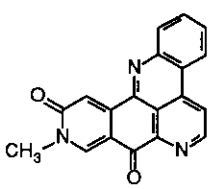
TOTAL SYNTHESIS OF KUANONIAMINE A, 11-HYDROXY-ASCIDIDEMIN, AND NEOCALLIACTINE ACETATE[1]

Yoshiyasu Kitahara, Shinsuke Nakahara, Takanobu Yonezawa, Masanori Nagatsu, and Akinori Kubo*
Meiji College of Pharmacy, 1-35-23 Nozawa, Setagaya-ku, Tokyo 154, Japan

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 6-bromo-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.[2] Examples are amphimedine (**1**),[2a] cystodytin A,[2b] diplamine A,[2c] meridine (**2**),[2d] ascididemin (**3**),[2e] 11-hydroxyascididemin (**4**),[2d] and kuanoniamine A (**5**),[2f] which are derivatives of pyrido[2,3,4-*kl*]acridine possessing iminoquinolinequinone structure (**6**). Neocalliactine acetate[3] was also obtained as a derivative of calliactine isolated from the sea anemone *Calliactis parasitica* in 1940.[4] The total synthesis of amphimedine (**1**),[5] cystodytin A,[6] and ascididemin (**3**)[7] 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.



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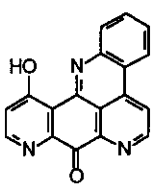

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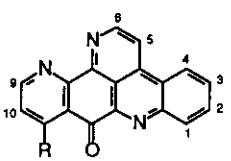
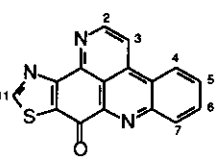


3: R=H
4: R=OH



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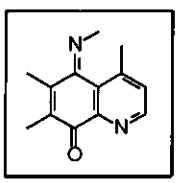

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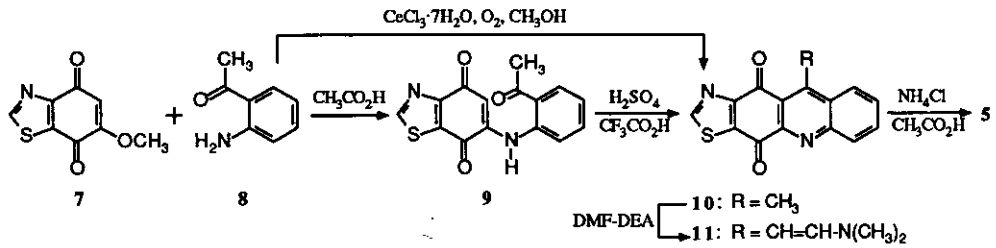
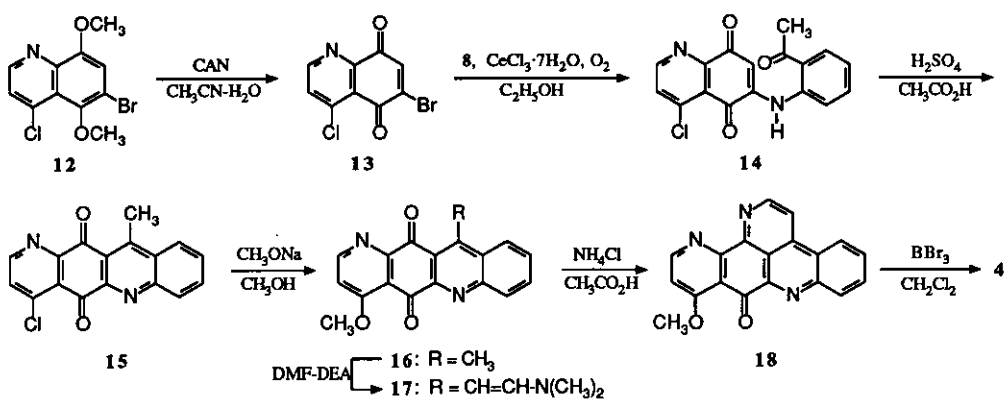
We first synthesized kuanoniamine A isolated from a Micronesian tunicate and its predator, a prosobranch mollusk *Chelynotus semperi*.[2f] 6-Methoxybenzothiazole-4,7-dione (**7**)[8] was treated with 2-aminoacetophenone (**8**) in refluxing acetic acid for 12 h to give **9** in 39% yield. The anilinoquinone (**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)[7a] 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**)[9] in 47% yield from **10**. The spectral data of synthetic iminoquinolinequinone (**5**) were identical with those of kuanoniamine A obtained from natural resources.

