# Synthesis of the Novel Anti-leukaemic Tetrahydrocyclopenta[*b*]benzofuran, Rocaglamide

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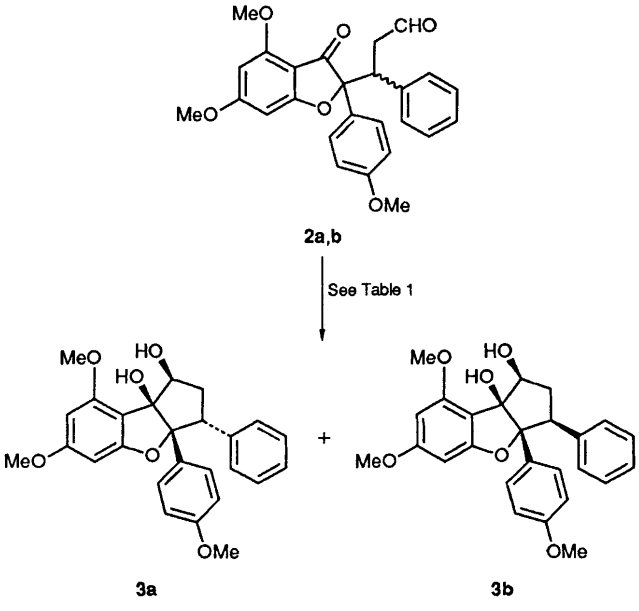
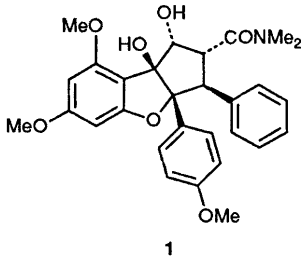
A total synthesis of the novel anti-leukaemic natural product, rocaglamide, in racemic form, is described, the key step involving an intramolecular keto-aldehyde pinacolic coupling; the synthetic route is short, proceeds from phloroglucinol, a readily-available starting material, and is well suited to the synthesis of analogues.

The anti-leukaemic natural product rocaglamide **1** was isolated from *Aglaia elliptifolia* Merr. and its structure determined by single crystal X-ray analysis in 1982.[1] From the synthetic viewpoint rocaglamide presents a considerable challenge, most notably involving the cyclopentane ring which contains five contiguous chiral centres, seven substituents and a *cis*-arrangement between the adjacent aryl and phenyl substituents. In 1987 we reported a number of synthetic approaches to the tricyclic rocaglamide skeleton[2,3] and in 1989 Kraus and Sy reported the synthesis of a di-*epi*-analogue of rocaglamide.[4] Recently, Trost *et al.* published a total synthesis of (−)-rocaglamide itself, which established the absolute configuration of the natural material.[5] The purpose of this communication is to give details of our own successful synthesis of rocaglamide. The key step in the synthesis is the intramolecular keto-aldehyde pinacolic coupling[3] shown in Scheme 1.

There has been a great deal of recent interest in the synthesis of cycloalkane-1,2-diols by intramolecular pinacol coupling.[6–10] We surveyed the utility of some of these methods for the conversion of the keto-aldehyde diastereoisomers **2a, b** into the tricyclic pinacol products **3a, b** as shown in Table 1. As can be seen, the zinc-based systems[8,10] gave no detectable pinacol products but the reduced titanium methods introduced by Corey *et al.*[9] proved to be more successful. With ($C_5H_5$) $TiCl_3$–$LiAlH_4$, the diastereoisomeric mixture **2a, b** was converted into the required all-*cis*-isomer **3b** in 26% yield together with 21% of the *trans*-isomer **3a** and reduced acyclic compounds.† Samarium iodide[4,6] gave similar results with the 1 : 1 diastereoisomeric mixture **2a, b** and a 59% yield of **3b** was obtained starting with a chromatographically enriched sample of **2b**.‡ With the pinacol coupling methodology established we



