Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 8793–8795
Tetrahedron Letters

An expedient synthesis of (+)-quinolactacin A2

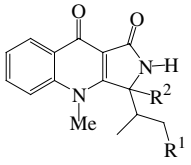
Su-Jin Park,[a] Kwang-Nym Cho,[a] Won-Gon Kim[b] and Kee-In Lee[a,*]

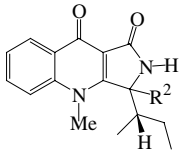
[a]*Bio-Organic Science Division, Korea Research Institute of Chemical Technology, PO Box 107, Yusong, Taejon 305-600, Korea*
[b]*National Research Laboratory of Antioxidant, Korea Research Institute of Bioscience and Biotechnology, PO Box 115, Yusong, Taejon 305-600, Korea*

Received 1 September 2004; accepted 1 October 2004

Abstract—An expedient synthesis of quinolactacin A2 from *N*-methylisatoic anhydride and *N*-Boc-(2*S*,3*S*)-isoleucine has been achieved. The key step involves the Friedländer-type annulation of isatoic anhydride and β-ketoester derived from isoleucine.

Quinolactacin A, B, and C containing a novel pyrrolo[3,4-*b*]quinolone skeleton were isolated from the fermentation broth of the fungal strain, *Penicillium* sp. EPF-6.[1] The structure of quinolactacins is unique in that a quinolone skeleton is conjugated with a γ-lactam ring. While a series of quinolactacins exhibited very weak anti-microbial activity, quinolactacin A showed inhibitory activity against tumor necrosis factor production induced by murine peritoneal macrophage. More recently, two diastereomeric quinolactacin A1 and A2, as shown in Figure 1, were isolated from solid-state fermentation of *Penicillium citrinum* 90684.[2] It has been reported that quinolactacin A2 exhibited 14 times higher anti-acetylcholinesterase activity than its diastereomer quinolactacin A1, and selective inhibitory activity for acetylcholinesterase against butyrylcholinesterase.





Quinolactacin A : R^1 = Me, R^2 = H
Quinolactacin B : R^1 = H, R^2 = H
Quinolactacin C : R^1 = Me, R^2 = OH

Quinolactacin A1 : R^2 = β-H
Quinolactacin A2 : R^2 = α-H

Figure 1. Structures of quinolactacin A–C and diastereomeric quinolactacin A1 and A2.

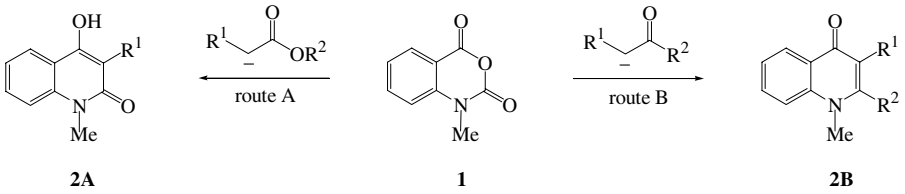
The first biomimetic synthesis of quinolactacin B suggests that quinolactacins might be biologically synthesized from three components, amino acids, anthranilic acid, and acetic acid.[3] This synthesis enlightens a general route to the many quinolactacin analogs. Recently, the enantioselective syntheses of (+)-quinolactacin A2 and (+)-quinolactacin B have been made through Winterfeldt oxidation of the Pictet–Spengler adducts starting from tryptamine and the corresponding aldehydes.[4]

It has been known that isatoic anhydride **1** is susceptible to nucleophilic attack, normally at the 'acid' 4-carbon.[5] In case of malonates, the reaction proceeds with concomitant removal of alcohol to afford quinoline-2,4-dione **2A** (route A, Scheme 1). Whereas, β-ketoesters react with **1** and further undergo ring closure by enamine formation with the β-keto group to produce 4-oxoquinoline **2B** (route B). We envisioned that a Friedländer-type annulation of isatoic anhydride and β-ketoesters derived from amino acids would offer the most concise synthetic route to quinolactacins. Here we would like to report an expedient synthesis of quinolactacin A2.

