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Concise Enantioselective Syntheses of Quinolactacins A and B through Alternative Winterfeldt Oxidation

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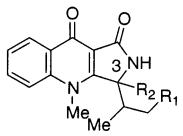
Abstract: Enantioselective total syntheses of (+)-quinolactacin B and (+)-quinolactacin A2 through asymmetric Pictet−Spengler cyclization and KO_2 oxidation—an alternative Winterfeldt condition—are described.

Novel quinolone antibiotics, quinolactacins A−C (Figure 1) were first discovered from the cultured broth of *Penicillium* sp. EPF-6, which was isolated from the larvae of the mulberry pyralid (*Margaronia pyloalis* Welker).[1] Quinolactacin A shows inhibitory activity against tumor necrosis factor (TNF) production by murine macrophages and macrophage-like J774.1 cells stimulated with lipopolysaccharide (LPS). More recently, the two quinolactacin A diastereomers were isolated from solid-state fermentation of *Penicillium citrinum* 90648 and named quinolactacin A1 and quinolactacin A2 (Figure 2).[2] The relative configuration of quinolactacin A2 is assumed to be the same as that of the originally assigned quinolactacin A from the cultured broth of *Penicillium* sp. EPF-6 on the basis of spectroscopic analysis. Quinolactacin A1 is the C-1′ diastereomer of A2. It is interesting that quinolactacin A2 showed 14 times higher *anti*-acetylcholinesterase activity than its diastereomer quinolactacin A1. The quinolactacins are the first pyrrolo[3,4-*b*]quinoline-type compounds isolated from microbial metabolites. The structures are unique in that a quinolone skeleton is conjugated with a γ-lactam ring. A biomimetic total synthesis of quinolactacin B has been reported by Tatsuta's group.[3] The synthesis suggests that quinolactacins might be biologically synthesized from three components, amino acids, anthranilic acid, and acetic acid. This synthesis also provides a general route to the analogues of quinolactacin-type antibiotics.

These unique structures elicited our interest in the quinolactacin alkaloids as targets for total synthesis. We envisioned that the total synthesis of quinolactacin B would confirm its absolute configuration as assigned by the literature.[1b,2] More importantly, the first total synthesis of quinolactacin A will establish both absolute configurations of A1 and A2, which have not been clearly determined. In view of synthetic strategy, the functional



R_1 = Me, R_2 = H, quinolactacin A
R_1 = H, R_2 = H, quinolactacin B
R_1 = Me, R_2 = OH, quinolactacin C

FIGURE 1. Structures of quinolacatacins A−C.

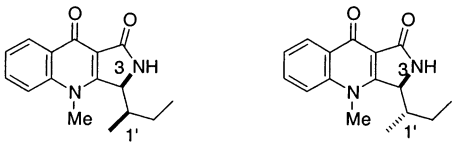


FIGURE 2. Diastereomeric quinolacatacins A1 and A2.

quinolone skeletons might be assembled by the application of an alternative Winterfeldt oxidation of β-carbolines as recently developed in our group.[4] In this paper, we describe an efficient enantioselective syntheses of quinolactacin B and quinolactacins A1 and A2.

A retrosynthetic analysis that outlines the implementation of our synthetic protocol is shown in Scheme 1. Thus, it was envisioned that quinolone **1** possessing the necessary functionalities could be furnished from β-carboline precursor **2** by KO_2 oxidation. The construction of β-carboline **2** could be achieved by diastereoselective Pictet−Spengler cyclization of the indole **3**. It should be noted that various indoles **3** could be prepared by condensation of commercially available tryptamine with the corresponding aldehydes (RCHO). This methodology should have potential in the synthesis of a series of quinolactacin analogues.

We first investigated the diastereoselective syntheses of chiral β-carboline-type structures **5** (Scheme 2). Asymmetric Pictet−Spengler reactions on the precursors **4** by employing chiral methyl benzyl or chiral naphthylethyl groups as chiral auxiliaries have been reported in the literature.[5] However, these methods when employed on our substrates resulted in very low diastereoselectivities of the cyclization adducts. We were then attracted by Waldmann's asymmetric Pictet−Spengler cyclization methodology using *N*,*N*-phthaloyl-protected amino acid chlorides as chiral auxiliaries.[6] Thus, the synthetic route to (+)-quinolactacin B is shown in Scheme 3. Compound **8a** was prepared according to Waldmann's protocol using

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(1) (a) Kakinuma, N.; Iwai, H.; Takahashi, S.; Hmano, 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) (a) Jiang, W.; Zhang, X.; Sui, Z. *Org. Lett.* **2003**, *5*, 43. (b) Zhang, X.; Jiang, W.; Sui, Z. Asymmetric total syntheses of quinolactacin A and B through an improved Winterfeldt Oxidation. *Abstracts of Papers*; 224th ACS National Meeting, Boston, MA, 18−22 Aug, 2002; American Chemical Society: Washington, DC, 2002.

