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# A Biomimetic Approach to the Synthesis of Rocaglamide Based on a Photochemical [2+2] Cycloaddition of a Cinnamate Unit to a Flavone.

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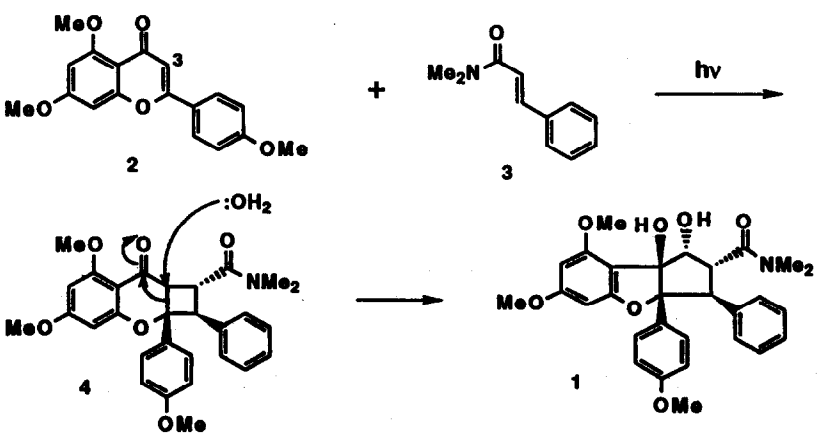
***Abstract:*** *In attempting a biomimetic synthesis of rocaglamide,we have discovered the first examples of photochemically induced cycloaddition reactions involving a flavone system.*

Our interest in the photochemically induced [2+2]-cycloaddition reactions of flavonoids arose from an idea for the biosynthesis of the antileukaemic metabolite, rocaglamide **1**.[1] In our proposed biosynthesis (Scheme 1), cycloaddition of a flavonoid unit, **2**, with a cinnamate unit, **3**, generates a bicyclo [6:4] fused ring system, which could subsequently undergo a rearrangement to form the [5:5] fused ring system found in the natural product. A ***biomimetic*** total synthesis of rocaglamide based on this approach would provide a short alternative to conventional synthetic approaches.[2] We have therefore investigated the feasibility of the proposed [2+2] cycloaddition step.



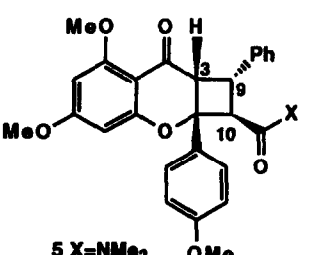

Scheme 1 Proposed Biosynthesis of Rocaglamide

Coumarins and chromones[3] have been reported to undergo photochemically-induced [2+2]-cycloaddition reactions, but there is no precedent for such a reaction involving a flavone. In contrast, there is a very rich literature of [2+2] cycloaddition reactions involving cinnamates, predominantly to form homodimers, but also to generate heteroadducts in the presence of another alkene.[4] The reaction of a cinnamate can be complicated by isomerisation of the double bond from *trans* to *cis*. Also regioisomers and stereoisomers of the desired [2+2] cycloadducts are often produced, leading to complex mixtures. These side reactions can severely limit the synthetic utility of the photochemical reaction.

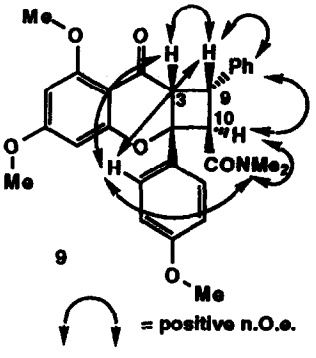
**Irradiations in Solution.**

Exploratory studies were carried out with the fully methylated derivative **2** of the flavone and the dimethylamino derivative **3** of the cinnamate. All the irradiations were carried out in a quartz immersion well photoreactor, using a medium pressure mercury lamp (450 watts) which emitted strongly up to 290 nm with further weaker emission up to about 350 nm. Solutions were made as concentrated as possible in order to minimise isomerisation of the cinnamate at the expense of cycloaddition. In these initial experiments in a range of solvents (hexane, $CH_2Cl_2$, MeCN, toluene), the flavone was either recovered unchanged or it suffered degradation to *p*-methoxybenzaldehyde. Only in aqueous solution was there any detectable formation of a heteroadduct, which proved to be **5** (see later for the elucidation of this structure). Although this had the 'wrong' regiochemistry, having the 'head to tail' arrangement of its units rather than the required 'head to head", its formation was most encouraging in that it provided the first evidence that a flavone would undergo a photochemically-induced [2+2] cycloaddition reaction.

