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A new analogue of rocaglamide by an oxidative dihydrofuran synthesis†

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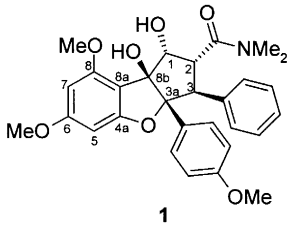
Abstract

A new analogue of rocaglamide **1** has been synthesised. The tricyclic core structure that is lacking the C-8b hydroxy group was generated in an oxidative addition of 1,3-cyclohexanedione to a cyclopentene moiety forming a tricyclic dihydrofuran system. Further transformation gave analogue **12** with the desired configuration. Although this C-8b deoxy derivative exhibits no insecticidal activity, it provides important information in understanding the structure–activity relationship.

The natural product rocaglamide **1** which was isolated from *Aglaia elliptifolia* in 1982 and described to exhibit antileukemic activity,[1] was rediscovered about 10 years later due to its insecticidal activity.[2–5] Meanwhile, the first total syntheses have been described.[6–8] Still, a shorter synthesis that allows an agrochemical application is needed. In particular, the synthesis of the tricyclic core structure bearing a highly functionalised cyclopentane moiety with five stereogenic centres is a challenge.



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In the investigation of the structure–activity relationship we have been interested in a facile access to analogues of the cyclopentabenzofuran structure. The synthetic approach we investigated was based on the idea of connecting a benzene moiety and a cyclopentane system in a furan synthesis. We have been able to realise this idea by an oxidative addition of a 1,3-dicarbonyl compound to a cyclopentene in an oxidative fashion.

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† This paper is dedicated to Pol Bamelis on the occasion of his 60th birthday.

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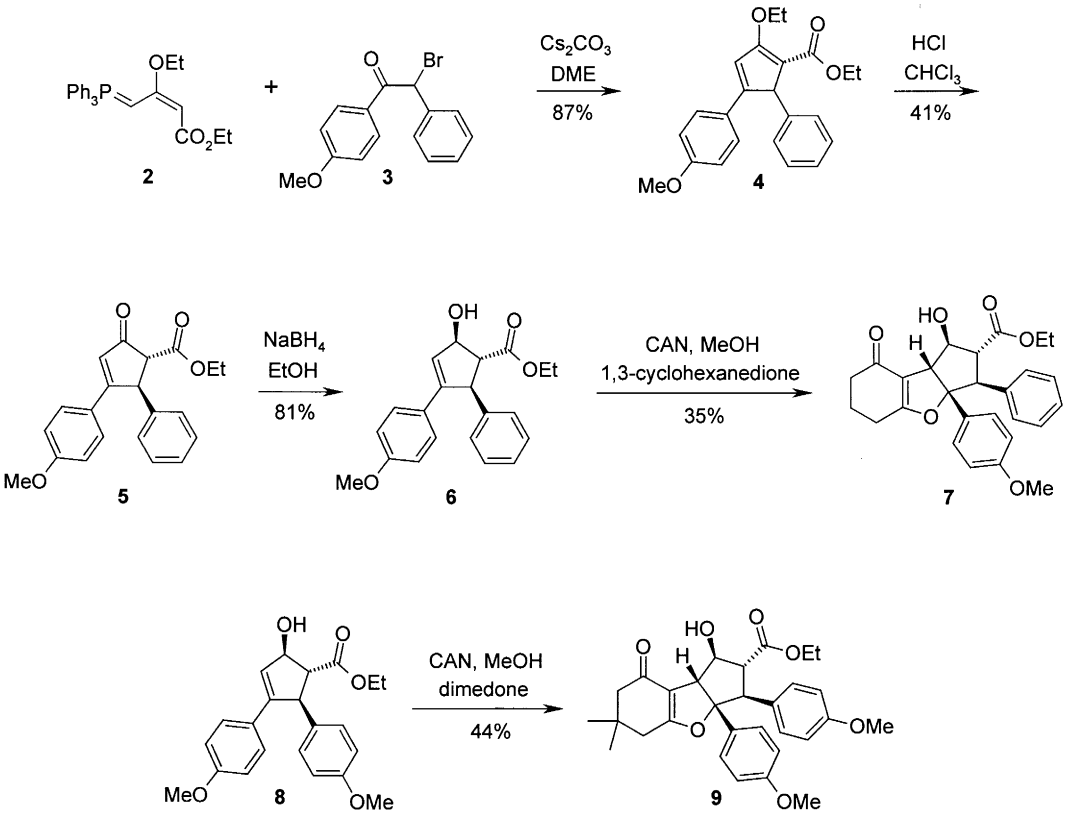
Starting from allylidenetriphenylphosphorane **2**[9] the cyclopentadiene **4** was prepared in one step and 87% yield by alkylation with bromoketone **3**[10] and intramolecular Wittig reaction in the presence of cesium carbonate (Scheme 1). The vinyl ether **4** was cleaved with HCl to give ketone **5** and reduction with $NaBH_4$ in ethanol yielded alcohol **6** as a single diastereoisomer (81%). According to literature protocols[11,12] olefin **6** was subjected to a reaction of 1,3-cyclohexanedione and cerium ammonium nitrate (CAN). Despite some side product formation the major compound turned out to be the desired *cis*-fused dihydrofuran **7** which was isolated in 35% yield. The stereochemical assignment was possible by crystallisation and X-ray analysis of dihydrofuran **9** which was obtained from dimedone and cyclopentene **8** in 44% yield (Fig. 1). The X-ray structure demonstrates that the two aryl substituents are in the desired *cis* arrangement and the ester is in an *anti* orientation. However, the stereocentre at C-1 has the opposite configuration compared to rocaglamide **1**.