(5) (a) Kawate, T.; Yamanaka, M.; Nakagawa, M. *Heterocycles* **1999**, *50*, 1033. (b) Soe, T.; Kawate, T.; Fukui, N.; Hino, T.; Nakagawa, M. *Heterocycles* **1996**, *42*, 347. (c) Gremmen, C.; Willemse, B.; Wanner, M.; Koomen, G.-J. *Org. Lett.* **2000**, *2*, 1955. (d) Jiang, W.; Sui, Z.; Chen, X. *Tetrahedron Lett.* **2002**, *43*, 8941.

(6) (a) Waldmann, H.; Schmidt, G.; Henke, H.; Burkard, M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2402. (b) Schmidt, G.; Waldmann, H.; Henke, H.; Burkard, M. *Chem. Eur. J.* **1996**, *2*, 1565.

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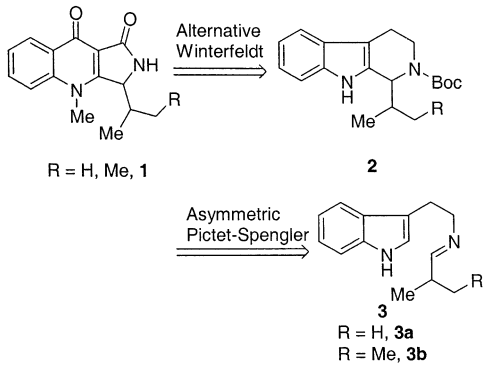
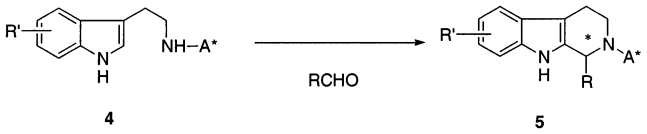
SCHEME 1. Retrosynthetic Analysis of Quinolactacins A and B

