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SIMPLE TOTAL SYNTHESSES OF MARINE ALKALOIDS, BATZELLINE C, ISOBATZELLINE C, DAMIRONE A, AND MAKALUVAMINE A¹

Fumio Yamada, Shin Hamabuchi, Aya Shimizu, and Masanori Somei*

Faculty of Pharmaceutical Sciences, Kanazawa University,

13-1 Takara-machi, Kanazawa 920, Japan

Abstract ----- Batzelline C and isobatzelline C were synthesized in eight (or nine) steps from indole-3-carboxaldehyde. Syntheses of damirone A and makaluvamine A are also reported.

Marine alkaloids having 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline as a common skeleton are of great interest owing to their potent biological activities,²⁻⁴ such as cytotoxic and topoisomerase II inhibition. Isobatzelline C³ (protonated form of **1**) and batzelline C⁴ (**2**) are members of those alkaloids and their total syntheses have already been achieved.⁵ However, they are still laborious and require long steps. We have intended to attain total syntheses of natural products as simple as possible^{6a} by creating suitable reactions.^{6,7} Now, we wish to report simple syntheses of **1** and **2** starting from readily available indole-3-carboxaldehyde (**3**). Total syntheses of damirone A⁸ (**4 b**) and makaluvamine A^{2,9} (**5**) are also reported.

In the preceding communication,⁷ we reported three (or four) step synthesis of 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (**7**, Scheme 1) through 4-nitroindole-3-acetonitrile (**6**). Treatment of **7** with *N*-chlorosuccinimide (NCS, 1 mol eq.) in CH₂Cl₂ produced 8-chloro (**8 a**), 6-chloro (**8 b**), and 6,8-dichloro compound (**8 c**) in 12, 60, and 5% yields, respectively. The structures of **8 a** and **8 b** were readily determined by their spectral data and reactivities with Ac₂O and pyridine. At room temperature, **8 a** afforded **9 a** in 99% yield, while **8 b** did not react at all. Whereas heating at 60°C for 4 h **8 b** converted to **9 b** in 99% yield. Treatment of **9 b** with NaH and then with MeI produced **10** in 98% yield. Subsequent hydrolysis of **10** with aq. NaOH gave **13 b** in 95% yield.

In shorter steps, synthesis of **13 b** was alternatively attained as follows. Making the most of acetylation of **7** with Ac₂O and pyridine affording **11** in 89% yield, the compound (**11**) was prepared in an one-pot operation from **6** in 56% yield by the catalytic hydrogenation with 10% Pd/C at 5 atm, followed by the treatment with Ac₂O and pyridine. Methylation of **11** with NaH and MeI gave 1-methyl derivative (**12 a**) in 97% yield. Hydrolysis of **12 a** with aq. NaOH produced **12 b** in a quantitative yield. Chlorination of **12 b** with NCS (1 mol eq.) in CH₂Cl₂ afforded 8-chloro (**13 a**), 6-

chloro (**13 b**), and 6,8-dichloro compound (**13 c**) in 17, 70, and 5% yields, respectively. Subsequent oxidation of **13 b** with Fremy's salt produced **14** in 77% yield. Interestingly, under similar reaction conditions with Fremy's salt, **12 b** did not afford the desired pyrroloiminoquinone.

Introduction of nitrogen moiety into the 7-position of **14** was a troublesome step. During examination of various reagents (NH₄OH, NH₄Cl, and amines), we disclosed that NaN₃ reacted with **14** in THF at room temperature to produce **1**, **2**, and **15** in 16, 9, and 58% yields, respectively. Alternatively, oxidation of **14** with dioxxygen exclusively produced **15** in 40% yield. Finally, we have newly found¹⁰ that benzylamine hydrochloride was a reagent of choice reacting with **14** in MeCN-MeOH (1:1) in the presence of NaHCO₃ to produce **1** and batzellin C (**2**) in 41 and 10% yields, respectively, and under these reaction conditions formation of **15** was not detected at all. Thus, total syntheses of **1** and **2** were achieved in eight steps from **3**. Originality rate^{6b} of the present syntheses for **1** and **2** is 44%.

Concerning isobatzelline C, the following new facts were found.

