 2 steps

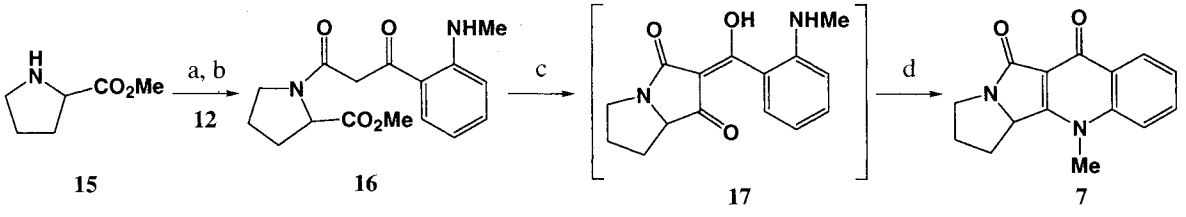
N-methyl derivative **10** in 3 steps as shown in Scheme 1. The activated thio ester **11**, which was prepared from **10** according to COREY's procedures,[3] reacted with the lithium enolate of *tert*-butyl thioacetate[4] to give the *β*-keto thio ester **12**.

For the synthesis of **1**, L-valine methyl ester (**3**) hydrochloride was coupled with **12** in the presence of CuI[5] and Et_3N to afford the corresponding *β*-keto amide **13**, which was *N*-deprotected by hydrogenolysis to **2**. This was submitted to Dieckmann cyclization[6] to the intermediary 3-acyltetramic acid **14**, which was followed by treatment with silica gel. The second cyclization proceeded smoothly with dehydration to give a racemate of the tricyclic compound **1**. This was identical with the natural product **1** in the spectral and chromatographic analyses, confirming the structure.

Now, we turned our attention to the synthesis of the analogs **7**~**9** by using proline, arginine and glutamic acid in place of valine.

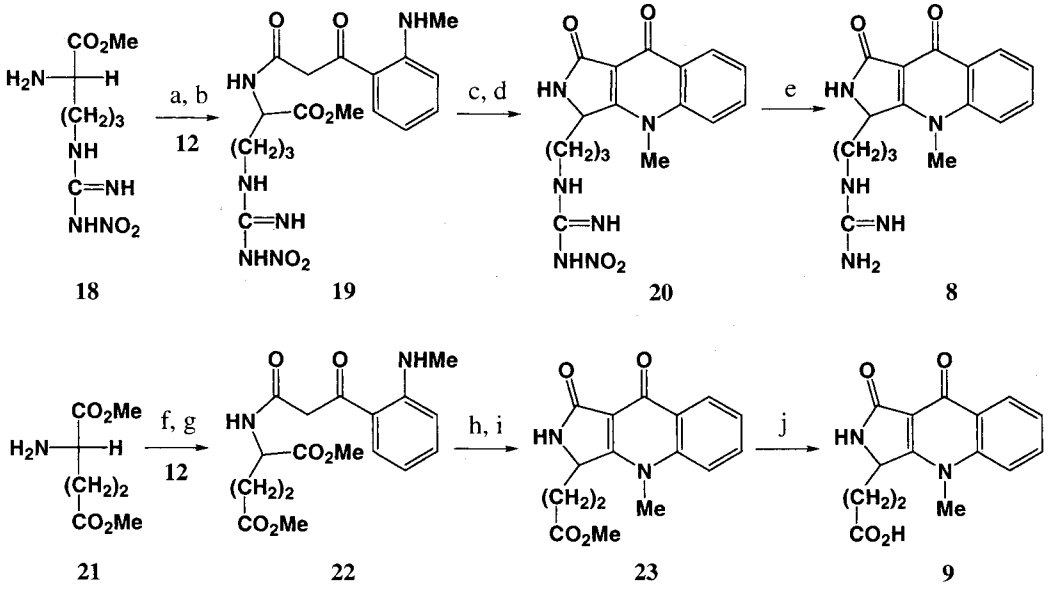
L-Proline methyl ester (**15**) hydrochloride and the aforesaid thio ester **12** was coupled under the same conditions as described in Scheme 2 to give the *β*-keto amide **16**, which was converted through the intermediate **17**

Scheme 2.



Conditions; (a) Et_3N, CuI/THF, rt, 30 minutes; 77% (b) H_2, Pd-C/EtOH, rt, 1 hour; 97% (c) NaOMe/MeOH, rt, 12 hours (d) AcOH, rt, 30 minutes; 84% in 2 steps

Scheme 3.



Conditions; (a) Et_3N, CuI/THF, rt, 30 minutes; 78% (b) H_2, Pd-C/EtOH, rt, 1 hour; 98% (c) NaOMe/MeOH, rt, 30 minutes (d) AcOH, rt, 30 minutes; 84% in 2 steps (e) H_2, $Pd(OH)_2$/10% AcOH-MeOH, rt, 30 minutes; 96% (f) Et_3N, CuI/THF, rt, 30 minutes; 79% (g) H_2, Pd-C/EtOH, rt, 1 hour; 93% (h) NaOMe/MeOH, 60°C, 4 hours (i) AcOH, 60°C, 5 minutes; 81% in 2 steps (j) NaOH/MeOH-H_2O, 60°C, 1 hour; 83%

into the tetracyclic analog **7**.

