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Enantioselective total synthesis of (*S*)-(−)-quinolactacin B

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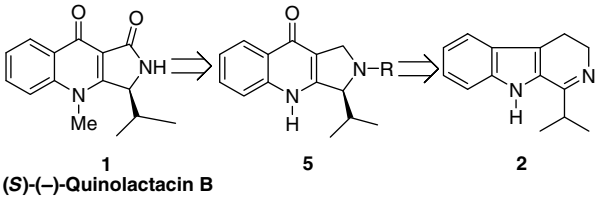
ABSTRACT

The enantioselective total synthesis of (−)-quinolactacin B (−)-**1** was performed in seven steps and 33% overall yield from tryptamine. The synthesis features the use of ruthenium catalytic asymmetric hydrogen reaction to introduce the chirality in dihydro-β-carboline **2**. Based on Noyori's work, the hydrogenation using the (*R*,*R*)-TsDPEN-Ru complex produces dihydro-β-carbolines possessing the (*S*) absolute configuration, the corrected asymmetric center of the natural product. The synthetic quinolactacin B displayed optical rotations that was in accordance with that of the natural product, thereby supporting the (*S*) configuration for natural quinolactacin B. The final product's stereochemical assignment is in agreement with that proposed by Nakagawa and co-workers.

Quinolactacin B (**1**) shows an interesting pyrrolo-quinolone moiety conjugated with a γ-lactam ring, as depicted in Scheme 1.[1] The unusual structure present in these compounds exhibited activity against tumor necrosis factor production, and biomimetic synthesis of **1** by Tatsuta et al. was suggested to undergo biologically through anthranilic acid, valine, and acetic acid.[2] In 2003, Zhang et al. reported a chiral auxiliary-based approach to this class of compounds,[3] and in 2004, Lee and coworkers achieved the synthesis of (+)-quinolactacin A2 from isatoic anhydride and *N*-Boc-(2*S*,3*S*)-isoleucine utilizing Friedlander-type annulation.[4]

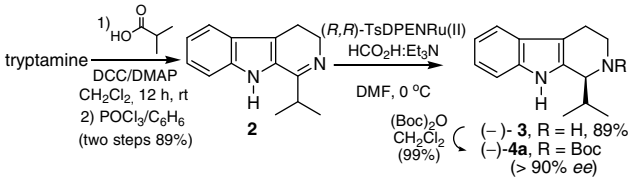
Inspired by its unusual structure, we undertook the stereoselective synthesis of **1** by taking advantage of the Noyori asymmetric hydrogen-transfer reaction of appropriately functionalized β-carboline derivative **2**.[5,6] Our strategy to quinolactacin B can be seen through the retrosynthetic analysis depicted in Scheme 1. In principle, the chirality in the molecule can be inserted through Noyori asymmetric hydrogenation of imine **2**. Then, protected β-carboline system can be converted to the pyrrolo–quinolone moiety by oxidative rearrangement of an appropriately functionalized precursor (**4**) through the unexplored Winterfeldt oxidation.[7]



Scheme 1. Retrosynthetic analysis of (−)-quinolactacin B (**1**).

We envisioned assembling the quinolactacin core of **1** by either a transition metal-catalyzed or an anodic oxidation to introduce the pyrrolo moiety. Then, an anodic oxidation reaction followed by further oxidation of resulting alcohol was appealing for its simplicity. The *N*-Boc carbamate C-ring of compound similar **6** was expected to give readily an alcohol intermediary on the pyrrolo ring.

We first set out to the introduction of the chirality in the β-carboline system through the imine **2**. Following the sequence depicted in Scheme 2, triptamine was converted in the imine **2** by exposure to isobutyric acid and DCC with catalytic amount of DMAP affording the corresponding amide. The crude amide in CH_2Cl_2 was acidified with diluted HCl, washed with H_2O, dried, evaporated, and used with no further purification. Treatment of the amide with $POCl_3$ promoted the Bischler–Napieralsky cyclization to give imine **2** in 89% yield (two steps). Having prepared imine **2**, the next step was set to introduce the required asymmetry in the molecule through the Noyori asymmetric hydrogenation (NAH) reaction. The NAH reaction uses an azeotropic mixture (HCO_2H–Et_3N) as



Scheme 2. Noyori asymmetric hydrogenation of imine **2**.

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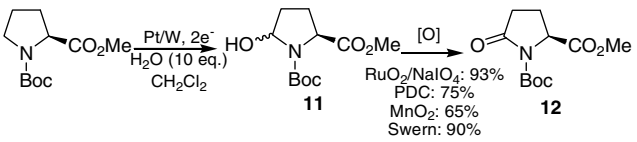
the source of hydrogen and allows a convenient, general route to natural and unnatural β-carboline alkaloids depending on the configuration of chiral ligand employed.

