A Novel 1,3-Dithiane-based Cyclopenta-annellation Procedure: Synthesis of the Rocaglamide Skeleton

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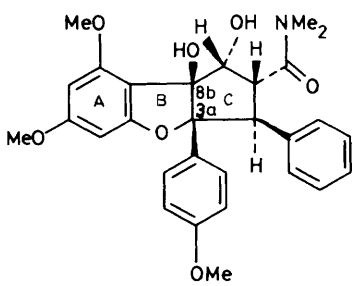
A novel three carbon cyclopentanone annellation procedure, based on direct 1,3-dithiane lithiation followed by intramolecular carbonyl addition, has been employed in a synthetic approach to the anti-cancer compound, rocaglamide.

Cyclisations involving 1,3-dithiane-derived anions are normally based on intramolecular alkylation reactions.[1] The only literature examples of ring closure *via* dithianyl anion to carbonyl addition involve the use of 2-trimethylsilyl-dithianes and fluoride-induced cyclisation.[2] The problem with the direct cyclisation of 2-(ω-oxoalkyl)-dithianes is that the strong bases required for dithiane deprotonation would normally be expected to undergo preferential reaction with the carbonyl group, either by addition or by enolisation.[1] However, in planning a total synthesis of rocaglamide (**1**), a recently discovered,[3] anti-leukaemic 1*H*-cyclopenta[*b*]benzofuran, we were hopeful that the novel cyclopentanone annellation procedure[4] outlined in Scheme 1 could be employed for the



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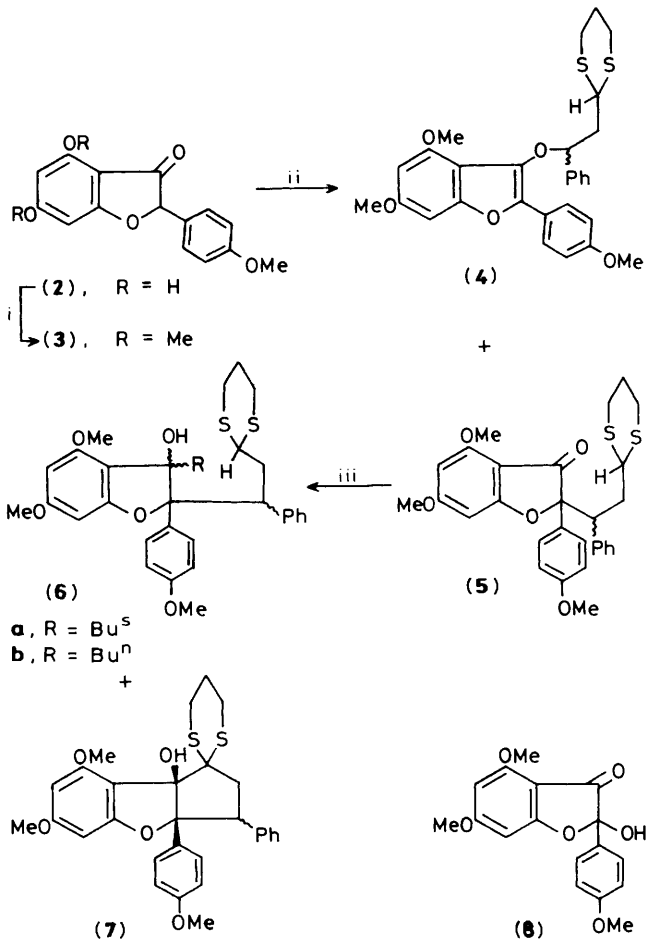
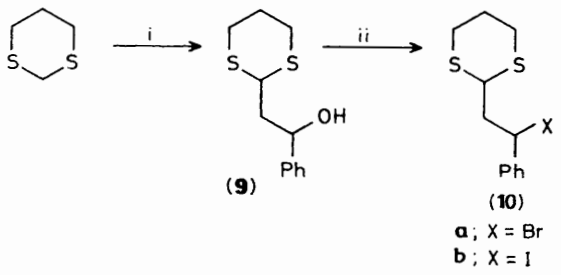


Scheme 1. *Reagents:* i, Me_2SO_4 then HCl, MeOH (91%); ii, NaH, (**10b**) [yield (**5**) 61%, (**4**) *ca.* 5%]; iii, see Table 1 [max. yield (**7**) 76%].

