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Total synthesis of (±)-rocaglamide and some aryl analogues

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Abstract—The insecticidal activity found for rocaglamide and its congeners, prompted us to establish a short and efficient synthesis of the natural product and some synthetic 'halo-aryl' analogues. Pd-catalysed cross-coupling reactions of the bromo analogue were then explored in order to gain a suitable access to a broad range of unnatural analogues. The key step of our approach is a keto-aldehyde acyloin ring-closure followed by a Stiles carboxylation.

Recently, members of the plant genus *Aglaia* (*A. elliptica*, *A. odorata* and *A. roxburghiana*) were shown to contain more than 20 novel insecticidal constituents of the rocaglamide type featuring its unique cyclopentatetrahydrobenzofuran skeleton.[1–4] These compounds inhibit larval growth and are insecticidal to both variegated cutworms and Asian armyworms. This interesting biological activity prompted us to investigate a reliable synthetic approach to the natural products and a broad range of unnatural analogues. In order to evaluate the contribution of the various functional groups to the biological activity of **1**, we focused on the derivatisation of both aryl groups and the amide function (Fig. 1).

Despite the existence of several synthetic approaches to the carbon framework of **1**,[5–10] a shorter, more convergent synthesis that allows an agrochemical application was needed. We were able to realise this idea by applying a keto-aldehyde acyloin ring-closure step and a Stiles[11,12] carboxylation.

The starting point of our synthesis was the Michael addition of benzofuranone **2** to cinnamaldehyde (**3**) as reported by Tayler et al.[8,9] yielding the desired *syn*-arranged product **4** in 57% yield (Scheme 1).

The intramolecular pinacol coupling reaction of **4** using reductive cyclisation procedures had been extensively studied in the past[8–10] and indeed following the literature, a multigram quantity of **7** was synthesised by treatment of **4** with SmI_2 followed by Parikh–Doering oxidation (Scheme 2). However, the method was rather elaborate and incompatible with substituents sensitive to reduction, which were of high interest for our SAR study.

Therefore we planned to achieve the final annelation step through an *Umpolungs* sequence. In fact Taylor et al. reported a successful ring-closure of the dithiane derivative of **4**,[7–9] but failed to hydrolyse it afterwards.[13] In light of these results, we favoured a

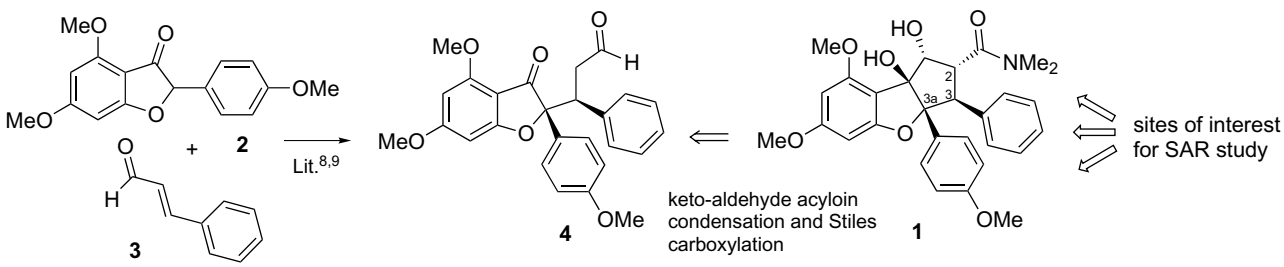

Figure 1.

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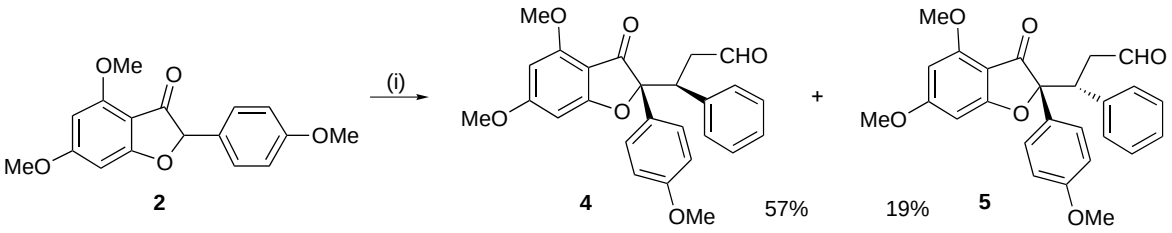


