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Synthesis of the Carbocyclic Analogue of (±)-Rocaglamide.

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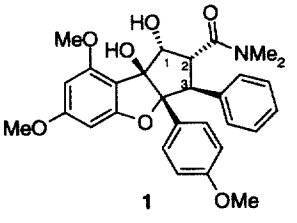
Abstract: The carbocyclic analogue of (±)-Rocaglamide **1**, in which the ring oxygen of the 2,3-dihydrobenzofuran has been replaced by a methylene group, was synthesised in 10 steps from cyclopentanone. A key feature of this route is a highly efficient intramolecular condensation reaction which cleanly leads to the tricyclic skeleton.

Keywords: Condensation; Cyclopentane

Rocaglamide **1** is a naturally occurring *1H*-cyclopenta[*b*]benzofuran which was isolated in 1982 from *Aglaia elliptifolia* Merr.[1]. It exhibits both anti-leukaemic activity (against P388 cells [1]) and insecticidal activity (against *Peridroma* [2-4] and *Spodoptera* [4]). The absolute stereochemistry was established by synthesis of the natural (-)-enantiomer in 1990 [5].



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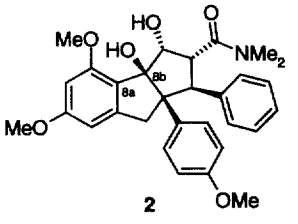

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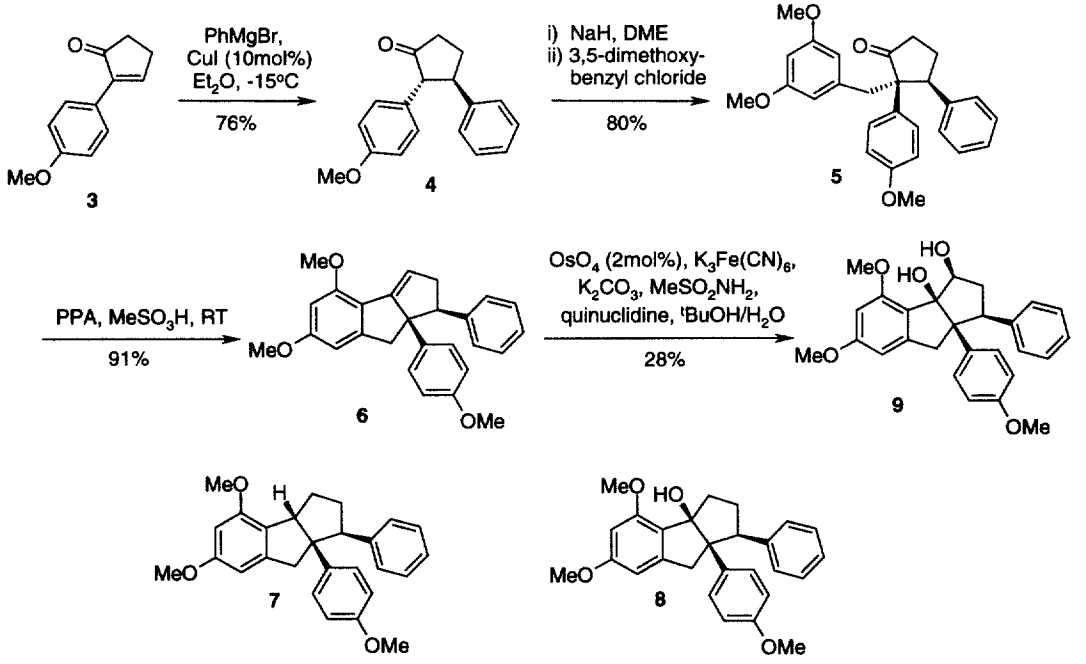
Despite several synthetic approaches to **1** [6-9], it remains a challenging target for synthesis by virtue of the highly functionalised cyclopentane ring containing five contiguous chiral centres and the *syn*-arrangement between the adjacent *p*-anisyl and phenyl substituents.

As part of our work on bioactive natural products we wished to prepare the Rocaglamide carbocyclic analogue **2**; firstly to evaluate the contribution of the various functional groups to the biological activity of **1** and secondly, since **2** represented a potentially equipotent yet synthetically more accessible target than **1**. We chose to base our approach to **2** on a strategy requiring formation of the C(8a)-C(8b) bond to close the tricyclic ring system with the two aryl groups already in a *syn*-arrangement to each other before further elaborating the skeleton.

Beginning from 2-(*p*-anisyl)-2-cyclopentenone **3** [10][3], copper-mediated Michael addition of phenylmagnesium bromide gave *anti*-biarylcyclopentanone **4** in 76% yield after allowing the initially formed *syn*-product to epimerise during workup (Scheme 1). Reaction of **4** with sodium hydride followed by trapping of the enolate with 3,5-dimethoxybenzyl chloride proceeded in a regiospecific and stereospecific manner to give a good yield of the 2,2,3-trisubstituted cyclopentanone **5**. Our initial attempts to effect cyclocondensation of **5** using neat polyphosphoric acid (PPA) [11] and prolonged heating resulted in a low yield of the desired product **6** (28%) together with a small amount (9%) of saturated product **7**.



