SIMPLE TOTAL SYNTHESES OF MARINE ALKALOIDS, BATZELLINE C, ISOBATZELLINE C, DAMIRONE A, AND MAKALUVAMINE A[1]

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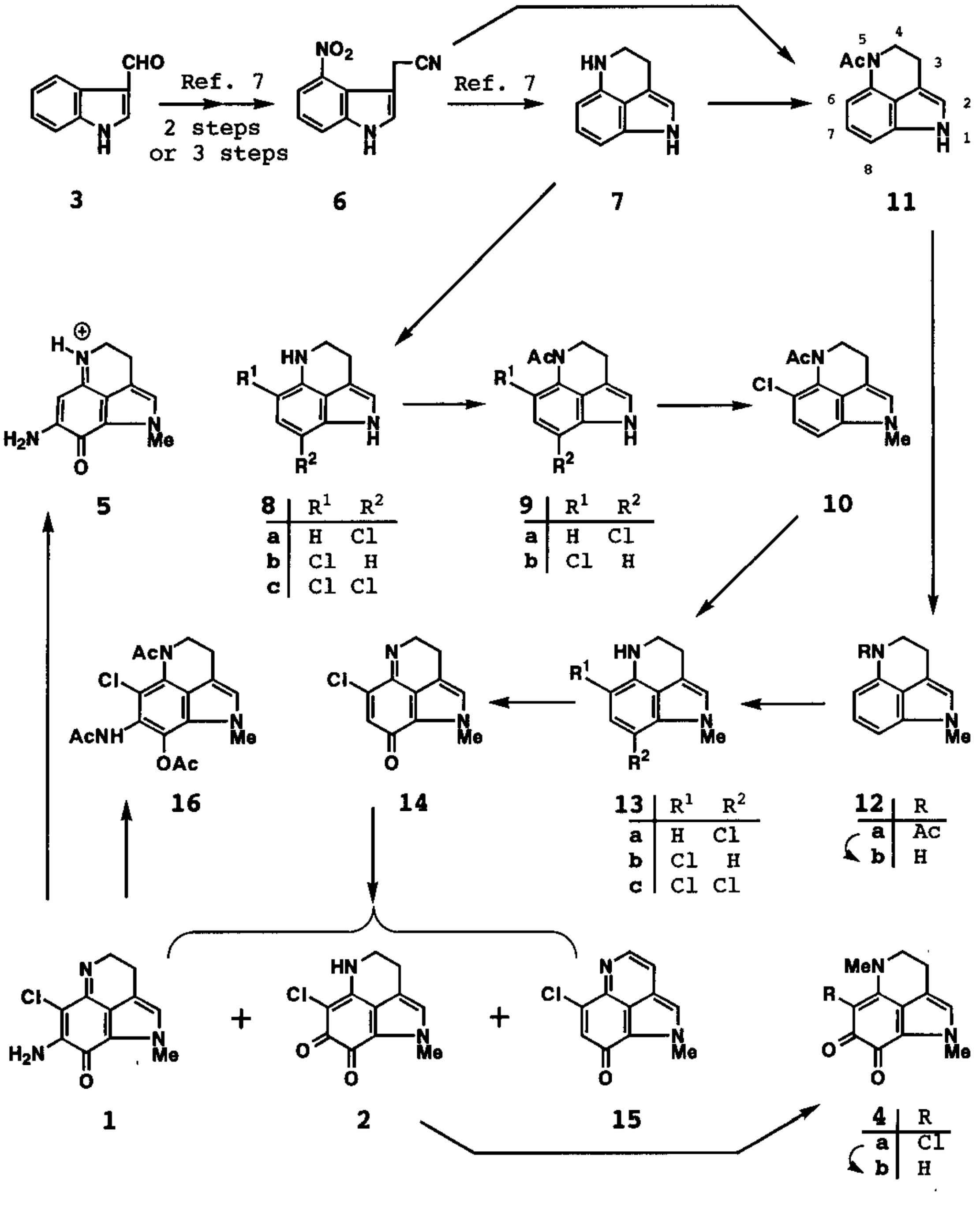
Abstract ------ Batzelline C and isobatzelline C were synthesized in eight (or nine) steps from indole-3-carboxaldehyde. Syntheses of damirone A and makaluvamine A are also reported.

