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First Total Synthesis of the Proposed Structures of Orisuaveolines A and B†

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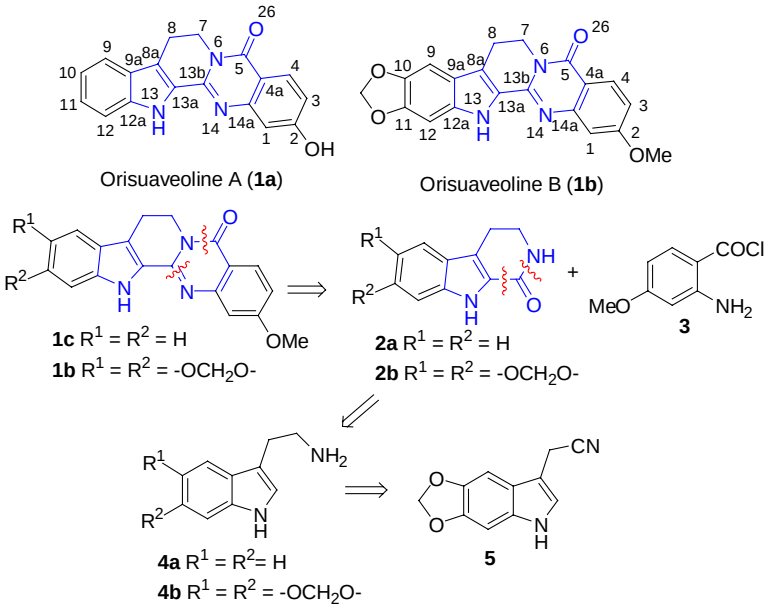
First total synthesis of the proposed structures of *β*-indoloquinazoline alkaloids orisuaveolines A and B is reported. The key steps of the synthesis included a Pictet-Spengler reaction to build a six-member lactam which further transformed into target molecular by a one-pot condensation. This synthesis provided an access to the proposed structures of orisuaveolines A and B in a short and convenient manner from inexpensive, commercially available starting materials. The structures of our synthesized products were confirmed by 2D-NMR experiments.

Keywords orisuaveolines A and B, indoloquinazoline alkaloids, Pictet-Spengler reaction, one-pot condensation

Introduction

Indole alkaloids are an important class of natural products that are widely distributed in nature.[1] Two new *β*-indoloquinazoline alkaloids orisuaveolines A (**1a**) and B (**1b**) were isolated from Cameroonian rainforest medical plants, *Oricia suaveolens* (Engl.) Verd. (Rutaceae).[2] Orisuaveoline A (**1a**) possesses cytotoxicity against lung adenocarcinoma A549 cell line. Orisuaveoline B (**1b**) is of inhibitory activity upon activation with serum opsonized zymosan.[2] Due to their important biological value, the syntheses of the two compounds are attractive. Many synthetic methods towards *β*-indoloquinazoline alkaloids have been developed over a long period.[3-6] Due to the diverse range of the physiological activities of *β*-indoloquinazoline alkaloids and their derivatives, many methods have been developed to construct their skeleton.[7,8] However, there is no report on the total synthesis of compounds **1a** and **1b** (Scheme 1).

Scheme 1 *β*-Indoloquinazoline alkaloids orisuaveolines A and B and their retrosynthetic analysis



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† Dedicated to the Memory of Professor Weishan Zhou.

Results and Discussion

As compounds **1a** and **1b** share the same *β*-indoloquinazoline skeleton, they could be synthesized through a common process. The retrosynthetic analysis of orisuaveolines A (**1a**) and B (**1b**) is demonstrated in Scheme 1. Quinazoline ring could be easily built from 2-amino-4-methoxybenzoyl chloride (**3**) and lactam **2a** or **2b**. The lactam could be accessible from amine **4a** or **4b** with triphosgene and acid, which goes through a spirocyclic lactam intermediate. Amine **4b** could be prepared from indole acetonitrile derivative **5**.

