# TWO-DIRECTIONAL SYNTHESIS OF 2,6-DIMETHYLPYRROLO-[2,3-*f*]INDOLE-4,8-DIONE BY DOUBLE CLAISEN REARRANGEMENT AND NITRENE CYCLIZATION †

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Abstract – Double Claisen rearrangement of the bis-allyl ether of 2,5-dichloro-1,4-hydroquinone, followed by alkene isomerization, oxidation and double chloride displacement with azide gives   2,5-diazido-3,6-dipropenyl-1,4-benzoquinone. Upon heating, a double nitrene cyclization occurs completing a high yielding, two-directional route to the pyrrolo[2,3-*f*]indole-4,8-dione ring system.

The indole heterocycle is ubiquitous among biologically active compounds, both naturally occurring indole alkaloids and synthetic medicinal compounds. One interesting subset of indoles are the pyrroloindoles (benzodipyrroles), particularly the symmetrical pyrrolo[2,3-*f*]indoles (Figure 1). Interest in this class of indoles has been heightened by the structure of terreusinone, a UV-protective natural product isolated from the marine fungus *Aspergillus terreus*.[1, 2] In keeping with their structure, the synthesis of pyrrolo[2,3-*f*]indoles is best approached through a strategy that takes advantage of the symmetry, and a number of such approaches have been developed. These include oxidative cyclization of 2,5-di(2-aminoethyl)-1,4-hydroquinones,[3] a double Leimgruber-Batcho synthesis starting from 2,5-dinitro-*p*-xylene,[4] and a Rh(I) catalyzed intramolecular hydroamination reaction of 2,5-diethynyl-*p*-phenylenediamine.[5] A related Au(I) catalyzed double intramolecular hydroamination has recently been reported for the two-directional synthesis of terreusininone itself.[6] We now report a complementary, new two-directional approach to pyrrolo[2,3-*f*]indoles based on a double Claisen rearrangement and nitrene cyclization. Routes to symmetrical pyrrolo[2,3-*f*]indole-4,8-diones are also known, for example from 2,5-diamino-3,6-dibromobenzoquinones.[7]
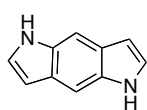

pyrrolo[2,3-*f*]indole
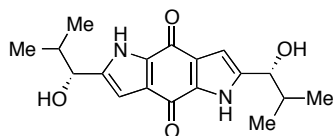
terreusinone

Figure 1. The pyrrolo[2,3-*f*]indole ring system, and the natural product terreusinone.

The starting point for the synthesis was 2,5-dichloro-1,4-hydroquinone that was converted into its diallyl ether (**1**) in excellent yield by reaction with allyl bromide and sodium hydride in DMF. On heating to 220 °C under microwave irradiation in 1,2-dichlorobenzene a double Claisen rearrangement ensued to give bis-allyl hydroquinone (**2**) in good yield (Scheme 1). Rearrangement under microwave conditions was generally superior to conventional heating, although the reaction could be carried out at room temperature albeit in lower yield (35%) by treatment with diethylaluminium chloride Lewis acid. Although the aromatic Claisen rearrangement is well known,[8] there are relatively few examples involving a double (or

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† Dedicated with respect and affection to Professor Victor Snieckus, Queen's University, Canada

