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# SYNTHESIS OF 5-METHYLINDOLE-4,7-QUINONE THROUGH A NEW CONSTRUCTION OF THE FUNCTIONALIZED INDOLE RING BASED ON THE ALLENE-MEDIATED ELECTROCYCLIC REACTION INVOLVING THE PYRROLE [*b*]-BOND

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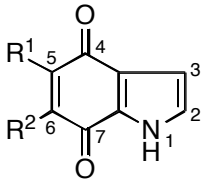
**Abstract** − A new synthesis of an indole ring based on an electrocyclic reaction of a 2-alkenyl-3-allenylpyrrole intermediate generating from 2-ethenyl-3-propargylpyrrole was established. A synthesis of 5-methylindole-4,7-quinone (**1**) was completed in seven steps from the 4-oxygenated 5-methylindole (**13a**). It was demonstrated that the structure of natural product (**1**), isolated from *Dropella fragum*, is not at least 5-methylindole-4,7-quinone (**1**).

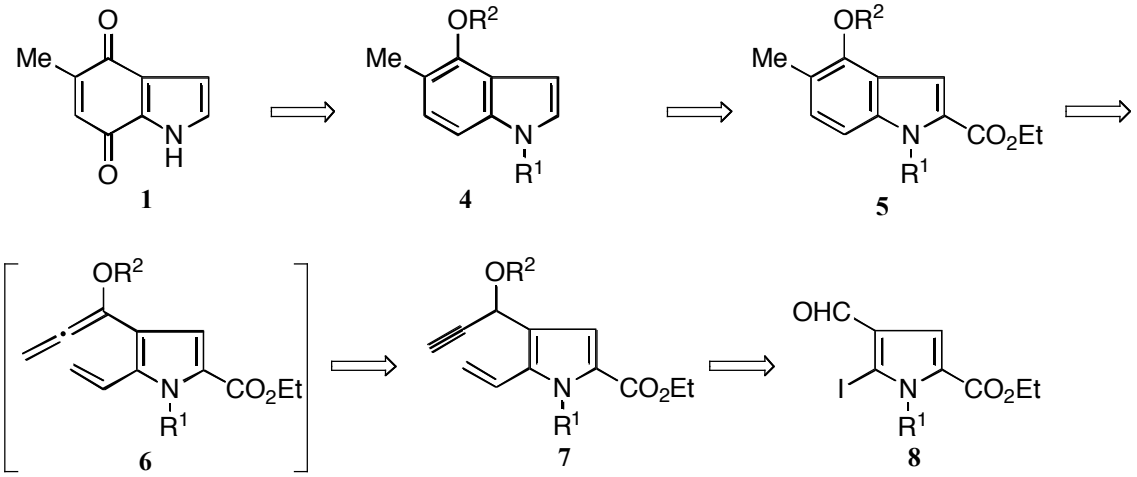
Three new antimicrobial indolequinones, 5-methylindole-4,7-quinone (**1**), 6-methoxyindole-4,7-quinone (**2**), and 5-methoxyindole-4,7-quinone (**3**), were isolated from the mid-intestinal gland of the muricid gastropod *Drupella fragum* (Figure 1) in 1998.[1] Although, the structures of 6-methoxyindole-4,7-quinone (**2**) and 5-methoxyindole-4,7-quinone (**3**) were determined by means of total syntheses and NMR spectroscopic analyses, the structure of **1** was elucidated mainly by NMR spectroscopic analyses.




