## TOTAL SYNTHESIS OF KUANONIAMINE A, 11-HYDROXY-ASCIDIDEMIN, AND NEOCALLIACTINE ACETATE<sup>1</sup>

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Abstract — A pentacyclic aromatic alkaloid, kuanoniamine A (5) was synthesized from 6-methoxybenzothiazole-4,7-dione (7) and 2-aminoacetophenone (8). Similarly, 11-hydroxyascididemin (4) was prepared from 6bromo-4-chloro-5,8-dimethoxyquinoline (12). The structure of neocalliactine acetate, a derivative of calliactine, was determined as 19 by total synthesis from 6-methoxy-5,8-quinolinedione (23) and 2-amino-5-methoxyacetophenone (24).

During the past ten years a series of structurally related polycyclic aromatic alkaloids has been isolated from marine organisms.<sup>2</sup> Examples are amphimedine (1),<sup>2a</sup> cystodytin A,<sup>2b</sup> diplamine A,<sup>2c</sup> meridine (2),<sup>2d</sup> ascididemin (3),<sup>2e</sup> 11-hydroxyascididemin (4),<sup>2d</sup> and kuanoniamine A (5),<sup>2f</sup> which are derivatives of pyrido[2,3,4-*kl*]acridine possessing iminoquinolinequinone structure (6). Neocalliactine acetate<sup>3</sup> was also obtained as a derivative of calliactine isolated from the sea anemone *Calliactis parasitica* in 1940.<sup>4</sup> The total synthesis of amphimedine (1),<sup>5</sup> cystodytin A,<sup>6</sup> and ascididemin (3)<sup>7</sup> was achieved among these alkaloids. Now we wish to report the first total synthesis of pentacyclic alkaloids, kuanoniamine A (5) and 11-hydroxy-ascididemin (4), and structure determination of neocalliactine acetate by synthesis.



We first synthesized kuanoniamine A isolated from a Micronesian tunicate and its predator, a prosobranch mollusk *Chelynotus semperi*.<sup>2f</sup> 6-Methoxybenzothiazole-4,7-dione  $(7)^8$  was treated with 2-aminoaceto-phenone (8) in refluxing acetic acid for 12 h to give 9 in 39% yield. The anilinoquinone (9) was refluxed with concentrated sulfuric acid in trifluoroacetic acid for 75 min to furnish the cyclization product (10) in 36% yield. When 7 was refluxed with 8 in methanol containing cerium (III) chloride under air for 18 h, the

cyclization product (10) was directly obtained in 73% yield. The tetracyclic quinone (10) was heated with  $N_{,N}$ -dimethylformamide diethyl acetal (DMF-DEA) in  $N_{,N}$ -dimethylformamide (DMF)<sup>7a</sup> at 110°C for 30 min to give 11. Treatment of 11 with ammonium chloride in acetic acid at 110°C for 30 min furnished the pentacyclic iminoquinolinequinone (5)<sup>9</sup> in 47% yield from 10. The spectral data of synthetic iminoquinolinequinone (5) were identical with those of kuanoniamine A obtained from natural resources.



Next, we synthesized 11-hydroxyascididemin (4) isolated from *Leptoclinides* sp. from Truk Lagoon.<sup>2d</sup> Oxidative demethylation of 6-bromo-4-chloro-5,8-dimethoxyquinoline (12)<sup>10</sup> with cerium (IV) ammonium nitrate (CAN) in aqueous acetonitrile (20°C, 10 min) gave 5,8-quinolinedione (13) in 56% yield. The quinone (13) was condensed with 2-aminoacetophenone (8) in ethanol containing cerium (III) chloride under air (20°C, 4 h) to give 14 in 74% yield. The cyclization of 14 with 10% sulfuric acid in acetic acid (62-63°C, 1 h) gave the tetracyclic quinone (15) in 69% yield. On treating with sodium methoxide in methanol (20°C, 30 min), the chlorine atom in 15 was substituted by a methoxyl group in a quantitative yield. Treatment of 16 with DMF-DEA in DMF (120°C, 15 min) followed by ammonium chloride in acetic acid (120°C, 10 min) furnished the pentacyclic iminoquinolinequinone (18) in 31% yield. The methyl ether in 18 was cleaved with boron tribromide in dichloromethane ( $-10 - -20^{\circ}$ C, 1 h) to furnish 4.<sup>11</sup> The spectral data of synthetic 4 were identical with those of 11-hydroxyascididemin obtained from a natural resource.



Finally, we determined the structure of neocalliactine acetate by unambiguous total synthesis. Neocalliactine acetate is a derivative prepared from calliactine, a pigment isolated from the sea anemone Calliactis parasitica,

and four alternative structures (19-22) were proposed.<sup>3</sup> Last year, Schmitz *et al.* reported further structural elucidation of neocalliactine acetate by a comparison with <sup>1</sup>H- and <sup>13</sup>C- nmr spectral data of meridine (2), ascididemin (3), and 11-hydroxyascididemin (4).<sup>2d</sup> They ruled out 21 and 22 possessing the meridine ring array unequivocally, and slightly preferred 19 of the two remaining structures having the overall skeletal outline of ascididemin (3). Thus, we studied the synthesis of 19.