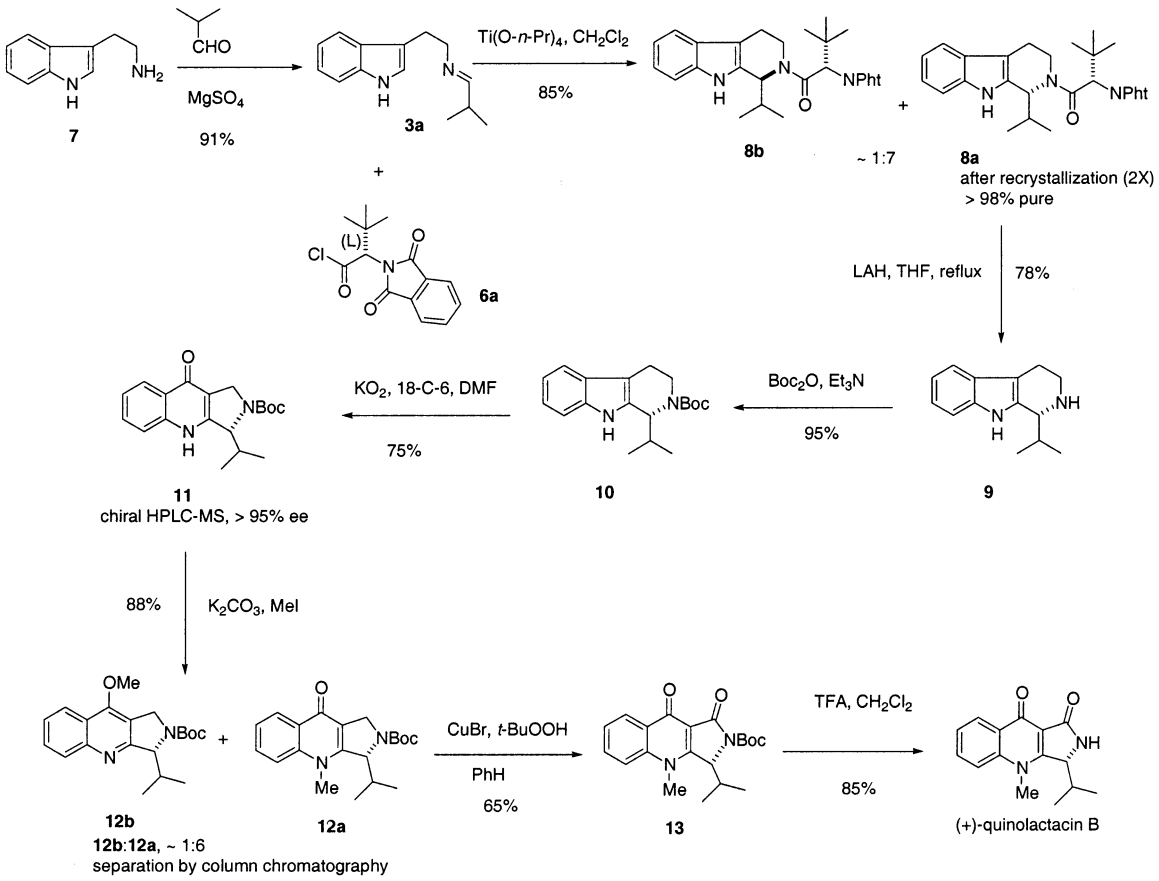


SCHEME 2. Asymmetric Pictet−Spengler Cyclization

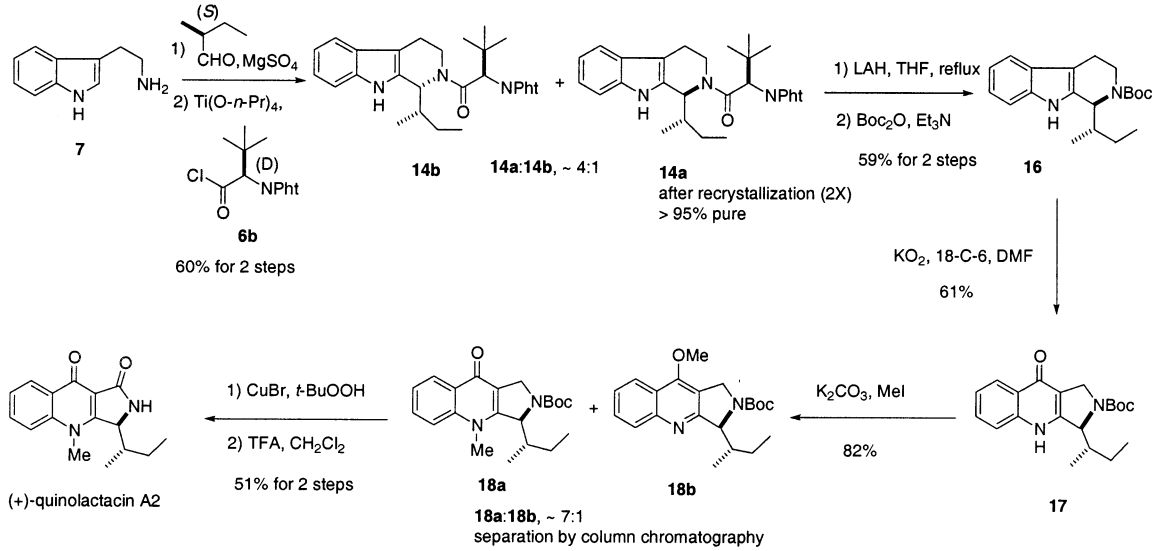


N,*N*-phthaloyl-protected amino acid chloride **6a** derived from L-(+)-*tert*-leucine[7] as chiral auxiliary in 68% yield from tryptamine (**7**) and ~7:1 ratio to its C-3 diastereomer.[6b] Because L-(+)-*tert*-leucine-derived chiral auxiliary was used for the formation of the intermediate acyl iminium species, the absolute stereochemistry of C-3 in the β-carboline **8a** was assigned as the *R* configuration according to the studies by Waldmann.[6] The chiral auxiliary of the Pictet−Spengler adduct **8a** could be readily removed by cleavage of the amide bond of **8a** with $LiAlH_4$ to give the enantiomerically pure tetrahydro-β-carboline **9** in 78% yield. Protection of the *sec*-amine group of **9** with Boc_2O and Et_3N (95% yield),[8] followed by modified Winterfeldt oxidation (KO_2, 18-C-6) of the resulting protected indole **10** gave the quinolone **11** in 75% yield. This is consistent with our previous findings that KO_2 is an efficient and mild reagent for transformation of β-carbolines to pyrroloquinolones.[4] Traditional Winterfeldt oxidation conditions using a strong base[9,10] such as *t*-BuOK or NaH were avoided in our synthesis due to the possibility of epimerization in the course of the rearrangement. It is known that the oxidation of β-carbolines under Winterfeldt conditions results in a ketone amide intermediate, which could be very sensitive to base-induced epimerization.[11] To evaluate the mildness of KO_2 and 18-C-6 combination, we determined the ee value of **11** by chiral HPLC. After integration of the peak of chiral **11** on HPLC using *rac*-**11**[12] as the standard, the ee of chiral **11** was determined as >95%. This result demonstrated that there was no epimerization in the process of the rearrangement by using KO_2 condition. The quinolone **11** was then methylated with MeI in the presence of K_2CO_3 to afford the methylated quinolone **12a** and the methylated pyridine **12b** in 6:1 ratio (88% yield). The isomers **12a** and **12b** were easily separated by column chromatography. The desired quinolone **12a** was then subjected to the allylic oxidation conditions to

SCHEME 3. Asymmetric Total Synthesis of (+)-Quinolactacin B



SCHEME 4. Asymmetric Total Synthesis of Quinolactacin A2