**1**: $R^1$=Me, $R^2$=H
**2**: $R^1$=H, $R^2$=OMe
**3**: $R^1$=OMe, $R^2$=H

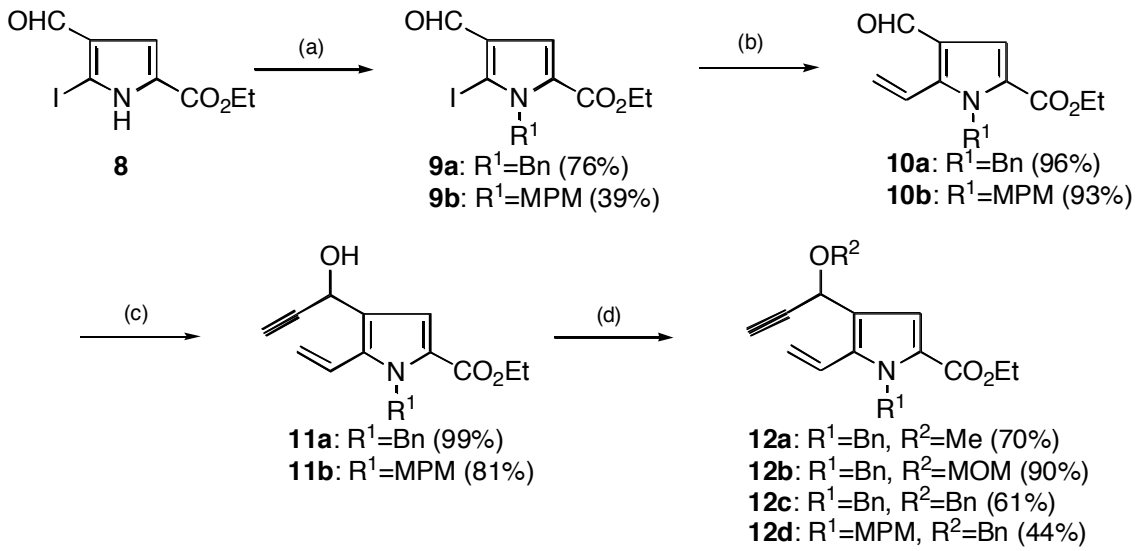
**Figure 1**

We are interested in a new indole synthesis through a benzo-annulation using the pyrrole [*b*]-bond. In the present paper, we describe a new construction of a functionalized indole ring (**4**) based on an application of our electrocyclic reaction[2] of an allenyl intermediate (**6**) involving the pyrrole 2,3-bond, and a synthesis of 5-methylindole-4,7-quinone (**1**) *via* an oxidation step. We planned a synthesis of 4-oxygenated 5-methylindole (**4**) as a precursor of indole-4,7-quinone system (**1**) through 2-ethenyl-3-propargylpyrrole (**7**) derived from the known ethyl 3-formyl-2-iodopyrrole-5-carboxylate (**8**),[3] as shown in retro-synthetic analysis (Scheme 1).



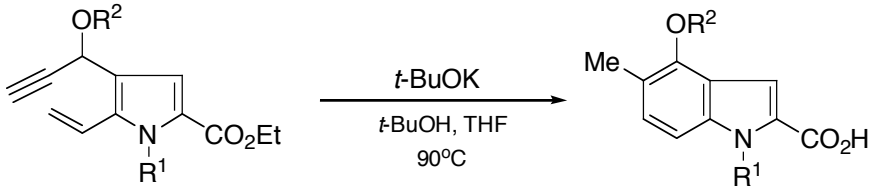
**Scheme 1**

For the synthesis of 4-oxygenated 5-methylindole, treatment of the pyrrole (**8**) with benzyl (Bn) bromide or 4-methoxybenzyl (MPM) chloride in the presence of $K_2CO_3$ gave the *N*-benzylpyrrole (**9a**) (76%) or *N*-MPM-pyrrole (**9b**) (39%)[4], respectively (Scheme 2). The palladium-catalyzed cross-coupling reaction of **9a** or **9b** with tributyl(ethenyl)tin in the presence of $PdCl_2(PPh_3)_2$ and $Et_4NCl$ in DMF at 80°C afforded 2-ethenylpyrroles (**10a**; 96% or **10b**; 93%), which were treated with ethynylmagnesium bromide to yield the propargyl alcohols (**11a**; 99% or **11b**; 81%). *O*-Alkylation of **11a** or **11b** with methyl iodide, chloromethyl methyl ether (MOMCl), or benzyl chloride furnished the propargyl ethers (**12a**; 70%, **12b**; 90%, **12c**; 61%, or **12d**; 44% yields, respectively). Four kinds of propargyl ethers (**12a-d**) were subjected to electrocyclic reaction in the presence of potassium *t*-butoxide at 90°C to afford the desired 4-oxygenated 5-methylindoles (**13a-d**) in moderate to excellent yields (Table 1) *via* ester hydrolysis. In the ring closure, protection of the pyrrole nitrogen and hydroxy groups of **12a-d** with Bn, MOM-, and MPM-groups was attempted and all the groups were found to be equally effective. Moreover, the amounts of 3 to 10 equivalents of potassium *t*-butoxide provided efficient results, respectively, as reported previously regarding the carbazole synthesis.[3]



