Synthesis of the Novel Anti-leukaemic Tetrahydrocyclopenta[*b*]benzofuran, Rocaglamide and Related Synthetic Studies

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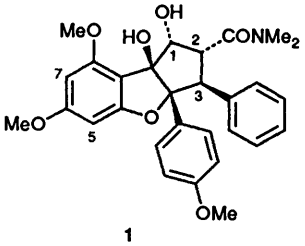
Two approaches to the rocaglamide tricyclic skeleton are described. The first, which employs an unusual intramolecular dithianyl anion to carbonyl addition reaction, provides access to α-phenyl rocaglamide analogues. The second route involves an intramolecular keto aldehyde pinacolic coupling in the key step and can be used for the preparation of a whole range of rocaglamide analogues possessing both α- and β-phenyl substituents. A total synthesis of rocaglamide, in racemic form, is described using this second approach. The synthetic route commences with phloroglucinol, an inexpensive and readily-available starting material, and takes only 8/9 steps giving an overall yield of >6%. The synthesis of 1-*epi*-rocaglamide **29b** is also described.

The anti-leukaemic natural product rocaglamide **1** was isolated from *Aglaia elliptofolia* 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.



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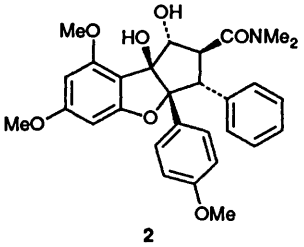

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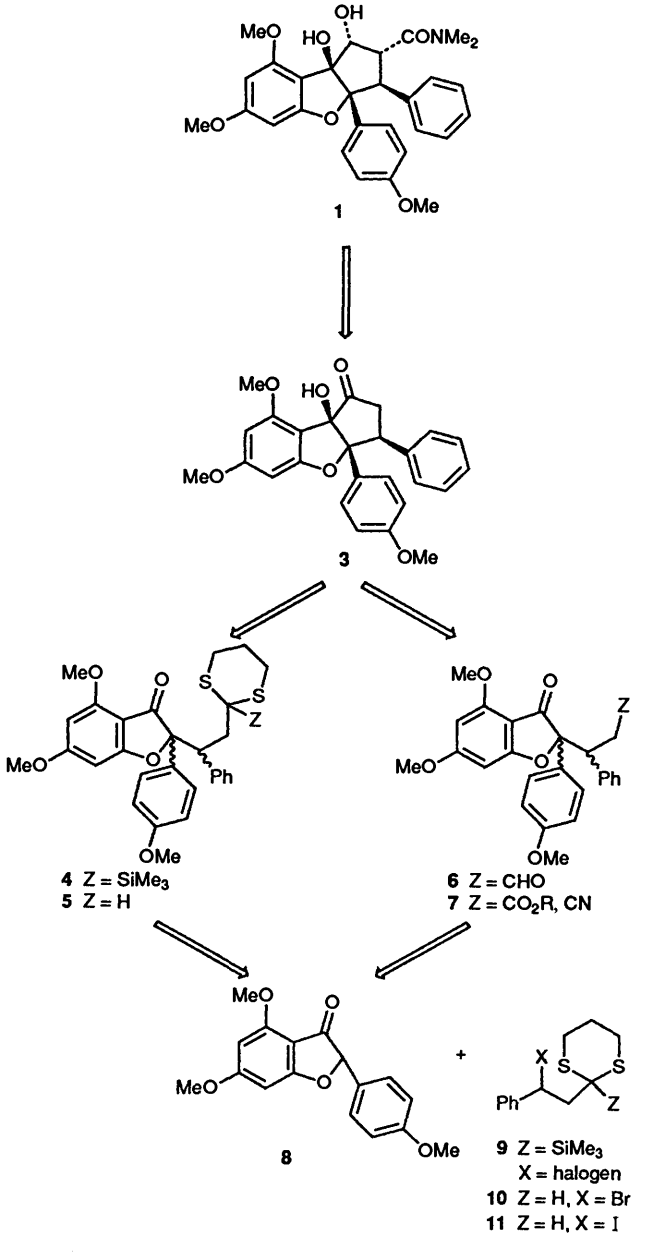
In 1987 we reported a number of synthetic approaches to the tricyclic rocaglamide skeleton[2,3] and in 1989 Kraus and Sy reported the synthesis of the di-*epi*-analogue **2** of rocaglamide.[4] Recently, Trost *et al.* published a total synthesis of (−)-rocaglamide itself which established the absolute configuration of the natural material as shown in structure **1**.[5a] In addition, a radical-mediated cyclisation approach has recently been employed to prepare simplified rocaglamide analogues.[5b] The present paper gives full details of our own successful synthesis of racemic rocaglamide[6] and related synthetic studies. Our original retrosynthetic analysis is shown in Scheme 1.

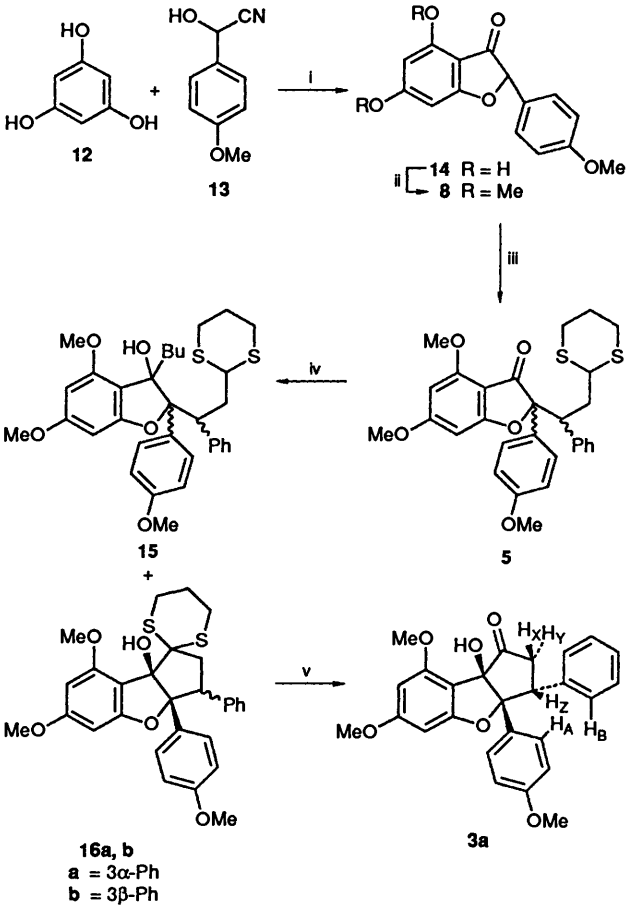
Given that cyclopentanone **3** is a logical rocaglamide precursor, and the dihydroxy version of benzofuranone **8** is a known compound,[7] we decided to concentrate our attention on cyclopenta-annellation procedures as illustrated in Scheme 1. We intended to utilise Grotjahn and Andersen's fluoride mediated cyclisation methodology[8] with silyl-dithiane **4** but were unable to prepare the requisite alkylating agent **9** for reasons described elsewhere.[9] The first approach to be explored in depth was therefore the direct cyclisation of keto dithiane **5**, alkylating agents **10** and **11** being readily available.[9] These investigations are shown in Scheme 2.†

The Hoesch reaction between phloroglucinol **12** and cyanohydrin **13**[10] is not always reproducible but generally proceeds in fair yields (50–76%) to give benzofuranone **14**. In our hands,

† All synthetic compounds are racemic. Rocaglamide numbering (see structure **1**) is used for all tricyclic compounds.



Scheme 1



Scheme 2 *Reagents and conditions:* i, HCl gas, ether then dil. HCl, reflux (50–76%); ii, Me_2SO_4, K_2CO_3, acetone, heat then dil. HCl, heat (91%); iii, NaH, DMF–C_6H_6, **11** (61% + *ca.* 5% **18**); iv, 28–84.5% (see text and Table 1); v, $HgCl_2$, MeCN, aq. $CaCO_3$ (32%) or PbO_2, BF_3·Et_2O, aq. THF (37% + 21% **21**)

the yields diminished when zinc chloride was employed in this reaction, contrary to literature[7] indications. It should also be noted that we are not able to confirm that the use of the α-chloro nitrile derived from **13** gives improved yields of benzofuranone **14**; when we followed this literature[7] procedure we obtained variable yields of **14** up to a maximum of 16%, lactone **17** being isolated as a major by-product. All attempts to carry out the Hoesch reaction on phloroglucinol trimethyl or dimethyl ether were unsuccessful. Treatment of benzofuranone **14** with dimethyl sulfate–K_2CO_3 in de-oxygenated acetone gave a trimethylated product, resulting from concomitant enol ether formation, in high yield. Hydrolysis of this crude product in acidic aqueous methanol produced the required ketone **8** as a crystalline solid in 91% overall yield. Alkylation of **8** with sodium hydride followed by iododithiane **11** gave the required *C*-alkylated product **5** in 61% yield (*ca.* 1:1 ratio of diastereoisomers) along with 5% of the *O*-alkylated adduct **18**. The amount of *O*-alkylated adduct increased dramatically when bromide **10** was employed (34% using NaH as base, 60% using K_2CO_3). It is also important to exclude oxygen from these reactions; if they are not rigorously de-gassed the 2-hydroxylated product **19** is formed. With precursor **5** in hand we turned our attention to the cyclisation reaction. Although this annellation relies on the unprecedented deprotonation of a dithiane in the presence of a nearby carbonyl group we felt that there was a realistic chance of success as the carbonyl group is non-enolisable and deactivated, both sterically and electronically, to nucleophilic attack. The results of this study, in which a range of bases were employed, are collected in Table 1. In the

Table 1 Treatment of dithianes **5** with base

Base (equiv.)	*T*/°C[c]	Yield (%) **16a, b**	Yield (%) **15**	Recovered **5** (%)
LDA (1)	−78 to reflux	—	—	100
Bu^{t}Li (1.1)[a] TMEDA (1.2)	−78 to room temp.	—	—	85
Bu^{s}Li (3)	−78 to room temp.[d]	—	42	—
BuLi (1)[b]	−78 to room temp.	—	—	55
BuLi (1.1)	−78 to −10	—	34	37
KOBu^t (1)				
BuLi (1.1) HMPA (2)	−78 to −10	28	14	31
BuLi (2) HMPA (2)	−78 to −10	45	24	31
BuLi (2) HMPA (2)	−96 to −10	55	12	10
BuLi (1.3) HMPA (2)	−96 to room temp.	84.5	—	—
Bu^{t}Li (1.2) HMPA (2)	−96 to −10	—	91	—

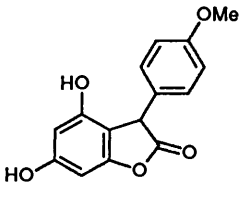
[a] The use of Bu^{t}Li alone gave a complex mixture of products. [b] A similar result was obtained using hexane in place of tetrahydrofuran (THF) in the presence of TMEDA. [c] Solvent THF where indicated otherwise. [d] Solvent THF–Et_2O (5:1).

initial reactions using LDA, Bu^{t}Li, Bu^{s}Li BuLi and BuLi–KOBu^t either unchanged starting material was recovered or butyl carbinols **15** were obtained. Success was observed, however, when BuLi was employed in the presence of HMPA (hexamethylphosphoramidide). As can be seen from Table 1, this reaction was eventually optimised so that the required tricycle **16a, b** was obtained exclusively, as a *ca.* 1:1 mixture of α- and β-Ph-diastereoisomers, in 84% yield. In order to gain information about the mechanism of this cyclisation process the reaction mixture was stirred for 1 h at −96 °C after BuLi addition and then quenched with D_2O. To our great surprise the only deuteriated product isolated was **20**, obtained in 72% yield. This result suggests that initial deprotonation occurs at the benzofuranone C-7 (rocaglamide C-5) position. It was also surprising to discover that treatment of the de-phenyl analogue of **5** under the optimum BuLi–HMPA conditions gave only products corresponding to carbinols **15** (Ph = H). Further studies are obviously needed before the mechanism of the unprecedented conversion of **5** into **16a, b** can be discussed with confidence.

