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Regioselective Preparation of 2-Substituted 3,4-Diaryl Pyrroles: A Concise Total Synthesis of Ningalin B

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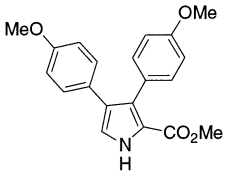
Methylisocyanoacetate undergoes a 2 + 3 cycloaddition with α,β-unsaturated nitriles to provide a regioselective synthesis of 2-substituted 3,4-diaryl pyrroles. The ease of preparation of α,β-unsaturated nitriles allows the rapid synthesis of pyrroles with varied substituents. Using this method, a key intermediate (**1**) for the synthesis of the marine natural products lukianol A, lamellarin O, and lamellarin Q was prepared in two steps. A total synthesis of ningalin B (**11**) was also accomplished utilizing this methodology.

Introduction

The biological activities of 2-substituted 3,4-diaryl pyrroles reported in the recent literature have demonstrated the importance of these molecules.[1−4] Many of these substituted pyrroles are incorporated as the nucleus of natural products, especially in the tunichrome family of marine natural products, first isolated during the 1990s.[5−8] We were particularly interested in the preparation of lukianol A, lamellarin O, lamellarin Q, and ningalin B, which have been recently synthesized using a variety of synthetic methods.[1,4,9−12]

Wong et al. published a highly regioselective synthesis of 2-substituted 3,4-diaryl pyrroles using N-protected 3,4-trimethylsilyl pyrrole for α-lithiation of the pyrrole, which reacted with methyl chloroformate to give an ester at the two position.[11] The authors then proceed through an iodination and palladium cross-coupling reaction sequence to substitute the three position of the pyrrole and then repeat this sequence to substitute the four position. This method of diarylation combined with pyrrole nitrogen protection/deprotection and preparation of the trimethylsilyl pyrrole starting material extends this synthesis to several steps. The authors use this reaction scheme to prepare the marine natural product lukianol A through the Fürstner intermediate **1**. Fürstner used this key structure in the first synthesis of marine natural products lukianol A and lamellarin O.[12]



1, Fürstner intermediate

Banwell et al. have also prepared this intermediate in a three-step sequence starting from *N*-triisopropylsilyl pyrrole, which is first dibrominated at positions three and four, and next, the 2-lithio species is generated and reacted with methyl chloroformate, followed by a diarylation via a Suzuki coupling.[10] Although this procedure is concise, the diarylation leads to compounds where both aromatic rings are identical. As an alternative to the Suzuki reaction, the authors twice perform a lithiation followed by a Negishi cross-coupling to differentiate the aromatic rings, but this doubles the number of steps for this synthetic route.

Kim et al.[13] recently modified a procedure pioneered by Gupton and Sikorski[14] that uses a vinylogous amide derived from a condensation of DMF−dimethylacetal with commercially available α-(*p*-methoxyphenyl)-*p*-methoxyacetophenone. The Fürstner pyrrole is then

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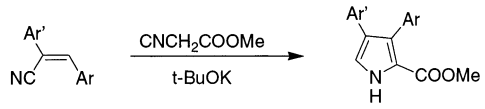
SCHEME 1



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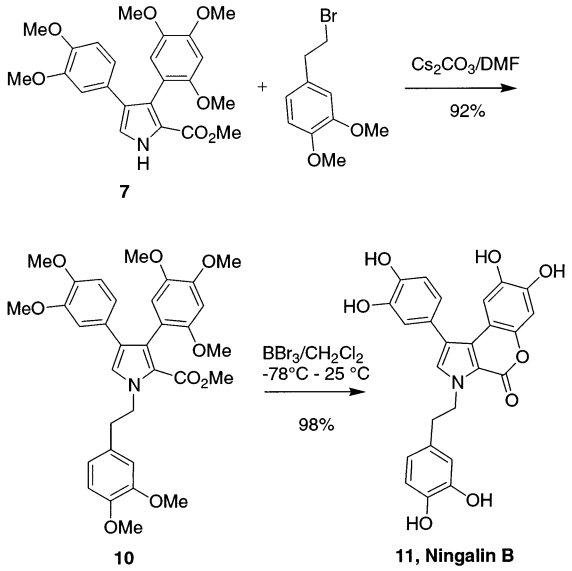


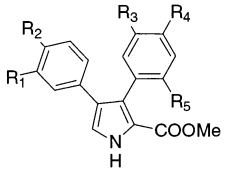
prepared through a cyclocondensation reaction between dimethyl aminomalonate and this vinylogous amide. Although this procedure constructs this compound in two steps from commercially available starting material, other analogues would require additional syntheses to obtain the appropriate starting materials. Furthermore, the scope of this reaction with other aromatic substituents was not reported.