**Scheme 2** *Reagents and conditions*: (a) RX, $K_2CO_3$, DMF; (b) $CH_2$=$CHSnBu_3$, $PdCl_2(PPh_3)_2$, DMF, 80°C, 3 h; (c) HC≡CMgBr, THF, rt, 1 h; (d) RX, NaH or *i*$Pr_2NEt$.

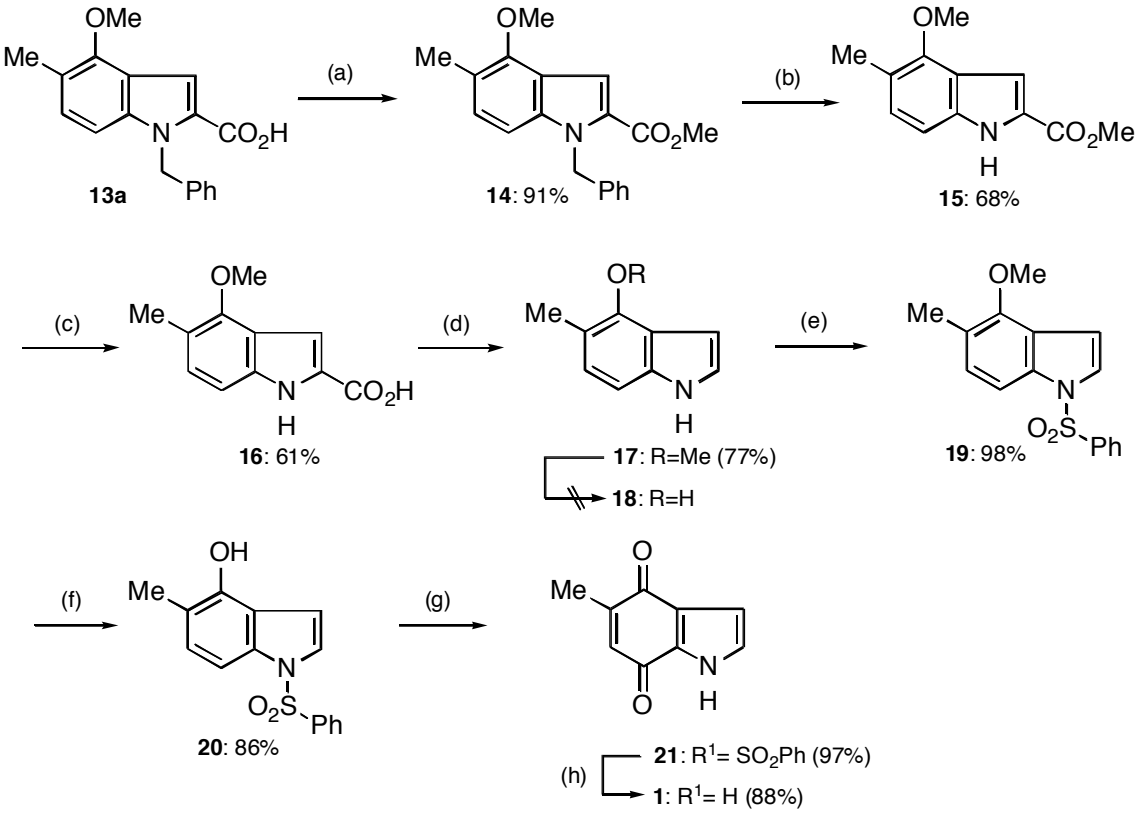
**Table 1**




**12a**: $R^1$=Bn, $R^2$=Me
**12b**: $R^1$=Bn, $R^2$=MOM
**12c**: $R^1$=Bn, $R^2$=Bn
**12d**: $R^1$=MPM, $R^2$=Bn

**13a**: $R^1$=Bn, $R^2$=Me
**13b**: $R^1$=Bn, $R^2$=MOM
**13c**: $R^1$=Bn, $R^2$=Bn
**13d**: $R^1$=MPM, $R^2$=Bn

| Run | Starting Material | *t*-BuOK | Time | Products | |
|---|---|---|---|---|---|
| | | | | No. | Yield (%) |
| 1 | **12a** | 3 eq. | 1 h | **13a** | 49 |
| 2 | **12a** | 7 eq. | 1 h | **13a** | 83 |
| 3 | **12a** | 10 eq. | 15 min | **13a** | 95 |
| 4 | **12b** | 3 eq. | 1 h | **13b** | 64 |
| 5 | **12b** | 10 eq. | 15 min | **13b** | 83 |
| 6 | **12c** | 3 eq. | 1 h | **13c** | 78 |
| 7 | **12c** | 10 eq. | 30 min | **13c** | 87 |
| 8 | **12d** | 3 eq. | 1 h | **13d** | 85 |




**Scheme 3** *Reagents and conditions*: (a)MeI, 25%NaOH, HMPA, rt, 0.5 h; (b) $AlCl_3$, benzene, 0°C, 4 h; (c) 3%NaOH, MeOH, rt, 16 h; (d) Cu, quinoline, 200°C, 2 h; (e) $PhSO_2Cl$, NaH, DMF, rt, 2 h; (f)$BBr_3$, $CH_2Cl_2$, -78°C→rt, 5 h; (g) CAN, MeCN, $H_2O$, 0°C, 15 min; (h) $NaHCO_3$, MeOH, 60°C, 30 min.

Next, the synthesis of 4-hydroxyindole (**20**) in this further experiment was carried out as follows. The deprotection of the *N*-benzyl group of indole-2-carboxylic acids (**13a-d**) under various conditions was attempted, but none of the conditions allowed the deprotection to proceed. On the other hand, treatment of the ester (**14**), derived from **13a**, with aluminum chloride[5] in benzene successfully