Having established an efficient route to the tricyclic dithiane **16a, b**, all that remained to complete a synthesis of rocaglamide (and 3-*epi*-rocaglamide) was dithiane hydrolysis, introduction of the C-2 dimethylcarboxamide group and carbonyl reduction. Unfortunately, we experienced great difficulty with the first step. A wide range of published[11] procedures were applied to the hydrolysis of dithiane **16a, b** (and the corresponding monosulfoxide) but in all cases the yields were low and only the α-phenyl diastereoisomer **3a** could be isolated. For example, this compound was obtained in up to 32% yield using $HgCl_2$–MeCN–aq. $CaCO_3$.[12] The structure of compound **3a** was unambiguously established by 400 MHz NMR spectroscopic studies summarised in Table 2; the 7% nuclear Overhauser effect (NOE) between H_A and H_Z (see structure **3a**) being conclusive. On the assumption that the required β-phenyl diastereoisomer of **3a** was being formed but preferentially destroyed under the reaction conditions, various mild hydrolytic conditions were investigated. The only procedure which produced a second major product was PbO_2–BF_3·Et_2O[13] and in this case the by-product, rather surprisingly, was the unsaturated ketone **21**. When the PbO_2–BF_3·Et_2O reaction was carried out for 10 min a 37% yield of saturated ketone **3a** and a 21% yield of

Table 2 NOE difference studies and *J* values for **3a**

	NOE (%)	*J*/Hz
H_X–H_Y	25	$J_{X,Y}$ 15.7
H_X–H_Z	5	$J_{X,Z}$ 6.7
H_Y–H_Z	<1	$J_{Y,Z}$ 14.9
H_A–H_Z	7	
H_B–H_Z	3	



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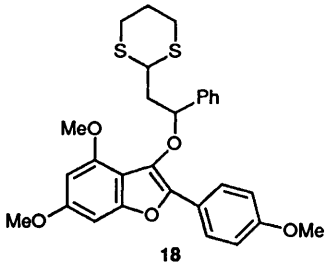

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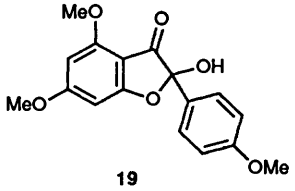

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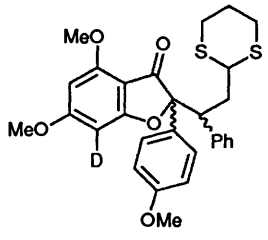

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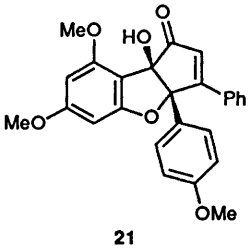

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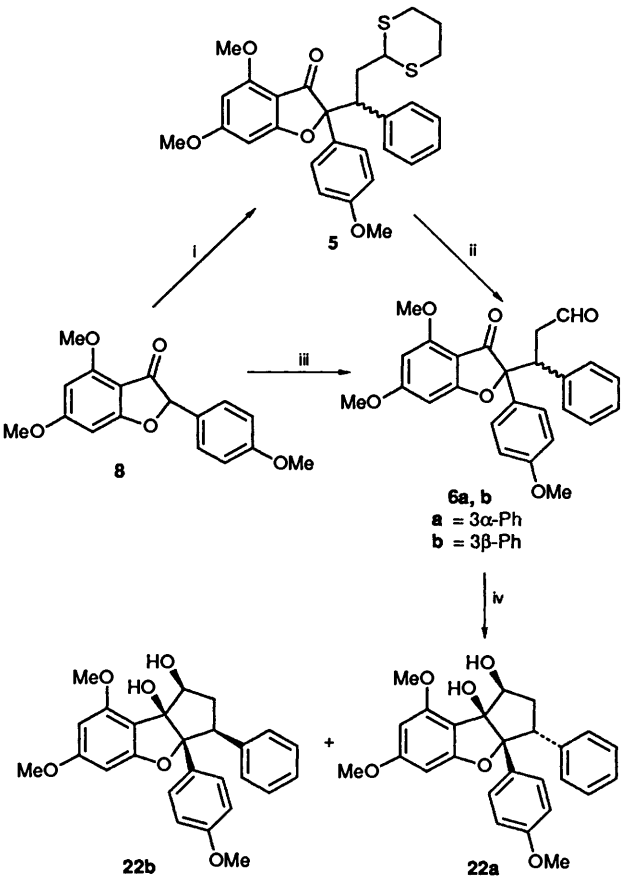
unsaturated ketone **21** were obtained. Longer reaction times led to a reduction in the amount of **21**, however, and leaving the reaction for 1 h gave only ketone **3a** (43%).

The α-phenyl diastereoisomer **3a** is obviously of interest in its own right as a precursor both to α-phenyl isomers of rocaglamide, *e.g.* **2**,[4] and, by inversion of the phenyl group *via* a dehydrogenation–hydrogenation sequence,[5a] to rocaglamide itself. However, our attempts to hydrogenate the unsaturated ketone **21** in order to obtain the β-phenyl diastereoisomer of **3a** were unsuccessful and so we turned our attention to the alternative strategy outlined in Scheme 1, *i.e.* the intramolecular pinacolic coupling approach. We made the initial decision to investigate the cyclisation reactions of keto-aldehyde diastereoisomers **6**, rather than the corresponding esters/nitriles **7**, a fortunate choice in view of a later publication.[4] Keto aldehyde **6a**, **b** was prepared in two ways as shown in Scheme 3. In contrast to the observations with the cyclic dithiane **16a**, **b** referred to earlier, hydrolysis of dithiane **5** to give keto aldehyde **6a**, **b** proceeded efficiently. The same product could be prepared directly from benzofuranone **7** by treatment with *E*-cinnamaldehyde–Triton B. Under standard conditions both reactions produced **6a**, **b** as a *ca.* 1:1 diastereoisomeric mixture. Attempts to modify the Michael reaction[14] in order to obtain a predominance of the required diastereoisomer **6b** are summarized in Table 3. The only selectivity observed on changing the base to LDA was 2:1 in favour of diastereoisomer **6a** (max.



Scheme 3 *Reagents:* i, NaH, DMF–C_6H_6 (61%); ii, $HgCl_2$, $CaCO_3$, aq. MeCN (82%); iii, *E*-PhCH=CHCHO, Triton B, Bu^{t}OH (69%, **6a**:**6b** = 1:2.25; see Table 3); iv, see Table 4.

yield, 44%). Attempts to influence the ratio by using *Z*-cinnamaldehyde were unsuccessful. However, it was subsequently discovered that by carrying out the reaction under dilute conditions (0.04 mol dm^{-3} *vs.* 0.22 mol dm^{-3} in *tert*-butyl alcohol–Triton B, a 1.0:2.25 ratio of **6a**:**6b** could be obtained. In addition, the unwanted isomer **6a** could be isomerised to a 1.0:1.7 mixture of **6a**:**6b** (49% recovery) on treatment with Triton B. To our knowledge,[14] this is the first report of a concentration effect upon the stereoselectivity of a Michael reaction and, although additional work is needed to establish the causes and implications of this finding, it is of potential value to others working in this area.

There has been a great deal of recent interest in the synthesis of cycloalkane-1,2-diols by intramolecular pinacol coupling.[15–20] We surveyed the utility of some of these methods for the conversion of the keto aldehyde diastereoisomers **6a**, **b** into the tricyclic pinacol products **22a**, **b** as shown in Table 4. As can be seen, the zinc-based systems gave no detectable pinacol products but the reduced titanium methods introduced by Corey *et al.*[19] proved to be more successful. With $CpTiCl_3$–$LiAlH_4$, the diastereoisomeric mixture **6a**, **b** was converted into the required all *cis*-isomer **22b** in 26% yield together with 21% of the *trans*-isomer **22a** and reduced acyclic compounds. Samarium iodide[4,16] gave similar results with the 1:1 diastereoisomeric mixture **6a**, **b** and a 58% yield of **22b** was obtained starting with a chromatographically enriched sample of **6b**. The formation of *cis*-diols in the tricyclic products was to be expected.[16]

Given the success of the ketoaldehyde cyclisation reactions we decided to look at the cyclisation reactions of the corresponding keto nitriles **23a**, **b**[4] as shown in Scheme 4. These

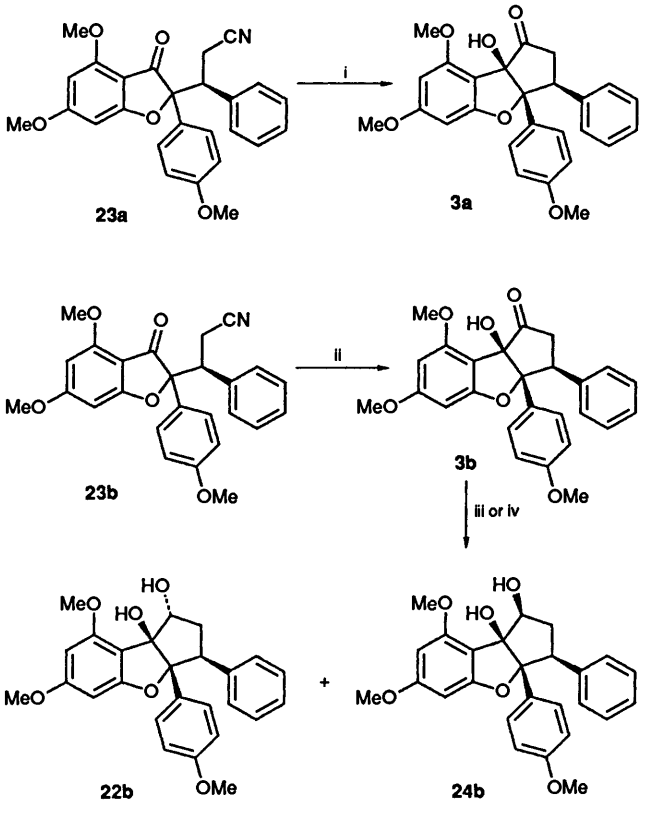
Table 3 Michael reactions to produce keto aldehydes **6a, b** from benzofuranone **8**

Cinnamaldehyde	Reaction conditions	Isolated yield (%)	Ratio **6a**:**6b**
trans	LDA, THF, −78 °C then 2 h at room temp.	44	1:1
trans	LDA, THF, −78 °C then −78 °C → room temp. over 2 d then 2 d at room temp.	39	1.75:1
cis	LDA, THF, −78 °C then 2 d at room temp.	0	—
trans	Triton B, Bu^{t}OH, 50 °C 2.5 h (0.22 mol dm^{-3})	60	1:1
trans	Triton B, Bu^{t}OH, 50 °C 2.5 h (0.04 mol dm^{-3})	69	1:2.25

Table 4 Reductive cyclisation reactions of keto aldehydes **6a, b**

Reaction conditions	Starting material[a]	Product [Yield (%)] results
Zn–Me_3SiCl [18]	**6a, b**	multi-component mixture
Zn–$TiCl_4$ [20]	**6a, b**	extensive decomposition
Mg(Hg)–$TiCl_4$ [19]	**6a**	**22a** (22)
$LiAlH_4$–$CpTiCl_3$ [19]	**6a, b**	**22a** (21)[b] + **22b** (26)[b] + acyclic reduced products (14)
SmI_2 [16]	**6a, b**	**22a** (29)[b] + **22b** (33)[b]
	6a, b, 10:90	**22a** (9) + **22b** (58)

[a] Approx. 1:1 ratio unless otherwise stated. [b] These are the best yields obtained for these reactions; lower yields were obtained on other occasions.

