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First total synthesis of the marine alkaloids purpurone and ningalin C†

Christian Peschko and Wolfgang Steglich*

Department Chemie der Ludwig-Maximilians-Universität, Butenandtstraße 5-13, Haus F, D-81377 Munich, Germany

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Abstract

Purpurone is obtained from 3-(3,4-dimethoxyphenyl)pyruvic acid, 2-(4-methoxyphenyl)ethylamine and 2′,2′,2′-trichloroethyl 2-bromo-2-(3,4-dimethoxyphenyl)acetate in seven steps with an overall yield of 11%. Ningalin C is synthesized from 1-[2-(3,4-dimethoxyphenyl)ethyl]-3,4-bis-(3,4-dimethoxyphenyl)-1*H*-pyrrole and methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate in five steps with a total yield of 19%. © 2000 Published by Elsevier Science Ltd.

Keywords: purpurone; ningalins; marine natural products; ACL inhibitors; pyrrole alkaloids.

In 1993 Chan, Faulkner and co-workers[1] reported the isolation and structural elucidation of the marine alkaloid purpurone (**1**) from an Indopacific sponge of the genus *Iotrochota*. In the course of the bioassay-guided fractionation of the extracts, purpurone was identified as a potent ATP-citrate lyase (ACL) inhibitor[2] ($IC_{50}=25$ μg/mL). The compound probably represents the aglycon of more complex sugar or protein conjugates as it is liberated only after acidic hydrolysis. Later, an hydroxy derivative of **1**, ningalin D (**2**), was discovered by Kang and Fenical[3] in an unidentified ascidian of the genus *Didemnum* together with three biogenetically related analogues including ningalin C (**3**).

* Corresponding author. Fax: (+49) 89-2180-7756; e-mail: wos@cup.uni-muenchen.de

† Dedicated to Professor Harry H. Wasserman on the occasion of his 80th birthday.

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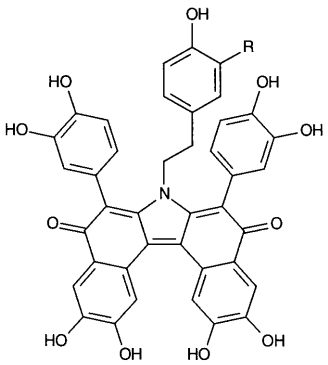
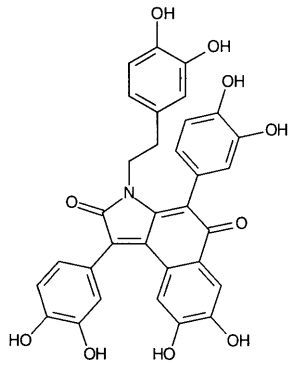
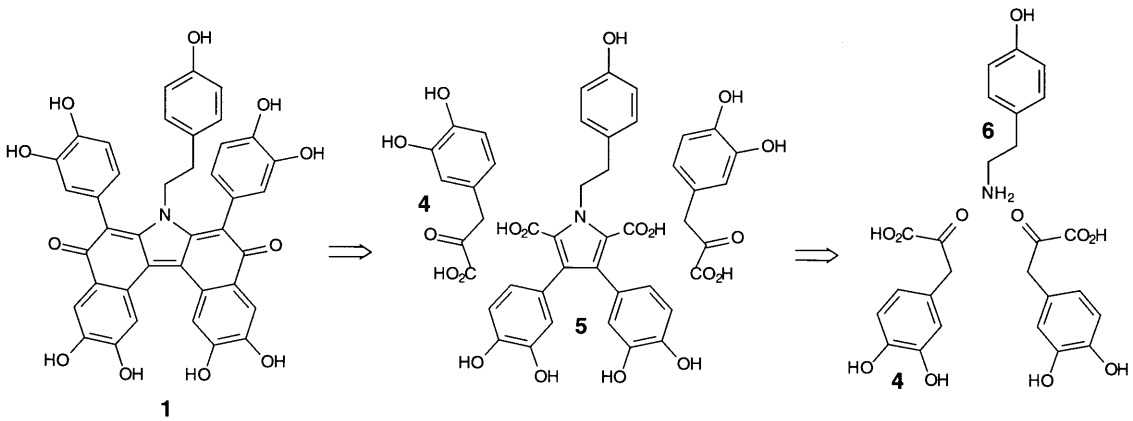