Commercially available starting material **5**[9,10] could be prepared from heliotropin.[11,12] The reductions of compound **5** to amine **4b** came across some troubles. Reduction reagents such as $LiAlH_4$ only led to complex results. Pd/C catalyzed hydrogenation resulted in the reduction of indole ring. Finally Raney-Ni catalyzed hydrogenation provided quantitative reduction of cyano group without any side reaction (Scheme 2).

According to the report[7] on the transformation of amine **4a** to **2a**, we realized transformation of **4b** to **2b** could be accomplished similarly. In this process, **4a** first reacted with triphosgene to generate the isocyanate intermediate **10** *in situ*, which underwent intramolecular nucleophilic attack by the indole moiety under the catalysis of hydrobromicacidinacetic acid to afford the corresponding tetrahydro-*β*-carbolin-1-one (**2a**, Scheme 2).[1,8,13,14]

Acyl chloride **3**, the reaction partner of **2a** or **2b**, was prepared by refluxing commercially available 2-amino-4-methoxybenzoic acid with $POCl_3$. Condensation between compounds **2a** and **3** furnished compound **1c** (Scheme 2). Condensation between compound **2b** and **3** was taken in THF, which afforded the desired orisuaveoline B (**1b**). After removing methoxyl group of compound **1c**, the synthesis of orisuaveoline B (**1b**) was accomplished. However, to our surprise, the ^{13}C NMR spectra data of our synthesized products are different from those reported for the natural products,[2] despite that the HRESIMS spectra data are correct. Besides, the spectral data of compound **1c** are in agreement with natural product isolated by Christopher and co-workers.[17] In order to confirm the framework of our synthesized products, COSY, HMQC, HMBC, and NOE experiments of **1c** and **1b** were conducted (Figure 1). Indeed, a weak NOE relevance between H-8 and H-9 indicates that the structures of our synthesized products are **1a** and **1b** (Scheme 2).

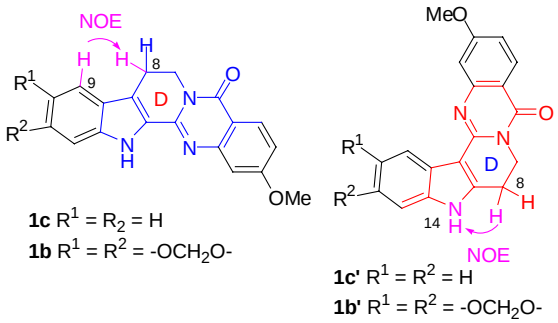


Figure 1 8-H's NOE effect.

Conclusions

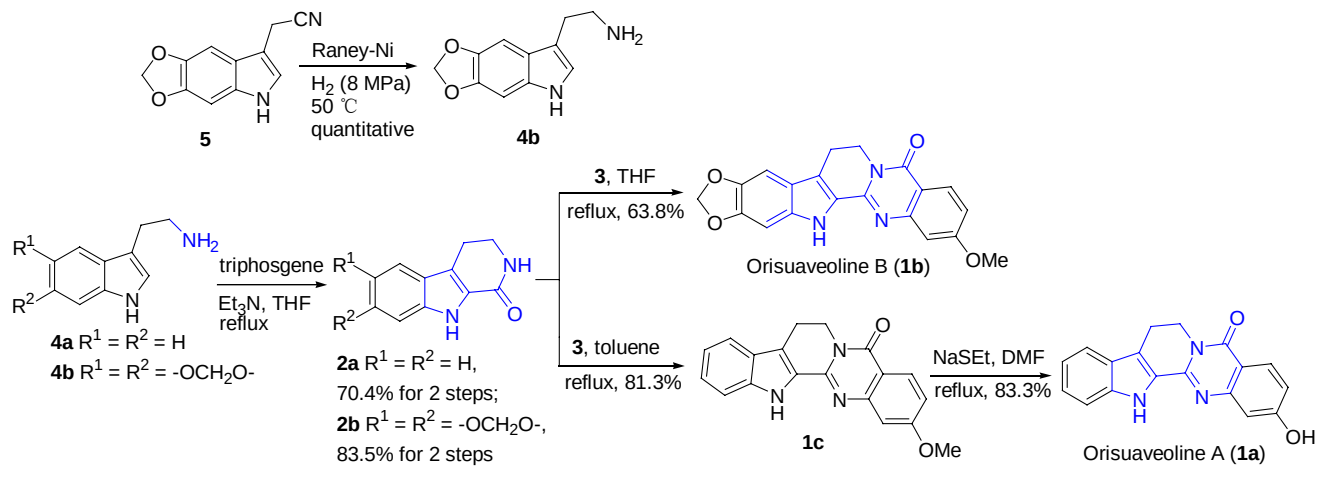
In conclusion, both of the proposed structures of orisuaveolines A and B were synthesized in 3 steps from inexpensive, commercially available starting material. Differences of ^{13}C NMR data between our synthesized products and those reported for the nature products indicated that the structures of the natural products have been assigned incorrectly.

