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Synthesis of novel 1,7-annulated 4,6-dimethoxyindoles

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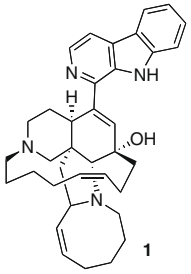
ABSTRACT

A range of new 1,7-annulated indole derivatives has been prepared via a ring-closing metathesis approach starting from *N*-allyl-7-formyl indoles.

Many natural and synthetic products containing functionalized medium-sized rings display potent biological activities. For example, the natural alkaloid manzamine A **1** possesses significant antileukaemic and antimicrobial activities.[1] Paullones **2** are cyclin-dependent kinase inhibitors[2] while bisindolylmaleimides **3** have been developed to treat diabetic complications.[3]



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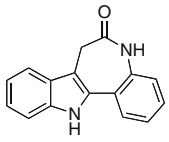

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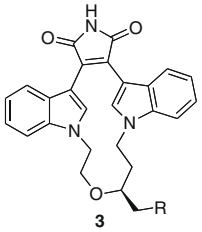

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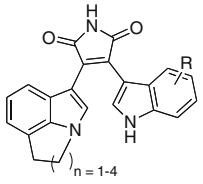
Medium-sized ring 1,7-annulated indoles, however, have not been extensively studied. Thus, synthetic approaches towards these structures are currently limited. Al-awar and co-workers reported the synthesis of 1,7-annulated bisindolyl maleimides **4** and related indolocarbazoles from the 7-bromoindole via Stille coupling with tributylvinyltin followed by N-alkylation with 5-bromopentene and subsequent ring-closing metathesis.[2] Conversely, van Wijingaarden et al. began with a tetrahydrobenzazepine or a tetrahydroquinoline derivative, reacting with ethyl bromopyruvate and then with magnesium chloride to produce annulated indoles **5**.[4]



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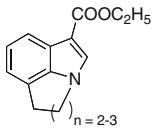

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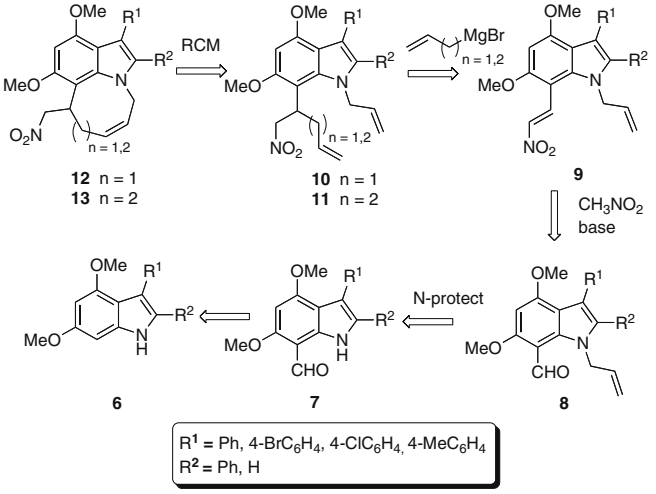
Therefore, developing versatile synthetic routes to functionalized medium-sized ring 1,7-annulated indoles is of interest. In general, routes to 1,7-annulated indoles are restricted by the lack of



12 n = 1
13 n = 2
10 n = 1
11 n = 2
9
6
7
8

Scheme 1.

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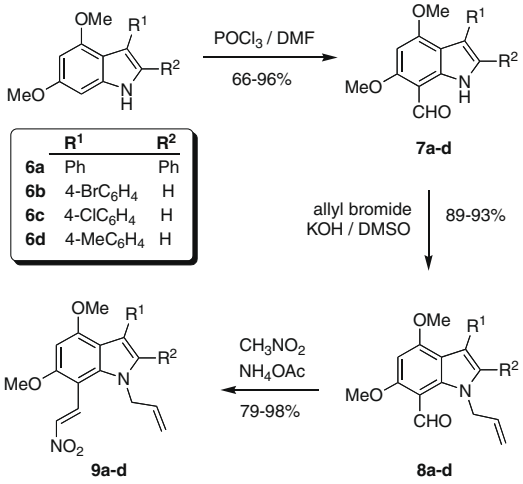
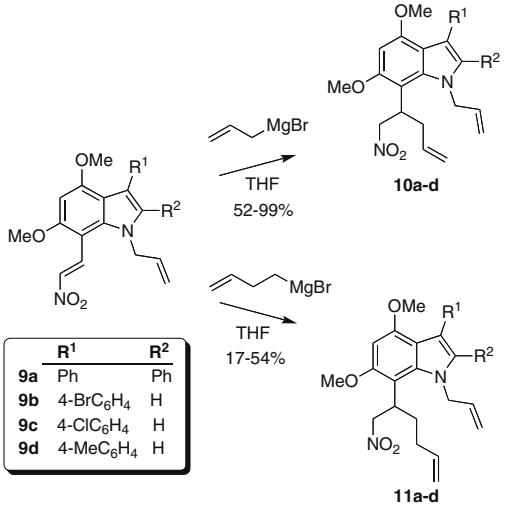


Scheme 2.