In general, regioselectivity in the synthesis of these 2-substituted 3,4-diaryl pyrroles continues to be the obstacle in the majority of this literature, which involves multistep syntheses to diversify the substitutions on the pyrrole. Our synthetic approach involves a two-step preparation of this key Fürstner intermediate (**1**) that allows effortless variation of the substituents of the two aromatic rings.

Results and Discussion

We have a simple regiocontrolled synthesis of 2-substituted 3,4-diaryl pyrroles that can be used to prepare these compounds in two steps from commercially available starting materials (Scheme 1). The key feature of this chemistry is in utilizing the leaving group ability of the nitrile, which allows these reactions to occur at low temperatures. The addition of methyl isocyanoacetate to α,*β*-unsaturated nitriles with subsequent ring closure was disclosed in a 1989 patent, where only a single compound (3,4-bis(4-fluorophenyl)pyrrole-2-ethyl ester) was reported.[15] Similarly, other researchers have used α,*β*-unsaturated sulfones and nitroalkenes as Michael acceptors to synthesize 2-substituted 3,4-diaryl pyrroles

TABLE 1. Yields of Pyrrole Formation



product	R_1	R_2	R_3	R_4	R_5	yield
1	H	OMe	H	OMe	H	55
2	H	CF_3	H	CF_3	H	59
3	H	CF_3	H	OMe	H	60
4	H	OMe	H	CF_3	H	59
5	H	OMe	H	H	H	51
6	H	H	H	H	H	54
7	OMe	OMe	OMe	OMe	OMe	57

in good yields.[16−18] However, the need for preparation of the α,*β*-unsaturated sulfones or nitroalkenes limits the scope of these reactions.

Preparation of the α,*β*-unsaturated nitriles can be performed through literature procedures by heating the appropriate benzaldehyde and phenylacetonitrile with either potassium carbonate[19] or sodium methoxide[20] in methanol. The pyrroles can be synthesized by a slow dropwise addition of a solution of the α,*β*-unsaturated nitrile and methyl isocyanoacetate to an excess of potassium *tert*-butoxide at 0 °C. Yields are typically 50−60% regardless of the electron-withdrawing or electron-releasing substitutions on each aromatic ring (Table 1).

We were able to substitute both aromatic rings with a strongly electron-releasing methoxy group (**1**), or a strongly electron-withdrawing trifluoromethyl group (**2**) without affecting the product yields. We also combined the activating and withdrawing effects of these substituents by placing the methoxy on one aromatic ring and the trifluoromethyl on the opposite aromatic ring (**3**). We could also reverse the electronics (**4**) without affecting the yields of these reactions. Further, synthesis of compound **5** with only one of the aromatic rings substituted or compound **6** with both aromatic rings unsubstituted proceeds in similar yield. This reaction was also carried out with multiple substituents and where R_5 is substituted with a methoxy group (**7**), which sterically crowds the Michael addition.

Inspired by the work of Boger et al,[1] we decided to apply this chemistry to the synthesis of ningalin B to further demonstrate the usefulness of this pyrrole formation reaction. Boger's synthesis involves a preparation of an intermediate pyrrole (**8**), which contains an orthogonally protected phenolic group. Deprotection of this methoxymethyl ether resulted in spontaneous lactonization of the phenol with the adjacent ester. The remaining ester is then selectively hydrolyzed and subsequently removed by decarboxylation. Exhaustive demethylation of the six methoxy groups generates ningalin B.