provided the *N*-deprotected indole (**15**) in 68% yield. Hydrolysis of **15** with 3% NaOH, followed by decarboxylation with cupper in quinoline at 200°C afforded the simple 4-methoxy-5-methylindole (**17**) (47% from **15**). The *N*-protection of **17** with the phenylsulfonyl group was carried out, because a direct conversion of the 4-methoxyindole (**17**) into 4-hydroxyindole (**18**) by boron tribromide failed. The indole (**17**) was reacted with phenylsulfonyl chloride and sodium hydride to yield the *N*-phenylsufonylindole (**19**) (98%), which was subsequently treated with boron tribromide in dichloromethane to produce the required 4-hydroxyindole (**20**) (86%) (Scheme 3).

Finally, oxidation of **20** with CAN (ceric ammonium nitrate)[6] in an aqueous acetonitrile provided the *N*-phenylsulfonyl-5-methylindole-4,7-quinone (**21**) in 97% yield. Treatment of **21** with sodium hydrogen carbonate in an aqueous methanol produced the 5-methylindole-4, 7-quinone (**1**) (88%). However, the data of synthetic **1**[7] did not agree with those of natural **1**[1] in all respects. Especially, it has been reported that the correlation between C3-H and C4-C was observed in the heteronuclear multibond connectivity (HMBC) spectrum of natural **1** as depicted in Figure 2, and similar correlations were not observed in the HMBC spectra of 6-methoxyindole-4,7-quinone (**2**) and 5-methoxyindole-4,7-quinone (**3**), respectively.[1] In contrast, a similar correlation was not observed in the HMBC spectrum between C3-H and C4-C of synthetic **1** (Figure 2). Direct comparison of synthetic **1** with natural **1** was impossible, because they have no natural **1**.