deliver the ketone lactam functionality in the target molecule. Several attempts to oxidize **12a** to **13** with common oxidants such as SeO_2, MnO_2, and RuO_2 were unsuccessful. However, treatment of **12a** with PDC (0.2 equiv) and *t*-BuOOH (2.0 equiv) in PhH resulted in the desired ketone lactam **13** in 25% yield.[13] We then optimized the reaction using CuBr as the catalyst to improve the yield to 65%.[14] After deprotection of Boc group from **13** by the treatment with TFA in CH_2Cl_2, (+)-quinolactacin B was obtained in 85% yield [$[\alpha]^{20}_D$ +5.8 (*c* 0.2, DMSO) [lit.[1b] $[\alpha]^{25}_D$ −3.3 (*c* 0.15, DMSO)]]. Our synthetic quinolactacin B showed spectral data identical with that of the natural product reported. The optical rotation of our synthetic product is the opposite of the natural product, which demonstrates that our product is the enantiomer of the natural product. Thus, the result confirmed that the absolute stereochemistry of C-3 in natural (−)-quinolactacin B is the *S* configuration, as assigned by the biomimetic synthesis.[3] Utilizing the same route, the natural product can be synthesized by using the D-amino acid derived chiral auxiliary.

Due to the indetermination of absolute stereochemistry of quinolactacin A, we extended the above synthetic route to the synthesis of quinolactacin A. We assumed that C-1′ stereochemistry of quinolactacin A2 (reported first in ref 1b as quinolactacin A) could be derived from a natural amino acid. Thus, (*S*)-(+)-2-methylbutanal[15] was used as the aldehyde component for the synthesis. The detailed synthetic route to (+)-quinolactacin A2 is shown in Scheme 4. Coupling tryptamine (**7**) with (*S*)-(+)-2-methylbutanal gave the Schiff base **3b** (structure not shown in Scheme 4). Asymmetric Pictet−Splengler cyclization of **3b** using the more expensive D-amino acid derived chiral auxiliary **6b** in the presence of $Ti(O\text{-}n\text{-}Pr)_4$ afforded the β-carboline **14a** and **14b** in 4:1 ratio. Thus, asymmetric induction by the D-chiral auxiliary resulted in the *S* configuration at C-3 of the major diastereomer **14a**. Removal of the chiral auxiliary from **14a** by LAH provided the chiral β-carboline **15** (structure not shown). Reprotection of the corresponding *sec*-amine with Boc_2O (**16**), followed by KO_2 oxidation, gave the quinolone **17** in 61% yield. After methylation of **17** to **18**a and **18b** (separated by column chromatography), allylic oxidation of the desired quinolone **18a** to **19** and deprotection of Boc group of **19** (structure not shown), (+)-quinolactacin A2 was obtained as a single enantiomer [$[\alpha]^{20}_D$ +19.5 (*c* 0.4, DMSO) [lit.[1b] $[\alpha]^{25}_D$ +17.9 (*c* 0.13, DMSO)]]. Spectroscopic data for synthetic (+)-quinolactacin A2 are in full accordance with the data as reported in the literature.[1b,2] Both C-3 and C-1′ stereochemistry are established as the *S* configuration.