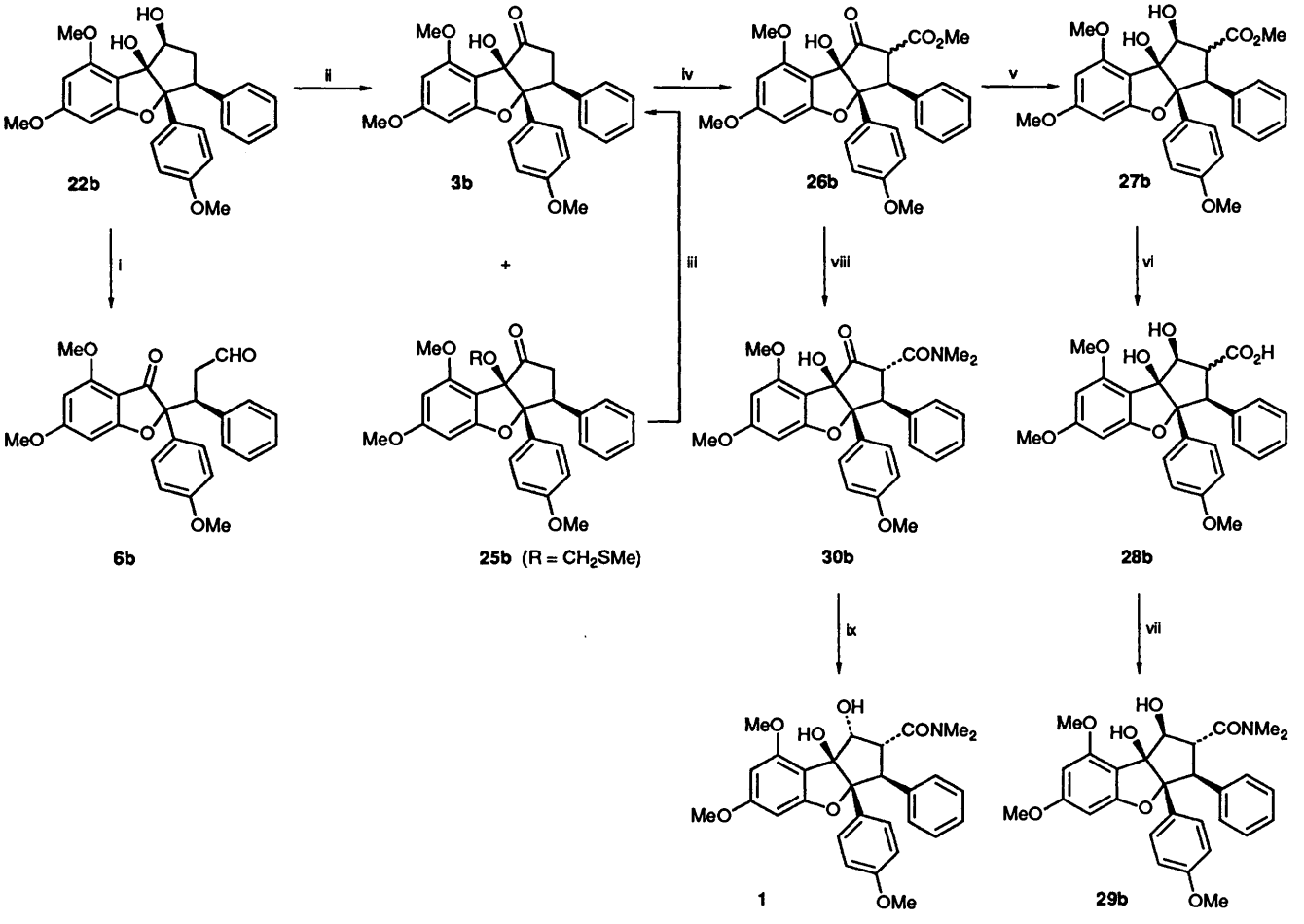


Scheme 4 *Reagents:* i, SmI_2 (60–80%); ii, SmI_2 (*ca.* 13.5%); iii, DIBAL, THF (99.5%); iv, $NaBH_4$, MeOH (**22b**:**24b** *ca.* 1:1, 93%)

nitriles were used by Kraus and Sy in their synthesis of rocaglamide analogue **2**.[4] We prepared nitriles **23a, b** (*ca.* 2.3:1 ratio) following Kraus and Sy's procedure and were able to separate the diastereoisomers and study their individual reactions with samarium iodide. It is interesting to note that, in our hands, nitrile **23a**, corresponding to aldehyde **6a**, also undergoes SmI_2 coupling efficiently (60–80%) to give ketone **3a**, identical (by ^1H NMR spectroscopy) with the sample prepared in Scheme 2 whereas the β-phenyl nitrile **23b**, corresponding to aldehyde **6b**, gives much lower yields of the required coupled product (< 13.5% in a very messy reaction). This observation accords with Kraus and Sy's report[4] that cyclisation of a diastereoisomeric mixture of nitriles **23a, b** gave a 5:1 product mixture and that they used the major isomer to prepare rocaglamide isomer **2**. The decision to study the pinacol coupling reactions of the keto aldehydes **6a, b** in our route was therefore extremely fortuitous. With small quantities of ketone **3b** in hand we briefly investigated its reduction reactions to produce the de-amido rocaglamide analogue **24b** shown in Scheme 4. Reduction of ketone **3b** using DIBAL gave the previously obtained alcohol **22b** in a highly stereoselective process. Reduction using sodium borohydride, however, gave an inseparable mixture (*ca.* 1:1) of alcohols **22b** and the required **24b** in high yield.

With the pinacol coupling methodology established we were then in a position to complete the synthesis of rocaglamide **1** and 1-*epi*-rocaglamide **29b** (Scheme 5). Diols **22a** and **22b** can be readily separated by chromatography but to our great consternation, oxidation of diol **22b** with pyridinium chlorochromate gave an almost quantitative yield of keto aldehyde **6b**. Similar chromium-induced cleavage reactions have been observed before.[21] The required ketone **3b** was obtained by use of the Swern oxidation procedure. Small quantities (10–15%) of the methylthiomethyl ether **25b** were also isolated but they could be hydrolysed[22] to give additional quantities of **3b**. The next challenge involved the introduction of the dimethylcarboxamido substituent. All attempts to effect this transformation directly by treatment of the enolate derived from **3b** (or from the *O*-silylated derivative of **3b**) with carbamoyl chloride or $NCCONMe_2$, proved unsuccessful. We therefore used the CS_2-based procedure utilised by Kraus and Sy.[4]. Thus, silylation of ketone **3b**, followed by enolate formation, sequential addition of carbon disulfide and iodomethane, and treatment with sodium methoxide gave β-keto ester **26b**, which exists as a 65:35 keto–enol mixture, in good overall yield. The direct conversion of ketone **3b** into the bis(thiomethyl)methylene adduct could also be achieved in 41% yield using CS_2–KF/Al_2O_3–MeI.[23] This procedure, which has not been optimised, avoids the need for hydroxy protection and for the use of LDA–HMPA.

Surprisingly, in view of published[5,24] results and the reduction studies referred to above (Scheme 3), reduction of β-keto ester **26b** using $Me_4NBH(OAc)_3$ or sodium borohydride gave only the 1β-alcohol **27b**. In the former process only the β-methoxycarbonyl epimer was obtained whereas sodium borohydride gave a mixture of methoxy carbonyl epimers (*ca.* 1:1). The fact that intramolecular hydride delivery is apparently not occurring in this transformation when $Me_4NBH(OAc)_3$ is employed is of interest given the reliability of this reagent for the reduction of acyclic β-hydroxy ketones.[24] However, these observations enabled us to prepare 1-*epi*-rocaglamide **29b** as outlined in Scheme 5. Saponification of ester **27b** produced acid **28b** which gave 1-*epi*-rocaglamide **29b** after DCC (dicyclohexylcarbodiimide) coupling with dimethylamine·HCl (in order to achieve reproducibility in this reaction it was necessary to use freshly sublimed amine hydrochloride).



Scheme 5 *Reagents:* i, $PyH{\cdot}CrO_3Cl$, CH_2Cl_2 (93%); ii, $(COCl)_2$, DMSO, Et_3N (**23b**, 81% + **25b**, 15%); iii, $HgCl_2$, aq. MeCN (50% +45% unchanged starting material); iv, (*a*) TMSOTf (*b*) LDA, HMPA, CS_2 then MeI (*c*) MeONa, THF (>55% from **3b**); v, $NaBH_4$, MeOH (76%) or $Me_4NBH(OAc)_3$, AcOH–MeCN (68%); vi, KOH, aq. MeOH (quant.); vii, $Me_2NH{\cdot}HCl$, DMAP, DCC (70%); viii, Me_2NLi, THF (89%); ix, $Me_4NBH(OAc)_3$, AcOH–MeCN (81%)

Table 5 Selected NMR spectroscopic data ($CDCl_3$) for rocaglamide and its isomers

	δ_H (*J*/Hz)			
	1-H	2-H	3-H	NMe_2
2,3-Diepi **2**[4]	4.82	3.57	4.25 ($J_{1,2}$ 10; $J_{2,3}$ 12)	2.89, 2.99
1-Epi **29β**	4.78	3.81	3.91 ($J_{1,2}$ 7.5; $J_{2,3}$ 13.4)	2.87, 3.27
Natural **1** *	4.93	4.05	4.55 ($J_{1,2}$ 6.5; $J_{2,3}$ 13.5)	2.94, 3.32
Synthetic **1**	4.93	4.04	4.54 ($J_{1,2}$ 6.5; $J_{2,3}$ 13.5)	2.93, 3.31

Natural **1**[4] (Synthetic **1**) 169 (169.5) 163.5 (163.9) 161 (161.1) 158 (158.6) 157.5 (157.2) 138.3 (137.6) 129 (128.9) 128 (127.8) 128 (127.7) 126.5 (127.1, 126.3) 112.8 (112.7) 108 (107.6), 101.5 (101.5) 93.8 (94) 92.8 (92.5) 89 (89.3) 78.5 (78.6) 56 (56) 56 (55.6) 55.5 (55.6) 55 (55) 47 (47.6) 36.9 (37) 35.7 (35.7)

After considerable experimentation β-keto ester **26b** was converted into β-keto amide **30b** using $LiNMe_2$ in THF.[25] Other methods such as Weinreb's $Me_2NAlMeCl$ reagent[26] and $Me_2NH{\cdot}DMAP$[27] were unsuccessful. Compound **30b** exists exclusively in the keto form and predominantly as a single diastereoisomer, presumably the α-carboxamide shown. In this system the final reduction was achieved with high stereoselectivity using $Me_4NBH(OAc)_3$[5] giving racemic rocaglamide **1** as a white crystalline solid (m.p. 119–120 °C, lit.,[1] 118–119 °C) with ^1H NMR spectroscopic data identical with the natural material[4,*] and different to isomeric compounds (Table 5).