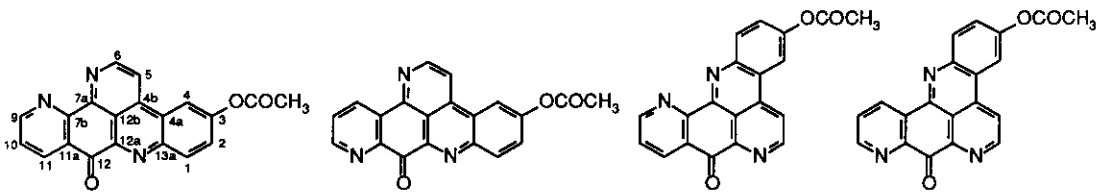


Next, we synthesized 11-hydroxyasciddemin (**4**) isolated from *Leptoclinides* sp. from Truk Lagoon.[2d] Oxidative demethylation of 6-bromo-4-chloro-5,8-dimethoxyquinoline (**12**)[10] with cerium (IV) ammonium nitrate (CAN) in aqueous acetonitrile (20°C, 10 min) gave 5,8-quinolinedione (**13**) in 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°C, 1 h) to furnish **4**.[11] The spectral data of synthetic **4** were identical with those of 11-hydroxyasciddemin obtained from a natural resource.



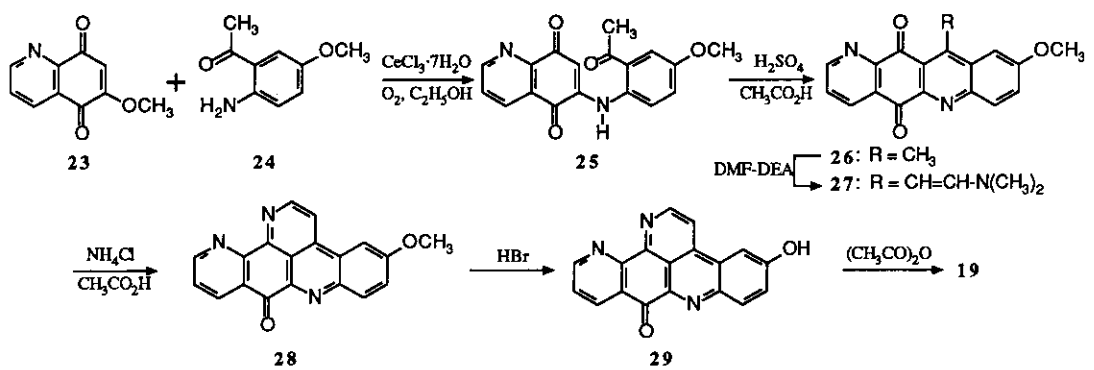
Finally, we determined the structure of neocalliactine acetate by unambiguous total synthesis. Neocalliactine acetate is a derivative prepared from calliactine, a pigment isolated from the sea anemone *Calliactis parasitica*,

and four alternative structures (**19-22**) were proposed.[3] Last year, Schmitz *et al.* reported further structural elucidation of neocalliactine acetate by a comparison with ^{1}H- and ^{13}C- nmr spectral data of meridine (**2**), ascididemin (**3**), and 11-hydroxyascididemin (**4**).[2d] 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**.