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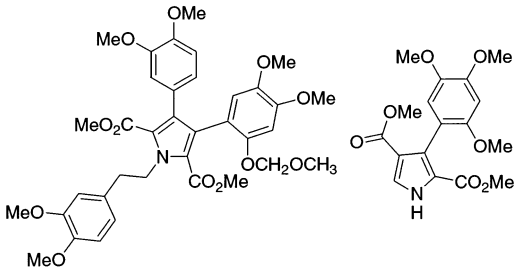

8 **9**

Our initial attempts to synthesize compound **7** were unsuccessful under our normal reaction conditions. Since the yields of compounds **1**−**6** were not influenced by electronic effects, we presumed that the 2-methoxy group was hindering the initial Michael addition reaction. Performing the reaction at 25 °C in an attempt to circumvent this problem did not produce compound **7** either. However, when the reaction was repeated under normal conditions but this time allowed to warm slowly to 25 °C overnight, compound **7** was obtained in good yield. Interestingly, structure **9** was also isolated as a slower moving peak during column chromatography purification. This side-product presumably arises from our initial Michael addition undergoing a retro-Michael with the leaving group being 3,4-dimethoxyphenylacetonitrile (not detected in the final workup). This methyl α-isocyanoacrylate intermediate then reacts with another equivalent of methyl isocyanoacetate and proceeds to product. Similarly, these types of diester compounds have been prepared in the literature through reaction of methyl α-isocyanoacrylates with an equivalent of methyl isocyanoacetate[21]

Compound **7** was alkylated with dimethoxyphenethyl bromide[22] using potassium carbonate in DMF but would not go to completion even after heating at 70 °C for 24 h. Substituting cesium carbonate for potassium carbonate allowed the reaction to proceed easily to compound **10** in 91% yield. We envisioned demethylating all seven methoxy groups of compound **10**, which would subsequently cyclize to the lactone in one step to give ningalin B (**11**). This procedure worked well, giving us compound **11** (ningalin B) in a 51% overall yield (three steps). The structure was confirmed by comparison of the spectroscopic data to the literature data for ningalin B.

Conclusions

We have explored the scope of a simple and concise route to 2-substituted 3,4-diaryl pyrroles using a 2,3-cycloaddition reaction. This route can be used to effectively prepare a key intermediate (**1**) to several marine natural products such as lukianol A, lamellarin O, and lamellarin Q. Since this reaction demonstrates good tolerance to electronic changes for both aromatic rings, it should be very amenable for the synthesis of a variety of analogues of these natural products.

We have completed a high yield synthesis of ningalin B that significantly reduces the number of synthetic steps required for its preparation and allows for the large-scale preparation of this and related compounds. This scheme offers a significant improvement over the existing methodologies to regioselectively prepare 2-substituted 3,4-diaryl pyrrole natural products

Experimental Section

General Procedure for the Formation of α,*β*-Unsaturated Acetonitriles (A). A mixture of benzaldehyde (1 mmol), phenylacetonitrile (1 mmol), and K_2CO_3 (1.2 mmol) was refluxed in MeOH (2 mL) for 4 h under N_2. The mixture was cooled, poured into H_2O (2 mL), and stirred for 20 min. The precipitate was collected by filtration, washed with H_2O (2 × 5 mL) and petroleum ether (2 × 5 mL), and air-dried. The material was used in the next step without further purification.

General Procedure for the Formation of α,*β*-Unsaturated Acetonitriles (B). A mixture of benzaldehyde (0.11 mol), phenylacetonitrile (0.1 mol), and NaOMe (20 mL, 25% in MeOH) was refluxed in MeOH (500 mL) for 24 h under N_2. The mixture was cooled and the precipitate collected by filtration and air-dried. The material was used in the next step without further purification.

General Procedure for the Pyrrole Ring Formation. A solution of α,*β*-unsaturated acetonitrile (3.7 mmol) and methyl isocyanoacetate (3.7 mmol) in THF (15 mL) was added dropwise to a stirred solution of 1 N potassium *t*-butoxide (6.7 mL, 1.0 N in THF, 6.7 mmol) at 0 °C under N_2. After stirring at 0 °C for 1 h, the reaction mixture was diluted with H_2O (10 mL) and extracted into EtOAc (20 mL, 2 × 10 mL). The combined organics were washed with water (20 mL) and then brine (20 mL). **Caution: the water layer contains KCN and should be kept basic and disposed of properly.** Evaporation of the solvent, followed by purification on SiO_2 (35 g) eluting with a gradient of 5−20% EtOAc in hexane afforded the pyrrole. An analytically pure sample was prepared by recrystallization from methanol.

3,4-Bis-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (1). The general method was followed to afford an off-white solid (0.69 g, 55% yield): mp 176−177 °C (lit.[11] 169−171 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.19 (br, NH), 7.2 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 3.3 Hz, 2H) 6.86 (d, J = 8.3 Hz, 2H), 6.76, (d, J = 8.4 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H); MS (M + 1, 338). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 70.96; H, 5.69; N, 3.91.