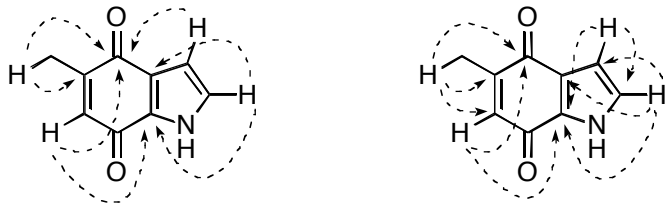
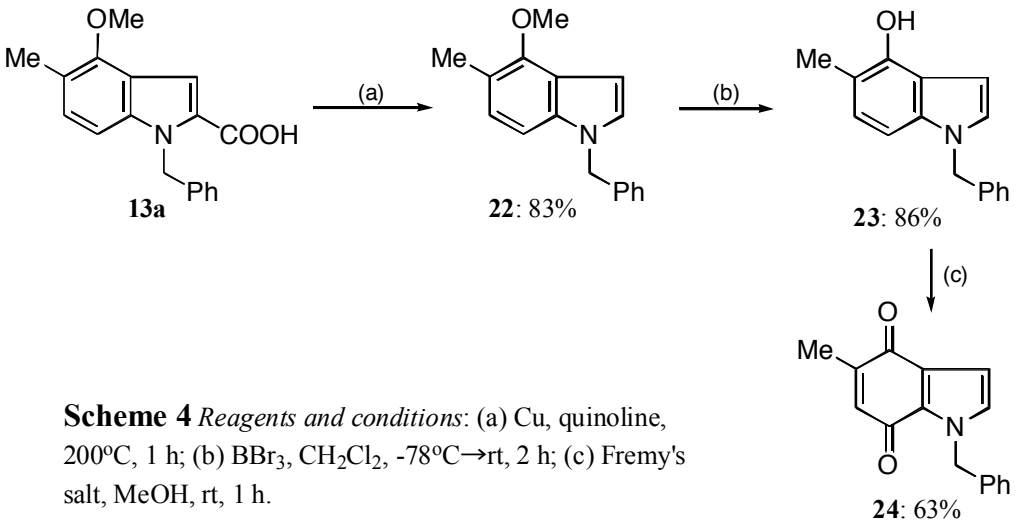



**Figure 2** : $^{1}H$-$^{13}C$ HMBC Correlations




**Scheme 4** *Reagents and conditions*: (a) Cu, quinoline, 200°C, 1 h; (b) $BBr_3$, $CH_2Cl_2$, -78°C→rt, 2 h; (c) Fremy's salt, MeOH, rt, 1 h.

On the basis of this result, we aimed a conversion of the cyclization product, indole-2-carboxylic acid (**13a**) into *N*-benzyl-5-methylindole-4,7-quinone (**24**) for further structure confirmation. Namely, the indole-2-carboxylic acid (**13a**) was heated with copper in quinoline at 200°C to give *N*-benzylindole (**22**) (83%) with loss of carbon dioxide, which was treated with boron tribromide in dichloromethane to yield *N*-benzyl-4-hydroxyindole (**23**) (86%). Oxidation of **23** with Fremy's salt[8] in an aqueous methanol afforded *N*-benzyl-5-methylindole-4,7-quinone (**24**) (63%) (Scheme 4). The assignments of protons and carbons of **24**[9] in NMR spectrum were supported by the interactions observed in the 2D-Nuclear Overhauser Effect (NOESY) and HMBC spectrum as illustrated by arrows (Figure 3). A correlation between C3-H and C4-C of **24** was also not observed in the HMBC spectrum in this case, and the NOESY spectrum showed spatial connectivity between the methylene proton of *N*-benzyl group and C2-H. In the light of the above spectral data, the structure of **24** has been deduced to be *N*-benzylindole-4,7-quinone (**24**). Consequently, the structure of synthetic **1** was also determined to be 5-methylindole-4,7-quinone (**1**).