Similarly, the analogs **8** and **9** were synthesized from nitro-L-arginine (**18**) hydrochloride and L-glutamic acid dimethyl ester (**21**) hydrochloride, respectively, through the corresponding intermediates (**19**, **20**, **22** and **23**) and the proper deprotections as depicted in Scheme 3.

Their biological evaluations will be reported in due course.

Acknowledgment

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Table 1. Physico-chemical properties of compounds.

Compds.	Mp (°C)	^{1}H-NMR (300, 400 or 600 MHz; δ ppm; *J* Hz)
1	244-246(decomp.) rods(from MeOH)	$(CD_3)_2SO$: δ 0.46(3H, d, *J*=6.8), 1.14(3H, d, *J*=7.0), 2.45(1H, m), 3.84(3H, s), 4.81(1H, dd, *J*=1.0&3.2), 7.48(1H, ddd, *J*=2.0, 6.4&7.8), 7.78-7.86(2H, m), 8.09(1H, br s), 8.25(1H, dd, *J*=1.2&7.8)
2	foam	$CDCl_3$: δ 0.93(3H, d, *J*=7.2), 0.94(3H, d, *J*=7.0), 2.20(1H, m), 2.93(3H, d, *J*=5.0), 3.73(3H, s), 3.90(1H, d, *J*=16.0), 3.99(1H, d, *J*=16.0), 4.59(1H, dd, *J*=5.0&8.8), 6.60(1H, dd, *J*=8.0&8.0), 6.71(1H, d, *J*=8.4), 7.36-7.50(2H, m), 7.77(1H, dd, *J*=1.2&8.0), 8.77(1H, br s)
7	249-251(decomp.) needles(from MeOH)	$(CD_3)_2SO$: δ 1.48(1H, m), 2.10-2.26(2H, m), 2.46(1H, m), 3.12(1H, m), 3.50(1H, m), 3.82(3H, s), 4.88(1H, dd, *J*=6.6&9.8), 7.48(1H, ddd, *J*=1.6, 6.4&7.6), 7.77-7.92(2H, m), 8.26(1H, dd, *J*=1.6&7.6)
8•AcOH	233-234(decomp.)	D_2O: δ 1.34(1H, m), 1.60(1H, m), 1.90(3H, s), 2.04(1H, m), 2.20(1H, m), 3.12(2H, dd, *J*=7.2&7.2), 3.98(3H, s), 5.11(1H, dd, *J*=3.6&5.6), 7.64(1H, ddd, *J*=1.0, 7.2&8.4), 7.88-7.98(2H, m), 8.36(1H, dd, *J*=1.6&8.4)
9	>290 needles(from AcOH-MeOH)	$(CD_3)_2SO$: δ 1.80(1H, m), 2.21-2.42(3H, m), 3.86(3H, s), 4.87(1H, dd, *J*=1.4&7.4), 7.49(1H, ddd, *J*=2.4, 6.0&8.4, 7.79-7.84(2H, m), 8.13(1H, br s), 8.26(1H, d, *J*=8.4)
16	foam	$CDCl_3$: δ 1.90-2.12(3H, m), 2.24(1H, m), 2.90(3H, d, *J*=5.0), 3.51-3.71(2H, m), 3.72(3H, s), 4.03(1H, d, *J*=15.0), 4.10(1H, d, *J*=15.0), 4.56(1H, dd, *J*=3.6&8.0), 6.60(1H, dd, *J*=7.2&7.2), 6.69(1H, d, *J*=8.4), 7.39(1H, ddd, *J*=1.8, 7.2&8.4), 7.78(1H, dd, *J*=1.8&7.2), 8.75(1H, br s)
19	75-78	CD_3CO_2D: δ 1.65-2.10(4H, m), 2.91(3H, s), 3.18-3.43(2H, m), 3.75(3H, s), 4.74(1H, dd, *J*=3.6&5.2), 6.60(1H, dd, *J*=7.2&8.0), 6.74(1H, d, *J*=8.6), 7.41(1H, dd, *J*=7.2&8.6), 7.76(1H, d, *J*=8.0)
22	oil	$CDCl_3$: δ 1.96(1H, m), 2.18(1H, m), 2.26-2.44(2H, m), 2.86(3H, s), 3.59(3H, s), 3.67(3H, s), 3.84(1H, d, *J*=16.0), 3.88(1H, d, *J*=16.0), 4.61(1H, ddd, *J*=5.2, 8.0&8.0), 6.54(1H, dd, *J*=7.8&8.0), 6.64(1H, d, *J*=9.0), 7.34(1H, dd, *J*=7.8&9.0), 7.41(1H, br d, *J*=8.0), 7.67(1H, d, *J*=8.0)

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