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

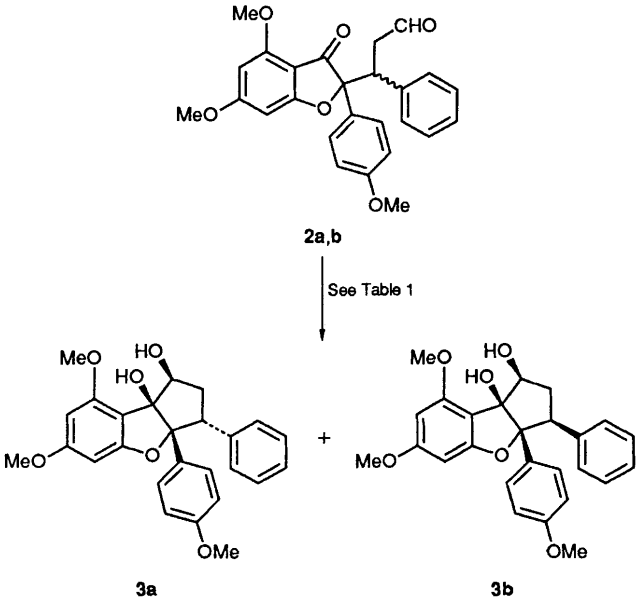
Andrew E. Davey, Marcel J. Schaeffer and Richard J. K. Taylor*

School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, UK

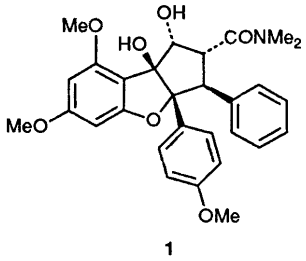
A total synthesis of the novel anti-leukaemic natural product, rocaglamide, in racemic form, is described, the key step involving an intramolecular keto-aldehyde pinacolic coupling; the synthetic route is short, proceeds from phloroglucinol, a readily-available starting material, and is well suited to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



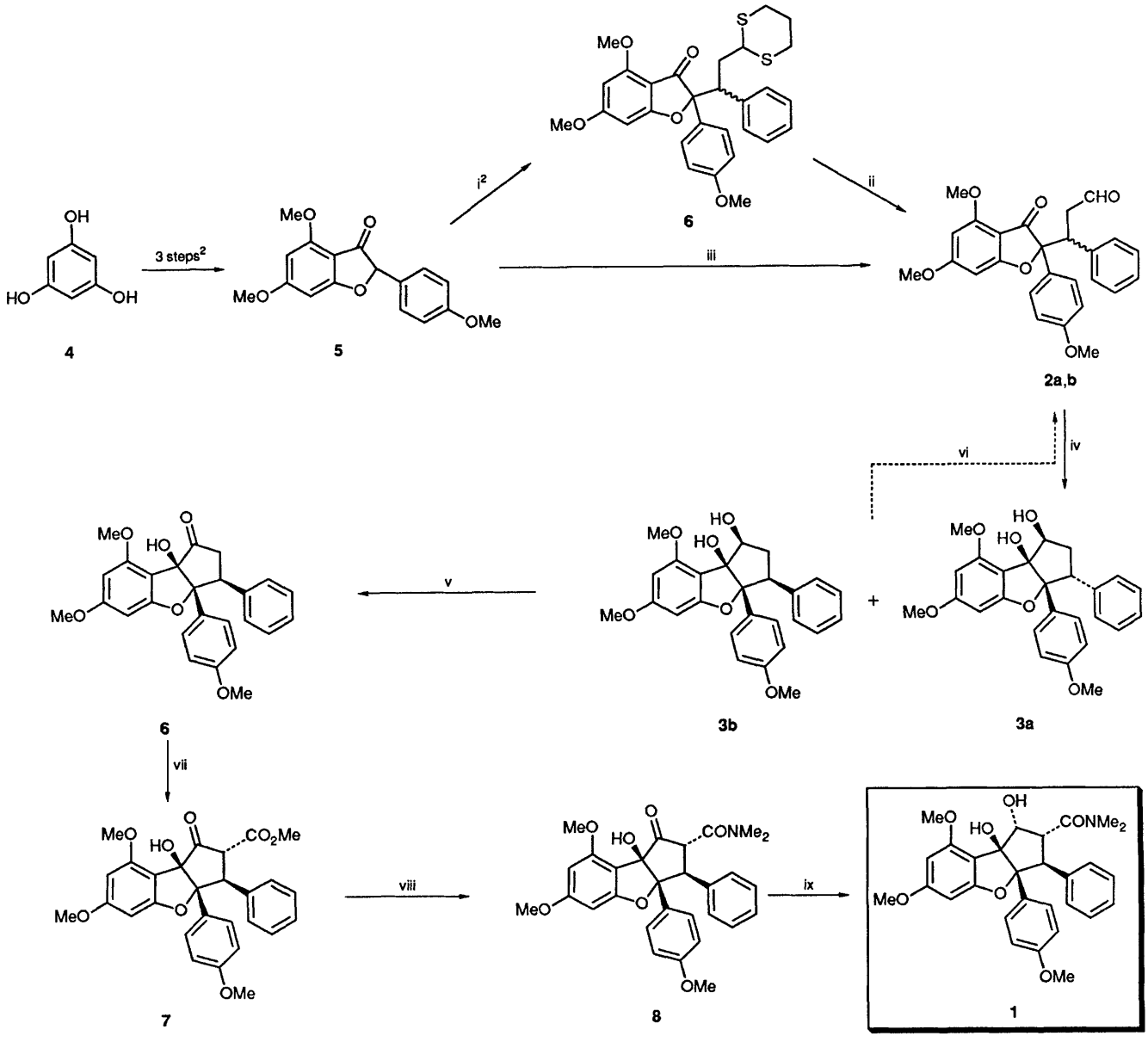
Scheme 1 a, α-Ph; b, β-Ph. All compounds are racemic