Table 1. Attempted cyclisation reactions [(**5**) to (**7**)].

Base (equiv.)	Temperature/°C[c]	Yield (**7**)/%	Recovery[e]
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]	–	(**6a**) (42%)
Bu^{n}Li (1)[b]	−78 to room temp.	–	[55%]
Bu^{n}Li (1.1) KOBu^t (1)	−78 to −10		(**6b**) (34%) [+37%]
Bu^{n}Li (1.1) HMPA (2)	−78 to −10	28	(**6b**) (14%) [+31%]
Bu^{n}Li (2) HMPA (2)	−78 to −10	45	(**6b**) (24%) [+13%]
Bu^{n}Li (2) HMPA (2)	−96 to −10	55	(**6b**) (12%) [+10%]
Bu^{n}Li (1.2) HMPA (2)	−96 to −10	64	(**6b**) (1%) [+16%]

[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) or in the presence of TMEDA. [c] Solvent THF except where indicated otherwise. [d] Solvent THF–Et_2O (5:1). [e] Recovery of (**5**) in square brackets.



Scheme 2. *Reagents:* i, BuLi then PhCHCH$_2$O (79%); ii, CBr_4–Ph_3P (*ca.* 83%) then NaI (*ca.* 74%).

construction of ring C. Although this annellation relies on dithiane deprotonation in the presence of a nearby carbonyl group we felt that there was a chance of success given that the carbonyl group in the cyclisation precursor (**5**) is non-enolisable and deactivated towards intermolecular nucleophilic addition both sterically and electronically.

The main advantage of this synthetic approach is the ready availability of benzofuranone (**2**),[5] which has the correct substituents for rings A and B of rocaglamide as well as reactive centres at C-3a and C-8b (rocaglamide numbering) suitable for the elaboration of ring C. Methylation of compound (**2**) gave the methyl enol ether corresponding to (**3**) but acidic hydrolysis produced the required dimethylated benzofuranone (**3**) in high yield.† The requisite alkylating agents (**10**) were easily prepared *via* the known[6] alcohol (**9**) using the procedure shown in Scheme 2.

Treatment of benzofuranone (**3**) with sodium hydride followed by alkyl iodide (**10b**) gave the *C*-alkylated product (**5**) in 61% yield along with *ca.* 5% of the *O*-alkylated isomer (**4**). When iodide (**10b**) was replaced by the corresponding bromide (**10a**) the amount of the *O*-alkylated product (**4**) increased dramatically (34% using NaH as base, 60% using K_2CO_3). It is important to exclude oxygen from these alkylation reactions; if the reactions are not rigorously degassed the 2-hydroxylated product (**8**) is also formed.

† All new compounds are racemic and gave spectral and analytical data consistent with the assigned structures.

With the key cyclisation precursor (**5**) in hand a number of attempts were made to effect its conversion into (**7**). The results of this study are summarised in Table 1. No reaction was observed when dithiane (**5**) was treated with lithium di-isopropylamide (LDA), an unsurprising observation given the relative pK_a values of 2-alkylated dithianes[1] and di-isopropylamine. The use of t-butyl-lithium alone gave a complex mixture of products whereas in the presence of tetramethylethylenediamine (TMEDA) starting material (**5**) was recovered unchanged. Changing to s-butyl-lithium or n-butyl lithium–KOBu^t produced addition products (**6**) but no cyclisation. Success was achieved when n-butyl-lithium was used in the presence of hexamethylphosphoramide (HMPA). The relative yields of the cyclisation and butyl addition products, (**7**) and (**6b**) respectively, varied according to reaction temperature and amount of butyl-lithium employed. The highest yield of cyclisation product (**7**), 64% (76% based on converted starting material), was obtained by treating compound (**5**) with 1.2 equiv. of n-butyl-lithium at −96 °C followed by warming to −10 °C over 1 h, and stirring at this temperature for 2 h. It is noteworthy that intramolecular carbonyl addition occurs almost exclusively when these conditions are employed. To our knowledge this is the first reported example of dithiane deprotonation in the presence of a carbonyl group.

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