Experimental

^1H NMR spectra (δ_H) were recorded using JEOL PMX 60 and JEOL FX 400/Bruker WH 400 (unless otherwise stated) spectrometers. ^{13}C NMR spectra (δ_C) were recorded using JEOL EX 90/FX 100 and JEOL FX 400 (unless otherwise stated) spectrometers. Samples for NMR spectrometry were prepared as solutions in $CDCl_3$, containing tetramethylsilane as an internal standard, unless otherwise stated. *J*-values are given in Hz. IR spectra (ν_{max}) were recorded on a Perkin-Elmer FT IR 1720X spectrophotometer as neat films (liquid samples) or emulsions in Nujol (solid samples). Mass spectra were recorded on a Kratos MS 25 (low resolution) or a Kratos VG ZAB-1F (high resolution) instrument. Light petroleum refers to the fraction of boiling range 40–60 °C, which was redistilled before use. Diethyl ether and THF were dried over sodium-benzophenone ketyl and distilled immediately before use. Dry DMSO (dimethyl sulfoxide) and CH_2Cl_2 were distilled from CaH_2 and stored over 4 Å molecular sieves. Butyllithium (in hexane) was purchased from Aldrich Chemical Company and was standardised at regular intervals using the double

* The ^1H NMR spectroscopic data for natural rocaglamide was kindly provided by Dr. J. P. Pachlatko of Ciba-Geigy, Basle, Switzerland.

titration method.[28] Other reagents were purchased from the Aldrich Chemical Company and used as received. Compounds **13**[10] and **23b**[4] were prepared by literature procedures. Moisture sensitive reactions were carried out under a nitrogen atmosphere using flame-dried apparatus. De-oxygenation of solvents, where specified, was carried out as follows. The stirred solvent was subjected to three cycles of evacuation (30 s), refilling with oxygen-free nitrogen. Sonications were performed using a Hilsonic bath. Standard extractive work-up refers to 2/3 extractions with the specified solvent, washing of the combined organic layers with water, drying ($MgSO_4$) and removal of the solvent on a rotary evaporator. Analytical thin layer chromatography (TLC) was performed on Merck 5554 aluminium-backed silica gel plates. Flash chromatography refers to the method described by Still *et al.*[29] M.p.s were recorded on a Kopfler hot-stage melting point apparatus and are uncorrected.

4,6-*Dihydroxy*-2-(4-*methoxyphenyl*)*benzofuran*-3(2H)-*one* **14**.[7]—A solution of the cyanohydrin **13**[10] (9.1 g, 55.8 mmol) and phloroglucinol **12** (dried *in vacuo* at 110 °C, 3 h) (7.7 g, 61.1 mmol) was stirred in dry ether (150 cm^3) at 0 °C while dry HCl gas was passed through for 1 h (a thick orange precipitate settled after 30 min). The mixture was then stored at 4 °C for 3 d, after which time the ether was decanted and the precipitate washed with dry ether (3 × 30 cm^3). The washed precipitate was dissolved in 0.1 mol dm^{-3} aqueous HCl (100 cm^3) and the solution refluxed for 3 h, during which time a white solid had settled. The solid was filtered, washed (water) and dried *in vacuo* to give the title compound **14** (11.5 g, 76%) as a white powder, m.p. 200–202 °C (lit.,[7] m.p. 216 °C) which was homogeneous by TLC (CH_2Cl_2–EtOH, 95:5, R_f 0.6). The product showed identical spectral parameters with those reported.[7] This reaction was not always reproducible, but generally yields of **14** were higher than 40%. When cyanohydrin **13** was replaced by the corresponding α-chloro nitrile,[7] compound **14** was obtained in only *ca.* 16% yield, the major reaction product being *lactone* **17** (25%) which was isolated as a white solid, m.p. 188–192 °C; R_f 0.71 (AcOEt); ν_{max}/cm^{-1} 3340, 1800 and 1625; δ_H(PMX 60; CD_3OD) 3.72 (3 H, s), 4.80 (3 H, s, 1 H exch.), 6.06 (1 H, d, *J* 2), 6.14 (1 H, d, *J* 2), 6.82 and 7.04 (4 H, AA'BB', *J* 8.5) (Found: C, 63.2; H, 5.2. $C_{15}H_{12}O_5 \cdot CH_3OH$ requires C, 63.15; H, 5.30%).

4,6-*Dimethoxy*-2-(4-*methoxyphenyl*)*benzofuran*-3(2H)-*one* **8**.—To a de-oxygenated suspension of potassium carbonate (11.60 g, 84 mmol) and dimethyl sulfate (10.66 g, 84.5 mmol) in acetone (60 cm^3) under nitrogen was added benzofuranone **14** (3.85 g, 14.1 mmol) in de-oxygenated acetone (90 cm^3) *via* a double-tipped needle. The mixture was heated at reflux under nitrogen for 30 min, methanol (15 cm^3) was added to destroy excess dimethyl sulfate and the mixture was refluxed for 1 h more. The red mixture was concentrated to an oil on a rotary evaporator, and methanol (75 cm^3) was added. The resultant clear solution was heated with vigorous stirring, whilst aqueous HCl (5% solution, 50 cm^3) was added dropwise through the reflux condenser at a slow enough rate to maintain clarity and refluxing was continued for 3 h. The solution was allowed to cool overnight whilst maintaining vigorous stirring during which time the product precipitated. Filtration and oven-drying *in vacuo* (6 h, 70 °C, 12 mmHg) gave *compound* **8** (3.84 g, 91%) as NMR pure white crystals, m.p. 117–123 °C. Recrystallisation (MeOH) provided analytically pure material (3.55 g, 84%), m.p. 120–122 °C; R_f 0.35 (CH_2Cl_2–EtOH, 98:2); ν_{max}/cm^{-1} 1700, 1620 and 1590; δ_H (PMX 60) 3.74 (3 H, s), 3.82 (3 H, s), 3.84 (3 H, s), 5.38 (1 H, s), 5.98 (1 H, d, *J* 2), 6.18 (1 H, d, *J* 2), 6.82 and 7.28 (4 H, AA'BB' *J* 8.5); *m/z* 300 (M^+) (Found: C, 67.9; H, 5.4. $C_{17}H_{16}O_5$ requires C, 67.99; H, 5.37%).

If the de-oxygenation procedure was not employed, chromatography (AcOEt–light petroleum, 1:9 to 7:3) of the crude reaction mixture gave 2-*hydroxy*-4,6-*dimethoxy*-2-(4-*methoxyphenyl*)*benzofuran*-3(2H)-*one* **19** as colourless crystals, m.p. 117.5–119 °C (Pr^i_2O) in yields up to 10%; R_f 0.4 (ether–light petroleum, 4:1); ν_{max}/cm^{-1} 1665 and 1635; δ_H(PMX 60) 3.46 (3 H, s), 3.81, 3.83 (6 H, 2 s), 5.86 (1 H, d, *J* 2), 6.15 (1 H, d, *J* 2), 6.96 and 7.86 (4 H, AA'BB', *J* 8.5) and 12.6 (1 H, s, exch.); δ_C(FX 100) 55.5 (q), 55.7 (q), 55.8 (q), 91.3 (d), 93.9 (d), 103.7 (s), 114.1 (d), 126.0 (s), 131 3 (d), 162.6 (s), 164.0 (s), 167.6 (s), 168.6 (s), 190.1 (s) and 197.3 (s) [Found: C, 64.4; H, 5.1%; M^+ (EI), 316.0947. $C_{17}H_{16}O_6$ requires C, 64.54; H, 5.10%; M^+, 316.094 69].

2-[2-(1,3-*Dithian*-2-*yl*)-1-*phenylethyl*]-4,6-*dimethoxy*-2-(4-*methoxyphenyl*)*benzofuran*-3(2H)-*one* **5**.—De-oxygenated toluene (7 cm^3) was added *via* a cannula to a mixture of granular sodium hydride (54 mg, 2.26 mmol, 4.5 equiv.), benzofuranone **8** (150 mg, 0.5 mmol) and alkyl iodide **11** (790 mg, 2.25 mmol, 4.5 equiv.) under nitrogen. The suspension was stirred at reflux for 1 h when a new white precipitate had formed. The reaction mixture was allowed to cool, filtered to remove solids, concentrated under reduced pressure and flash chromatographed (Et_2O–light petroleum, 1:3 to 4:1) to give recovered alkyl iodide **11** (477 mg) as a brown oil heavily contaminated by its dehydroiodination product, a colourless oil (42 mg) containing some *O*-alkylated product **18** (*ca.* 5%; other reactions gave higher amounts of **18** which was fully characterised) and the *title benzofuranone* **5** (inseparable mixture of diastereoisomers, α:β *ca.* 1:1.35 by ^1H NMR spectroscopy) (158 mg, 61%) as an amorphous foam, R_f 0.4 (ether–light petroleum, 4:1); ν_{max}/cm^{-1} 1700 and 1600; δ_H 1.71–1.85, 1.91–2.10, 2.24–2.38, 2.48–2.81 (8 H, 4 m), 3.38 (β-diastereoisomer, 0.43 H, d, *J* 3.1) and 3.41 (α-diastereoisomer, 0.57 H, d, *J* 2.6), 3.66, 3.84, 3.85 (β-diastereoisomer, 3 × 1.3 H, 3 s), 3.655, 3.78, 3.89 (α-diastereoisomer, 3 × 1.7 H, 3 s), 3.88–4.00 (1 H, m), 5.77 (β-diastereoisomer, 0.43 H, d, *J* 1.8) and 5.98 (α-diastereoisomer, 0.57 H, d, *J* 1.8), 6.21 (β-diastereoisomer, 0.43 H d, *J* 1.8) and 6.30 (α-diastereoisomer, 0.57 H, d, *J* 1.8), 6.62, 6.88, 7.33 and 7.62 (total 4 H, 2 AA'BB', *J* 9.0), 7.07–7.24 (4 H, m) and 7.30–7.36 (1 H, m); δ_C(FX 100; mixture of diastereoisomers) 25.8, 26.3, 28.8, 29.2, 29.7, 34.9, 43.7, 44.1, 48.9, 50.5, 55.1, 55.9, 88.3, 88.7, 92.6, 93.0, 94.5, 103.7, 104.3, 113.1, 113.9, 126.1, 127.0, 127.7, 128.0, 128.8, 129.1, 129.6, 136.6, 137.5, 158.7, 159.1, 159.2, 169.7, 174.3, 174.4, 195.2 and 195.7 [Found: C, 66.4; H, 5.8; S, 12.1% M^+ (EI), 522.1532. $C_{29}H_{30}O_5S_2$ requires C, 66.65; H, 5.79; S, 12.25%; *M*, 522.153 47]. The ratio of *C*-alkylated to *O*-alkylated product varied if other alkylation conditions were employed (see text).