19 **20** **21** **22**

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**)[14] were identical with those of neocalliactine acetate. Thus, we determined the structure of neocalliactine acetate to be **19**, *i.e.* 3-acetoxyascididemin.



23 **24** **25** **28** **29**

ACKNOWLEDGEMENT

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9. **5**: mp 258-259°C ($CHCl_3$) (lit.,[2f] mp 255-258°C (decomp.)). Ms *m/z* (%): 289 (M^+, 100). High-resolution ms Calcd for $C_{16}H_7N_3OS$: 289.0310. Found: 289.0315. ^{1}H-Nmr (270 MHz, DMSO-d_6) δ: 8.03 (1H, t, J = 8.3 Hz, C_5-H), 8.09 (1H, t, J = 8.3 Hz, C_6-H), 8.43 (1H, d, J = 8.3 Hz, C_7-H), 8.84 (1H, d, J = 5.9 Hz, C_3-H), 8.96 (1H, d, J = 8.3 Hz, C_4-H), 9.11 (1H, d, J = 5.9 Hz, C_2-H), 9.68 (1H, s, C_{11}-H).
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11. **4**: mp >260°C ($CHCl_3$) (lit.,[2d] mp >250°C). Ms *m/z* (%): 299 (M^+, 93), 271 (100). High-resolution ms Calcd for $C_{18}H_9N_3O_2$: 299.0695. Found: 299.0715. ^{1}H-Nmr (270 MHz, $CDCl_3$) δ: 7.15 (1H, d, J = 5.6 Hz, C_9-H), 8.00 (1H, dt, J = 8.3, 1.3 Hz, C_3-H), 8.07 (1H, dt, J = 8.3, 1.7 Hz, C_2-H), 8.59 (1H, d, J = 5.6 Hz, C_5-H), 8.65 (1H, dd, J = 8.3, 1.3 Hz, C_1-H), 8.73 (1H, dd, J = 8.3, 1.7 Hz, C_4-H), 8.90 (1H, d, J = 5.6 Hz, C_{10}-H), 9.32 (1H, d, J = 5.6 Hz, C_6-H), 13.06 (1H, s, OH).
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14. **19**: mp >270°C (decomp.) ($CHCl_3$-ether) (lit.,[3] no mp was given). Ms *m/z* (%): 341 (M^+, 13), 313 (22), 299 (100). High-resolution ms Calcd for $C_{20}H_{11}N_3O_3$: 341.0800. Found: 341.0800. ^{1}H-Nmr (270 MHz, $CDCl_3$-CD_3OD) δ: 2.39 (3H, s, CH_3), 7.66 (1H, dd, J = 7.9, 4.6 Hz, C_{10}-H), 7.72 (1H, dd, J = 8.9, 2.3 Hz, C_2-H), 8.42 (1H, d, J = 2.3 Hz, C_4-H), 8.47 (1H, d, J = 5.9 Hz, C_5-H), 8.54 (1H, d, J = 8.9 Hz, C_1-H), 8.72 (1H, dd, J = 7.9, 1.6 Hz, C_{11}-H), 9.08 (1H, dd, J = 4.6, 1.6 Hz, C_9-H), 9.18 (1H, d, J = 5.9 Hz, C_6-H). ^{13}C-Nmr (67.8 MHz, $CDCl_3$-CD_3OD) δ: 20.80 (CH_3), 115.03 (C_4), 117.18 (C_5), 117.72 (C_{12b}), 124.42 (C_{4a}), 125.82 (C_{10}), 126.71 (C_2), 128.81 (C_{11a}), 133.99 (C_1), 136.54 (C_{11}), 137.68 (C_{4b}), 143.20 (C_{13a}), 145.25 (C_{12a}), 149.24 (C_{7a}), 149.31 (C_6), 151.67 (C_{7b}), 152.24 (C_3), 155.15 (C_9), 169.05 (CH_3CO), 181.33 (C_{12}).

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