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Rhodium-catalyzed synthesis of a C(3) disubstituted oxindole: an approach to diazonamide A

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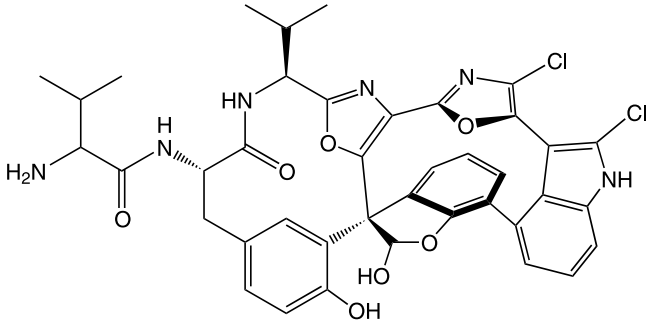
Abstract—A two step synthesis of a C(3) disubstituted oxindoles via the rhodium(II)-catalyzed coupling of diazoketone (**6**) and 3-methyloxindole (**9**) is reported.

As part of recent efforts directed toward a synthesis of diazonamide A, a secondary metabolite of the colonial ascidian *Diazona chinensis* that exhibits in vitro activity against human colorectal carcinoma and murine melanoma cancer cell lines (IC_{50} <15 ng/ml against HCT-116 and B-16),[1] we reported the use of a Rh(II) catalyzed cyclopropanation/ring-opening reaction for assembling the C10 quaternary.[2] Subsequent to this report and a decade after the original disclosure of the diazonamide structures, Harran and co-workers synthesized the originally reported structure (**1**), found it to be in error,[3] and postulated the structural revision illustrated as structure **2**.[4] One year after Harran's report, Nicolaou and co-workers reported the first total synthesis of the revised structure **2** and found it to be identical to natural diazonamide A.[5–7]

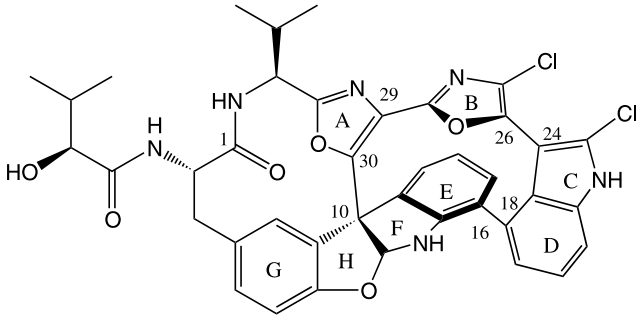
Based on our original strategy and in accord with Harran's structural revision, we began developing a modified approach to diazonamide A (Scheme 1) that relies on conversion of a tripeptide (**4**) to indole precursor **3** which, in turn, serves as the substrate for a tandem cycloproponation-ring opening that would deliver the C10 quaternary center.

To asses the feasibility of this approach we explored the Rh(II) catalyzed cyclopropanation of a 3-alkylindole (**5**) and known diazoketone (**6**).[8] In analogy to the benzofuran systems explored earlier,[2] these substrates combined to form 2-arylindole **7**,[9] a product which can be envisioned as arising via through-ring scission of the cyclopropane (**8**) followed by rearomatization (Scheme 2).

In an effort to redirect the ring opening, we turned to the silyloxy-containing substrate (**10**) produced upon treatment of 3-methyloxindole (**9**) with TBDMSOTf and Et_3N.[10] To our delight, **10** was found to undergo Rh(II)-promoted coupling with **6** to furnish oxindole **11** in good yield (Scheme 3)[11] via what is likely a Rh-promoted cyclopropanation followed by ring opening and silyl migration.