3,4-Bis-(4-trifluoromethylphenyl)-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (2). The general method was followed on a 1.5 mmol scale. Chromatography on SiO_2 eluting with CH_2Cl_2 afforded **2** (0.36 g, 59% yield) as a white solid: mp 206−209 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.35 (br, NH), 7.59 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.19−7.15 (m, 3H), 3.76 (s, 3H); MS (CI) *m*/*z* 436 (M^+ + Na). Anal. Calcd for $C_{20}H_{13}F_6NO_2$: C, 58.12; H, 3.17; N, 3.39. Found: C, 57.85; H, 3.00; N, 3.35.

3-(4-Methoxyphenyl)-4-(4-trifluoromethylphenyl)-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (3). The general method was followed on a 1.6 mmol scale. Chromatography on SiO_2 eluting with CH_2Cl_2 afforded **4** (0.37 g, 60% yield) as a white solid: mp 166−167 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (br, NH), 7.33−7.24 (m, 4H), 7.06 (d, J = 3.1 Hz, 1H) 7.01 (d, J = 8.7 Hz, 2H) 6.74 (d, J = 8.8 Hz, 2H) 3.76 (s, 3H), 3.72 (s, 3H); MS (M +1, 330). Anal. Calcd for $C_{20}H_{16}F_3NO_3$: C, 64.00; H, 4.30; N, 3.73. Found: C, 63.94; H, 4.28; N, 3.60.

4-(4-Methoxymethylphenyl)-3-(4-trifluoromethylphenyl)-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (4). The general method was followed to afford **3** (0.83 g, 59% yield) as a white solid: mp 151−152 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.27 (br, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.07 (d, J = 3.0 Hz, 1H), 6.99 (d, J = 8.5 Hz, 2H), 6.77 (d, J = 9.0 Hz, 2H), 3.79 (s, 3H), 3.75 (s, 3H); MS (M + Na, 398).

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Anal. Calcd for $C_{20}H_{16}F_3NO_3$: C, 64.00; H, 4.30; N, 3.73. Found C, 63.70; H, 4.01; N, 3.62.

3-(4-Methoxyphenyl)-4-phenyl-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (5). The general method was followed to afford **5** (0.59 g, 51% yield) as a white solid: mp 166−168 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.2 (br, NH), 7.30 (m, 5H), 7.07 (d, J = 3.0 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 6.73 (d, J = 8.4 Hz, 2H), 3.78 (s, 3H), 3.73 (s, 3H); MS (M + 1, 330). Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.12; H, 5.44; N, 4.35.

3,4-Diphenyl-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (6). The general method was followed to afford **6** (0.56 g, 54% yield) as a white solid: mp 130−131 °C (lit.[23] 125−126 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.288 (br, NH), 7.32−7.06 (m, 11H), 3.71 (s, 3H) MS (M + Na, 300). Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.97; H, 5.33; N, 4.89.

4-(3,4-Dimethoxyphenyl)-3-(2,4,5-trimethoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (7). After the addition was complete, the reaction was stirred for 1 h at 0 °C. No product was observed by TLC (10% MeOH in CH_2Cl_2), so stirring was continued for 18 h allowing the reaction to warm to 25 °C. Evaporation of the solvent, followed by purification on SiO_2 (35 g) eluting with a gradient of 1−5% MeOH in CH_2Cl_2, gave compound **7** (910 mg, 57% yield): mp 155−156 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.24 (br, NH), 7.11 (d, J = 3.2 Hz, 1H), 6.80−6.74 (m, 3H), 6.63 (d, J = 1.6 Hz, 1H), 6.53 (s, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 3.60 (s, 3H), 3.47 (s, 3H); MS (M + 1, 428). Anal. Calcd for $C_{23}H_{25}NO_7$: C, 64.63; H, 5.90; N, 3.28. Found: C, 64.41; H, 5.82; N, 3.18. A second peak was isolated from the column, and this compound was identified as **3-(2,4,5-trimethoxyphenyl)-1*H*-pyrrole-2,4-dicarboxylic acid dimethyl ester (9):** mp 135−138 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.55 (br, NH), 7.57 (d, J = 3.2 Hz, 1H), 6.79 (s, 1H), 6.59 (s, 1H), 3.94 (s, 3H), 3.83 (s, 3H), 3.71 (s, 3H), 3.70 (s, 3H), 3.68 (s, 3H) MS (M + 1, 350). Anal. Calcd for $C_{17}H_{19}NO_7$: C, 58.45; H, 5.48; N, 4.01. Found; C, 58.41; H, 5.53; N, 3.83.