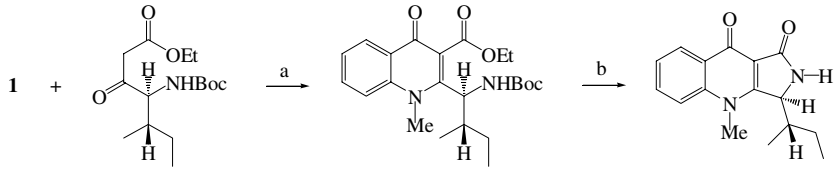
The required isoleucine derivative **3** was prepared from *N*-Boc-(2*S*,3*S*)-isoleucine according to the reference procedure.[6] After activation of its carboxyl group to the corresponding imidazolide (CDI, THF, 2 h), followed by the treatment with ethyl lithioacetate (EtOAc, LiHMDS, −78 °C, THF)[7] afforded the known β-ketoester **3**[8] in 81% yield. Next, we evaluated the Friedländer-type annulation of the readily available *N*-methylisatoic anhydride **1** with the β-ketoester **3** to secure the 4-oxoquinoline **4**, as shown in Scheme 2. After examining a number of bases commonly employed in such cyclization,[9] we found that DBU was the base of

Keywords: Isatoic anhydride; β-ketoester; Friedländer-type annulation; (+)-Quinolactacin A2.
* Corresponding author. Tel.: +82 42 860 7186; fax: +82 42 860 7160; e-mail: kilee@krict.re.kr

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.10.001



Scheme 1.



Scheme 2. Reagents and conditions: (a) DBU, molecular sieves 3 Å, CH_2Cl_2, 20 h, 42%; (b) Et_2O/H_2O/TFA, 2 h, 87%.

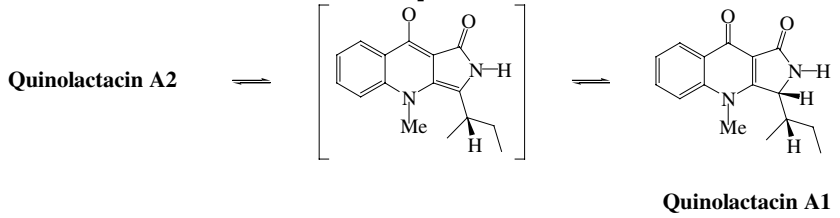


Figure 2. Epimerization of quinolactacin A2 into quinolactacin A1.

choice and the yield was improved by adding molecular sieves 3 Å as a dehydrating agent. In this way, the desired 4-oxoquinoline **4**[10] was realized in 42% yield without the formation of quinoline-2,4-dione. Unfortunately, we could not avoid the regeneration of *N*-methylanthranilic acid during the reaction. Finally, *N*-Boc amino ester **4** was subjected to deprotection of *N*-Boc group under acidic conditions (Et_2O/H_2O/TFA) and which in turn spontaneously cyclized to give the tricyclic compound **5** (87%) and its diastereomer at the ratio of ~8:1. The compound **5**[11] was matched with (+)-quinolactacin A2 in the spectral and optical data reported in the literatures; $[\alpha]_D^{21}$ +20.5 (*c* 0.26, DMSO) [lit. $[\alpha]_D^{25}$ +17.9 (*c* 0.13, DMSO)[1b] and $[\alpha]_D^{20}$ +19.5 (*c* 0.7, DMSO)[4]].

While an expedient synthesis of (+)-quinolactacin A2 from *N*-Boc-(2*S*,3*S*)-isoleucine had been achieved, it was prone to epimerized to its diastereomer with prolonged contact time with silica gel, protic solvents, and acidic media and vice versa (Fig. 2). To evaluate the epimerization of (+)-quinolactacin A2, the diastereomeric mixture was isolated by chiral HPLC (Chirex (R)-NGLY and DNB (4 × 250 mm)).[12] The epimer was totally matched with ^1H NMR and ^{13}C NMR data of quinolactacin A1 and thus identified as C-3 diastereomer to (+)-quinolactacin A2. This result clearly suggested that quinolactacin A2 and A1 are C-3 diastereomers each other.

In summary, we have achieved the expedient synthesis of (+)-quinolactacin A2 from isatoic anhydride and *N*-Boc-(2*S*,3*S*)-isoleucine utilizing Friedländer-type annulation. This route described herein may offer highly efficient approach to the total synthesis of quinolactacin family and analogs. Currently, a similar chemistry is ongoing to establish the absolute configurations of quinolactacins, which have not been clearly determined.