Experimental

General

THF was dried by distillation over Na/K. Other chemicals were used as received, and all reactions conducted under standard conditions were monitored by thin-layer chromatography (TLC) on gel GF254 plates. The silica gel (200—300 meshes) and alumina B (100—200 meshes) were used for column chromatography.

Scheme 2 Reported transformation to **2a** and our application to **2b**



^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-400 MHz instruments, and spectral data were reported relative to tetramethylsilane (TMS) as internal standard. Mass spectra (MS) were measured on spectrometer by direct inlet at 70 eV, and signals were given in *m*/*z* with relative intensity (%) in brackets. HRESIMS data were determined on a Bruker Daltonics APEXII 47e FT-ICR spectrometer. The melting points were measured by Yanaco MP-500, with thermometer unrevised.

2-(5*H*-[1,3]Dioxolo[4,5-*f*]indol-7-yl)ethanamine (4b) Raney-Ni (3 g) was added into a solution of compound **5** (1.935 g, 9.7 mmol) in methanol (250 mL). The hydrogenation proceeded under H_2 (8 MPa) at 50 ℃ for 7 h. And the catalyst was removed by short flash chromatography on silica eluting with EtOAc, which afforded **4b** (2.003 g) as a dark brown liquid quantitatively. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (s, 1H, NH), 6.97 (s, 1H, H-11), 6.89 (s, 1H, H-6), 6.81 (s, 1H, H-3), 5.92 (s, 2H, OCH_2O), 2.99 (t, J=6.6 Hz, 2H, H-14), 2.82 (t, J=6.6 Hz, 2H, H-13), 1.79 (s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.88 (C-1), 142.65 (C-2), 131.22 (C-4), 121.32 (C-11), 120.76 (C-5), 113.67 (C-12), 100.52 (C-8), 97.39 (C-6), 92.05 (C-3), 42.06 (C-14), 29.32 (C-13); IR (KBr) ν_{max}: 3324, 3284, 2954, 2923, 2864, 1692, 1455, 1347, 1223, 745 cm^{-1}. HRESIMS ([M]+ H^+ at *m*/*z* 205.0971, calcd 205.0972).