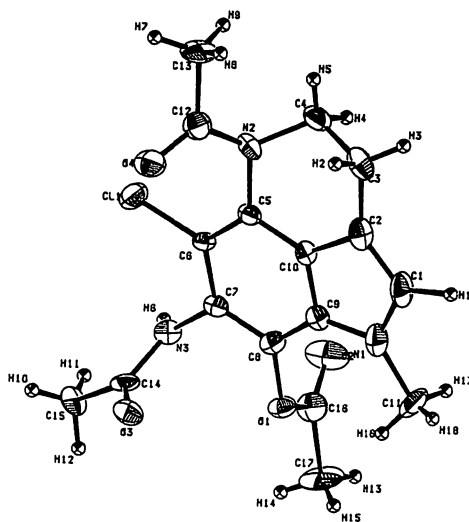
The spectral data¹¹ (¹³C-, ¹H-nmr, uv, and ir) of our synthetic **1** are identical with those of Yamamura's,⁵ but they are partly different from those of isobatzelline C.³ We made a salt of **1** with HCl. The ¹³C- and ¹H-nmr, and ir spectral data¹² of the salt were completely identical with those of natural product. In addition, we confirmed the structure of our synthetic **1** as follows. Fortunately, we could find that treatment of **1** with zinc and Ac₂O produced triacetyl compound (**16**), which was suitable prisms for X-ray crystallographic analysis and the results shown in Figure 1 proved the structure unequivocally.

Consequently, we concluded that isobatzelline C is a protonated salt of **1**, although the anion is not known.¹³

Further treatment of **2** with MeI and K₂CO₃ afforded **4 a** in 97% yield. Removal of chlorine was achieved by catalytic hydrogenation with 10% Pd/C, followed by stirring in the air, to give damirone A^B (**4 b**) in 24% yield together with 54% yield of recovery. Similarly, makaluvamine A^{2,9} (**5**) was produced in 40% yield together with 46% yield of recovery by catalytic hydrogenation with 10% Pd/C, followed by stirring in the air. Spectral data of **2**, **4 b**, and **5** are identical with those of the reported alkaloids.^{2,4,8}

Total syntheses of other related marine alkaloids are in progress using **7** and **11** as common synthetic intermediates.

Figure 1
ORTEP Drawing of **16**



REFERENCES AND NOTES

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- We believe that one step formation of **1** was attained as follows. Initially aminobenzoylation of **1 4** occurred at 7-position, followed by oxidation, to afford benzylideneamine, and its subsequent hydrolysis produced **1**.
- mp 221-223°C (decomp., brown needles from MeOH). ¹³C-Nmr (CD₃OD:CDCl₃, 1:1) δ : 18.7, 35.7, 49.3, 105.1, 118.2, 122.7, 122.8, 129.1, 145.0, 153.5, 169.7. ¹H-Nmr (CD₃OD:CDCl₃, 1:1) δ : 2.73 (2H, t, J=7.9 Hz), 3.93 (3H, s), 4.03 (2H, t, J=7.9 Hz), 6.79 (1H, s). Ir : 3320, 2940, 1649, 1589, 1428, 1342, 1307, 1195, 1090, 840, 820 cm⁻¹. Ms m/z : 237 (M⁺), 235 (M⁺), 208, 173, 145, 129. Uv λ_{max}^{MeOH} nm (ε) : 244 (16000), 333 (16400). Anal. Calcd for C₁₁H₁₀N₃OCl: C, 56.06; H, 4.28; N, 17.83. Found: C, 55.96; H, 4.27; N, 17.59.
- mp 210-212°C (decomp., greenish brown powder from MeOH-Ether). ¹³C-Nmr (CD₃OD:CDCl₃, 1:1) δ : 19.0, 36.6, 43.8, 93.8, 119.8, 122.5, 123.6, 131.9, 152.7, 154.5, 166.3. ¹H-Nmr (CD₃OD:CDCl₃, 1:1) δ : 3.00 (2H, t, J=7.8 Hz), 3.95 (2H, t, J=7.8 Hz), 3.98 (3H, s), 7.10 (1H, s). Ir : 3410, 3000, 1678, 1606, 1424, 1347, 1320, 1205, 1144, 837, 811 cm⁻¹. Uv λ_{max}^{MeOH} nm (ε) : 247 (20600), 339 (13300), 348 (shoulder, 13000), 400 (shoulder, 5330). Anal. Calcd for C₁₁H₁₀N₃OCl·HCl: C, 48.55; H, 4.07; N, 15.44. Found: C, 48.27; H, 3.99; N, 15.34. These data of pure synthetic sample suggest that natural product included some impurities.
- We have informed these facts and sent copies of our spectral data to Dr. H. H. Sun for discussing.