The Noyori hydrogenation of imine **2** was accomplished with preformed (*R*,*R*)-TsDPEN-Ru(II) complex in DMF, and a HCO_2H–Et_3N mixture[6a] that achieved amine (−)-**3** in 89% yield and >90% ee as determined by HPLC analysis using a ChiralPack OD column. According to Noyori's work, the absolute stereochemistry of **3** is expected to be (*S*). The optical rotation, $[\alpha]_D$ −83 (*c* 1.0, MeOH), is in accordance with that reported in the literature for the expected (*S*)-(−)-**3**.[3,8] Another approach to **3** was using the chloroformate of 8-phenylmenthyl as chiral auxiliary (Scheme 3). The in situ formation of the corresponding *N*-acyliminium ion **9** by adding the chloroformate of 8-phenylmenthyl to imine **2** in CH_2Cl_2 at room temperature, then cooling the mixture to −78 °C, and subsequent Pd–H reduction using $PdCl_2/Et_3SiH$ protocol[9] afforded **4b** in good yield (88%). The absolute configuration of **4b** was determined to be (*R*) after chiral auxiliary removal using $HCl/CHCl_3$ (2 M) that gave (+)-**3** in 89% yield, $[\alpha]_D$ 65 (*c* 1.0, MeOH). As mentioned above, the ee% for (+)-**3** was 75% ee as determined by HPLC, and it is in accordance with (*R*)-(+)-**3**. The chiral auxiliary 8-phenylmenthol was recovered in 95% yield with no decrease of its optical rotation. The selectivity obtained in the chiral auxiliary mediated reduction of **2** to **3** was rationalized by transition state depicted in Scheme 3, which is in accordance with the reduction of the *N*-acyliminium ion **9** through its *Si*-face.

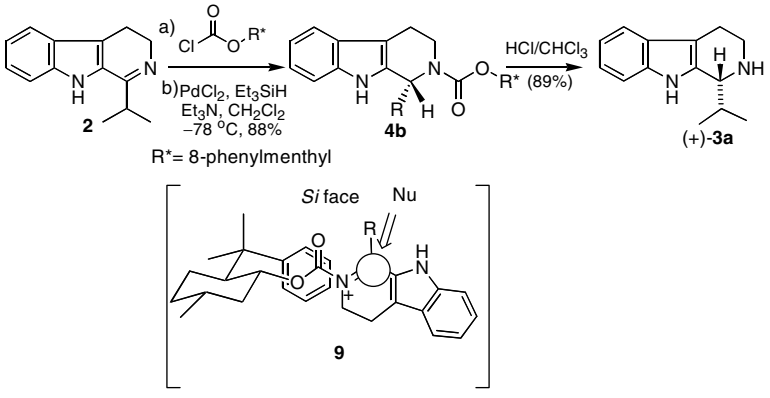
Further, with an efficient approach to the corrected asymmetric center into the quinolactacin moiety secured by NAH, the stage was now set for the Winterfeldt rearrangement. Treatment of (−)-**3** with $(Boc)_2O$ and Et_3N in CH_2Cl_2 gave *N*-carbamate(−)-**4a** in 99% yield (Scheme 2). Winterfeldt reaction of (−)-**4** with 18-crown-6-ether and NaO_2 or KO_2 gave quinolone (−)-**5** in 75% (>90% ee) and 73% (>90% ee), respectively, as depicted in Scheme 4.[10] The enantiomeric excesses were determined by HPLC to assure that no epimerization was occurred in the reaction due to basic conditions. NMR and HRMS spectra were in agreement with previously reported.[3,10] Then, the secondary amine (−)-**5** was methylated by addition of HCHO in CH_2Cl_2 at 0 °C for 15 min affording the iminium ion, which was reduced in an one-pot manner by Et_3SiH and catalytic amount of $PdCl_2$ at −78 °C for 30 min. The resulting *N*-methylquinolone (−)-**6** was obtained in 91% yield, $[\alpha]_D$ −183 (*c* 0.5, MeOH). Another approach also tested consisted by using **5** and NaHMDS (1.1 equiv, 1 h, THF, −78 °C), followed by addition of methyl iodide (−78 °C to rt, 2 h)[11] affording (−)-**6** in 90% yield as the sole product, $[\alpha]_D$ −185 (*c* 0.5, MeOH), Scheme 4.[3]

With asymmetry incorporated in the pyrrolo–quinolone moiety, we turned our attention to the exploration of anodic oxidation method for α-oxidation of carbamate (−)-**6**. Previously, the feasibility of the oxidation route was evaluated through a model system (Scheme 5) that would in turn be generated by electrochemically functionalizing the corresponding proline derivative.[12] The available *N*-Boc-proline under anodic oxidation conditions at −40 °C gave the α-hydroxy-derivative **11**[13] that was oxidized under several conditions: MnO_2 and 65%, PDC and 75%, $RuO_2/NaIO_4$ and 93%.[14] Finally, Swern conditions afforded **12** in 90% yield with no epimerization of the proline center. Trying the direct oxidation of *N*-Boc-proline ester to **12** with $RuO_2/NaIO_4$ gave a complex mixture. This model study showed that although the anodic oxidation can take place readily, temperature and reaction times needed to be controlled. Regioselective hydroxylation occurred exclusively at the less substituted carbon of the *N*-carbamate, and the hydroxy-derivative **11** showed to be very unstable to chromatography purification in silica gel.