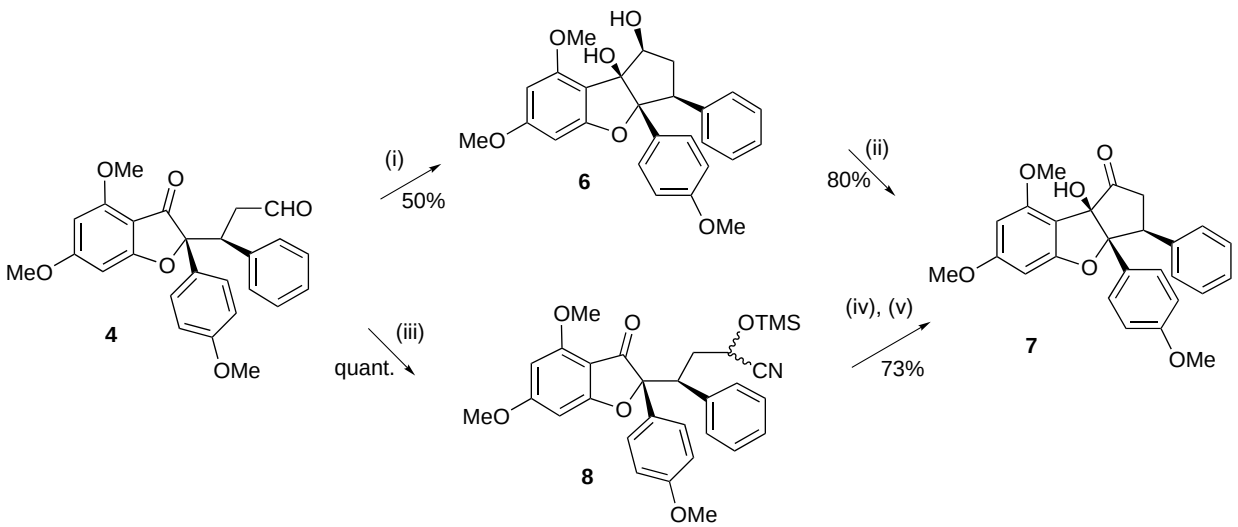
Scheme 1. *Reagents and conditions*: (i) (*E*)-cinnamaldehyde (**3**), triton B, THF, rt, 1 h.

cyanohydrin *Umpolungs* intermediate. Aldehyde **4** was subjected to TMSCN to yield the cyanohydrin **8** in quantitative yield. Formation of the acyloin **7** was initiated by addition of LDA to **8**. Subsequent deprotection of the resulting mixture with K_2CO_3 yielded **7** in high overall yield as shown in Scheme 2.

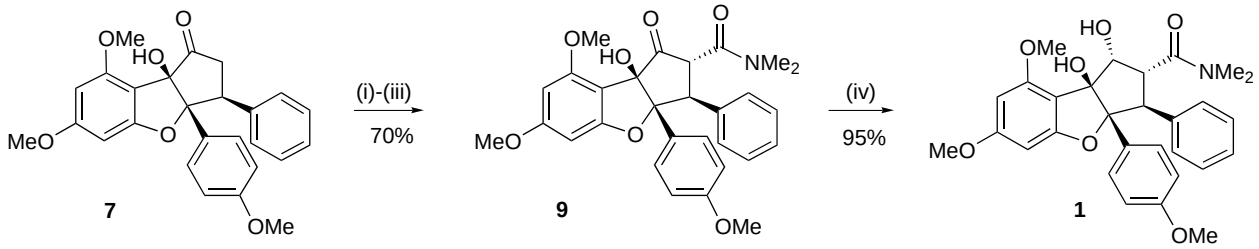
According to the published syntheses of **1** and its derivatives,[8–10] the introduction of the dimethylcarboxamido substituent requires at least a four-step sequence. We aimed for a two-step process not requiring the protection of the tertiary hydroxyl group by utilising Stiles reagent[11,12] for the direct carboxylation of the acyloin **7**. However we were aware of the fact, that cyclopentanone derivatives were reported[14] to be rather sluggish substrates for magnesium chelate-mediated carboxylation reactions. Gratifyingly, treatment of **7** with a 2-fold excess of a 2.5 M solution of magnesium methylcarbonate in DMF at 100°C followed by acid hydrolysis, resulted in the quantitative formation of the desired β-ketoacid. The excess of reagent proved to be critical in driving the reaction to completion. The crude product was immediately converted to the ketoamide **9** by Py·BOP-mediated condensation. Competing decarboxylation of the ketoacid back to the parent ketone **7** occurred only to a minor extent. Evans-type directed borane reduction of **9** completed our short synthesis of the natural product **1** (Scheme 3).