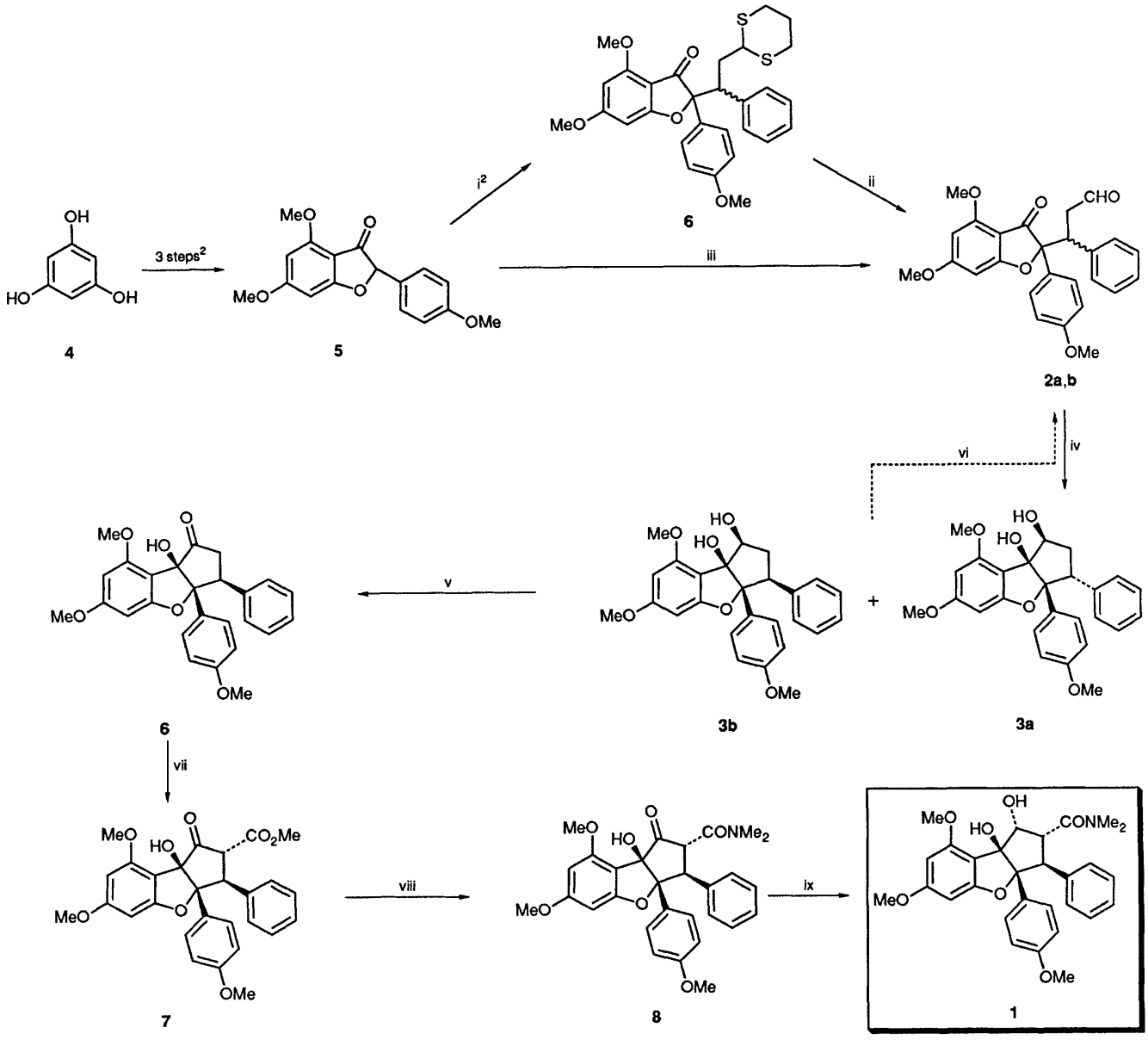

**Scheme 1** **a**, α-Ph; **b**, β-Ph. All compounds are racemic




**1**

† All new compounds gave spectral and analytical or high resolution mass spectrometric data consistent with the assigned structures.

‡ It is interesting to note that, in our hands, the nitrile corresponding to aldehyde **2a** also undergoes $SmI_2$ coupling efficiently (60–80%) whereas the nitrile corresponding to aldehyde **2b** gives much lower yields of the required coupled products (<10%). Given that Kraus and Sy used these nitriles in their approach to the rocaglamide skeleton,[4] this observation presumably explains their production of an isomer of rocaglamide with Ar and Ph groups *trans* to each other.