References and notes

1. (a) Kakinuma, N.; Iwai, H.; Takahashi, S.; Hamano, K.; Yanagisawa, T.; Nagai, K.; Tanaka, K.; Suzuki, K.; Kirikae, F.; Kirikae, T.; Nakagawa, A. *J. Antibiot.* **2000**, *53*, 1247; (b) Takahashi, S.; Kakinuma, N.; Iwai, H.; Yanagisawa, T.; Nagai, K.; Suzuki, K.; Tokunaga, T.; Nakagawa, A. *J. Antibiot.* **2000**, *53*, 1252.
2. Kim, W.-G.; Song, N.-K.; Yoo, I.-D. *J. Antibiot.* **2001**, *54*, 831.
3. Tatsuta, K.; Misawa, H.; Chikauchi, K. *J. Antibiot.* **2001**, *54*, 109.
4. Zhang, X.; Jiang, W.; Sui, Z. *J. Org. Chem.* **2003**, *68*, 4523.
5. (a) Coppola, G. M. *Synthesis* **1980**, 505; (b) Coppola, G. M.; Hardtmann, G. E. *J. Heterocycl. Chem.* **1979**, *16*, 1605.
6. (a) Hamada, Y.; Kondo, Y.; Shibata, M.; Shioiri, T. *J. Am. Chem. Soc.* **1989**, *111*, 669; (b) Harris, B. D.; Joullié, M. M. *Tetrahedron* **1988**, *44*, 3489.
7. Rathke, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3222.

8. (a) Paris, M.; Fehrentz, J.-A.; Heitz, A.; Loffet, A.; Martinez, Z. *Tetrahedron Lett.* **1996**, *47*, 8489; (b) Shioiri, T.; Hayashi, K.; Hamada, Y. *Tetrahedron* **1993**, *49*, 1913.
9. (a) Dorma, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G. R.; McWilliams, J. C.; Reider, P. J.; Sager, J. W.; Volante, R. P. *J. Org. Chem.* **2003**, *68*, 467; (b) Vasse, J.-L.; Levacher, V.; Bourguignon, J.; Dupas, G. *Tetrahedron* **2003**, *59*, 4911; (c) Camps, P.; Gómez, E.; Muñoz-Torrero, D.; Arnó, M. *Tetrahedron: Asymmetry* **2001**, *12*, 2909.
10. Satisfactory analytical data were obtained for the compound **4**: ^{1}H NMR ($CDCl_3$) δ 8.44 (1H, dd, $J = 7.5$, 1.4 Hz), 7.68 (1H, ddd, $J = 8.2$, 7.5, 1.4 Hz), 7.56 (1H, d, $J = 8.1$ Hz), 7.39 (1H, dd, $J = 7.7$, 7.5 Hz), 6.23 (1H, d, $J = 9.3$ Hz), 4.95 (1H, dd, $J = 10.1$, 2.3 Hz), 4.42 (2H, q, $J = 7.2$ Hz), 4.01 (3H, s), 1.82–1.75 (2H, m), 1.45 (3H, t, $J = 7.1$ Hz), 1.43 (9H, s), 0.94 (3H, t, $J = 7.4$ Hz), 0.81 (3H, d, $J = 6.7$ Hz); ^{13}C NMR ($CDCl_3$) δ 175.3, 169.8, 155.7, 153.8, 141.7, 132.8, 126.7, 126.6, 124.2, 116.8, 116.5, 80.0, 61.9, 66.0, 38.8, 36.5, 28.3, 26.4, 15.7, 14.1, 11.4; EIMS *m*/*z* (rel intensity) 416 (M^+, 75), 387 (18), 360 (20), 343 (15), 331 (52), 303 (27), 271 (45), 259 (30), 241 (56), 213 (100); HREI-MS Calcd for $C_{23}H_{32}N_2O_5$: 416.2311, Found: 416.2309.
11. To a solution of 10 mL of Et_2O/H_2O/TFA (1/1/3) was added **4** (658 mg, 1.57 mmol) at room temperature. The reaction mixture was stirred for 2 h. Saturated $NaHCO_3$ was added, and the aqueous layer was extracted three times with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give the tricyclic compound **5** and its diastereomer at the ratio of 8:1. The diastereomeric mixture was isolated by preparative TLC (silica gel, THF/$CHCl_3$ = 6:1) to give **5** as a white solid (369 mg, 87%). The ^{1}H NMR and ^{13}C NMR of **5** identical with the data of (+)-quinolactacin A2 reported in Ref. 1b: $[\alpha]_D^{21}$ +20.5 (*c* 0.26, DMSO) [lit. $[\alpha]_D^{25}$ +17.9 (*c* 0.13, DMSO)[1b] and $[\alpha]_D^{20}$ +19.5 (*c* 0.7, DMSO)[4]].
12. HPLC conditions: column, Chirex (R)-NGLY and DNB (4×250 mm), Phenomenex; eluent, MeOH–H_2O (45:50); flow rate, 1 mL/min; UV absorbance at 315 nm; retention time, (+)-quinolactacin A1 (9.8 min) and (+)-quinolactacin A2 (10.7 min). (+)-quinolactacin A1: $[\alpha]_D^{21}$ +10.8 (*c* 0.39, DMSO).