Following the outlined protocol several unnatural analogues were synthesised by either varying the Michael donor or acceptor and through ketoamide formation with different amines. The bromo analogue **11**, synthesised using **10**[15] as the Michael donor and HN(MeO)Me to form the ketoamide (Fig. 2), was not only of special interest for itself to explore its biological activity, but was also our preferred template for the following cross-coupling reactions (Scheme 4).

The Pd-mediated cross-coupling reactions of the highly functionalised bromo analogue **11**, applying Buchwald's protocol,[16–19] worked surprisingly well. The described reaction conditions, using ligand **15**, turned out to be superior to other 'standard' Suzuki and Buchwald–Hartwig conditions described in the literature.[16] The Suzuki reaction with ligand **15** proceeded at room temperature, but was heated to 100°C to reach completion. The desired coupling products **12** and **14** could be obtained in moderate to good yields.



Scheme 2. *Reagents and conditions*: (i) SmI_2, anisole, 70°C, 15 min; (ii) $Py{\cdot}SO_3$, CH_2Cl_2, rt, 6 h; (iii) TMSCN, ZnI_2, CH_3CN, benzene, rt, 12 h; (iv) LDA, THF, −78°C, 1 h; (v) K_2CO_3, MeOH, rt, 15 min.



Scheme 3. *Reagents and conditions*: (i) Stiles reagent (2 equiv.), DMF, rt, 24 h; (ii) 6N HCl, 0°C, 15 min; (iii) $HNMe_2$, Py·BOP, CH_2Cl_2, rt, 16 h; (iv) $Me_4NBH(OAc)_3$, MeCN, AcOH, rt, 18 h.

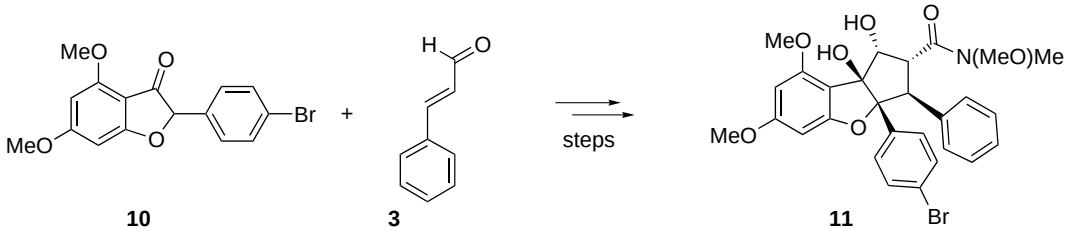
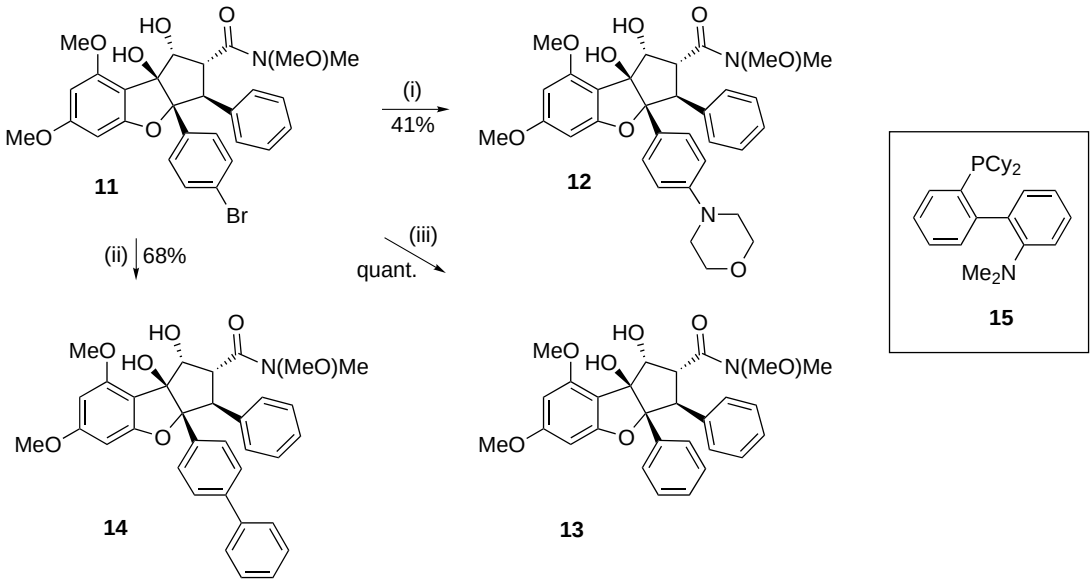