Originally Reported Structure of Diazonamide A (**1**)



Revised Structure of Diazonamide A (**2**)

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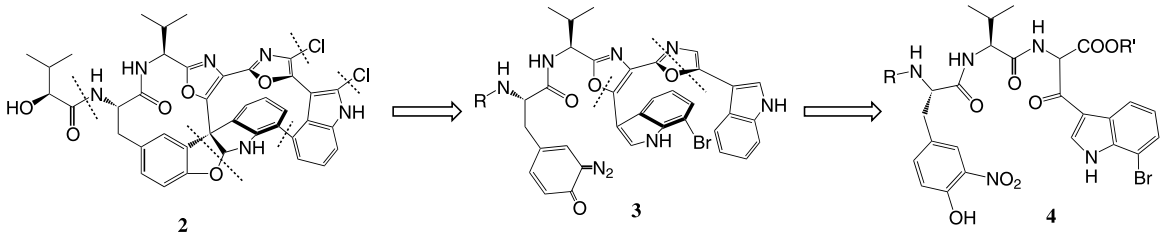
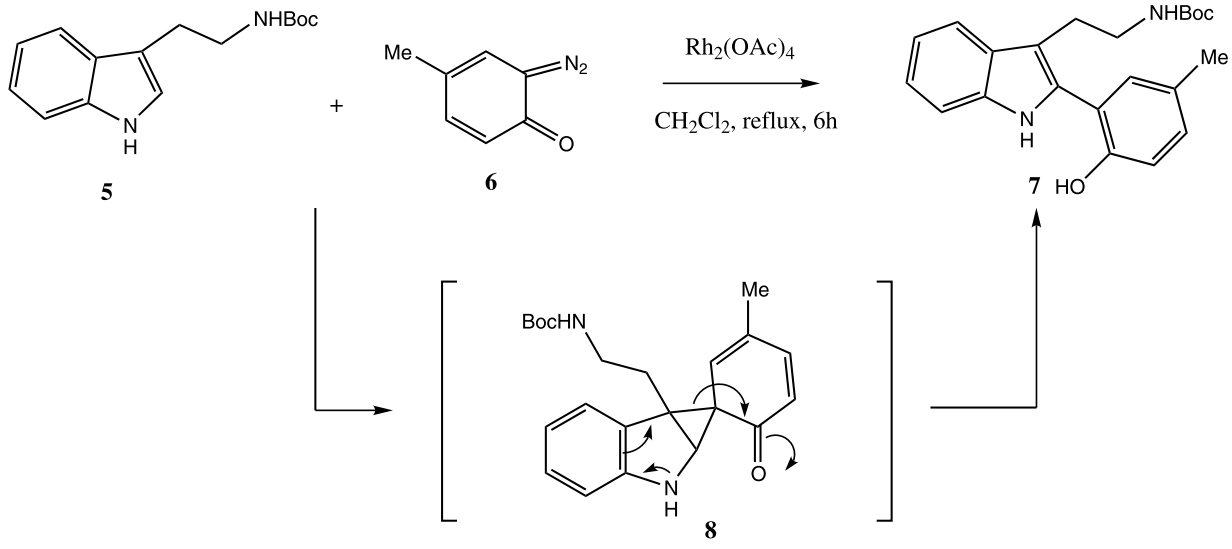
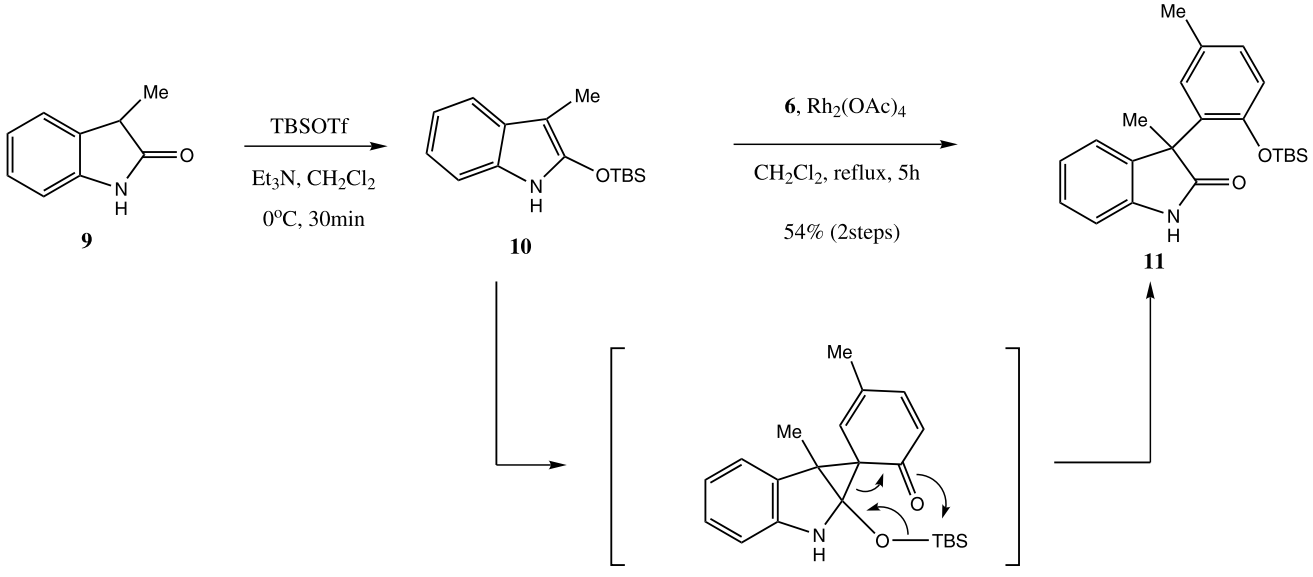
doi:10.1016/S0040-4039(03)01038-4