tandem) rearrangement of bis(allyloxy)arenes.[9-11] Hydroquinone (**2**) was treated with palladium(II) chloride bis(acetonitrile) in catalytic amount to give the isomerized hydroquinone (**3**) in excellent yield. Oxidation with cerium(IV) ammonium nitrate gave dichloroquinone (**4**) in good yield, which was treated with sodium azide to give diazidoquinone (**5**) in excellent yield. Finally, heating in toluene at 85 °C gave dipyrrolobenzoquinone (**6**) in quantitative yield (Scheme 1). The structure of pyrrolo[2,3-*f*]indole (**6**) was confirmed both by NMR spectroscopy and mass spectrometry. The appearance of a broad singlet at 12.18 ppm for the NH groups, a singlet at 6.14 ppm for the CH groups and a singlet at 2.20 ppm for the methyl groups in the ^{1}H-NMR spectrum were in agreement with the symmetrical structure of (**6**).
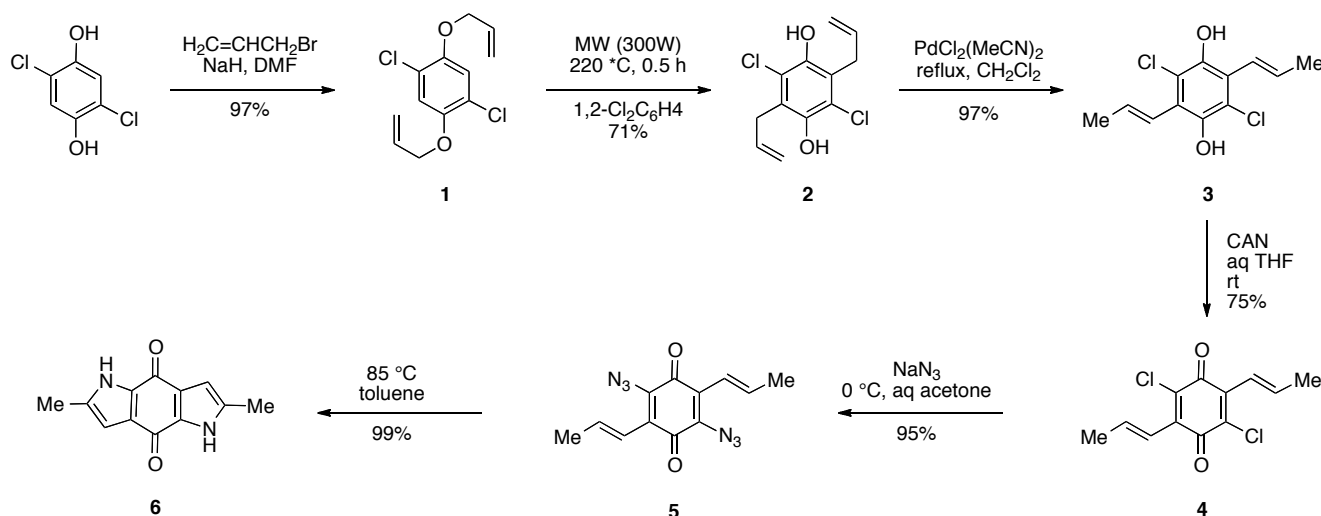
Scheme 1. Double Claisen rearrangement and nitrene cyclization.

The proposed mechanism for the cyclization involves the thermolysis of the azide group with loss of nitrogen and formation of a nitrene intermediate; a six-electron electrocyclic ring closure followed by [1,5]-sigmatropic hydrogen shift, gives the fused pyrrole (Scheme 2). This mechanism is preferred over a direct nitrene insertion into the alkene C-H bond.[12, 13] It is not known whether the two nitrene cyclizations occur simultaneously or sequentially, but in combination with the double Claisen rearrangement it constitutes a very convenient, high yielding two-directional route to the pyrrolo[2,3-*f*]indole core structure.
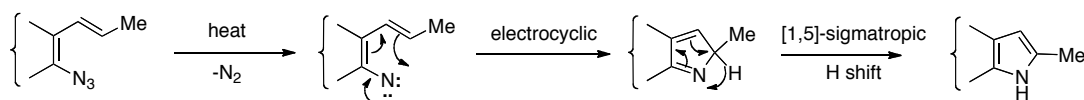
Scheme 2. Proposed mechanism of nitrene cyclization.

EXPERIMENTAL
Commercially available reagents were used throughout without purification unless otherwise stated. All anhydrous solvents were used as supplied, except dichloromethane that was freshly distilled according to standard procedures. Reactions were routinely carried out under an argon atmosphere unless otherwise stated, and all glassware was flame-dried before use. Light petroleum refers to the fraction with bp 40-60 ºC.
Analytical thin layer chromatography was carried out on aluminum backed plates coated with silica gel, and visualized under UV light at 254 and/or 360 nm and/or by chemical staining. Flash chromatography was carried out using silica gel, with the eluent specified. Infrared spectra were recorded using an FT-IR spectrometer over the range 4000-600 cm^{-1}.

NMR spectra were recorded at 400 MHz (^{1}H frequency, 100 MHz ^{13}C frequency). Chemical shifts are quoted in parts per million (ppm), and are referenced to residual H in the deuterated solvent as the internal standard. Coupling constants, *J*, are quoted in Hz. In the ^{13}C NMR spectra, signals corresponding to CH, CH$_2$, or CH$_3$ groups are assigned from DEPT. Mass spectra were recorded on a time-of-flight mass spectrometer using electrospray ionization (ESI).