Purpurone (**1**), R=H
Ningalin D (**2**), R=OH



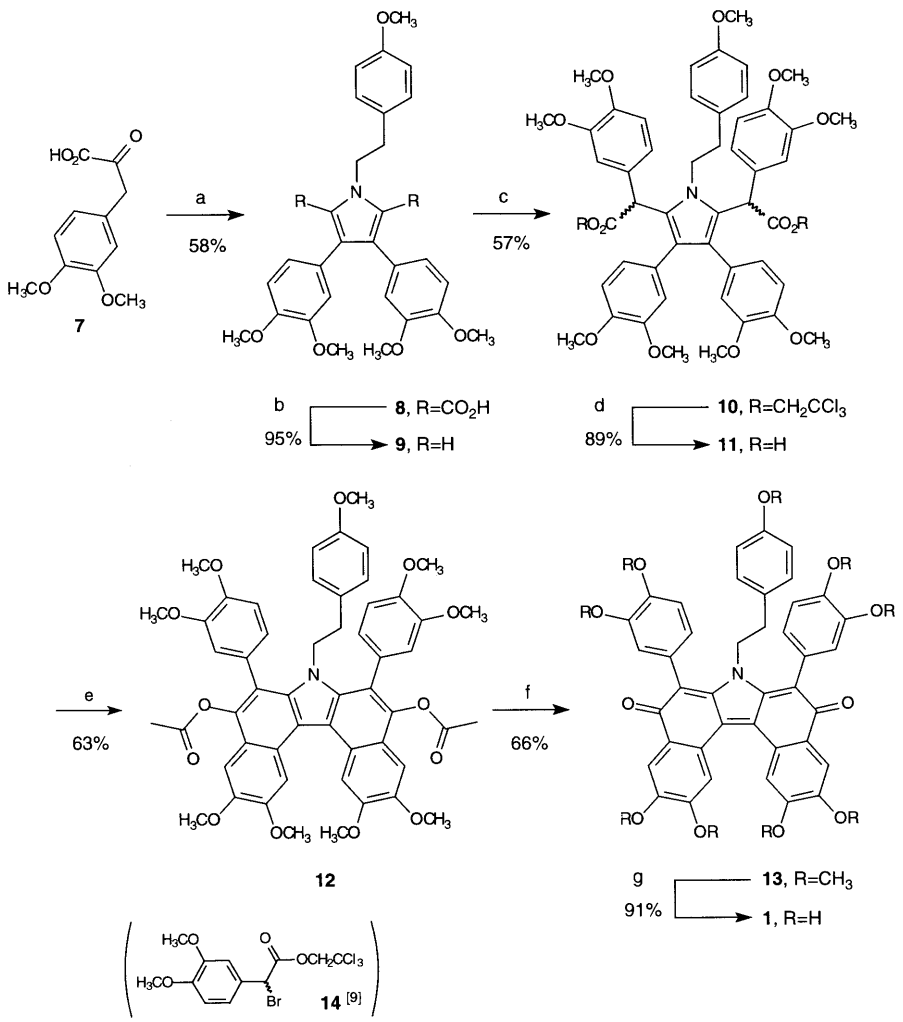
Ningalin C (**3**)

Retrobiosynthetic analysis suggests that purpurone (**1**) is built-up from five aromatic amino acid residues[4] (Scheme 1). The core unit is the *N*-substituted 3,4-diarylpyrrole-2,5-dicarboxylic acid **5**, which could be formed by oxidative dimerization of aryl pyruvic acid **4** followed by condensation of the resulting 1,4-diketone with tyramine **6**.[4] Attachment of two further molecules of **4** to the pyrrole ring in **5** would yield an intermediate, from which the purpurone system can be derived by decarboxylation and subsequent cyclization. In this paper we describe the syntheses of purpurone (**1**) and ningalin C (**3**) according to this proposal, a strategy which has already been successfully applied to the total syntheses of other marine pyrrole alkaloids like polycitrin A,[5] lamellarin G trimethyl ether,[4] lamellarin L[6] and storniamide A nonamethyl ether.[7]



Scheme 1. Retrobiosynthetic analysis of purpurone (**1**)