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 C[3] (protonated form of **1**) and batzelline C[4] (**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 A[8] (**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 CH_2Cl_2 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 Ac_2O 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 Ac_2O 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 Ac_2O 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 CH_2Cl_2 afforded 8-chloro (**13 a**), 6-

Scheme 1


CHO
Ref. 7
2 steps
or 3 steps
NO2
CN
Ref. 7
HN
AcN
3
6
7
11
5
4
3
2
1
6
7
8
H2N
Me
R1
R2
Cl
5
8 | R1 R2
a | H Cl
b | Cl H
c | Cl Cl
9 | R1 R2
a | H Cl
b | Cl H
10
AcNH
OAc
16
14
13 | R1 R2
a | H Cl
b | Cl H
c | Cl Cl
12 | R
a | Ac
b | H
RN
MeN
R
1
2
15
4 | R
a | Cl
b | H

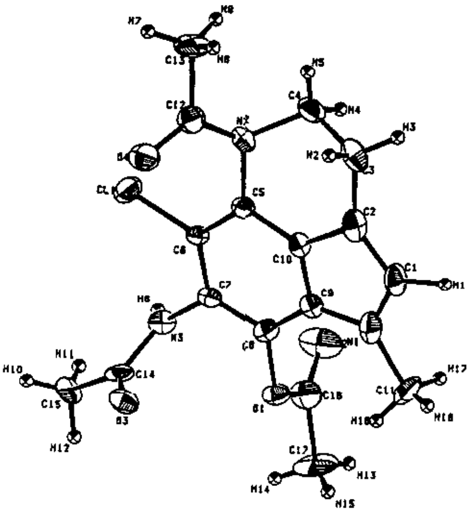
chloro (**13b**), and 6,8-dichloro compound (**13c**) in 17, 70, and 5% yields, respectively. Subsequent oxidation of **13b** with Fremy 's salt produced **14** in 77% yield. Interestingly, under similar reaction conditions with Fremy 's salt, **12b** did not afford the desired pyrroloiminoquinone.

Introduction of nitrogen moiety into the 7-position of **14** was a troublesome step. During examination of various reagents (NH_4OH, NH_4Cl, and amines), we disclosed that NaN_3 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 dioxygen exclusively produced **15** in 40% yield. Finally, we have newly found[10] that benzylamine hydrochloride was a reagent of choice reacting with **14** in MeCN-MeOH (1:1) in the presence of $NaHCO_3$ 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 data[11] (^{13}C-,^{1}H-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 ^{13}C- and ^{1}H-nmr, and ir spectral data[12] 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 treament of **1** with zinc and Ac_2O 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]

Figure 1

ORTEP Drawing of **16**



Further treatment of **2** with MeI and K_2CO_3 afforded **4a** 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[8] (**4b**) 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**, **4b**, 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.

REFERENCES AND NOTES

1. This paper is Part 74 of a series entitled "The Chemistry of Indoles". Part 73: M. Somei and T. Kawasaki, *Heterocycles*, memorial edition of Prof. Y. Ban, 1995, in press. All new compounds gave satisfactory spectral data *and elemental analyses for crystals or high resolution mass data for oils:* **8a**) mp 165-167°C (decomp.); **8b**) mp 176-177°C; **8c**) mp 187-188°C (decomp.); **9a**) mp 197-198°C; **9b**) mp 180-182°C (decomp.); **10**) colorless oil; **11**) mp 200-202°C; **12a**) mp 105-106°C; **12b**) colorless oil; **13a**) mp 82-83°C; **13b**) colorless oil; **13c**) mp 69-71°C; **14**) mp 127-129°C (decomp.); **15**) mp 180°C (decomp.); **16**) mp 233-234°C; **4a**) mp 223-225°C (decomp.).
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9. Synthesis of makaluvamine A: T. Izawa, S. Nishiyama, and S. Yamamura, *Tetrahedron*, 1994, **50**, 13593.
10. We believe that one step formation of **1** was attained as follows. Initially aminobenzylation of **14** occurred at 7-position, followed by oxidation, to afford benzylideneamine, and its subsequent hydrolysis produced **1**.
11. mp 221-223°C (decomp., brown needles from MeOH). ^{13}C-Nmr (CD_3OD:$CDCl_3$, 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. ^{1}H-Nmr (CD_3OD:$CDCl_3$, 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 $C_{11}H_{10}N_3OCl$: C, 56.06; H, 4.28; N, 17.83. Found: C, 55.96; H, 4.27; N, 17.59.
12. mp 210-212°C (decomp., greenish brown powder from MeOH-Ether). ^{13}C-Nmr (CD_3OD:$CDCl_3$, 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. ^{1}H-Nmr (CD_3OD:$CDCl_3$, 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 $C_{11}H_{10}N_3OCl \cdot HCl$: 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.
13. We have informed these facts and sent copies of our spectral data to Dr. H. H. Sun for discussing.

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