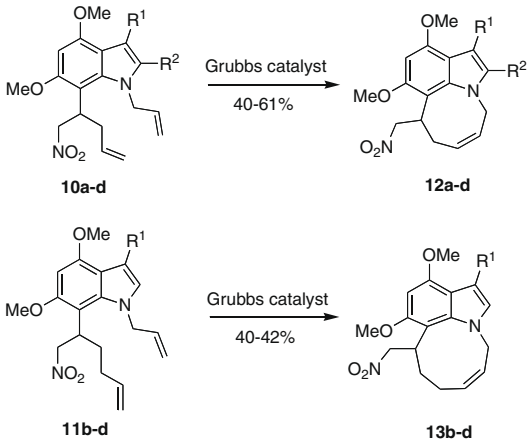


Scheme 3.

reactivity of indoles at C7. However, functionalization at C7 can be readily achieved through the use of specifically activated indoles.[5] We have used this synthetic strategy to construct 1,7-annulated five- and six-membered indoles.[6] Here, we report a facile route to functionalized eight- and nine-membered 1,7-annulated indoles from substituted 4,6-dimethoxyindoles.

Based upon the reports by Deb et al.[7] and Comer et al.,[8] it was envisaged that a ring-closing metathesis approach would allow access to the target compounds (Scheme 1). Ring-closing metathesis is a powerful and versatile approach to construct medium size rings.[9] The Michael addition to nitroalkenes used in this methodology is an efficient synthetic step to more complex molecules, and the nitro group also serves as a masked functionality which could be further transformed if desired.[10]

Formylation of indoles **6a–d** with one equivalent of the Vilsmeier reagent was regioselective and afforded the 7-carbaldehydes **7a–d** in good yields, without the formation of the 2-isomer. The



Scheme 4.

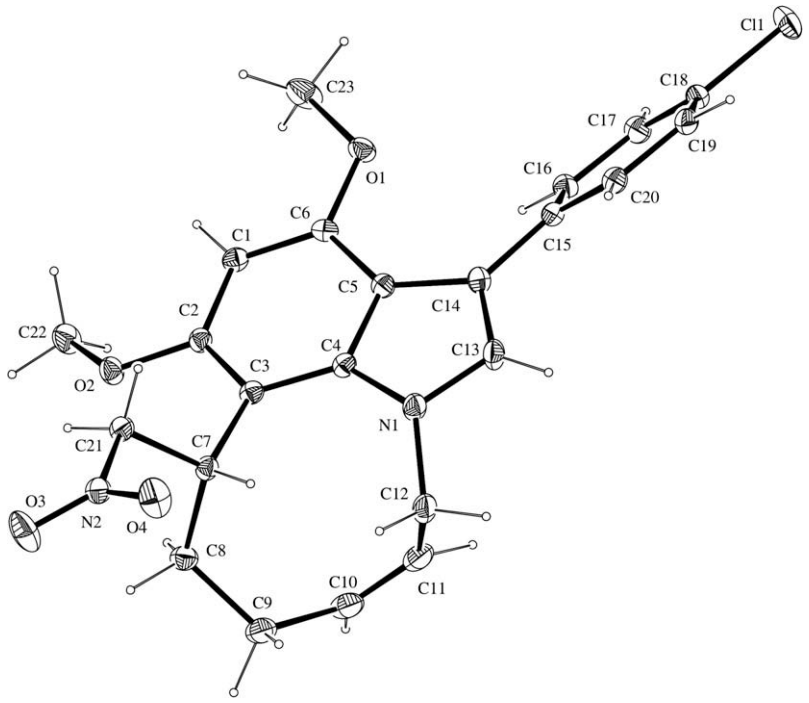


Figure 1. ORTEP diagram of compound **13c**.[13]

N-allyl derivatives **8a–d** were furnished in high yields through treatment with potassium hydroxide in dimethylsulfoxide followed by the addition of allyl bromide (Scheme 2).

Indoles **8a–d** then underwent a Henry reaction with refluxing nitromethane in isopropanol for 3 h. The nitroalkenes **9a–d** were obtained in high yields upon cooling (Scheme 2).

The next step was to introduce the second alkene unit in the preparation for the ring-closing metathesis. Different alkyl groups could be used at this point to provide access to rings of different sizes.

Initially nitroalkenes **9a–d** were stirred under inert conditions in dry THF with allylmagnesium bromide for 2–3 h to afford the Michael adducts **10a–d** in good yields as low melting solids (Scheme 3).[11] An extension of the alkenyl chain was attempted by the reaction of indoles **9a–d** with butenylmagnesium bromide. However, these reactions were noticeably slower and required approximately three days and a larger excess of the Grignard reagent to reach completion. Compounds **11a–d** were obtained as oils in significantly lower yields of 17–54% (Scheme 3).

