New Syntheses of Murrayaquinone A and Furostifoline

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Starting from 2-chloro-3-formylindole, new syntheses of murrayaquinone A and furostifoline were achieved by an allene-mediated electrocyclic reaction involving the indole 2,3-bond.

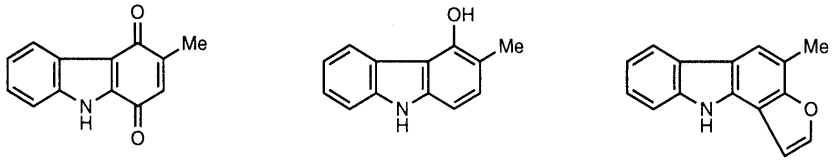
Key words murrayaquinone A; carbazole-1,4-quinone; furostifoline; furo[3,2-*a*]carbazole; synthesis; electrocyclic reaction

The carbazole-1,4-quinone alkaloid, murrayaquinone A (**1**), was isolated from the root bark of *Murraya eucrestifolia* HAYATA (Rutaceae) together with three related alkaloids (murrayaquinone B—D) by Furukawa and co-workers from 1983 to 1985.[1] The furo[3,2-*a*]carbazole alkaloid, furostifoline (**3**), was also isolated in 1990 from the same origin by the same group (Chart 1).[2] Extracts of the leaves and bark of this tree have been used as a folk medicine in Taiwan. Among these alkaloids, murrayaquinone A (**1**) has cardiotonic activity on guinea-pig papillary muscle.[3] Since they were isolated, synthetic studies of these alkaloids have been reported by many groups.[4,5]

We were also interested in the syntheses of the carbazole-1,4-quinone alkaloid, murrayaquinone A (**1**), and the novel furo[3,2-*a*]carbazole alkaloid, furostifoline (**3**), in the course of our synthetic studies. Recently, we reported the total syntheses of the 3-oxygenated and 3,4-dioxygenated carbazole alkaloids, carazostatins and carbazoquinocins (B—F), based on the thermal electrocyclic reaction of the 3-alkenyl-2-allenylindole intermediate derived from 3-alkenyl-2-propargylindole.[6]

In this paper, we describe the synthesis of 4-oxygenated carbazole (**2**) which consists of a formal total synthesis of murrayaquinone A (**1**) and a new total synthesis of the furo[3,2-*a*]carbazole, furostifoline (**3**), based on the thermal electrocyclic reaction of a new type of hexatriene system involving the 2-alkenyl-3-allenylindole intermediate derived from 2-alkenyl-3-propargylindole.

We chose 2-chloro-3-formylindole (**4**) as the common starting material for the syntheses of the two target molecules. The 2-chloroindole (**4**) was treated with benzyloxymethyl chloride (BOMCl) and K_2CO_3 to give the *N*-BOM-indole (**5**) (96%). The cross-coupling reaction of **5** with tributylvinyltin in the presence of $PdCl_2(PPh_3)_2$ and tetraethylammonium chloride in DMF at 80 °C was carried out to yield the 2-ethenylindole (**6**) (78%). The subsequent Grignard reaction of 3-formylindole (**6**) with ethynylmagnesium bromide followed by treatment with BOMCl afforded