8b-*Hydroxy*-6,8-*dimethoxy*-3a-(4-*methoxyphenyl*)-3-*phenyl*-2,3,3a,8b-*tetrahydro*-1H-*cyclopenta*[b]*benzofuran*-1-*spiro*-2'-(1',3'-*dithiane*) **16a**, **b**.—Optimum reaction conditions only are presented below. For a full list of conditions used, see Table 1. Butyllithium in hexane (2.58 mol dm^{-3}; 6.05 cm^3, 15.6 mmol, 1.3 equiv.) was added dropwise to a well stirred mixture of the dithianylbenzofuranone **5** (6.26 g, 12.0 mmol) and HMPA (hexamethylphosphoramidite) (4.00 cm^3, 24.0 mmol, 2.0 equiv.) in dry THF (70 cm^3) at −96 °C (methanol–liq. N_2 bath) under nitrogen at such a rate to keep the internal temperature below −90 °C. The brown mixture was stirred at this temperature for 10 min, allowed to warm to room temp. over 4 h and acidified with aqueous 5% HCl. Standard extractive work-up (Et_2O) and precipitation from diisopropyl ether gave a first crop of the *title compound* **16a**, **b** (3.43 g, 55%) as an amorphous pale yellow foam, m.p. 201–209 °C; R_f 0.26 (Et_2O–light petroleum, 1:1); ν_{max}/cm^{-1} 3550, 1610 and 1500; δ_H(FX 400) 1.97–2.11 (2 H, m), 2.48–2.70 (1 H, m), 2.87–3.14 (4 H, m), 3.05 (0.5 H, d, *J* 13.4), 3.43 (0.5 H, d, *J* 14.2), 3.64 (1.5 H, s), 3.78 (3 H, s), 3.80 (1.5 H, s),

3.84 (1.5 H, s), 3.843 (1.5 H, s), 4.28 (0.5 H, dd, *J* 5.2 and 13.4), 4.51 (0.5 H, dd, *J* 5.9 and 14.2), 6.03 (0.5 H, d, *J* 1.8), 6.06 (0.5 H, d, *J* 2.1), 6.15 (0.5 H, d, *J* 1.8), 6.25 (0.5 H, d, *J* 2.1), 6.58 and 6.87 (2 H, AA'BB', *J* 8.9), 7.04 and 7.41 (2 H, AA'BB', *J* 8.6), 7.04–7.09 (2 H, m) and 7.12–7.20 (3 H, m); δ_C(FX 100) 25.0 (m), 25.5 (m), 27.3 (m), 28.0 (m), 28.8 (m), 41.1 (t), 44.0 (t), 51.7 (d), 52.7 (d), 54.8 (q), 55.0 (q), 55.4 (q), 64.6 (s), 65.4 (s), 88.0 (d), 91.7 (d), 93.7 (s), 94.4 (s), 103.0 (s), 105.9 (s), 107.4 (s), 112.1 (d), 113.1 (d), 125.9 (s), 126.7 (s), 127.6 (s), 127.9 (s), 128.2 (s), 128.5 (s), 128.9 (s), 129.2 (s), 137.2 (s), 138.4 (s), 158.5 (s), 158.8 (s), 161.5 (s), 163.4 (s) and 163.6 (s) [Found: C, 66.7; H, 5.85; S, 12.3%; M^+ (EI), 522.1533. $C_{29}H_{30}O_5S_2$ requires C, 66.65; H, 5.79; S, 12.25%; *M*, 522.153 47].

Concentration of the mother liquors under reduced pressure and flash chromatographic purification (Et_2O–light petroleum, 2:1) gave a further 1.86 g of product (total yield 5.29 g, 84.5%). The diastereoisomeric ratios of both crops of product **16a, b** and of the starting material **5** were almost identical (α:β *ca.* 1:1.3) by ^{1}H NMR spectroscopic analysis.

8b-*Hydroxy*-6,8-*dimethoxy*-3a-(4-*methoxyphenyl*)-3-*phenyl*-2,3-3a,8b-*tetrahydrocyclopenta*[b]*benzofuran*-1-*one* **3a**.—(*a*) *By mercury*(II) *chloride-mediated hydrolysis of dithiane compound* **16a, b**. A solution of tricyclic dithiane **16a, b** (156 mg, 0.30 mmol, *ca.* 1:1 mixture of diastereoisomers) in acetonitrile (2 cm^3) was added to a well-stirred solution of mercury(II) chloride (168 mg, 0.62 mmol) in acetonitrile–water (1:2, 6 cm^3) containing calcium carbonate (62 mg, 0.62 mmol) under nitrogen. The mixture was refluxed for 1 h, when TLC analysis (Et_2O–light petroleum, 4:1) showed very little starting material. The cooled reaction mixture was filtered through a plug of Celite and washed through with ether. Washing with saturated aqueous ammonium acetate and the standard extractive work-up (ether) and flash chromatography (ether–petroleum, 1:1 to 4:1, then dichloromethane–ethanol, 49:1) gave impure starting material **16a, b** as a yellow foam (27 mg) followed by the *title compound* **3a** (41 mg, 32%) as an amorphous white solid, m.p. 146–147 °C (ether); R_f 0.3 (ether–petroleum, 4:1); ν_{max}/cm^{-1} 3500, 1745, 1600br and 1500; δ_H 2.70 (1 H, dd, *J* 15.7 and 6.7), 3.29 (1 H, dd, *J* 15.7 and 14.9), 3.50 (1 H, s), 3.76, 3.77, 3.78 (9 H, 3 s), 4.02 (1 H, dd, *J* 14.9 and 6.7), 6.00 (1 H, d, *J* 2.0), 6.14 (1 H, d, *J* 2.0), 6.88 and 7.32 (4 H, AA'BB', *J* 8.9), 7.05–7.11 (2 H, m) and 7.23 (3 H, m) [Found (EI): M^+, 432.1575. $C_{26}H_{24}O_6$ requires M^+, 432.1573].

(*b*) *By lead*(IV) *oxide-mediated hydrolysis of dithiane compound* **16a, b**. To a solution of lead(IV) oxide (140 mg, 0.585 mmol) in THF (1 cm^3) and water (0.02 cm^3) under nitrogen at room temp. was added boron trifluoride–diethyl ether (0.145 cm^3, 167 mg, 1.2 mmol). A solution of compound **16a, b** (205 mg, 0.39 mmol, an ~1:1 diastereoisomeric mixture) in THF (1 cm^3) was then added dropwise. A slightly exothermic reaction took place. After stirring for 10 min, the reaction was quenched by addition of aqueous 1 mol dm^{-3} HCl (5 cm^3). Standard extractive work-up (dichloromethane) gave a brown oil. Flash chromatography (ether–light petroleum, 4:1) gave ketone **3a** (62.3 mg, 37%), which was identical with the previous mixture by ^{1}H NMR spectroscopy, followed by the *conjugated ketone* **21** (35.2 mg, 21%), R_f 0.25 (ether–light petroleum, 4:1); m.p. 176–177 °C; ν_{max}/cm^{-1} 3540, 3450, 1715, 1600 and 1530; δ_H 3.08 (1 H, s), 3.74 (3 H, s), 3.79 (3 H, s), 3.81 (3 H, s), 6.05 (1 H, d, *J* 2.0), 6.14 (1 H, d, *J* 2.0), 6.88 and 7.30 (4 H, AA'BB', *J* 8.9), 6.90 (1 H, s), 7.30–7.38 (3 H, m) and 7.63–7.69 (2 H, m) [Found (EI): M^+, 430.1416. $C_{26}H_{22}O_6$ requires *M*, 430.141 64].

3-[4,6-*Dimethoxy*-2-(4-*methoxyphenyl*)-3-*oxo*-2,3-*dihydrobenzofuranan*-2-*yl*]-3-*phenylpropanal* **6a, b**.—(*a*) *From cinnamaldehyde and benzofuranone* **8** *by a Michael reaction*. Benzofuranone **8** (5.75 g, 19.15 mmol) was suspended in *tert*-butyl alcohol (500 cm^3). The mixture was evacuated and de-gassed with nitrogen three times. The suspension was then heated to 50 °C under nitrogen and benzyltrimethylammonium hydroxide in methanol (40%, 0.47 cm^3, 188 mg, 1.12 mmol) was added, followed by the rapid addition of cinnamaldehyde (4.8 cm^3, 5.03 g, 38.1 mmol). The mixture was stirred for 2.5 h at 50 °C, allowed to cool to room temp. and concentrated to a brown oil on a rotavapor. Addition of 1 mol dm^{-3} hydrochloric acid (50 cm^3) followed by standard extractive work-up (dichloromethane) gave a yellow oil. Flash chromatography (ether–light petroleum, 4:1) gave a diastereoisomeric mixture of keto aldehydes **6a, b** (*ca.* 1:2.25 by ^{1}H NMR spectroscopy) (5.69 g, 69%) as a white powder (Found: C, 71.8; H, 5.5. $C_{26}H_{24}O_6$ requires C, 72.21; H, 5.59%).

Careful, repeated flash chromatography (ether–light petroleum, 4:1) allowed separation of the two diastereoisomers **6a** and **6b**. Keto aldehyde **6a** was obtained as white crystals, m.p. 213–214 °C (ether–light petroleum, 4:1); R_f 0.25 (ether–light petroleum, 4:1); ν_{max}/cm^{-1} 1730 and 1620; δ_H 2.65 (1 H, dd, *J* 3.7 and 16.8), 3.00 (1 H, ddd, *J* 2.9, 11.0 and 16.8), 3.69 (6 H, s), 3.89 (3 H, s), 4.14 (1 H, dd, *J* 3.7 and 11.0), 5.99 (1 H, d, *J* 1.8), 6.30 (1 H, d, *J* 1.8), 6.68 and 7.39 (4 H, AA'BB', *J* 8.9), 7.08–7.18 (5 H, m) and 9.47 (1 H, d, *J* 1.8). Keto aldehyde **6b** was obtained as a white solid, m.p. 74–75 °C; R_f 0.3 (ether–light petroleum, 4:1); ν_{max}/cm^{-1} 1750 and 1710; δ_H 2.68 (1 H, ddd, *J* 1.2, 4.3 and 17.3), 3.03 (1 H, ddd, *J* 2.1, 10.5 and 17.3), 3.69 (3 H, s), 3.78 (3 H, s), 3.84 (3 H, s), 4.20 (1 H, dd, *J* 4.3 and 10.7), 5.80 (1 H, d, *J* 1.8), 6.21 (1 H, d, *J* 1.8), 6.89 and 7.65 (4 H, AA'BB', *J* 8.9), 7.06–7.16 (3 H, m), 7.30–7.32 (2 H, m) and 9.39 (1 H, dd, *J* 1.2 and 2.1).