The ring-closing metathesis reactions were achieved by refluxing the Michael adducts **10a–d** in dry, degassed toluene in the presence of 5–10 mol % of Grubbs' 2nd generation catalyst. The reactions reached completion within 4 h, and upon work up produced the indole-fused eight-membered ring compounds **12a–d** in moderate yields (Scheme 4).[12] The ring-closing metathesis of indoles **11b–d** was also successful under similar conditions, forming the corresponding indole-fused nine-membered rings **13b–d** in 40–42% yield (Scheme 4).

The structures of all the 1,7-annulated indoles were established on the basis of 1D and 2D NMR spectroscopy data. The 1,7-annulated structure of compound **13c** was confirmed by X-ray crystallography (Fig. 1).

In summary, the unique reactivity of 4,6-dimethoxyindoles has been utilized to produce a range of novel eight- and nine-membered 1,7-annulated indoles. This methodology is an effective and flexible route to 1,7-annulated indoles and enables a systematic evaluation of their biological properties.

Acknowledgements

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11. Representative procedure for compound **10b**: Indole **9b** (0.30 g, 0.68 mmol) was dissolved in dry THF (15 ml), cooled in a salt/ice bath and placed under an argon atmosphere. Allylmagnesium bromide (3 ml, 1 M) in dry THF (5 ml) was added dropwise. The reaction mixture was stirred at room temperature for 3 h before being quenched with saturated NH_4Cl solution (10 ml) and then with water (50 ml). The solution was extracted with CH_2Cl_2 (3×10 ml) and the combined organic layers were dried over Na_2SO_4 and reduced in vacuo to give **10b** as a brown solid (0.33 g, 99%). Mp 72–74 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.64 (t, J = 7.3 Hz, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.18 (m, 1H, CH), 5.05 (m, 8H, $4 \times CH_2$), 5.66 (m, 1H, CH), 6.13 (m, 1H, CH), 6.33 (s, 1H, H7), 6.82 (s, 1H, H2), 7.38 (d, J = 9.0 Hz, 2H, H_{aryl}), 7.45 (d, J = 9.0 Hz, 2H, H_{aryl}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.9, 35.2, 36.6, 51.9, 54.9, 56.2, 78.6, 89.3, 103.6, 112.5, 115.9, 116.6, 117.3, 119.5, 128.9, 130.3, 131.2, 134.0, 134.8, 135.8, 136.3, 153.6, 155.7. IR (KBr): ν_{max} 3415, 3075, 2936, 2839, 1609, 1585, 1548, 1463, 1403, 1375, 1336, 1204, 1127, 1070, 1047, 1008, 918, 832, 797 cm^{-1}. UV–vis (MeOH): λ_{max} 203 nm (ε 39,100 cm^{-1} M^{-1}), 226 (28,100), 295 (13,100). HRMS (+ESI): $C_{24}H_{25}BrN_2O_4$ $[M+Na]^+$ requires 507.0890, found 507.0892.
12. Representative procedure for compound **12b**: Indole **10b** (0.22 g, 0.45 mmol) was dissolved in dry, degassed toluene (30 ml) and placed under an argon atmosphere. Grubbs' 2nd generation catalyst (5–10 mol %) was added and the reaction mixture was refluxed for 4.5 h. The solution was reduced in vacuo and the crude product was column chromatographed using 50:50 CH_2Cl_2/hexane to give **12b** as an off-white solid (83 mg, 40%). Mp 164–166 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.62 (m, 1H, CH_2), 2.86 (m, 1H, CH_2), 3.78 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.33 (dd, J = 8.0 Hz, J = 15.2 Hz, 1H, CH), 4.84 (dd, J = 3.1 Hz, J = 12.9 Hz, 1H, CH), 5.08 (m, 2H, CH_2), 5.47 (dd, J = 8.0 Hz, J = 15.2 Hz, 1H, CH), 5.74 (m, 2H, CH_2), 6.27 (s, 1H, H5), 6.83 (s, 1H, H2), 7.39 (d, J = 8.7 Hz, 2H, H_{aryl}), 7.45 (d, J = 8.7 Hz, 2H, H_{aryl}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.2, 34.7, 46.1, 54.1, 55.4, 79.7, 88.5, 103.5, 111.6, 115.0, 118.6, 122.4, 127.8, 128.4, 129.5, 130.0, 130.1, 132.2, 133.7, 136.9, 152.9, 153.4. IR (KBr): ν_{max} 3547, 3474, 3414, 2929, 2834, 1613, 1587, 1547, 1510, 1463, 1375, 1337, 1201, 1178, 1125, 1070, 1051, 1007, 795 cm^{-1}. UV–vis (MeOH): λ_{max} 203 nm (ε 38,900 cm^{-1} M^{-1}), 227 (24,100), 298 (13,200). HRMS (+ESI): $C_{22}H_{21}BrN_2O_4$ $[M+Na]^+$ requires 479.0577, found 479.0581.
13. Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 755940 (**13c**). X-ray crystal structures were obtained by Mohan Bhadbhade, Crystallography Laboratory, UNSW Analytical Centre, Sydney, Australia.