4-(3,4-Dimethoxyphenyl)-1-[2-(3,4-dimethoxyphenyl)-ethyl]-3-(2,4,5-trimethoxyphenyl)-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (10). Compound **7** (600 mg, 1.4 mmol), 3,4-dimethoxyphenethyl bromide[22] (1.0 g, 4.2 mmol), and Cs_2CO_3 (1.4 g, 4.2 mmol) were heated to 60 °C in DMF (15 mL). After 2.5 h, the reaction was cooled, diluted with water (30 mL), and extracted into EtOAc (50 mL, 2 × 20 mL). The combined organics were washed with water (4 × 10 mL) and then brine (10 mL) and dried (Na_2SO_4). After evaporation of the solvent, the oil was dissolved in toluene (5 mL) and purified on SiO_2 (35 g) eluting with a gradient of 50−70% EtOAc in hexane to give **10** (0.76 g, 92% yield) as a light yellow solid. Recrystallization provided **10** as colorless crystals: mp 140−141 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.86 (d, J = 8.9 Hz, 1H), 6.79−6.76 (m, 2H), 6.70 (d, J = 8.2 Hz, 1H), 6.66 (s, 1H), 6.63−6.59 (m, 2H), 6.52−6.50 (m, 2H) 4.53 (br, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.72 (s, 3H), 3.61 (s, 3H), 3.58 (s, 3H), 3.50 (s, 3H), 3.07 (t, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 162.5, 151.9, 149.2, 149.0, 148.6, 148.0, 147.4, 143.0, 131.5, 128.2, 127.0, 126.3, 124.3, 121.2, 120.0, 119.8, 117.2, 116.3, 112.6, 111.7, 111.3, 111.3, 98.2, 56.8, 56.8, 56.4, 56.2, 56.1, 56.0, 55.7, 52.1, 51.1, 38.2; MS (M + Na, 614). Anal. Calcd for $C_{33}H_{37}NO_9$: C, 66.99; H, 6.30; N, 2.37. Found: C, 66.86; H, 6.20; N, 2.12.

1-(3,4-Dihydroxyphenyl)-3-[2-(3,4-dihydroxyphenyl)-ethyl]-7,8-dihydroxy-3*H*-5-oxa-3-aza-cyclopenta[a]naphthalen-4-one (11), Ningalin B. Compound **10** (60 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (25 mL), and 1 N BBr_3 (1.6 mL, 1 N BBr_3 in CH_2Cl_2, 0.16 mmol) was added dropwise at −78 °C. The solution was stirred overnight allowing the temperature to slowly warm to 25 °C. The reaction was quenched with H_2O (5 mL) and the mixture concentrated in vacuo. The mixture was extracted into EtOAc (3 × 15 mL), and the organics were washed with brine (10 mL), dried (Na_2SO_4), and evaporated to a dark yellow solid (46 mg, 98%): ^{1}H NMR (20% MeOH-d_4/DMSO-d_6, 400 MHz) δ 7.23 (s, 1H), 7.12 (s, 1H), 6.85 (d, J = 7.8 Hz, 1H), 6.82 (d, J = 2.0 Hz, 1H), 6.8 (s, 1H), 6.67 (d, J = 8.1 Hz, 1H), 6.48 (dd, J = 2.0, 8.1 Hz, 1H), 6.64 (d, J = 2.0 Hz, 1H), 6.48 (dd, J = 2.0, 8.1 Hz, 1H), 4.54 (t, J = 7.0 Hz, 2H), 2.92 (t, J = 7.4 Hz, 2H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 154.5, 146.0, 145.2, 145.1, 144.7, 144.7, 143.8, 142.1, 132.7, 128.9, 126.1, 125.0, 120.5, 119.4, 118.9, 116.9, 116.2, 115.8, 115.5, 113.7, 109.4, 108.5, 103.4, 49.7, 37.0; MS (M + 1, 462), FAB−HRMS (M + 1, 462.1174, $C_{25}H_{20}NO_8$, requires 462.1189). Anal. Calcd for $C_{25}H_{19}NO_8 \cdot 1.75\ H_2O$: C, 60.91; H, 4.60; N, 2.84. Found: C, 61.00; H, 4.33; N, 2.75.

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Supporting Information Available: ^{1}H NMR spectra of compounds **1**−**7** and **9**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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