(*b*) *From cinnamaldehyde and benzofuranone* **8** *by a Michael reaction under concentrated conditions*. Procedure (*a*) was repeated using benzofuranone **8** (10.0 g, 33.3 mmol), *tert*-butyl alcohol (150 cm^3), benzyltrimethylammonium hydroxide in methanol (40%, 1.8 cm^3, 720 mg, 4.29 mmol) and cinnamaldehyde (4.4 cm^3, 4.91 g, 34.9 mmol). The reaction and work-up were carried out as in (*a*). Flash chromatography (ether–light petroleum, 4:1) gave a diastereoisomeric mixture of keto aldehydes **6a, b** (*ca.* 1:1 by ^{1}H NMR spectroscopy) (8.64 g, 60%) as a white powder.

(*c*) *By equilibration procedure*. To a stirred solution of keto aldehyde **6a** (1.125 g, 2.60 mmol) in de-gassed *tert*-butyl alcohol (150 cm^3) at 50–55 °C under nitrogen was added benzyltrimethylammonium hydroxide in methanol (40%; 0.061 cm^3, 24 mg, 0.15 mmol). The reaction was stirred at the same temperature for 3 h, cooled to room temp. and the solvent evaporated on a rotavapor. Addition of 1 mol dm^{-3} hydrochloric acid (50 cm^3) followed by standard extractive work-up (dichloromethane) gave a yellow oil. Flash chromatography (ether–light petroleum, 4:1) gave the two diastereoisomers **6a** and **6b** (202 mg, 18% and 346 mg, 31% respectively) identical with the previous samples by ^{1}H NMR spectroscopy.

(*d*) *By hydrolysis of the corresponding dithiane compound* **5**. A solution of dithianylbenzofuranone **5** (2.20 g, 4.21 mmol, α:β *ca.* 1:1.35 diastereoisomeric mixture) in acetonitrile (40 cm^3) was added at room temp. under nitrogen to a well stirred suspension of mercury(II) chloride (5.02 g, 18.5 mmol) and calcium carbonate (1.85 g, 18.5 mmol) in acetonitrile–water (1:1, 40 cm^3). The mixture was refluxed for 24 h, allowed to cool to room temp., filtered through a plug of Celite and washed through with ether (100 cm^3). The organic phase was washed with saturated aqueous ammonium acetate (40 cm^3) and water (40 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure to an oil which after flash chromatographic separation (ether–light petroleum, 4:1) gave a white solid **6a, b** (1.49 g, 82%, *ca.* 1:1.3 diastereoisomeric mixture) which was identical with the previous mixture by ^{1}H NMR spectroscopy.

(*e*) *By oxidative cleavage of diol* **22b**. To a solution of

pyridinium chlorochromate (140 mg, 0.65 mmol) in dichloromethane (1 cm^3) was added at room temp. under nitrogen a solution of diol **22b** (187 mg, 0.43 mmol) in dichloromethane (1 cm^3). After stirring for 1 h at room temp. anhydrous ether (20 cm^3) was added and then decanted from the resulting heavy brown oil. The oil was washed twice with anhydrous ether (20 cm^3) and the combined organic solution was filtered through a short plug of silica gel, evaporation of the solvents giving a white solid (175 mg, 94%). ^1H NMR spectroscopy showed it to be only keto-aldehyde **6b**.

6,8-*Dimethoxy*-3a-(4-*methoxyphenyl*)-3-*phenyl*-2,3,3a,8b-*tetrahydrocyclopenta*[b]*benzofuran*-1,8b(1H)-*diol* **22a** *and* **22b**.—(*a*) *By samarium*(II) *iodide coupling of keto aldehydes* **6a, b**. A solution of diiodoethane (1.83 g, 6.5 mmol) in THF (7 cm^3) was added dropwise under nitrogen to flame-dried samarium powder (1.92 g, 12.8 mmol). After stirring for 0.5 h at room temp. the dark blue mixture was sonicated for 2 h. Freshly distilled benzene (25 cm^3) was then added and the sonication was continued for a further 2 h. Keto aldehyde **6a, b** (1.40 g, 3.24 mmol, **6a**:**6b** *ca.* 1:9) in freshly distilled benzene (45 cm^3) was then added quickly. Sonication was continued for a further 3 h during which time the colour changed from blue to yellow or dark grey. The solution was allowed to stand overnight. The reaction was quenched by the addition of 1 mol dm^{-3} aqueous HCl solution (30 cm^3). Standard extractive work-up (ether) gave a yellow foam. Flash chromatography (ether–light petroleum, 4:1) gave *diol* **22a** (130 mg, 9%) as colourless crystals (ether–petroleum, 4:1), m.p. 237–238 °C; R_f 0.5 (ether–petroleum, 4:1); ν_{max}/cm^{-1} 3550 and 1620; δ_H 2.13 (1 H, ddd apparent dt, *J* 3.2 and 13.5), 2.21 (1 H, dd, *J* 6.2 and 7.2), 3.78 (3 H, s), 3.807 (3 H, s), 3.809 (3 H, s), 4.26 (1 H, dd, *J* 6.2 and 13.5), 4.57 (1 H, d, *J* 3.2), 6.03 (1 H, d, *J* 2.1), 6.09 (1 H, d, *J* 2.1), 6.91 and 7.42 (4 H, AA′BB′, *J* 8.9), 6.99–7.02 (2 H, m) and 7.17–7.20 (3 H, m); δ_C 163.72, 162.22, 158.97, 157.47, 137.97, 129.87, 128.85, 128.13, 127.68, 126.62, 113.49, 106.70, 100.87, 91.83, 89.62, 87.83, 74.37, 55.59, 55.44, 55.20, 53.06 and 34.76 (Found: C, 71.7; H, 6.0. $C_{26}H_{26}O_6$ requires C, 71.87; H, 6.03%). This was followed by *diol* **22b** (816 mg, 58%) as a white solid, m.p. 148.5–149.5 °C; R_f 0.45 (ether–light petroleum, 4:1) ν_{max}/cm^{-1} 3440 and 1610; δ_H 2.36 (1 H, ddd, *J* 7.9, 13.5 and 14.6), 2.56 (1 H, br s), 2.62 (1 H, dd, *J* 6.7 and 13.5), 3.12 (1 H, d, *J* 3.2), 3.45 (1 H, dd, *J* 6.7 and 14.6), 3.70 (3 H, s), 3.83 (3 H, s), 3.84 (3 H, s), 4.80 (1 H, dt, *J* 2.6 and 7.9), 6.09 (1 H, d, *J* 2.0), 6.25 (1 H, d, *J* 2.0), 6.69 and 7.19 (4 H, AA′BB′, *J* 9.0), 6.98–7.01 (2 H, m) and 7.05–7.11 (3 H, m); δ_C 153.74, 160.05, 158.40, 157.67, 138.17, 128.63, 128.04, 127.60, 127.22, 126.25, 112.75, 110.58, 102.31, 92.23, 89.11, 86.35, 72.57, 55.60, 55.53, 55.00, 49.68 and 36.62; *m/z* 434 (M^+, 2.0%) (Found: C, 72.1; H, 6.1. $C_{26}H_{26}O_6$ requires C, 71.87; H, 6.03%). This reaction was not very reproducible, total yields of **22a, b** up to 67% were obtained but more commonly the yield ranged from 45 to 60% (see Table 4).

(*b*) *By titanium coupling of keto aldehydes* **6a, b**. A solution of $LiAlH_4$ (44 mg, 1.15 mmol) in ether (2 cm^3) was added dropwise at room temp. under N_2 and with stirring to a solution of cyclopentadienyltitanium trichloride (314 mg, 1.43 mmol) in THF (2 cm^3). The mixture was then heated for 30 min at 30–40 °C. After cooling to room temp., a solution of keto aldehyde **6a, b** (*ca.* 1:1) (108 mg, 0.25 mmol) in THF (1 cm^3) was added dropwise. The reaction mixture was stirred at room temp. for 3 h and then quenched by the addition of a saturated aqueous potassium carbonate (5 cm^3). The mixture was stirred for 30 min and then filtered through a plug of Celite and washed through with ether (10 cm^3) and dichloromethane (40 cm^3). Drying ($MgSO_4$) and removal of solvents under reduced pressure gave a yellow foam. Flash chromatography (ether–light petroleum, 4:1) gave a white solid (38 mg) containing diol **22a** (21%) contaminated with acyclic reduced starting material (14%), followed by diol **22b** (28.5 mg, 26%) as a white solid identical with the previous sample by TLC and ^1H NMR spectroscopy.

(*c*) *By amalgam coupling of keto aldehydes* **6a, b**. To a stirred suspension of Mg (195 mg, 3.9 mmol) in dry THF (3 cm^3) under N_2 and with stirring was added solid $HgCl_2$ (60 mg, 0.22 mmol) and the reaction mixture sonicated for 30 min. The solvent was then removed with a syringe and the remaining solid washed with dry THF (3 × 5 cm^3). The solid was then cooled to −10 °C and $TiCl_4$ (0.57 g, 3.0 mmol) added dropwise to give a yellow slurry. On addition of keto aldehyde **6a** (476 mg, 1.1 mmol) the reaction mixture turned to a dark brown colour. The reaction mixture was warmed to room temp. and stirred for a further 2 h. The reaction was then quenched by the addition of saturated aqueous potassium carbonate (25 cm^3). The mixture was stirred for 30 min, filtered directly through a plug of Celite and washed through with ether (30 cm^3) and dichloromethane (80 cm^3). Drying ($MgSO_4$) and removal of solvents under reduced pressure gave a yellow foam. Flash chromatography (ether–light petroleum, 4:1) gave a multitude of unknown compounds as well as diol **22a** as a white solid (107 mg, 22%) identical with the previous sample by ^1H NMR spectroscopy.

(*d*) *By diisobutylaluminium hydride reduction of the corresponding ketone* **3b**. To a solution of the ketone **3b** (52 mg, 0.12 mmol) in THF (10 cm^3) at −78 °C under nitrogen was added diisobutyl aluminium hydride in hexane (1 mol dm^{-3}; 0.6 cm^3, 0.6 mmol). The reaction mixture was stirred for 30 min at −78 °C, then allowed to warm to room temp. over 3 h. The reaction was quenched with aqueous 1 mol dm^{-3} HCl (15 cm^3). Standard extractive work-up (dichloromethane) followed by flash chromatography (ether–light petroleum, 4:1) gave pure *cis*-diol **22b** (52 mg, 99.5%) as evidenced by 400 MHz ^1H NMR spectroscopy.