Quinolactacin A1 has been assigned as the diastereomer of A2 on the basis of its spectral data. Although quinolactacin A1 was isolated concurrently with A2 from the same microbial metabolites, it is still not clear whether they are real diastereomers at C-1′. Due to the unavailability of optically pure (*R*)-(−)-2-methylbutanal, we took advantage of commercially available *rac*-2-methylbutanal as starting material. Following the synthetic route described, a pair of C-1′ diastereomers were obtained. Chiral HPLC was used for separation of these two diastereomers (see the Experimental Section). The column was eluted with 2-propanol at a flow rate of 1 mL/min to afford quinolactacin A2 with a retention time of 4.276 min and its C-1′ diastereomer at 5.706 min. From ^1H NMR of the diastereomeric mixture, the C-1′ diaste-

(7) For preparation of the chiral auxiliary, see: Sheehan, J.; Chapman, D.; Roth, R. *J. Am. Chem. Soc.* **1952**, *74*, 3822.
(8) Lounasmaa, M.; Karvinen, E.; Koskinen, A.; Jokela, R. *Tetrahedron* **1987**, *43*, 2135.
(9) Winterfeldt, E. *Liebigs Ann. Chem.* **1971**, *745*, 23.
(10) (a) Warneke, J.; Winterfeldt, E. *Chem. Ber.* **1972**, *105*, 2120. (b) Boch, M.; Korth, T.; Nelke, J. M.; Pike, D.; Radunz, H.; Winterfeldt, E. *Chem. Ber.* **1972**, *105*, 2126.
(11) (a) Demerson, C. A.; Humber, L. G. *Can. J. Chem.* **1979**, *57*, 3296. (b) Carniaux, J.-F.; Han-Fan, C.; Royer, J.; Husson, H.-P. *Synlett* **1999**, *5*, 563.
(12) *rac*-**11** was prepared from *rac*-**9**, available from acid-catalyzed Pictet−Spengler cyclization of tryptamine and isobutyraldehyde.
(13) Schultz, A. G.; Taveras, A. G.; Harrington, R. E. *Tetrahedron Lett.* **1988**, *29*, 3907.
(14) Salvador, J. A. R.; Sá e Melo, M. L.; Campos Neves, A. S. *Tetrahedron Lett.* **1997**, *38*, 119.
(15) For preparation of (*S*)-(+)-methylbutanal, see: Jauch, J.; Czesla, H.; Schurig, V. *Tetrahedron* **1999**, *55*, 9787.
(16) Gremmen, C.; Willemse, B.; Wanner, M.; Koomen, G. J. *Org. Lett.* **2000**, *2*, 1955.
(17) Kawate, T.; Nakagawa, M.; Yamazaki, H.; Hirayama, M.; Hino, T. *Chem. Pharm. Bull.* **1993**, *41*, 287.

reomer of quinolactacin A2 could be differentiated by comparison of the spectrum of A2. The spectrum is in agreement with the data of quinolactacin A1 reported in ref 2. This result confirms quinolactacin A1 is the C-1′ diastereomer of A2.

In conclusion, we have achieved the enantioselective total syntheses of (+)-quinolactacin B and (+)-quinolactacin A2. The route described herein affords (+)-quinolactacin B in overall 16% yield over eight steps from tryptamine and (+)-quinolactacin A2 in 8% yield. The synthetic protocol is highlighted by asymmetric Pictet−Spengler cyclization and KO_2 oxidation reactions. We also confirmed that quinolactacin A1 is the C-1′ diastereomer of A2. The present synthesis should be amenable to provide general access to members of the quinolactacin family and analogues.