No photochemical reaction was observed when solutions containing the potential photosensitisers, acetone or benzophenone were irradiated. Although both **2** and **3** readily formed solid complexes when treated with boron trifluoride etherate, attempts to induce the desired reaction by irradiating solutions of **2** plus **3** in the presence of this Lewis acid catalyst proved unsuccessful: the starting flavone was recovered unchanged but, remarkably, the alkene double bond of the cinnamate was reduced to give the corresponding propanamide in good yield (57 %). Also, attempts to carry out the required photoreaction in the solid state, with **2** and **3** adsorbed on silica gel, or co-crystallised, failed to yield products.




**5** X=$NMe_2$
**6** X=OMe
**7** X=OPh
**8** X=OH




**Irradiations in Micelles.**

Neither of the reactants, **2** or **3**, is readily soluble in aqueous solution, so it is not surprising that the yield of heteroadduct **5** is low. It has been shown that micelles can be used to overcome this problem, and also that they may alter the preferred regiochemistry of the cycloaddition by favouring a different form of association between the reactants.[5] Two surfactants which have proved useful with other systems were tested, a cationic detergent, cetyl trimethylammonium bromide (CTAB), and an anionic counterpart, sodium dodecyl sulphate (SDS). Although the yield of heteroadduct was markedly increased in both cases, the higher yield was obtained when SDS was used (experiment 1, Table). In a control experiment the flavone showed no

tendency to undergo homodimerisation when irradiated on its own under the same conditions. In a second control, the cinnamate on its own showed its usual tendency to form a homodimer, but its main reaction under these conditions was *trans-cis* isomerisation. It is interesting that heteroadduct formation took precedence over this isomerisation in the mixed reaction with the flavone.

Different derivatives of the cinnamate component were investigated next (see Table). Both the methyl ester and the phenyl ester reacted with the flavone to give heteroadducts, **6** and **7**. The *t*-butyl ester was hydrolysed to give cinnamic acid, which was isolated as a mixture a mixture of *cis*-and *trans*- isomers. The free acid was also investigated using CTAB, rather than SDS, as the micelle forming agent. At pH 7 starting materials were recovered from the irradiation mixture, but under acidic conditions (pH 3), a [2+2] cycloaddition reaction occurred to give the heteroadduct **8**. No photochemical reaction was observed with either the 2,4-dinitrophenyl ester of cinnamate or the imidazole derivative, showing that an electron deficient aromatic ring placed at the acyl end of the cinnamate unit did not promote the desired reaction. Other cinnamate derivatives which failed to give heteroadducts with **2** in the presence of SDS micelles included the cinnamate esters of *p*-chlorophenol, 2,4-dichlorophenol, pentafluorophenol, and glycollic acid. Finally, cinnamyl alcohol was examined but it failed to react in the desired manner.

Table Results of Irradiation of Mixtures of Cinnamate Derivatives with Flavone **2** in Aqueous Solution Containing SDS or CTAB (1%).

| Expt. | Cinnamate derivative | Conditions: compound [concentration]; | Results: product [yield %] |
|---|---|---|---|
| 1 | N,N-dimethylamide | **2** [6.4 mM]; amide [9.6 mM] | **5** [72%] |
| 2 | methyl ester | **2** [5.0 mM]; ester [10.0 mM] | **6** [77%] |
| 3 | phenyl ester | **2** [1.6 mM]; ester [2.0 mM] | **7** [35%] |
| 4 | t-butyl ester | **2** [1.5 mM]; ester [1.5 mM] | cinnamic acids |
| 5 | free acid | **2** [1.1 mM]; acid [2.3 mM]; pH 3 | **8** [16%] |
| 6 | 2,4-dinitrophenyl ester | **2** [1.3 mM]; ester [1.3 mM] | no reaction |
| 7 | acyl imidazole | **2** [1.6 mM]; imidazolide [3.4 mM] | no reaction |