Treatment of 6-methoxy-5,8-quinolinedione  $(23)^{12}$  with 2-amino-5-methoxyacetophenone  $(24)^{13}$  in ethanol containing cerium (III) chloride under air (20°C, 1 h) gave 25 in 46% yield. The anilinoquinone (25) was heated with concentrated sulfuric acid in acetic acid (90°C, 30 min) to give the cyclization product (26) in 94% yield. Reaction of 26 with DMF-DEA in DMF (120°C, 30 min) followed by treatment with ammonium chloride in acetic acid (120°C, 30 min) furnished 28 in 64% yield. The methyl ether (28) was refluxed in 48% hydrobromic acid for 4 h to give 29. The acetylation of phenol (29) with acetic anhydride in pyridine (20°C, 2 h) furnished the acetate (19) in 39% yield from 28. The spectral data of synthetic acetate (19)<sup>14</sup> were identical with those of neocalliactine acetate. Thus, we determined the structure of neocalliactine acetate to be 19, *i.e.* 3-acetoxyascididemin.



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- 9. 5: mp 258-259°C (CHCl<sub>3</sub>) (lit.,<sup>2f</sup> mp 255-258°C (decomp.)). Ms m/z (%): 289 (M<sup>+</sup>, 100). High-resolution ms Calcd for C<sub>16</sub>H<sub>7</sub>N<sub>3</sub>OS: 289.0310. Found: 289.0315. <sup>1</sup>H-Nmr (270 MHz, DMSO-d<sub>6</sub>) δ: 8.03 (1H, t, J = 8.3 Hz, C<sub>5</sub>-H), 8.09 (1H, t, J = 8.3 Hz, C<sub>6</sub>-H), 8.43 (1H, d, J = 8.3 Hz, C<sub>7</sub>-H), 8.84 (1H, d, J = 5.9 Hz, C<sub>3</sub>-H), 8.96 (1H, d, J = 8.3 Hz, C<sub>4</sub>-H), 9.11 (1H, d, J = 5.9 Hz, C<sub>2</sub>-H), 9.68 (1H, s, C<sub>11</sub>-H).
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- 4: mp >260°C (CHCl<sub>3</sub>) (lit.,<sup>2d</sup> mp >250°C). Ms m/z (%): 299 (M<sup>+</sup>, 93), 271 (100). High-resolution ms Calcd for C<sub>18</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>: 299.0695. Found: 299.0715. <sup>1</sup>H-Nmr (270 MHz, CDCl<sub>3</sub>) δ: 7.15 (1H, d, J = 5.6 Hz, C<sub>9</sub>-H), 8.00 (1H, dt, J = 8.3, 1.3 Hz, C<sub>3</sub>-H), 8.07 (1H, dt, J = 8.3, 1.7 Hz, C<sub>2</sub>-H), 8.59 (1H, d, J = 5.6 Hz, C<sub>5</sub>-H), 8.65 (1H, dd, J = 8.3, 1.3 Hz, C<sub>1</sub>-H), 8.73 (1H, dd, J = 8.3, 1.7 Hz, C<sub>4</sub>-H), 8.90 (1H, d, J = 5.6 Hz, C<sub>10</sub>-H), 9.32 (1H, d, J = 5.6 Hz, C<sub>6</sub>-H), 13.06 (1H, s, OH).
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- 14. **19**: mp >270°C (decomp.) (CHCl<sub>3</sub>-ether) (lit.,<sup>3</sup> no mp was given). Ms m/z (%): 341 (M<sup>+</sup>, 13), 313 (22), 299 (100). High-resolution ms Calcd for C<sub>20</sub>H<sub>11</sub>N<sub>3</sub>O<sub>3</sub>: 341.0800. Found: 341.0800. <sup>1</sup>H-Nmr (270 MHz, CDCl<sub>3</sub>-CD<sub>3</sub>OD) & 2.39 (3H, s, CH<sub>3</sub>), 7.66 (1H, dd, J = 7.9, 4.6 Hz, C<sub>10</sub>-H), 7.72 (1H, dd, J = 8.9, 2.3 Hz, C<sub>2</sub>-H), 8.42 (1H, d, J = 2.3 Hz, C<sub>4</sub>-H), 8.47 (1H, d, J = 5.9 Hz, C<sub>5</sub>-H), 8.54 (1H, d, J = 8.9 Hz, C<sub>1</sub>-H), 8.72 (1H, dd, J = 7.9, 1.6 Hz, C1<sub>1</sub>-H), 9.08 (1H, dd, J = 4.6, 1.6 Hz, C<sub>9</sub>-H), 9.18 (1H, d, J = 5.9 Hz, C<sub>6</sub>-H). <sup>13</sup>C-Nmr (67.8 MHz, CDCl<sub>3</sub>-CD<sub>3</sub>OD) & 20.80 (CH<sub>3</sub>), 115.03 (C<sub>4</sub>), 117.18 (C<sub>5</sub>), 117.72 (C<sub>12b</sub>), 124.42 (C<sub>4a</sub>), 125.82 (C<sub>10</sub>), 126.71 (C<sub>2</sub>), 128.81 (C<sub>11a</sub>), 133.99 (C<sub>1</sub>), 136.54 (C<sub>11</sub>), 137.68 (C<sub>4b</sub>), 143.20 (C<sub>13a</sub>), 145.25 (C<sub>12a</sub>), 149.24 (C<sub>7a</sub>), 149.31 (C<sub>6</sub>), 151.67 (C<sub>7b</sub>), 152.24 (C<sub>3</sub>), 155.15 (C<sub>9</sub>), 169.05 (CH<sub>3</sub>CO), 181.33 (C<sub>12</sub>).