**Scheme 2** **a**, α-Ph; **b**, β-Ph. All compounds are racemic. *Reagents and conditions*: i, NaH, 2-(2-iodo-2-phenyl)-1,3-dithiane (61%);[2] ii, $HgCl_2$, $CaCO_3$, aq. MeCN (82%); iii, (*E*)-PhCH=CHCHO, Triton B, $Bu^tOH$ (62%); iv, see Table 1; v, $(COCl)_2$, $Me_2SO$, $Et_3N$ (81%); vi, $PyHClCrO_3$, $CH_2Cl_2$ (**2b**, 94%); vii, (*a*) $Me_3SiOSO_2CF_3$, (*b*) $LiNPr^i_2$, hexamethylphosphoric triamide, (*c*) MeONa, tetrahydrofuran (THF) (89% from **6**); viii, $Me_2NLi$, THF (78%); ix, $Me_4NBH(OAc)_3$, MeCN–AcOH (59%).

were then in a position to complete the synthesis of rocaglamide (Scheme 2).

The benzofuranone **5**, readily prepared from phloroglucinol **4** *via* literature procedures,[2,11] could be converted into the cyclisation precursor **2a, b** in two ways. Alkylation of the benzofuranone enolate with 2-(2-iodo-2-phenylethyl)-1,3-dithiane gave adduct **6**[2] which was hydrolysed to give keto-aldehyde **2a, b**. The same transformation could be achieved directly by treating benzofuranone **5** with cinnamaldehyde–Triton B. Under standard conditions both reactions produce **2a, b** as a *ca.* 1 : 1 diastereoisomeric mixture. We are currently exploring modifications which give a predominance of the required diastereoisomer **2b**. After pinacolic coupling (Table 1), diols **3a** and **b** can be readily separated by chromatography. To our consternation, oxidation of diol **3b** with pyridinium chlorochromate ($PyHClCrO_3$) gave an almost

**Table 1** Reductive cyclisation reactions of keto-aldehydes **2a, b**

| Conditions | Starting material[a] | Products or results |
|---|---|---|
| Zn–$Me_3SiCl$[c] | **2a, b** | Multi-component mixture |
| Zn–$TiCl_4$[d] | **2a, b** | Extensive decomposition |
| Mg(Hg)–$TiCl_4$[e] | **2a** | **3a**, 22% |
| $LiAlH_4$–($C_5H_5$) $TiCl_3$[e] | **2a, b** | **3a**, 21%[b] + **3b**, 26%[b] + acyclic reduced products, 14% |
| $SmI_2$[f] | **2a, b** | **3a**, 29%[b] + **3b**, 33%[b] |
| | **2a, b**, 10 : 90 | **3a**, 10% + **3b**, 59% |

[a] *Ca.* 1 : 1 ratio unless otherwise stated. [b] These are the best yields obtained for these reactions; lower yields were obtained on other occasions. [c] Ref. 8. [d] Ref. 10. [e] Ref. 9. [f] Ref. 6.

quantitative yield of keto-aldehyde **2b**.[12] The required ketone **6** was obtained by use of the Swern oxidation procedure and we were then in a position to introduce the dimethylcarboxamido substituent. All attempts to effect this transformation directly by treatment of the enolate derived from **6** (or from the *O*-silylated derivative of **6**) with carbamoyl chloride or $NCCONMe_2$ have so far proved unsuccessful. We therefore used the $CS_2$-based procedure developed by Kraus and Sy[4] to convert ketone **6** into β-keto ester **7**, which exists as a 65 : 35 keto–enol mixture. After considerable experimentation ester was converted into amide **8** using $LiNMe_2$ in THF.[13] Compound **8** exists exclusively in the keto form and predominantly as a single diastereoisomer, presumably the α-carboxamide shown. The final reduction was achieved with high stereoselectivity using $Me_4NBH(OAc)_3$[5]§ giving racemic rocaglamide as a white crystalline solid (m.p. 119–120 °C, lit.[1] 118–119 °C) with identical $^1H$ and $^{13}C$ NMR data to the natural material.

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§ Surprisingly, when the same reaction conditions were employed to reduce β-keto ester **7**, only the β-hydroxy derivative was obtained (68%).

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