(*e*) *By sodium borohydride reduction of ketone* **3b**. To a solution of ketone **3b** (100 mg, 0.23 mmol) in methanol (10 cm^3) at 0 °C under nitrogen was added solid sodium borohydride (132 mg, 3.5 mmol). The reaction mixture was stirred for 6 h at 0 °C, maintained at 5 °C overnight, then warmed to room temp. and stirred for a further 2 h. The reaction was then quenched with aqueous 1 mol dm^{-3} HCl (10 cm^3). Standard extractive work-up (dichloromethane) followed by flash chromatography (ether–light petroleum, 4:1) gave a mixture of diols **22b** and **24b** (93 mg, 0.21 mmol, 93%, *ca.* 1:1 by 60 MHz ^1H NMR spectroscopy), δ_H(PMX 60) 2.30–3.00 (2 H, m), 3.45 (1 H, t, *J* 7), 3.70 (3 H, s), 3.80 (6 H, s), 4.80 (0.5 H, t, *J* 7), 4.80 (0.5 H, t, *J* 7), 6.06 (1 H, d, *J* 2), 6.22 (1 H, d, *J* 2), 6.64 and 7.17 (4 H, AA′BB′, *J* 9), 7.03 (2 H, br s) and 7.09 (3 H, br s).

8b-*Hydroxy*-6,8-*dimethoxy*-3a-(4-*methoxyphenyl*)-3-*phenyl*-2,3,3a,8b-*tetrahydrocyclopenta*[b]*benzofuran*-1-*one* **3b**.—(*a*) *By Swern oxidation of diol* **22b**. Oxalyl chloride (0.262 cm^3, 381 mg, 3.0 mmol) was added to THF (10 cm^3) at −78 °C under nitrogen, followed by dropwise addition of DMSO (0.238 cm^3, 262 mg, 3.35 mmol) with vigorous stirring. Stirring was continued for 5 min and then a solution of diol **22b** (860 mg, 0.92 mmol) in THF (30 cm^3) was added dropwise. The mixture was stirred at −78 °C for 30 min, then triethylamine (3.5 cm^3, 2.97 g, 29.3 mmol) was added quickly. The solution was allowed to reach room temp. slowly and the reaction was quenched by addition of 1 mol dm^{-3} HCl (30 cm^3). Standard extractive work-up (dichloromethane) gave a white solid. Flash chromatography (light petroleum–ether, 4:1) gave methylthiomethyl-ether-protected ketone **25b** as a slightly yellow solid (145 mg, 15%), m.p. 80–81 °C; R_f 0.6 (ether–light petroleum, 4:1); ν_{max}/cm^{-1} 1750 and 1620; δ_H 1.62 (3 H, s), 2.85 (1 H, m), 3.05 (1 H, m), 3.63 (3 H, s), 3.83 (3 H, s), 3.86 (3 H, s), 3.65–4.00 (3 H, m), 6.15 (1 H, d, *J* 2), 6.35 (1 H, d, *J* 2), 6.65 (2 H, BB′ part of an AA′BB′, *J* 9) and 6.60–7.30 (7 H, m); *m/z* 492 (M^+, 2.4%)

followed by the *title ketone* **3b** as a white solid (690 mg, 81%), m.p. 150.5–151.5 °C; R_f 0.45 (ether–light petroleum, 4:1); ν_{max}/cm^{-1} 3450 and 1750; δ_H 2.97 (1 H, dd, *J* 12.2 and 19.6), 3.05 (1 H, dd, *J* 9.7 and 19.6), 3.08 (1 H, s), 3.70 (3 H, s), 3.82 (3 H, s), 3.84 (3 H, s), 3.89 (1 H, dd, *J* 10.0 and 12.3), 6.10 (1 H, d, *J* 2.0), 6.33 (1 H, d, *J* 2.0), 6.67 and 6.95 (4 H, AA'BB', *J* 8.9), 6.92–6.94 (2 H, m) and 7.09–7.13 (3 H, m); δ_C 210.59, 164.65, 161.14, 158.71, 158.40, 137.19, 127.95, 127.82, 126.74, 125.81, 113.05, 112.74, 106.50, 101.18, 92.56, 89.66, 88.70, 55.64, 55.51, 55.02, 48.51 and 39.78 (Found: C, 72.0; H, 6.0%; M^+ (EI), 432.1573. $C_{26}H_{24}O_6$ requires C, 72.20; H, 5.60%; *M*, 432.157 29).

(*b*) *By samarium*(II) *iodide-coupling of keto cyanide* **23b**. A solution of diiodoethane (388 mg, 1.4 mmol) in THF (2.2 cm^3) was added dropwise under nitrogen to flame-dried samarium powder (361 mg, 2.4 mmol). After sonicating for 1 h at room temp. the mixture was stirred for 30 min. The solution then turned dark blue in colour. After sonication for a further 4 h, freshly distilled benzene (40 cm^3) was added and the sonication was continued for a further 3 h. A solution of keto cyanide **23b**[4] (475 mg, 1.1 mmol) in freshly distilled benzene (40 cm^3) was then added quickly *via* a double-tipped needle. Sonication was continued for a further 1 h, by which time the solution had turned light yellow. The reaction was quenched by the addition of 1 mol dm^{-3} aqueous HCl (40 cm^3), standard extractive work-up (ether) giving a yellow foam. Flash chromatography (ether–light petroleum, 4:1) gave recovered starting material (36%) together with ketone **3b** as a white foam (64 mg, 13.5%) identical with the previous sample by ^1H NMR spectroscopy. This reaction was not reproducible, on subsequent trials no better yields than 12% could be achieved.

Methyl 8b-*Hydroxy*-6,8-*dimethoxy*-3a-(4-*methoxyphenyl*)-1-*oxo*-3-*phenyl*-2,3,3a,8a-*tetrahydrocyclopenta*[b]*benzofuran*-2-*carboxylate* **26b**.—(*a*) To a solution of ketone **3b** (158 mg, 0.365 mmol) in dry toluene (10 cm^3) at 0 °C under a nitrogen atmosphere was added diisopropylethylamine (0.17 cm^3, 126 mg, 0.98 mmol) dropwise, followed by the dropwise addition of trimethylsilyl trifluoromethanesulfonate (0.125 cm^3, 144 mg, 0.65 mmol). The reaction mixture was stirred at 0 °C for 30 min, allowed to warm to room temp., diluted with hexanes (100 cm^3) and filtered. The filtrate was concentrated under reduced pressure to give a light yellow solid. The crude silylated material was not purified further and was normally used immediately.

(*b*) Butyllithium in hexane (1.4 mol dm^{-3}; 1.1 cm^3, 1.5 mmol) was added dropwise to diisopropylamine (0.22 cm^3, 155 mg, 1.5 mmol) under a nitrogen atmosphere at −40 °C. The resulting lithium diisopropylamide was stirred for 15 min, and then HMPA (1.5 cm^3, 1.45 g, 8.6 mmol) in THF (5 cm^3) was added rapidly. After 30 min, a solution of the silylated starting material from (*a*) in dry THF (5 cm^3) was added dropwise. The orange solution was stirred for 1.25 h at −40 °C, then carbon disulfide (0.65 cm^3, 823 mg, 10.8 mmol) was added rapidly. The reaction mixture was stirred for 5 h, then methyl iodide (0.9 cm^3, 2.05 g, 14.5 mmol) was introduced rapidly. The reaction mixture was allowed to warm to room temp. overnight. Water (50 cm^3) was added and a standard extractive work-up (light petroleum) followed by flash chromatography (light petroleum–ether, 1:1) gave the *silylated bis*(*thiomethyl*)*methylene adduct* (140 mg, 63%) as a yellow foam, m.p. 56–57 °C; R_f 0.7 (ether–light petroleum, 4:1); ν_{max}/cm^{-1} 1700, 1620 and 1600; δ_H −0.43 (9 H, s), 2.03 (3 H, s), 2.52 (3 H, s), 3.64 (3 H, s), 3.78 (3 H, s), 3.85 (3 H, s), 4.30 (1 H, s), 6.04 (1 H, d, *J* 2.0), 6.30 (1 H, d, *J* 2.0), 6.51 and 6.87 (4 H, AA'BB', *J* 9.0), 6.70–6.80 (2 H, br s) and 6.92–6.95 (3 H, m); δ_C 193.13, 164.49, 161.42, 158.71, 158.14, 156.06, 138.74, 131.59, 128.85, 128.66, 127.97, 127.18, 125.90, 112.00, 107.34, 100.34, 92.29, 89.78, 89.22, 60.10, 55.55, 55.11, 55.02, 19.72, 18.04 and 0.67 (Found: C, 63.3; H, 6.2; S, 10.7. $C_{32}H_{36}O_6S_2Si$ requires C, 63.13; H, 5.96; S, 10.53%); *m*/*z* 608 (M^+, 2.2%). Changing the eluent to ether–light petroleum, 9:1 gave the desilylated *bis*(*thiomethyl*)*methylene adduct* (31 mg, 16%) as a yellow foam, m.p. 89.5–90.5 °C; R_f 0.3 (ether–light petroleum, 4:1); ν_{max}/cm^{-1} 3400, 1690 and 1600; δ_H(PMX 60) 2.13 (3 H, s), 2.48 (3 H, s), 3.62 (3 H, s), 3.76 (3 H, s), 3.79 (3 H, s), 4.50 (1 H, s), 6.01 (1 H, d, *J* 2), 6.25 (1 H, d, *J* 2), 6.50 (2 H, BB' part of an AA'BB', *J* 9.0) and 6.70–7.20 (7 H, m); *m*/*z* 536 (M^+, 4.2%). It should be noted that (i) the yields in the next step were much lower if chromatographic purification was not carried out, and (ii) the chromatographed, desilylated product could also be employed in the next step.

(*c*) To a solution of the silylated bis(thiomethyl)methylene adduct (120 mg, 0.197 mmol) in dry THF (5 cm^3) at 0 °C under nitrogen was added MeOH (0.4 cm^3) followed by sodium (45 mg, 2.0 mmol). The reaction mixture was stirred for 30 min at 0 °C, then the solution was allowed to warm to room temp. After stirring for 2 h at room temp. the reaction was quenched with 1 mol dm^{-3} aqueous HCl. Standard extractive work-up (dichloromethane) followed by flash chromatography (light petroleum–AcOEt, 1:4) gave the *title compound* **26b** (keto–enol mixture; *ca.* 65:35 by ^1H NMR spectroscopy) as a white solid (85 mg, 88%), m.p. 87.5–89.5 °C; R_f 0.5–0.1 (ether–light petroleum, 4:1); ν_{max}/cm^{-1} 3540, 1760, 1740 and 1670; δ_H 3.58 (1.05 H, s), 3.65 (1.05 H, s), 3.66 (1.95 H, s), 3.71 (1.95 H, s), 3.79 (1.05 H, s), 3.81 (1.95 H, s), 3.82 (1.05 H, s), 3.85 (1.95 H, s), 4.06 (0.65 H, d, *J* 13.2), 4.24 (0.65 H, d, *J* 13.2), 4.47 (0.35 H, s), 6.04 (0.35 H, d, *J* 1.8), 6.11 (0.65 H, d, *J* 2.1), 6.20 (0.35 H, d, *J* 1.8), 6.35 (0.65 H, d, *J* 2.1), 6.57 and 7.02 (1.4 H, AA'BB', *J* 8.9), 6.68 and 6.94 (2.6 H, AA'BB', *J* 9.0), 6.90–6.95 (2 H, m) and 7.07–7.11 (3 H, m) [Found: C, 68.7; H, 5.2%; $M^+ - H_2O$ (EI): 472.1522. $C_{28}H_{26}O_8$ requires C, 68.56; H, 5.34%; $M - H_2O$: 472.152 20].