Scheme 1.

Treatment of **7** with iodine in methanol led to the formation of the methyl ether and the aromatisation in one step to give intermediate **10** (Scheme 2). Because of side product formation, the reaction was stopped before complete conversion, yielding 33% aromatised product **10** and recovered starting material (30%). To invert the configuration at C-1, alcohol **10** was subjected to an oxidation–reduction sequence. While Swern oxidation resulted in low yields, oxidation of **10** by Dess–Martin periodinane afforded ketoester **11** in 63% yield. In a final reduction **11** was transformed to the hydroxyester **12**. Standard conditions ($NaBH_4$, ethanol) resulted in low conversion and poor diastereoselectivity (3:1). Instead, dichloromethane and Bu_4NBH_4 gave better conversions and a selectivity of 5.5:1 yielding **12** in 37% after purification.

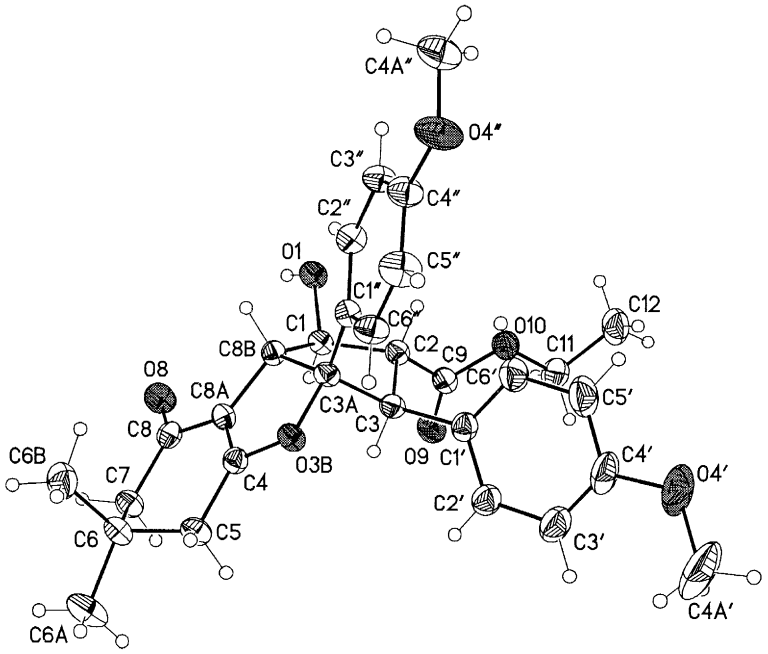
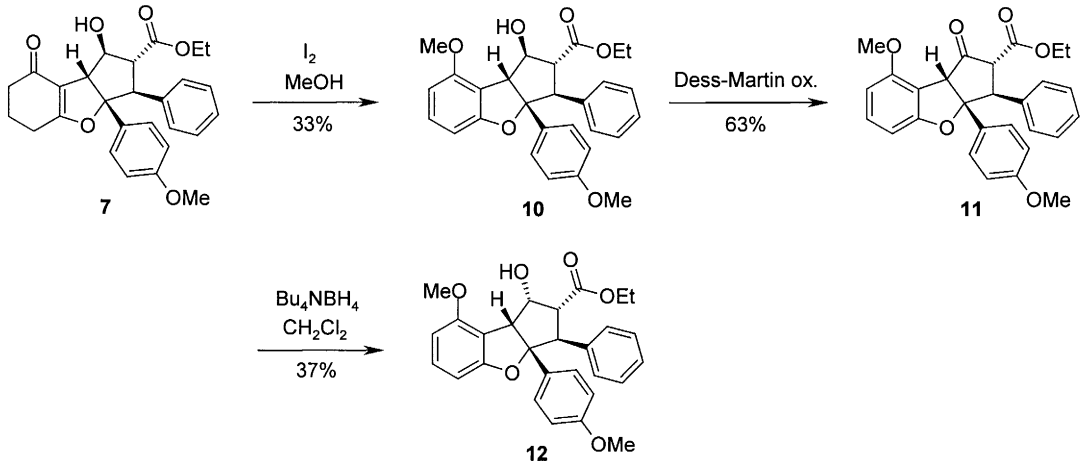


Fig. 1. X-Ray structure of dihydrofuran **9**[13]



Scheme 2.

The relative configuration of analogue **12** was assigned by ^{1}H NMR data in comparison to the epimer **10**. The configuration of C-2 is confirmed by the coupling constant of **12** ($J_{2,3}$=14.1 Hz) indicating the ester substituent to be *trans* to the 3-aryl substituent as in compound **10** ($J_{2,3}$=13.6 Hz). The coupling constant $J_{1,2}$ is larger for the epimer **10** (**10**: $J_{1,2}$=9.1 Hz, **12**: $J_{1,2}$=5.0 Hz) as seen in the rocaglamide series.[7] The configuration of C-1 was also assigned by comparing the chemical shifts. A low field shift at 5.14 ppm of compound **12** compared to the signal at 4.73 ppm of epimer **10** indicated a configuration at C-1 that no longer orientates the carbinol proton in the anisotropic cone of the benzofuran moiety.

Interestingly, when analogue **12** was tested against *Spodoptera littoralis*, no insecticidal activity was observed. Although the influence of the C-6 methoxy substituent of rocaglate esters is not clear, it seems

most likely that the drastic loss in activity is due to the missing hydroxy group at the bridgehead atom C-8b.

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13. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre (CCDC 138222).