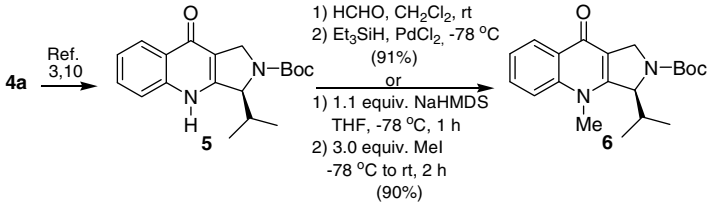
Thus, with the electrolysis approach optimized we performed the reaction with compound (−)-**6**. As expected by model studies,



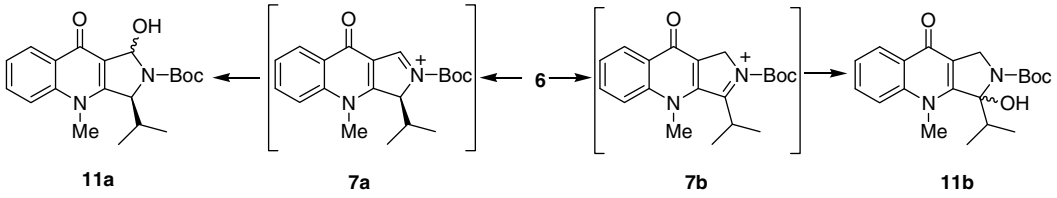
Scheme 5. Model studies of anodic/Swern oxidations with *N*-Boc-proline ester.



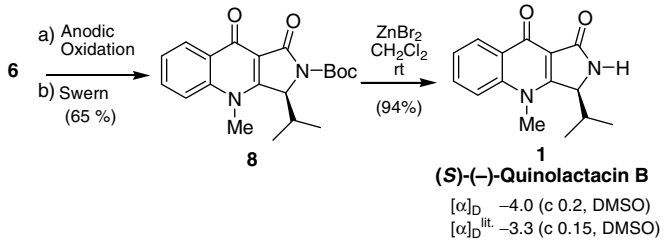
Scheme 3. Proposed facial discrimination in the chiral auxiliary-mediated Pd-hydride reduction of the *N*-acyliminium ion derived from **2**.



Scheme 4. Winterfeldt oxidation and *N*-methylation to give (−)-**6**.



Scheme 6. Proposed intermediates for the formation of **8** from **11a** and (±)-**6** from **11b**.



Scheme 7. Anodic/Swern oxidations of **6** followed by $ZnBr_2$ deprotection to give (−)-quinolactacin B.

the anodic oxidation proceeded smoothly at −78 °C giving an unstable product, which was then readily converted into the desired pyrrolo compound (−)-**8**, $[\alpha]_D$ −85 (*c* 0.5, MeOH), as depicted in Scheme 7. The expected regioselectivity of hydroxylation to less substituted α-nitrogen carbon in cyclic carbamates has been extensively studied.[13] The mechanism behind the high regiocontrol to *N*-protected carbamates was recently proposed by Onomura,[13h] and suggested that stabilities of iminium ions might determine the regioselectivities observed. *N*-acyliminium ion **7a** is somewhat stable compared with **7b** by DFT calculations, thereby affording to hydroxylation on the less substituted side (Scheme 6). As an interesting side note, it was found that temperatures higher than −30 °C and longer reaction times in the anodic oxidation led to a decrease in the yields (determined by gas-chromatography), and formation of (±)-**6** was also observed.

The unusual formation of (±)-**6** could be explained by a radicalar process involving **6** or intermediates **7b**/**11b** in the electrochemical cell, Scheme 6. Herein, on-line ESI-MS analysis[15] of the reaction mixture suggested that a hydroxylated by-product at the tertiary carbon presenting a structure as **11b** was also formed. It was rationalized that kinetic formation of the α-hydroxy-*N*-carbamate was reversible under the reaction conditions. In accordance with time, the initial *N*-acyliminium ion **7a** would be, isomerized and might be trapped hydroxy at C-2 to give **7b**. Fortunately, it was possible to address both of these regioselectivity issues due to electron-withdrawing nature of the *tert*-butyl ester, regeneration of the iminium ion toward C-2 would be expected to be slow, effectively stopping the reaction.

Finally, deprotection of **8** to (−)-quinolactacin B requires only treatment with acidic conditions. This was best accomplished using $ZnBr_2/CH_2Cl_2$,[16] which afforded **1** in 94% yield (Scheme 7). Synthetic **1** displayed the same absolute configuration, $[\alpha]_D$ −4.0 (*c* 0.2, DMSO), when compared to natural **1**, $[\alpha]_D$ −3.3 (*c* 0.13, DMSO).[1]

In summary, a mild and efficient method for preparation of pyrrolo–quinolones **8** from **2** has been developed. The results described here provide an attractive route to pyrrolo–quinolones, and the utilization of this approach in the total synthesis of different alkaloids is undergoing in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.130.

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