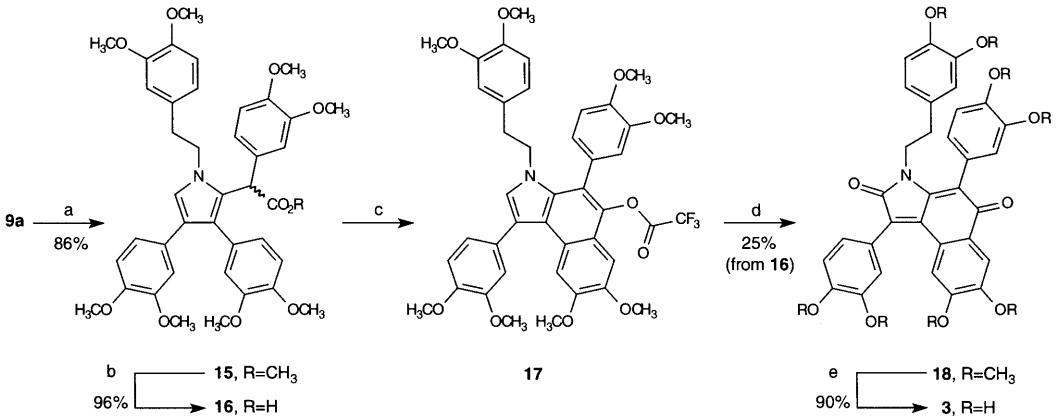
Our highly convergent total synthesis of purpurone (**1**) started with the one pot formation[4] of pyrrole–dicarboxylic acid **8** by oxidative dimerization of two molecules of 3-(3,4-dimethoxyphenyl)pyruvic acid (**7**) and subsequent condensation with 2-(4-methoxyphenyl)ethylamine (Scheme 2). Decarboxylation by treatment with trifluoroacetic acid[8] afforded pyrrole **9** in almost quantitative yield. The twofold Friedel–Crafts alkylation was accomplished by heating **9** with



Scheme 2. *Reagents and conditions*: (a) i) *n*-BuLi (2 equiv.), THF, −78°C; ii) I_2 (0.5 equiv.), −78 to 25°C; iii) 2-(4-methoxyphenyl)-ethylamine (3 equiv.), 4 Å molecular sieves, 18 h; (b) TFA (15 equiv.), $CHCl_3$, reflux, 10 h; (c) **14** (2.5 equiv.), acidic Al_2O_3 (40 equiv.), $CHCl_3$, reflux, 10 h; (d) Zn dust (50 equiv.), aq. NH_4OAc (1N, 4 equiv.), THF, 25°C, 1.5 h; (e) Ac_2O, KOAc (2.6 equiv.), reflux, 1.25 h; (f) 5% aq. NaOH, air, MeOH, 55°C, 0.5 h; (g) BBr_3 (10 equiv.), cyclohexene (20 equiv.), CH_2Cl_2, −78°C

bromoester **14**[9] in chloroform in the presence of acidic alumina (40 equiv.). The key compound **10** was thereby obtained in 57% yield.[10] Cleavage of the ester groups under mild conditions with Zn/aqueous NH_4OAc in THF[11] furnished the crude diacid **11** in 89% yield, which on heating with Ac_2O/KOAc[12] was regioselectively cyclized to the diacetate **12** (63% yield). Conversion of **12** to purpurone nonamethyl ether (**13**)[13] was achieved by saponification with aqueous sodium hydroxide in methanol under exposure to air in 66% yield. The synthesis was completed by cleavage of the *O*-methyl groups with an excess of boron tribromide[14] in dichloromethane under addition of cyclohexene as bromine scavenger.[15] Purpurone (**1**) was thereby obtained as an amorphous deep purple solid in 11% overall yield. Its spectroscopic data (UV, NMR, MS) agreed with those reported for the natural product.[1]

For the total synthesis of ningalin C (**3**), pyrrole **9a**[16] was monoalkylated by Rh(II)acetate catalyzed insertion of the carbene[17] generated from methyl 2-diazo-2-(3,4-dimethoxyphenyl)-acetate[18] (Scheme 3). Saponification of ester **15** and subsequent intramolecular Friedel–Crafts acylation[12] of crude acid **16** furnished the trifluoroacetate **17**. Formation of both the conjugated and the amide carbonyl groups of the ningalin C skeleton **18** was achieved in one step (25% from **16**) by simply subjecting the acylated phenol **17** to aqueous sodium hydroxide/methanol under exposure to air. The deep orange-colored permethyl ningalin C (**18**)[13] was converted to the natural product by methyl ether cleavage using boron tribromide in dichloromethane[14] to furnish **3** in a total yield of 19% from **9a**. The spectral data (IR, UV–vis, MS, ^1H, ^{13}C NMR) correspond to those given for the natural product.[3]



Scheme 3. *Reagents and conditions*: (a) Methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate (1.5 equiv.), cat. $[Rh(OAc)_2]_2$, CH_2Cl_2, 25°C, 2.5 h; (b) 5% aq. NaOH, EtOH, reflux, 1 h; (c) TFAA, KO_2CCF_3 (1.1 equiv.), CH_2Cl_2, 45°C, 4 h; (d) 10% aq. NaOH, MeOH, 25°C, 18 h; (e) BBr_3 (13 equiv.), CH_2Cl_2, −78 to 25°C, 18 h

Acknowledgements

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9. Preparation of **14**: (a) (3,4-dimethoxyphenyl)acetic acid, DCC (1.1 equiv.), DMAP (0.1 equiv.), 2,2,2-trichloroethanol (2.5 equiv.), CH_2Cl_2, 25°C, 15 h; (b) CCl_4, NBS (1.05 equiv.), cat. AIBN, *hv*, 35°C, 1 h.
10. The NMR spectra indicate a mixture of stereoisomers.