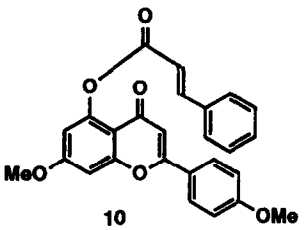
**Assignment of structures to the heteroadducts**

Four cinnamic acid derivatives gave heteroadducts with the flavone **2**. The structures of the products were established by a combination of X-ray diffraction, n.m.r., and chemical correlation. The structure of the methyl ester adduct, produced in experiment 2, was rigorously established as **2** by X-ray analysis of a crystal.[6] It was then possible to confirm that the adduct derived from the free acid had structure **8**, by methylation of the carboxyl group with diazomethane to give a methyl ester which was identical to **6**. The phenyl ester **7** (experiment 3) could also be converted to a product identical to **6**, by hydrolysis with $H_2O_2$ in dimethyl formamide, followed by treatment of the resulting acid with diazomethane.

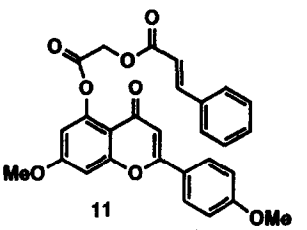
Attempts to correlate the amide **5**, with the acid **8** by hydrolysis failed, as did efforts to carry out the reverse reactions. In the absence of a rigorous chemical correlation, the structure of **5** was established by n.m.r studies. The pattern of n.O.e.'s for the protons of the amide derivative **5** are shown in structure **9**. Of particular relevance are the n.O.e.'s between the hydrogens attached to the *o*-postions of the *p*-methoxyphenyl ring of the flavone unit and two sites in the cinnamate unit: the hydrogens of the dimethylamino group and H-9 of the cyclobutane ring. The absence of an n.O.e. between these two hydrogens of the flavone unit and the hydrogens of the phenyl ring of the cinnamate unit is also significant. The combined evidence strongly supports the proposed structure **5**, which has the same regiochemistry and stereochemistry as the ester derivatives discussed above.

**Irradiations of linked molecules**

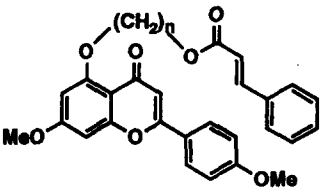
To summarise, four heteroadducts have been formed between the flavone unit **2** and various cinnamate units, but none has the correct regiochemistry for conversion to rocaglamide. To force the desired orientation in the cycloaddition, we next explored the use of covalently-linked reactants in which only the desired regiochemistry for cycloaddition would be allowed by geometric constraints. Of the many possible ways on which this strategy might realised, we chose to link the cinnamate ester residue to an oxygen substituent on the flavone ring, as in structures **10** - **13**. When irradiated in aqueous solution in the presence of SDS micelles, all compounds suffered the same fate - cleavage of the linking group, to give the hydroxyflavone together with recovered starting material. The failure of **10** and **11** to undergo the cycloaddition reaction might be caused by steric strain in the linking chain preventing the required sites for reaction from approaching sufficiently close, but this explanation is less convincing with **12** and **13**.




**10**




**11**




**12** n=2
**13** n=4

**Conclusion**

In conclusion, we have discovered the first examples of cycloaddition products formed from flavones, but these were exclusively head to tail adducts. The reluctance of theses two species to react head to head may be due to steric repulsion between the phenyl and methoxyphenyl rings of the two reactants, which may inhibit them from associating with the required regiochemistry. It may be better to tie the two aryl rings by a covalent link in future studies. An alternative strategy, which may provide the correct type of adduct, would be to use the 3-methoxy derivative of **2**.[7] The extra methoxy group at C-3 may bias the reaction towards the head to head adduct both by its steric effect and by its electronic effect, and its presence in **4** may also benefit the subsequent migration step of the proposed synthesis, by stablising the positive charge at the carbon from which the migrating group leaves. However, a ketone group would be generated from the methoxy group at the origin of the migration process, so a subsequent stereospecific reduction step would be required to reduce it to the hydroxyl group found at that site in the natural product **1**.

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***References and Notes***

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6. We thank Dr P. Raithby for solving the crystal structure.
7. This work is being followed up by Dr. R. J. K. Taylor, personal communication.

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