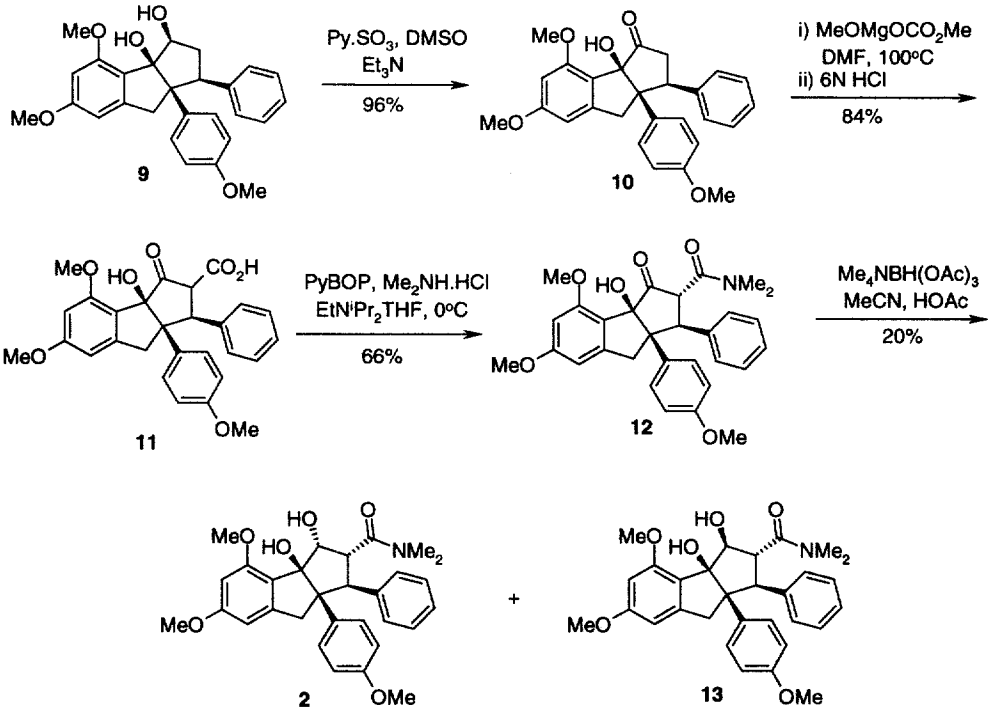
Scheme 1

[3] Prepared in two steps from cyclopentanone *via* Grignard addition/dehydration followed by allylic oxidation (SeO_2). For an alternative approach see ref. 10

The identity of **7** was confirmed by hydrogenation of **6** (H_2, $Pd(OH)_2/C$) to provide an identical sample. Using methanesulfonic acid as co-solvent (5:1 $MeSO_3H$: PPA) in the cyclocondensation led to dramatic improvements with the reaction occurring rapidly at room temperature to give **6** in excellent yield. A minor amount (2%) of the intermediate **8** was also isolated.

Dihydroxylation of olefin **6** was problematic due to slow hydrolysis of the intermediate osmate ester but two procedures gave moderate success; reaction of **6** with stoichiometric OsO_4 in pyridine [12] afforded diol **9** (37%) and a small amount of ketone **10** (8%) although this required a lengthy work-up procedure. A more convenient protocol used catalytic OsO_4 in a two phase system [13], this needed longer reaction times but work-up procedure was less hazardous. Generally the reaction was quenched after only partial conversion to afford **9** in adequate yield (28%) [63% based on recovered starting material] on a multigramme scale.

Oxidation of diol **9** (DMSO/Py.SO_3) gave ketone **10** in 96% yield (Scheme 2) which was converted to carboxylic acid **11** (84%) with Stiles reagent [14] at 100°C followed by acid hydrolysis. The crude acid was immediately converted to ketoamide **12** using PyBOP/Me_2NH (66%) although a competing decarboxylation of β-ketoacid **11** to ketone **10** (8%) was also observed. Compound **12** exists exclusively in the keto form with the amide substituent *anti* to the phenyl group.



Scheme 2

Rather disappointingly, reduction of **12** with $Me_4NBH(OAc)_3$ was extremely slow and unselective and only provided 20% of the target compound **2** despite a large excess of reducing agent (20 equiv.). Also isolated was the C-1 epimer **13** (<10%). This contrasts with the Rocaglamide series where this reagent has been employed by us and others [5,9] leading to excellent yields of *anti*-diols, however no attempts have been made to optimise this reaction.

The relative stereochemistries of the carbocyclic analogue **2** and of other compounds in the sequence were confirmed by a combination of NOESY experiments and direct comparison with ^1H NMR spectra of analogous compounds in the Rocaglamide series. In each case, the ^1H coupling constants suggest that the carbocyclic analogues exist in a similar confirmation to the corresponding Rocaglamide compounds (see Table 1 for selected examples).

Table 1.

Selected ^1H NMR Coupling Constants for Carbocyclic Rocaglamide Derivatives.

Compound	$J_{1,3}$(Hz)	$J_{2,3}$(Hz)
2	5.9 (6.4 [5])	13.0 (13.7 [5])
13	7.4 (7.5 [9])	13.3 (13.4 [9])

Figures in brackets refer to corresponding values for Rocaglamide series

In summary, a route to the carbocyclic analogue of (±)-Rocaglamide has been described which utilises inexpensive reagents and mild conditions.

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