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13. Selected spectroscopic data: **13**: UV (MeOH): λ_{max} (ε) = 226 (25 834), 283 (16 935), 498 nm (11 202). IR (KBr): $\tilde{\nu}$ = 1713 (m), 1618 (m), 1588 (s), 1558 (m), 1513 (s), 1464 (m), 1270 (s), 1027 cm^{-1} (m). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.84 (s, 2H), 7.68 (s, 2H), 6.96 (dd, J = 8.7, 1.8 Hz, 2H), 6.95 (d, J = 1.8 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.50 (d, J = 8.7 Hz, 2H), 6.43 (d, J = 8.7 Hz, 2H), 4.02 (s, 6H), 3.91 (s, 6H), 3.90 (s, 6H), 3.88 (s, 6H), 3.53 (s, 3H), 3.03 (t, J = 7.2 Hz, 2H), 2.27 (t, J = 7.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 182.99 (C=O), 158.14, 154.37, 151.12, 151.03, 149.06, 148.66, 131.15, 129.62 (CH), 129.37, 126.30, 125.42, 124.10, 123.73 (CH), 117.31, 114.24 (CH), 113.29 (CH), 110.89 (CH), 109.81 (CH), 108.65 (CH), 56.51 (CH_3), 56.21 (CH_3), 55.97 (CH_3), 55.88 (CH_3), 54.92 (CH_3), 46.85 (CH_2), 33.48 (CH_2). EIMS (170°C): m/z (rel. intensity) = 823 (100) [M^+], 702 (47), 690 (30), 689 (30), 658 (17). HREIMS calcd for $C_{49}H_{45}NO_{11}$ [M^+] 823.2958, found 823.2955. **18**: UV (MeOH): λ_{max} (ε) = 203 (54 833), 282 (13 514), 343 nm (8866). IR (KBr): $\tilde{\nu}$ = 1706 (s), 1626 (s), 1593 (s), 1515 (s), 1264 (s), 1235 (s), 1142 (s), 1027 cm^{-1} (s). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.62 (s, 1H), 7.17 (dd, J = 8.2, 2 Hz, 1H), 7.05 (d, J = 1.9 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.99–6.68 (br, 3H), 6.97 (s, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.39 (dd, J = 8, 2 Hz, 1H), 6.29 (d, J = 2 Hz, 1H), 3.95 (s, 6H), 3.94 (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H), 3.88–3.81 (br, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.53 (s, 3H), 2.52 (t, J = 8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 183.59 (C=O), 170.81 (C=O), 152.06, 150.68, 150.24, 149.36, 149.26, 148.79, 148.61, 147.63, 147.13, 134.31, 130.48, 130.31, 124.98, 124.48, 123.81, 123.71 (CH), 123.13, 122.91 (CH), 120.75 (CH), 118.92, 114.24 (CH), 112.69 (CH), 111.71 (CH), 111.36 (CH), 111.20 (CH), 110.87 (CH), 109.38 (CH), 107.76 (CH), 56.08 (CH_3), 56.07 (CH_3), 56.06 (CH_3), 56.00 (CH_3), 55.91 (CH_3), 55.86 (CH_3), 55.72 (CH_3), 55.67 (CH_3), 43.14 (CH_2), 34.85 (CH_2). EIMS (170°C): m/z (rel. intensity) = 693 (24) [M^+], 542 (24), 529 (100). HREIMS calcd for $C_{40}H_{39}NO_{10}$ [M^+] 693.2581, found 693.2579.
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15. Utilization of excess BBr_3 without the addition of cyclohexene resulted in partial mono-bromination of **1** at the 4-hydroxybenzene unit. **1** and its bromo derivative were easily separated by RP-18-HPLC (solvents: A: CH_3CN/H_2O 1:9+0.1% TFA, B: CH_3CN. Gradient: 100% A to 100% B within 50 min. Retention times: **1**: 21 min, bromo derivative: 22 min).
16. The synthesis of **9a** followed the procedure described for **9** with homoveratrylamine instead of 2-(4-methoxyphenyl)ethylamine.
17. (a) Maryanoff, B. E. *J. Org. Chem.* **1982**, *47*, 3000–3002; (b) Padwa, A.; Wisnieff, T. J.; Walsh, E. J. *J. Org. Chem.* **1989**, *54*, 299–308; (c) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765–1808.
18. Methyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate was obtained in 62% yield by stirring methyl 2-(3,4-dimethoxyphenyl)acetate with 4-toluenesulfonyl azide (1 equiv.) and DBU (1 equiv.) in CH_3CN for 15 h at ambient temperature.