1: murrayaquinone A **2** **3**: furostifoline

Chart 1

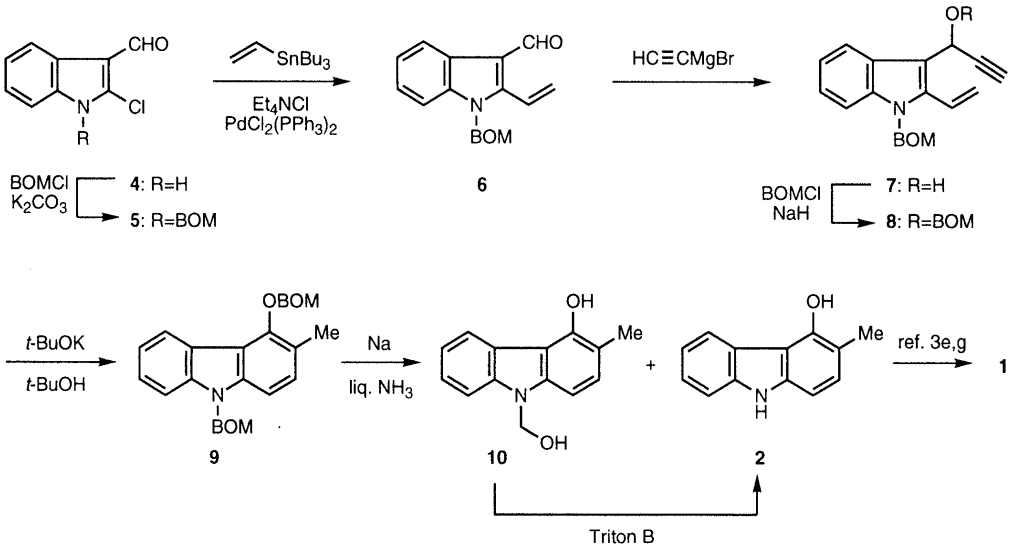


Chart 2

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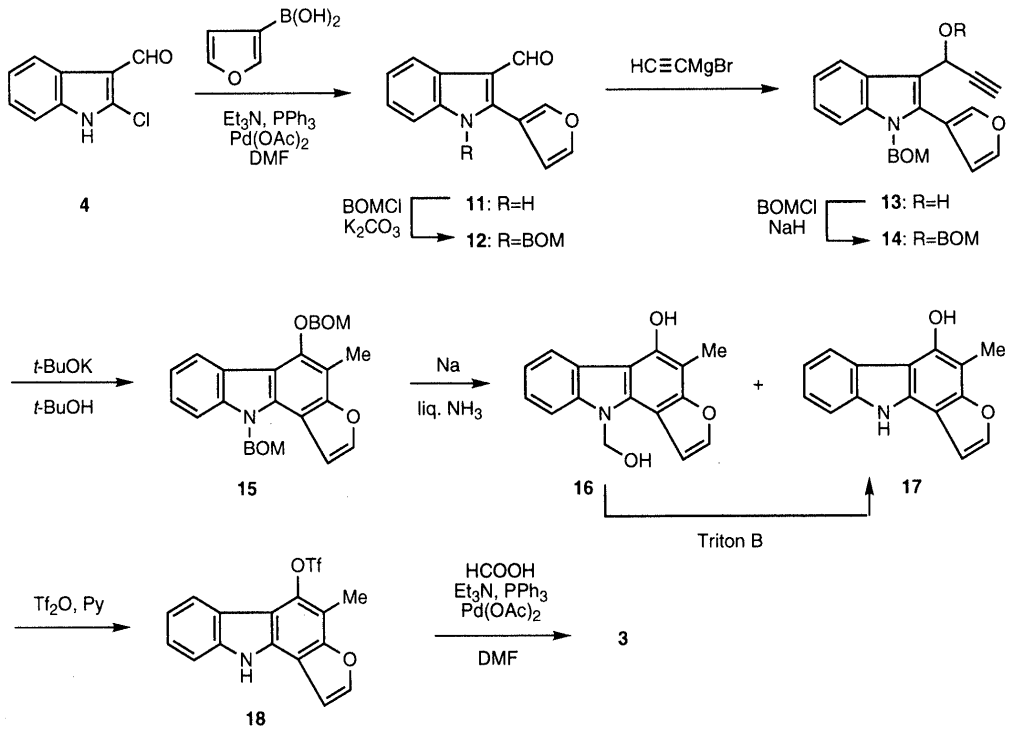

Chart 3

the 2-ethenyl-3-propargylindole (**8**) (56%) as a new precursor of the hexatriene system. The thermal electrocyclic reaction of **8** was carried out in the presence of potassium *t*-butoxide at 90 °C[6] to produce 3-methyl-4-oxygenated carbazole (**9**) (81%), which was deprotected with Birch conditions to give a separable mixture of the *N*-hydroxymethyl-4-hydroxy-3-methylcarbazole (**10**) (75%) and the 4-hydroxy-3-methylcarbazole (**2**) (22%). Treatment of **10** with Triton B[7] gave **2** [71%; mp 156—158 °C (Lit.,[3g] mp 161—163 °C)] (Chart 2). This compound was identical in all respects to the precursor (**2**) of murrayaquinone A (**1**), as reported previously.[3g] This constitutes the formal total synthesis of murrayaquinone A (**1**).

The cross-coupling reaction of 2-chloroindole (**4**) with furan-3-boronic acid[8] was carried out in the presence of $Pd(OAc)_2$, PPh_3, and triethylamine in DMF at 100 °C to obtain 2-(3-furyl)indole (**11**) (84%). After protection of the indole nitrogen atom with BOMCl, the subsequent Grignard reaction of **12** with ethynylmagnesium bromide gave the alcohol (**13**) (97%). The alcohol (**13**) was treated with BOMCl and NaH to yield the 2-(3-furyl)-3-propargylindole (**14**), which was subjected to the thermal electrocyclic reaction in the presence of potassium *t*-butoxide at 90 °C[6] to produce the 4-oxygenated tetracyclic furocarbazole (**15**) (65% yields from **13**). Birch reduction of **15** for the deprotection of *N*,*O*-bisBOM groups also gave a separable mixture of the *N*-(hydroxymethyl)furocarbazole (**16**) (41%) and the furocarbazole (**17**) (51%). Treatment of **16** with Triton B[7] afforded **17** (93%), which was converted into the triflate (**18**) (92%) with trifluoromethanesulfonic anhydride and pyridine. Finally, reductive elimination[9] of the 4-trifluoromethanesulfonyloxy group of **18** with HCOOH, triethylamine, $Pd(OAc)_2$, and PPh_3 in DMF at 60 °C afforded furostifoline (**3**) (98%) (Chart 3).[10] The synthetic furostifoline (**3**) was identical in all respects to natural[2] and synthetic[5] furostifoline.

Thus the new synthetic route to the carbazole-1,4-quinone, murrayaquinone A (**1**), has been established by a new type of allene-mediated electrocyclic reaction. Based on this methodology, the total synthesis of furostifoline (**3**) has also been completed.

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10) Furostifoline (**3**): mp 171—173 °C (Lit., mp 174—175 °C[5a] and 175 °C[5b]); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.68 (3H, d, J=1.1 Hz), 7.00 (1H, d, J=2.2 Hz), 7.26 (1H, dt, J=1.1, 8.1 Hz), 7.38 (1H, dt, J=1.1, 8.1 Hz), 7.49 (1H, br d, J=8.1 Hz), 7.73 (1H, d, J=2.2 Hz), 7.78 (1H, br s), 8.06 (1H, br d, J=8.1 Hz), 8.26 (1H, br s). Ms *m/z*: 221 (M^+).