1,4-Diallyloxy-2,5-dichlorobenzene 1

A stirred suspension of anhydrous, oil-free sodium hydride (60% in mineral oil; 2.23 g, 55.9 mmol) in DMF (56 mL) was treated dropwise with a solution of 2,5-dichloro-1,4-hydroquinone (5.00 g, 27.9 mmol) in DMF (56 mL) and allyl bromide (6.76 g, 55.9 mmol). The resulting reaction mixture was stirred at room temperature for 16 h, diluted with ethyl acetate (200 mL), washed with water (3 × 100 mL) and saturated aqueous sodium chloride (100 mL), dried (MgSO$_4$), filtered and the filtrate evaporated *in vacuo*. Flash chromatography of the residue on silica, eluting with ethyl acetate-light petroleum (1:9), gave the *title compound* (7.02 g, 97%) as a colourless solid; mp 62-64 °C; (Found: C, 55.44; H, 4.64. C$_{12}$H$_{12}$Cl$_2$O$_2$ requires C, 55.62; H, 4.67%); (Found: M+Na$^+$, 281.0107. C$_{12}$H$_{12}$^{35}Cl$_2$O$_2$ + Na$^+$ requires 281.0107); ν_{max} (CHCl$_3$)/cm^{-1} 3088, 2991, 2872, 1649, 1498, 1083, 997; δ_H (400 MHz; CDCl$_3$) 6.99 (2 H, s, ArH), 6.10-6.00 (2 H, m, ArOCH$_2$C$\underline{H}$=CH$_2$), 5.48-5.43 (2 H, m, ArOCH$_2$CH=CH$\underline{H}$), 5.34-5.30 (2 H, m, ArOCH$_2$CH=CH$\underline{H}$), 4.57-4.54 (4 H, m, ArOC$\underline{H}_2$CH=CH$_2$); δ_C (100 MHz; CDCl$_3$) 148.5 (C), 132.4 (CH), 121.7 (C), 118.2 (CH$_2$), 116.4 (CH), 70.7 (CH$_2$); *m/z* (ESI) 285/283/281 (M+Na$^+$, 9/61/100%).

2,5-Diallyl-3,6-dichlorobenzene-1,4-hydroquinone 2

A solution of 1,4-diallyloxy-2,5-dichlorobenzene (0.200 g, 0.771 mmol) in 1,2-dichlorobenzene (2 mL) in a sealed tube was heated at 220 °C for 30 min in a microwave reactor (300 W). The solvent was removed under reduced pressure, and purification of the residue by flash chromatography on silica, eluting with dichloromethane-light petroleum (2:8), gave the *title compound* (0.141 g, 71%) as a colourless solid; mp 120-122 °C; (Found: M+Na$^+$, 281.0097. C$_{12}$H$_{12}$^{35}Cl$_2$O$_2$ + Na$^+$ requires 281.0107); ν_{max} (CHCl$_3$)/cm^{-1} 3541, 3083, 2984, 2927, 1639, 1425, 1319, 1172; δ_H (400 MHz; CDCl$_3$) 5.98-5.88 (2 H, m, ArCH$_2$C$\underline{H}$=CH$_2$), 5.42 (2 H, s, OH), 5.10-5.05 (4 H, m, ArCH$_2$CH=C$\underline{H}_2$), 3.59-3.57 (4 H, m, ArC$\underline{H}_2$CH=CH$_2$); δ_C (100 MHz; CDCl$_3$) 143.6 (C), 134.0 (CH), 122.9 (C), 119.8 (C), 115.9 (CH$_2$), 32.2 (CH$_2$); *m/z* (ESI) 285/283/281 (M+Na$^+$, 10/62/100%).

2,5-Dichloro-3,6-di(prop-1-enyl)-1,4-hydroquinone 3

A solution of 2,5-diallyl-3,6-dichlorobenzene-1,4-hydroquinone (1.00 g, 3.86 mmol) and palladium(II) chloride bis(acetonitrile) (0.100 g, 0.386 mmol) in dichloromethane (100 mL) was heated under reflux for 3 h, filtered through Celite® and the filtrate evaporated *in vacuo* to give the *title compound* (0.974 g, 97%) as a colourless solid; mp 190-192 °C; (Found: M+Na$^+$, 281.0096. C$_{12}$H$_{12}$^{35}Cl$_2$O$_2$ + Na$^+$ requires 281.0107); ν_{max} (CHCl$_3$)/cm^{-1} 3527, 2916, 1602, 1430, 1415, 1318, 1253, 1176, 969; δ_H (400 MHz; DMSO-d_6) 8.78 (2 H, s, OH), 6.49-6.42 (4 H, m, C$\underline{H}$=C$\underline{H}$CH$_3$), 1.88 (6 H, d, *J* 5.3, CHCH$\underline{3}$); δ_C (100 MHz; DMSO-d_6) 144.2 (C), 133.1 (CH), 123.8 (CH), 123.3 (C), 120.1 (C), 19.4 (Me); *m/z* (ESI) 285/283/281 (M+Na$^+$, 10/64/100%).