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.

We thank the SERC for the award of a studentship (A. E. D) and Ciba-Geigy for generous financial support. We also thank the SERC mass spectrometry service centre, Swansea and the SERC WH-400 NMR spectroscopic service, Warwick for their invaluable assistance. In addition, we are most grateful to Professor G. A. Kraus (Iowa State University) for sending us unpublished experimental details concerning samarium iodide chemistry.

Received, 12th June 1991; Com. 1/02830H

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

References

1 M. L. King, C. C. Chiang, H. C. Ling, E. Fujita, M. Ochiai and A. T. McPhail, *Chem. Commun.*, 1982, 1150.
2 A. E. Davey and R. J. K. Taylor, *J. Chem. Soc., Chem. Commun.*, 1987, 25.
3 A. E. Davey, PhD thesis, University of East Anglia, 1987.
4 G. A. Kraus and J. O. Sy, *J. Org. Chem.*, 1989, **54**, 77.
5 B. M. Trost, P. D. Greenspan, B. V. Yang and M. G. Saulnier, *J. Am. Chem. Soc.*, 1990, **112**, 9022.
6 J. L. Chiara, W. Cabri and S. Hanessian, *Tetrahedron Lett.*, 1991, **32**, 1125 and references therein; G. A. Molander and C. Kenny, *J. Org. Chem.*, 1988, **53**, 2132.
7 J. E. McMurry and J. G. Rico, *Tetrahedron Lett.*, 1989, **30**, 1169.
8 E. J. Corey and S. G. Pyne, *Tetrahedron Lett.*, 1983, **24**, 2821.
9 E. J. Corey, R. L. Danheiser and S. Chandrasekaran, *J. Org. Chem.*, 1976, **41**, 260.
10 T. Mukaiyama, T. Sato and J. Hanna, *Chem. Lett.*, 1973, 1041.
11 C. Katamna, *Bull. Chim. Soc. Fr.*, 1970, 2309 and references therein.
12 A. Cisneros, S. Fernández and J. E. Hernández, *Synth. Commun.*, 1982, **12**, 833.
13 B. M. Bhawal, S. P. Khanapure and E. R. Biehl, *Synth. Commun.*, 1990, **20**, 3236.