Methyl 1,8b-*Dihydroxy*-6,8-*dimethoxy*-3a-(4-*methoxyphenyl*)-3-*phenyl*-2,3,3a,8b-*tetrahydrocyclopenta*[b]*benzofuran*-2(1H)-*carboxylate* **27b**.—To a solution of the keto ester **26b** (109 mg, 0.22 mmol) in methanol (25 cm^3) at 0 °C under nitrogen was added solid sodium borohydride (95 mg, 2.5 mmol). The reaction mixture was stirred for 3 h at 0 °C, and allowed to warm to room temp. overnight. The reaction was quenched with 1 mol dm^{-3} aqueous HCl (10 cm^3). Standard extractive work-up (dichloromethane) followed by flash chromatography (light petroleum–ether, 1:9) gave an inseparable mixture of epimeric esters **27b** (*ca.* 55:45 by ^1H NMR spectroscopy) (82 mg, 76%) as a white solid, R_f 0.5 (ether–light petroleum, 4:1); ν_{max}/cm^{-1} 3450, 1710, 1600 and 1510; δ_H 1.78 (0.45 H, s), 2.53 (0.55 H, s), 3.39 (0.55 H, d, *J* 3.5), 3.52 (0.55 H, dd, *J* 7.8 and 14.2), 3.61 (1.65 H, s), 3.64 (1.45 H, s), 3.68 (0.55 H, m), 3.70 (1.65 H, s), 3.71 (1.45 H, s), 3.83 (3 H, s), 3.84 (1.65 H, s), 3.86 (1.45 H, s), 3.89 (0.45 H, dd, *J* 6.6 and 14.2), 4.30 (0.45 H, d, *J* 14.2), 4.87 (0.55 H, dd, *J* 3.5 and 7.8), 5.02 (0.45 H, dd, *J* 1.5 and 6.6), 6.10 (0.55 H, d, *J* 2.0), 6.12 (0.45 H, d, *J* 2.0), 6.25 (0.55 H, d, *J* 2.0), 6.28 (0.45 H, d, *J* 2.0), 6.67 and 7.10 (1.8 H, AA'BB', *J* 9.0), 6.69 and 7.14 (2.2 H, AA'BB', *J* 9.0), 6.87–6.89 (2 H, m) and 7.03–7.07 (3 H, m) [Found (CI): $M^+ + 1$, 493.1862. $C_{28}H_{28}O_8$ requires $M + 1$, 493.186 24].

1,8b-*Dihydroxy*-6,8-*dimethoxy*-3a-(4-*methoxyphenyl*)-3-*phenyl*-2,3,3a,8a-*tetrahydrocyclopenta*[b]*benzofuran*-2(1H)-*carboxylic Acid* **28b**.—To a solution of keto ester **27b** (70 mg, 0.14 mmol) in MeOH (12.5 cm^3) and water (2.5 cm^3) was added solid potassium hydroxide (30 mg, 0.54 mmol) at room temp. under N_2 and with stirring. The reaction mixture was heated to 40 °C for 2 h. After cooling to room temp., 1 mol dm^{-3} HCl (10 cm^3) was added. Standard extractive work-up (dichloromethane) gave the title compound **28b** (65 mg, 97%) as an inseparable mixture of epimeric acids (*ca.* 55:45 by ^1H NMR spectroscopy)

as a slightly yellow solid, m.p. 194.5–195.5 °C; ν_{max}/cm^{-1} 3440, 3400, 1715, 1600 and 1520; δ_H 3.48 (0.45 H, dd, *J* 7.0 and 14.0), 3.52 (0.55 H, dd, *J* 7.6 and 14.0), 3.71 (1.45 H, s), 3.72 (1.65 H, s), 3.74 (0.55 H, m), 3.84 (3 H, s), 3.85 (1.65 H, s), 3.88 (1.35 H, s), 4.25 (0.45 H, d, *J* 14.0), 4.91 (0.55 H, d, *J* 7.6), 5.07 (0.45 H, d, *J* 7.0), 6.10 (0.55 H, d, *J* 1.8), 6.13 (0.45 H, d, *J* 1.8), 6.25 (0.55 H, d, *J* 1.8), 6.28 (0.45 H, d, *J* 1.8), 6.68 and 7.10 (1.8 H, AA'BB', *J* 8.9), 6.70 and 7.14 (2.2 H, AA'BB', *J* 8.9), 6.86–7.00 (2 H, m) and 7.05–7.07 (3 H, m) which was used without further characterisation.

1,8b-*Dihydroxy*-6,8-*dimethoxy*-3a-(4-*methoxyphenyl*)-N,N-*dimethyl*-3-*phenyl*-2,3,3a,8b-*tetrahydrocyclopenta*[b]*benzofuran*-2(1H)-*carboxamide* **29b**.—A solution of acid **28b** (40 mg, 0.084 mmol), freshly sublimed dimethylamine hydrochloride (21 mg, 0.26 mmol), DCC (50 mg, 0.24 mmol) and DMAP (dimethylaminopyridine) (74 mg, 0.61 mmol) in dry dichloromethane (25 cm^3) was stirred at room temp. under N_2 for 24 h and then quenched by the addition of 1 mol dm^{-3} HCl (10 cm^3). Standard extractive work-up (dichloromethane) gave a slightly yellow solid. Flash chromatography (AcOEt–light petroleum, 4:1) gave the *title amide* **29b** (30.1 mg, 71%) as a white solid, m.p. 150–151 °C; R_f 0.35 (AcOEt–light petroleum, 9:1); ν_{max}/cm^{-1} 3440, 1630, 1520 and 1500; δ_H 2.56 (1 H, br s), 2.87 (3 H, s), 3.27 (3 H, s), 3.46 (1 H, br s), 3.72 (3 H, s), 3.79 (3 H, s), 3.81 (1 H, dd, *J* 7.5 and 13.4), 3.82 (3 H, s), 3.91 (1 H, d, *J* 13.4), 4.78 (1 H, dd, *J* 3.0 and 7.5), 6.06 (1 H, d, *J* 1.9), 6.23 (1 H, d, *J* 1.9), 6.72 and 7.20 (4 H, AA'BB', *J* 8.9), 6.74–6.78 (2 H, m) and 7.00–7.04 (3 H, m); δ_C 171.73, 164.01, 159.99, 158.60, 157.58, 136.56, 128.74, 128.13, 127.73, 127.46, 126.56, 112.90, 110.52, 101.80, 92.55, 89.24, 84.83, 55.71, 55.57, 55.13, 53.48, 53.45, 49.97, 37.55 and 36.05 [Found (CI): $M^+ + 1$, 506.2179. $C_{29}H_{31}NO_7$ requires $M + 1$, 506.217 88].

8b-*Hydroxy*-6,8-*dimethoxy*-3a-(4-*methoxyphenyl*)-N,N-*dimethyl*-1-*oxo*-3-*phenyl*-2,3,3a,8b-*tetrahydrocyclopenta*[b]*benzofuran*-2(1H)-*carboxamide* **30b**.—To a solution of anhydrous dimethylamine (680 mg, 15.1 mmol) in dry THF (5 cm^3) at −78 °C under nitrogen was added butyllithium in hexane (1.25 cm^3; 1.5 mol dm^{-3}; 1.85 mmol). The mixture was stirred for 10 min at −78 °C, then a solution of keto ester **26b** (95 mg, 0.194 mmol) in dry THF (5 cm^3) was added dropwise. The reaction was stirred for 30 min at −78 °C and then allowed to warm to room temp. After stirring for 30 min at room temp. the reaction was quenched by the addition of methanol (1 cm^3), followed by slow addition of 1 mol dm^{-3} HCl (5 cm^3). Standard extractive work-up (dichloromethane) gave a brown oil. Flash chromatography (AcOEt–petroleum, 9:1) gave the *title keto amide* **30b** (87 mg, 89%) as a white solid, m.p. 121–122 °C; R_f 0.2–0.1 (ether); ν_{max}/cm^{-1} 3350, 1750, 1650 and 1620; δ_H 2.90 (3 H, s), 3.25 (3 H, s), 3.73 (3 H, s), 3.80 (3 H, s), 3.84 (3 H, s), 4.33 (1 H, d, *J* 13.2), 4.51 (1 H, d, *J* 13.2), 6.08 (1 H, d, *J* 2.1), 6.33 (1 H, d, *J* 2.1), 6.71 and 6.99 (4 H, AA'BB', *J* 9.0), 6.83–6.85 (2 H, m) and 7.08–7.09 (3 H, m) [Found (EI): $M^+ - H_2O$, 485.1838. $C_{29}H_{29}NO_7$ requires $M - H_2O$, 485. 183 84].

1,8b-*Dihydroxy*-6,8-*dimethoxy*-3a-(4-*methoxyphenyl*)-N,N-*dimethyl*-3-*phenyl*-2,3,3a,8b-*tetrahydrocyclopenta*[b]*benzofuran*-2(1H)-*carboxamide* **1**.—Acetonitrile (0.6 cm^3) was added at room temp. and under nitrogen to tetramethylammonium triacetoxyborohydride (273 mg, 1.04 mmol) followed by the addition of glacial acetic acid (0.6 cm^3). After stirring for 30 min at room temp., a solution of keto amide **30b** (60 mg, 0.119 mmol) in dry acetonitrile (1.5 cm^3) was added dropwise. The resulting mixture was stirred for 24 h at room temp. The reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate (30 cm^3). Standard extractive work-up (dichloromethane) gave a white solid. Flash chromatography (AcOEt) gave rocaglamide **1** (49 mg, 81%) as a white solid, m.p. 119–120 °C (lit.,[1] 118–119 °C); R_f 0.25 (AcOEt); ν_{max}/cm^{-1} 3600, 3490, 1630 and 1605; δ_H 2.93 (3 H, s), 3.31 (3 H, s), 3.70 (1 H, m), 3.83 (3 H, s), 3.85 (3 H, s), 4.04 (1 H, dd, *J* 6.5 and 13.5), 4.54 (1 H, d, *J* 13.5), 4.93 (1 H, d, *J* 6.5), 6.10 (1 H, d, *J* 2.0), 6.27 (1 H, d, *J* 2.0), 6.67 and 7.10 (4 H, AA'BB', *J* 9.0), 6.84–6.86 (2 H, m) and 6.97–7.05 (3 H, m); δ_C see Table 5 [Found: C, 68.6; H, 6.4; N, 2.55%; $M^+ + 1$ (CI), 506.2179. $C_{29}H_{31}NO_7$ requires C, 68.88; H, 6.18; N, 2.77%; $M + 1$, 506.217 88].

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