Figure 2. The key intermediate **11**.



Scheme 4. *Reagents and conditions*: (i) morpholine, $Pd_2(dba)_3$ (5 mol%), **15**, Cs_2CO_3 (1.5 equiv.), dioxane, 80°C, 16 h; (ii) $PhB(OH)_2$, $Pd(OAc)_2$ (5 mol%), **15**, CsF (1 equiv.), dioxane, 100°C, 24 h; (iii) H_2, Pd/C (cat.), ethyl acetate, rt, 24 h.

Accordingly several C-3 and C-3a *para*-substituted aryl analogues of **1** were synthesised and tested for their insecticidal and antifungal activity.[20] The detailed results of this SAR study will be published elsewhere.

In summary, the shortest and most efficient route today to the natural product and its aryl analogues has been described. Especially the use of Stiles reagent led to a considerable elegant improvement.

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20. All new compounds were completely characterised and gave satisfactory spectral and analytical data. Selected data: Compound **11** ^{1}H NMR δ: 7.18–7.22 (m, 2H), 6.97–7.07 (m, 5H), 6.80–6.84 (m, 2H), 6.29 (d, $J=1.9$ Hz, 1H), 6.09 (d, $J=2.1$ Hz, 1H), 4.99 (dd, $J=6.5$, 1.5 Hz, 1H), 4.41 (d, $J=14.0$ Hz, 1H), 4.19 (dd, $J=14.1$, 6.5 Hz, 1H), 3.99 (m, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.18 (s, 3H), 1.76 (s, 1H); ES-MS m/z 570 (M^+), 572 (M^{+2}).
Compound **12** ^{1}H NMR δ: 7.05–7.15 (m, 5H), 6.93 (m, 2H), 6.72 (d, $J=9.1$ Hz, 2H), 6.30 (d, $J=1.9$ Hz, 1H), 6.14 (d, $J=2.1$ Hz, 1H), 5.06 (dm, $J=6.8$ Hz, 1H), 4.47 (d, $J=13.8$ Hz, 1H), 4.26 (dd, $J=14.2$, 6.9 Hz, 1H), 4.09 (m, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 3.81–3.85 (m, 4H), 3.20 (s, 3H), 3.13–3.07 (m, 4H), 1.71 (s, 1H); ES-MS m/z 577 (M^{+1}).
Compound **13** ^{1}H NMR δ: 7.08–7.26 (m, 5H), 6.97–7.00 (m, 3H), 6.84–6.90 (m, 2H), 6.29 (d, $J=1.9$ Hz, 1H), 6.13 (d, $J=2.01$ Hz, 1H), 5.06 (d, $J=6.5$ Hz, 1H), 4.48 (d, $J=14.0$ Hz, 1H), 4.27 (dd, $J=14.0$, 6.5 Hz, 1H), 4.05 (m, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.18 (s, 3H), 1.77 (s, 1H); ES-MS m/z 492 (M^{+1}).
Compound **14** ^{1}H NMR δ: 7.24–7.51 (m, 9H), 7.00 (m, 3H), 6.91 (m, 2H), 6.31 (d, $J=1.9$ Hz, 1H), 6.12 (d, $J=2.0$ Hz, 1H), 5.08 (dm, $J=6.9$ Hz, 1H), 4.49 (d, $J=13.6$ Hz, 1H), 4.30 (dd, $J=13.6$, 6.9 Hz, 1H), 4.12 (m, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.18 (s, 3H), 1.74 (s, 1H); ES-MS m/z 568 (M^{+1}).