Scheme 1.



Scheme 2.



Scheme 3.

We have developed rhodium catalyzed cyclopropanation/ring-opening sequence for the construction of the C(3) quaternary carbon of oxindole **11**. This provides an efficient method to make the C(10) quaternary carbon of diazonamide A (**2**). Further efforts directed towards the total synthesis of **2** are currently underway.

Acknowledgements

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9. Although the yields of **7** obtained from successive runs were generally good (60–70%) inability to obtain analytically pure samples prevents our reporting them with certainty.
10. The structure of **10** was confirmed by the ^{1}H NMR of a crude product. ^{1}H NMR (C_6D_6, 400 MHz): δ 0.01 (6H, s), 0.96 (9H, s), 2.16 (3H, s), 6.66 (1H, br), 7.00 (1H, d, 7 Hz), 7.20–7.28 (2H, m), 7.52 (1H, d, 7 Hz).
11. Experimental procedure and spectral data of **11**: To a solution of 120 mg of 3-methyloxindole (**9**) and 0.4 ml of triethylamine in CH_2Cl_2 (2 mL), 0.21 mL of TBDMSOTf was added at 0°C. After stirring at 0°C for 30 min, the mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL), and 60 mg of $Rh_2(OAc)_4$ and a solution of 120 mg of diazoketone (**6**) in CH_2Cl_2 (5 mL) were added. After refluxing for 5 h, the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over Na_2SO_4, and concentrated. The residue was purified by silica-gel column chromatography (hexane:ethyl acetate = 5:1) to give 164 mg of **11** as a brown oil (54%); ^{1}H NMR (C_6D_6, 400 MHz): δ 0.16 (3H, s), 0.19 (3H, s), 1.07 (9H, s), 1.91 (3H, s), 1.96 (3H, s), 6.67 (1H, d, 8 Hz), 6.76 (1H, t, 8 Hz), 6.80 (1H, d, 8 Hz), 6.85 (1H, m), 6.92 (1H, t, 8 Hz), 7.06 (1H, d, 8 Hz), 7.44 (1H, m), 9.90 (1H, brs); ^{13}C NMR (C_6D_6, 100 MHz): δ –4.20, –4.17, 18.79, 20.25, 20.51, 26.18, 79.64, 110.90, 118.45, 122.28, 122.94, 124.96, 129.59, 131.27, 131.58, 133.39, 142.22, 143.84, 152.19, 178.97.