2,5-Dichloro-3,6-di(prop-1-enyl)-1,4-benzoquinone 4

A solution of cerium(IV) ammonium nitrate (2.60 g, 4.75 mmol) in water (50 mL) was added dropwise to a stirred solution of 2,5-dichloro-3,6-di(prop-1-enyl)-1,4-hydroquinone (0.492 g,

1.90 mmol) in THF (50 mL). The resulting reaction mixture was stirred at room temperature for 2 h, concentrated, and extracted with ethyl acetate (3 × 20 mL). The organic layer was dried (MgSO$_4$) and evaporated *in vacuo.* The residue was purified by flash chromatography on silica eluting with dichloromethane-light petroleum (2:8) to give the *title compound* (0.367 g, 75 %) as a bright red solid; mp 130-132 °C; (Found: C, 55.71; H, 3.90. C$_{12}$H$_{10}$Cl$_2$O$_2$ requires C, 56.06; H, 3.92%); (Found: M+Na$^+$, 278.9940. C$_{12}$H$_{10}$^{35}Cl$_2$O$_2$ + Na$^+$ requires 278.9950); λ_{max} (acetonitrile)/nm 255 (log ε 4.31), 340 (log ε 3.99); ν_{max} (CHCl$_3$)/cm^{-1} 2914, 1673, 1627, 1189, 1168, 966, 851; δ_H (400 MHz; CDCl$_3$) 7.19-7.10 (2 H, dq, *J* 15.9, 6.9, CH=C$\underline{H}$CH$_3$), 6.55-6.50 (2 H, dq, *J* 15.9, 1.7, C$\underline{H}$=CHCH$_3$), 2.01-1.99 (6 H, dd, *J* 6.9, 1.8, CHC$\underline{H}_3$); δ_C (100 MHz; CDCl$_3$) 177.8 (C), 144.3 (CH), 137.2 (C), 137.1 (C), 122.2 (CH), 20.7 (Me); *m/z* (ESI) 283/281/279 (M+Na$^+$, 10/63/100%).

2,5-Diazido-3,6-di(prop-1-enyl)-1,4-benzoquinone 5

A solution of 2,5-dichloro-3,6-di(prop-1-enyl)-1,4-benzoquinone (0.154 g, 0.599 mmol) in acetone (20 mL) was stirred at 0 °C while sodium azide (0.082 g, 1.26 mmol) in water (1 mL) was added dropwise. After 10 min, the solution was diluted with water (20 mL) and extracted with dichloromethane (3 x 20 mL). The organic layer was dried (MgSO$_4$), filtered and the filtrate and evaporated *in vacuo* to give the *title compound* (0.154 g, 95%) as a dark red solid; mp >300 °C; (Found: M+Na$^+$, 293.0753. C$_{12}$H$_{10}$N$_6$O$_2$ + Na$^+$ requires 293.0757); λ_{max} (acetonitrile)/nm 280 (log ε 4.60), 369 (log ε 4.24); ν_{max} (CHCl$_3$)/cm^{-1} 3012, 2115, 1658, 1626, 1550, 1362, 1316, 1249; δ_H (400 MHz; CDCl$_3$) 7.08-6.99 (2 H, dq, *J* 16.0, 6.9, CH=C$\underline{H}$CH$_3$), 6.41-6.36 (2 H, dq, *J* 15.9, 1.8, C$\underline{H}$=CHCH$_3$), 1.96-1.93 (6 H, dd, *J* 6.9, 1.8, CHC$\underline{H}_3$); δ_C (100 MHz; CDCl$_3$) 181.0 (C), 139.6 (CH), 137.4 (C), 123.2 (C), 120.3 (CH), 20.4 (Me).

2,6-Dimethylpyrrolo[2,3-*f*]indole-4,8(1H,5H)-dione 6

A stirred solution of 2,5-diazido-3,6-di(prop-1-enyl)-1,4-benzoquinone (0.460 g, 1.702 mmol) in toluene (100 mL) was heated at 85 °C for 1 h and then evaporated *in vacuo.* The solid obtained was washed with ethanol and the solvent was filtered off to give the *title compound* (0.364 g, 99%) as a dark red solid; mp >300 °C; (Found: M+Na$^+$, 237.0633. C$_{12}$H$_{10}$N$_2$O$_2$ + Na$^+$ requires 237.0634); λ_{max} (acetonitrile)/nm 243 (log ε 3.77); ν_{max} (CHCl$_3$)/cm^{-1} 3207, 1725, 1602, 1240; δ_H (400 MHz; DMSO-*d$_6$*) 12.18 (2 H, s, NH), 6.14 (2 H, s, CH), 2.20 (6 H, s, Me); δ_C (100 MHz; DMSO-*d$_6$*) 173.7 (C), 135.5 (C), 131.5 (C), 126.3 (C), 105.7 (CH), 12.5 (Me).

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