2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (2a) To a solution of Et_3N (0.35 mL, 2.5 mmol) and tryptamine **4a** (0.16 g, 1 mmol) in dry THF (8 mL) was slowly added a solution of triphosgene (0.118 g, 0.39 mmol) in dried THF (2 mL). After being stirred at room temperature for 1 h, to the mixture was added 0.23 mL hydrobromicacidinacetic acid and refluxed for 2.5 h. The reaction was quenched by adding water (5.5 mL) and EtOAc (5.5 mL). Water layer was adjusted to pH= 7 and extracted with EtOAc (10 mL×3). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The product was purified by flash chromatography eluting with Hex/EtOAc (1∶1, *V*∶*V*), which afforded **2a** (0.131 g, 70.4%) as a white solid, m.p. 185−188 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.41 (s, 1H, N-7), 7.60 (d, J=8.0 Hz, 1H, H-6), 7.51 (d, J=8.3 Hz, 1H, H-3), 7.33−7.25 (m, 1H, H-2), 7.14 (t, J=7.5 Hz, 1H, H-1), 6.64 (s, 1H, N-11), 3.73 (td, J= 7.1, 2.5 Hz, 2H, H-12), 3.07 (t, J=7.0 Hz, 2H, H-13); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.62 (C-10), 137.59 (C-4), 126.33 (C-8), 125.24 (C-5), 125.06 (C-2), 120.21 (C-1), 120.15 (C-6), 119.87 (C-9), 112.69 (C-3), 42.14 (C-12), 20.83 (C-13); IR (KBr) ν_{max}: 3211, 2936, 2870, 1664, 1542, 1514, 1489, 1456, 1414, 1329, 1219 cm^{-1}. MS (EI) *m*/*z*: 186 (M^+, 100), 161 (44.32), 129 (61.9), 85 (30.83), 71 (42.35), 70 (29.27), 57 (46.60), 43 (100).

2-Methoxy-7,8-dihydroindolo[2',3':3,4]pyrido-[1,2-*b*]isoquinolin-5(13*H*)-one (1c) To the suspension of 2-amino-4-methoxybenzoic acid (0.2 g, 1.2 mmol) in 40 mL dry toluene was added $POCl_3$ (1.0 mL) and 1−2 drops of $SOCl_2$. The mixture was refluxed at 110 ℃ for 2 h when the suspension became clear. After cooling down to room temperature, the mixture was added compound **2a** (0.19 g, 1 mmol) and refluxed over night. The reaction was quenched by strong ammonia to adjust to pH>7 and extracted with $CHCl_3$ (80 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. Further purification on alumina B chromatography using CH_2Cl_2/MeOH (20∶1, *V*∶*V*) afforded **1c** (0.257 g, 81.3%) as a light yellow solid, m.p. 268 − 269 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.82 (s, 1H, NH), 8.08−8.02 (m, 1H, H-4), 7.63 (d, J=8.0 Hz, 1H, H-12), 7.49 (d, J=8.3 Hz, 1H, H-9), 7.27 (dd, J=11.2, 4.0 Hz, 1H, H-11), 7.08 (t, J=7.4 Hz, 1H, H-10), 7.04 (td, J=4.8, 2.5 Hz, 2H, H-1 and H-3), 4.41 (t, J=6.9 Hz, 2H, H-7), 3.90 (s, 3H, OMe), 3.15 (t, J=6.9 Hz, 2H, H-8); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.89 (C-2), 160.09 (C-5), 149.39 (C-14a), 145.79 (C-13b), 138.62 (C-12a), 128.21 (C-4), 127.06 (C-13a), 124.86 (C-9a), 124.67 (C-11), 119.88 (C-9), 119.67 (C-10), 117.81 (C-8a), 115.15 (C-4a), 114.17 (C-3), 112.52 (C-12), 107.55 (C-1), 55.51 (OMe), 40.53 (C-7), 18.92 (C-8); IR (KBr) ν_{max}: 3338, 1646, 1611, 1493, 1461, 1395, 1212, 1163, 1099, 1022, 798, 760 cm^{-1}. HRESIMS ([M]+H^+ at *m*/*z* 318.1233, calcd 318.1237).