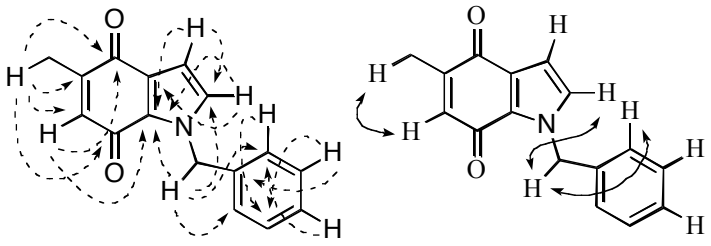


**Figure 3** : $^{1}$H-$^{13}$C HMBC Correlations (·----► ) and NOESY Interaction ( ◄——► ) of **24**

Thus, a new indole synthesis by the allene-mediated electrocyclic reaction involving the pyrrole 2,3-bond was realized. In addition, 5-methylindole-4,7-quinone (**1**) was synthesized from the functionalized indole (**13a**). However, it was found that the structure of natural **1**, isolated from *Drupella fragum*,[1] is not 5-methylindole-4,7-quinone (**1**) itself. Further investigations are now in progress.

**ACKNOWLEDGEMENT**

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7. Synthetic **1**: mp 162-165 °C (EtOAc-hexane). IR (KBr) ν 3228, 1662, 1646, 1604, 1490, 1403, 1378 $cm^{-1}$. $^{1}$H-NMR (DMSO-$d_6$, 500 MHz) δ: 1.99 (3H, d, *J*=1.55 Hz, Me), 6.50 (1H, d, *J*=1.55 Hz, H-6), 6.52 (1H, d, *J*=2.5 Hz, H-3), 7.19 (1H, d, *J*=2.5 Hz, H-2), 12.6 (1H, br s, H-1). $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) δ: 15.4 (Me), 107.4 (C-3), 125.1 (C-3a), 126.1 (C-2), 130.9 (C-7a), 132.6 (C-6), 146.3 (C-5), 177.3 (C-7), 183.0 (C-4). Natural **1**: mp 202-204 °C. IR (KBr) ν 3266, 1663, 1636, 1537, 1495, 1203, 1120 $cm^{-1}$. $^{1}$H-NMR (DMSO-$d_6$, 500 MHz) δ: 2.35 (3H, s, Me), 6.16 (1H, br s, H-6), 6.55 (1H, d, *J*=2.5 Hz, H-3), 7.16 (1H, d, *J*=2.5 Hz, H-2); $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) δ: 13.30 (Me), 107.67 (C-3), 123.74 (C-6), 123.98 (C-3a), 125.69 (C-2), 131.45 (C-7a), 154.58 (C-5), 174.26 (C-7), 178.96 (C-4).
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9. Compound (**24**): mp 88-90 °C (EtOAc-hexane). IR(KBr)ν 1660, 1650 $cm^{-1}$. $^{1}$H-NMR ($CDCl_3$, 500 MHz) δ 1.97 (3H, s), 5.60 (2H, s), 6.47 (1H, s), 6.57 (1H, d, *J*=2.5 Hz), 7.20-7.30 (2H, m), 7.30-7.40 (3H, m), 7.43 (1H, d, *J*=2.5 Hz); $^{13}$C-NMR ($CDCl_3$, 125 MHz) δ 15.2, 107.2, 126.3, 127.1(2C), 127.7, 128.3, 128.6(2C), 130.8, 133.4, 137.3, 145.8, 150.9, 177.7, 182.8.