Experimental Section

General Methods. All melting points were uncorrected. ^{1}H NMR spectra were obtained at 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz, with *d*-chloroform or DMSO-d_6 as solvent. Chemical shifts are reported in ppm downfield from TMS as an internal standard. Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ. Thin-layer chromatography was carried out using silica gel 60 (250 μM layer) plates with UV detection. Flash chromatography was done using EM science silica gel 60 (230−400 mesh). *N*,*N*-Phthaloyl-protected amino acid chlorides **6a** and **6b** were prepared according to the method reported by Sheeman.[7]

3-(*R*)-Isopropyl-9-oxo-1,3,4,9-tetrahydropyrrolo[3,4-*b*]-quinoline-2-carboxylic Acid *tert*-Butyl Ester (11). To a solution of **10** (105 mg, 0.334 mmol) and 18-crown-6 (88 mg, 0.334 mmol) in DMF (3 mL) was added KO_2 (95 mg, 1.34 mmol) [Caution! Explosive Material!] in one portion at room temperature. The reaction solution turned red. After 30 min, the red color disappeared and the reaction was stirred for another 2 h. The extra KO_2 was then quenched with saturated NH_4Cl, and EtOAc was added into the reaction. The aqueous phase was extracted five times with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. Flash column chromatography (silca gel, EtOAc) afforded **11** as a white solid (83 mg, 75%). The ee value is >95% on the basis of Chiral AD HPLC-MS analysis: mp 245−247 °C dec; $[\alpha]^{20}_D$ +191 (*c* 0.21, MeOH); ^{1}H NMR (DMSO-d_6) δ 8.16 (d, 1H, J = 7.5 Hz), 7.62 (m, 2H), 7.30 (d, 1H, J = 6.8 Hz), 5.05 (d, 1H, J = 13.5 Hz), 4.55 (d, 1H, J = 7.0 Hz), 4.21 (m, J = 13.5 Hz, 1H), 2.32 (m, 1H), 1.46 (s, 9H), 1.02 (d, 3H, J = 7.5 Hz), 0.82 (d, 3H, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 174.1, 154.6, 140.8, 131.6, 125.4, 125.0, 123.3, 119.0, 116.0, 115.5, 82.2, 66.9, 34.5, 33.2, 28.4, 19.7, 17.0, 11.5; IR (neat, cm^{-1}) 3395, 1684, 1620; MS (*m*/*z*) 329 [M + H]$^+$, 679 [2M + Na]$^+$; HRMS calcd for $C_{19}H_{24}N_2O_3$ (MH^+) 329.1865, found 329.1869. Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37. Found: C, 69.25; H, 7.34.

3-(*R*)-Isopropyl-4-methyl-9-oxo-1,3,4,9-tetrahydropyrrolo-[3,4-*b*]quinoline-2-carboxylic Acid *tert*-Butyl Ester (12a) and 3-(*R*)-Isopropyl-9-methoxy-1,3-dihydropyrrolo[3,4-*b*]-quinoline-2-carboxylic Acid *tert*-Butyl Ester (12b). To a solution of **11** (110 mg, 0.33 mmol) and K_2CO_3 (92 mg, 0.67 mmol) in DMF (5 mL) was added MeI (42 μL, 0.67 mmol) at room temperature. After 2 h, the mixture was diluted with EtOAc and water. The aqueous phase with extracted twice with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give the crude product. Flash column chromatography (silica gel, hexanes/EtOAc = 3:1, then 1:1) afforded **12b** as a yellow oil (15 mg, 13%) and **12a** as a white solid (86 mg, 75%). **12a**: mp 219−221 °C; $[\alpha]^{20}_D$ +168 (*c* 0.19, MeOH); ^{1}H NMR ($CDCl_3$) δ 8.52 (d, J = 7.5 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.48 (d, = 8.2 Hz, 1H), 7.42 (t, J = 7.9 Hz, 1H), 5.41 (s, 1H), 4.88 (d, J = 12.5 Hz, 1H), 4.42 (d, J = 12.5 Hz, 1H), 3.78 (s, 3H), 2.25 (m, 1H), 1.51 (s, 9H), 1.21 (d, J = 6.9 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.7, 155.9, 152.4, 142.1, 132.2, 127.2, 126.7, 123.9, 117.6, 115.6, 80.6, 67.5, 51.6, 36.7, 34.5, 28.8, 21.4, 16.2, 14.5; IR (neat, cm^{-1}) 1697, 1625; MS (*m*/*z*) 343 [M + H]$^+$, 365 [M + Na]$^+$; HRMS calcd for $C_{20}H_{26}N_2O_3$ (MH^+) 343.2022, found 343.2033. Anal. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65; N, 8.18. Found: C, 70.02; H, 7.71; N, 8.08. **12b**: ^{1}H NMR ($CDCl_3$) δ 8.21 (d, J = 7.5 Hz, 1H), 8.03 (d, J = 7.4 Hz, 1H), 7.68 (t, J = 6.8 Hz, 1H), 7.45 (t, J = 6.8 Hz, 1H), 5.38 (d, J = 10.5 Hz, 1H), 5.01 (s, 1H), 4.90 (d, J = 10.5 Hz, 1H), 4.22 (s, 3H), 2.42 (m, 1H), 1.55 (s, 9H), 0.98 (d, J = 6.9 Hz, 6H); IR (neat, cm^{-1}) 1692; MS (*m*/*z*) 343 [M + H]$^+$, 365 [M + Na]$^+$, 707 [2M + Na]$^+$.