Orisuaveoline A (1a) A solution of EtSH (400 μL, 5.4 mmol) in DMF (3 mL) was cooled to 0 ℃ and treated with NaH (60% in mineral oil, 204 mg, 5.1 mmol). The solution was stirred at room temperature for 30 min. This NaSEt solution (2.3 mL, *ca.* 3.4 mmol) was added to a solution of **1c** (54 mg, 0.17 mmol) in DMF (1 mL). The reaction was preceded at 90 ℃ for 10 h, which was quenched with saturated aqueous NH_4Cl and diluted with EtOAc (60 mL). The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated. Flash column chromatography (Hex∶EtOAc=1∶1, *V*∶*V*) afforded orisuaveoline A (43 mg, 83.3%) as a light yellow solid, m.p. 315−316 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.81 (b, 1H, NH), 10.52 (b, 1H, OH), 8.00 (d, J=8.4 Hz, 1H, H-4), 7.65 (d, J=8.0 Hz, 1H, H-12), 7.48 (d, J=8.4 Hz, 1H, H-9), 7.26 (t, J=7.6 Hz, 1H, H-11), 7.09 (t, J=7.6 Hz, 1H, H-10), 6.99 (d, J=2.0 Hz, 1H, H-1), 6.92 (dd, J= 8.8, 2.0 Hz, 1H, H-3), 4.40 (t, J=6.8 Hz, 2H, H-7), 3.15 (t, J=6.8 Hz, 2H, H-8); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 162.76 (C-2), 160.20 (C-5), 149.38 (C-14a), 145.56 (C-13b), 138.58 (C-12a), 128.51 (C-4), 127.22 (C-13a), 124.91 (C-9a), 124.62 (C-11), 119.90 (C-9), 119.69 (C-10), 117.65 (C-8a), 115.84 (C-3), 113.10 (C-4a), 112.52 (C-12), 109.91 (C-1), 40.47 (C-7), 19.01 (C-8). IR (KBr) ν_{max}: 3385, 2832, 1781, 1662, 1390, 1131, 739 cm^{-1}. HRESIMS ([M]+H^+ at *m*/*z* 304.1074, calcd 304.1081).

8,9-Dihydro-5*H*-[1,3]dioxolo[4,5-*f*]pyrido[3,4-*b*]-indol-6(7*H*)-one (2b) Following the procedure described for **2a**, compound **4b** (0.306 g, 1.5 mmol) was converted into **2b**. The product was purified by alumina B column chromatography (50% EtOAc in hexanes) to

furnish **2b** (0.288 g, 83.5%) as a dark liquid. ^{1}H NMR (400 MHz, methanol-d_4) δ: 6.93 (s, 1H), 6.86 (s, 1H), 5.93 (s, 2H), 3.60 (t, J=7.1 Hz, 2H), 2.93 (t, J=7.1 Hz, 2H); ^{13}C NMR (100 MHz, methanol-d_4) δ: 165.04 (C-10), 149.21 (C-2), 145.20 (C-1), 135.28 (C-4), 121.99 (C-8), 120.63 (C-9), 102.35 (OCH_2O), 98.75 (C-6), 93.45 (C-3), 42.93 (C-12), 21.85 (C-13); IR (KBr) ν_{max}: 3284, 2954, 2863, 1695, 1508, 1456, 1339, 1219, 752 cm^{-1}. HRESIMS ([M]+H$^+$ at m/z 231.0761, calcd 231.0764).

Orisuaveoline B (1b) The solvent was changed into dry THF for better solubility. Compound **2b** (92 mg, 0.4 mmol) was transformed into orisuaveoline B following the same procedure for **1c**. The product was purified by alumina B column chromatography (50% EtOAc in hexanes) to furnish synthesis of orisuaveoline B (92 mg, 63.8%) as a light yellow solid, m.p. 322—323 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.66 (br, 1H, NH), 8.03 (d, J=8.4 Hz, 1H, H-4), 7.09 (s, 1H, H-9), 7.01 (d, J=2.4 Hz, 1H, H-1), 6.99 (dd, J=8.4, 2.4 Hz, 1H, H-3), 6.91 (s, 1H, H-12), 6.01 (s, 2H, OCH_2O), 4.37 (t, J=6.8 Hz, 2H, H-7), 3.90 (s, 3H, OMe), 3.07 (t, J=6.8 Hz, 2H, H-8); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.90 (C-2), 160.16 (C-5), 149.64 (C-14a), 147.01 (C-11), 145.66 (C-13b), 143.06 (C-10), 134.65 (C-12a), 128.23 (C-4), 125.66 (C-13a), 118.90 (C-9a), 118.44 (C-8a), 114.74 (C-1), 113.91 (C-4a), 107.33 (C-3), 100.76 (OCH_2O), 97.67 (C-9), 92.42 (C-12), 50.50 (OMe), 40.46 (C-7), 19.06 (C-8); IR (KBr) ν_{max}: 3385, 2925, 1653, 1471, 1312, 1228, 1109, 739 cm^{-1}. HRESIMS ([M]+H$^+$ at m/z 362.1133, calcd 362.1135).

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References

[1] Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538.
[2] Wansi, J. D.; Mesaik, M. A.; Chiozem, D. D.; Devkota, K. P.; Gaboriaud-kolar, N.; Lallemand, M.-K.; Wandji, J.; Choudhary, M. I.; Sewald, N. *J. Nat. Prod.* **2008**, *71*, 1942.
[3] Bergman, J.; Bergman, S. *J. Org. Chem.* **1985**, *85*, 1246.
[4] Hamid, A.; Elomri, A.; Daïch, A. *Tetrahedron Lett.* **2006**, *47*, 1777.
[5] Mohanta, P. K.; Kim, K. *Tetrahedron Lett.* **2002**, *43*, 3993.
[6] Lee, C.-S.; Liu, C.-K.; Chiang, Y.-L.; Cheng, Y.-Y. *Tetrahedron Lett.* **2008**, *49*, 481.
[7] Bracher, F.; Hilderband, D. *Liebigs Ann. Chem.* **1992**, 1315.
[8] Judd, K. E.; Mahon, M. F.; Caggiano, L. *Synthesis* **2009**, 2809.
[9] Yang, L.-M.; Chen, C.-F.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 465.
[10] Marchi, I., Rebelo, R. A.; Maiochi, F. A. *Quim. Nova* **2007**, *30*, 763.
[11] Chen, C.-M.; Fu, Y.-F.; Yang, T.-H. *J. Nat. Prod.* **1995**, *58*, 1767.
[12] Rosa, F. A.; Rebelo, R. A.; Nascimento, M. G. *J. Braz. Chem. Soc.* **2003**, *14*, 11.
[13] Bracher, F.; Hilderband, D. *Pharmazie* **1993**, *48*, 695.
[14] Hamid, A.; Oulyadi, H.; Daich, A. *Tetrahedron* **2006**, *62*, 6398.
[15] Compound **1c**: 1D-NMR spectrum comparison between compound **1c** and reported nature products indicates that structure of our synthesized compound **1c** identically agrees with the one separated by Christopher and co-works. HMQC, and HMBC experiments were taken to further confirm the structure of **1c**. HMBC correlations between the signal of H-7 (δ 4.410) with C-8 (δ 18.92), C-8a (δ 117.83), C-13b (δ 145.81) and C-5 (δ 160.11) and between the signal of H-8 (δ 3.150) with C-7 (δ 40.54), C-8a (δ 117.83), C-13a (δ 127.08), C-9a (δ 124.87) and C-13b (δ 145.81) indicated the framework of our product should be in agreement with illustration in Scheme 1.
[16] Compound **1b**: HMBC correlations between the signal of H-7 (δ 4.368) with C-8 (δ 19.06), C-8a (δ 118.44) and C-5 (δ 160.16) and between the signal of H-8 (δ 3.069) with C-7 (δ 40.46), C-8a (δ 118.44), C-13a (δ 125.66), C-12a (δ 134.65) and C-13b (δ 145.66) indicate that the framework of our synthesized product should be **1b** (Scheme 1).
[17] Christophera, E.; Bedira, E.; Dunbara, C.; Khan, I. A.; Okunji, C. O.; Schusterd, B. M.; Iwu, M. M. *Helv. Chim. Acta* **2003,** *86*, 2914.

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