3-(*R*)-Isopropyl-4-methyl-1,9-dioxo-1,3,4,9-tetrahydropyrrolo[3,4-*b*]quinoline-2-carboxylic Acid *tert*-Butyl Ester (13). To a solution of **12a** (90 mg, 0.26 mmol) and CuBr (8 mg, 0.06 mmol) in PhH (6 mL) was added *t*-BuOOH (5.0 M in decane, 106 μL, 0.52 mmol) at room temperature. The mixture was then heated at 50 °C for 2 h and stirred at room temperature overnight. The solid was filtered through a pad of Celite. The filtrate was then concentrated to give a light green oil, which contained the crude product. Flash column chromatography (silica gel, EtOAc, then CH_2Cl_2/MeOH = 10:1) afforded **13** as a white solid (61 mg, 65%): mp 254−255 °C dec; $[\alpha]^{20}_D$ +75 (*c* 0.26, MeOH); ^{1}H NMR (DMSO-d_6) δ 8.46 (d, J = 7.9 Hz, 1H), 7.81 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 5.34 (d, J = 2.0 Hz, 1H), 3.89 (s, 3H), 2.43 (m, 1H), 1.58 (s, 9H), 1.24 (d, J = 6.8 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 173.5, 164.8, 163.1, 150.8, 141.0, 134.2, 126.5, 125.5, 124.2, 121.5, 114.8, 108.5, 79.5, 62.0, 34.9, 28.0, 27.6, 20.6, 14.5; IR (neat, cm^{-1}) 1753, 1625, 1605; MS (*m*/*z*) 357 [M + H]$^+$, 379 [M + Na]$^+$, 735 [2M + Na]$^+$; HRMS calcd for $C_{20}H_{24}N_2O_4$ (MH^+) 357.2178, found 357.2171.

(+)-Quinolactacin B. To a solution of **13** (50 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) was added TFA (0.5 mL) 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 CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give (+)-quinolactacin B as a white solid (31 mg, 85%). The product was pure enough for characterization without further purification. The ^{1}H NMR and ^{13}C NMR match the data reported in ref 1b: $[\alpha]^{20}_D$ +5.8 (*c* 0.12, DMSO) [lit.[1b] (−)-quinolactacin B, $[\alpha]^{25}_D$ −3.3 (DMSO)].

(+)-Quinolactacin A2: white solid; yield 85%; $[\alpha]^{20}_D$ +19.5 (*c* 0.7, DMSO) [lit.[1b] $[\alpha]^{25}_D$ +17.9 (*c* 0.13, DMSO)]. The ^{1}H NMR and ^{13}C NMR match the data reported in ref 1b.

Separation of Quinolactacin A1 and A2 by Analytical Chiral AD HPLC−MS. Diastereomeric quinolactacins A1 and A2 were prepared using the same synthetic route described in Scheme 4 from *rac*-2-methylbutanal. From ^{1}H NMR of the diasteromeric mixture (A1 and A2), spectra data of A1, compared with that of A2, matched the data in ref 2. HPLC−MS (Chiralpak AD column, 250 mm × 46 mm) was used for separation of the two diastereomers. The elution with 2-propanol at a flow rate of 1.0 mL/min on the column afforded A2 (peak 1) with a retention time at 4.276 min and A1 (peak 2) at 5.706 min. Quinolactacin A2 prepared from (*S*)-(+)- 2-methylbutanal was used for comparison.

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Supporting Information Available: Experimental details and characterizations for all new compounds; ^{1}H NMR and ^{13}C NMR spectra of all new compounds; ^{1}H NMR spectra of (+)-quinolactacin A2 and (+)-quinolactacin B. This material is available free of charge via the Internet at http://pubs.acs.org.

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