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An Intramolecular [2+2] Photocycloaddition-Fragmentation Approach Towards the Total Synthesis of Asteriscanolide

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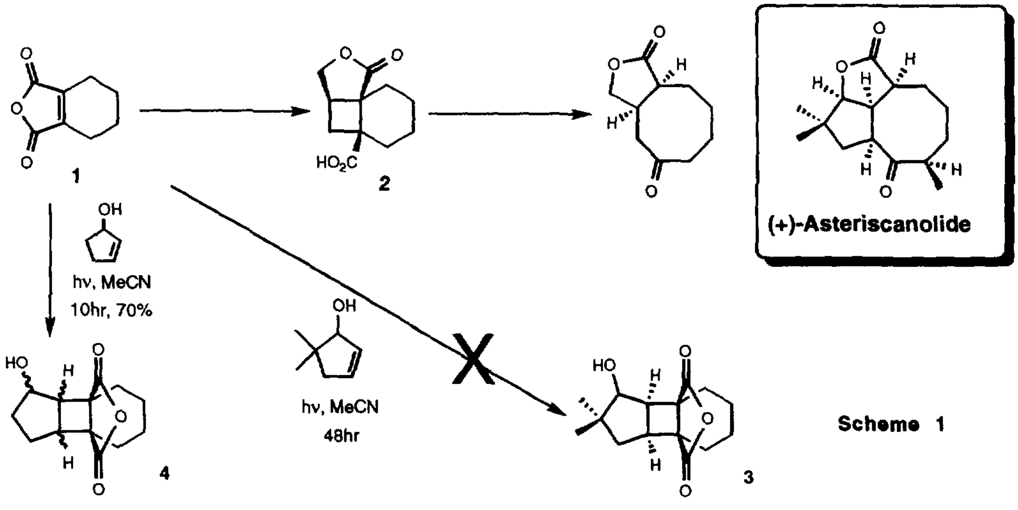
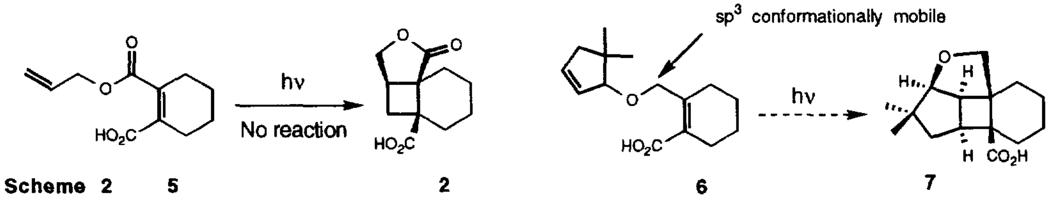
Abstract: A new route towards the Asteriscanolide skeleton is described. The key features include an efficient intramolecular [2+2] photocycloaddition of the α,β-unsaturated acid-ether **10** followed by a Curtius rearrangement/ ruthenium tetroxide/ fragmentation sequence to yield the cyclooctane lactones **13** and **14**.

Recently we described[1] an approach to the asteriscanolide skeleton which involved a novel aza de Mayo fragmentation of the cyclobutane acid-lactone **2**, which itself was prepared in three steps from tetrahydrophthalic anhydride (THPA, **1**) *via* intermolecular [2+2] photocycloaddition, hydrolysis and subsequent hydrogenation and lactonisation. However, attempts to extend this strategy towards a synthesis of the natural product by photolysis of THPA with 5,5-dimethyl-2-cyclopentenol[2] were unsuccessful and no intermolecular [2+2] photocycloaddition products (**3**) were observed. This was probably a result of unfavourable steric interactions involving the *gem*-dimethyl groups, as we found that THPA and 2-cyclopentenol readily underwent photolysis to give the photoadduct **4**. This was of limited synthetic value, however, as **4** was obtained as a complex mixture of stereoisomers (Scheme 1).



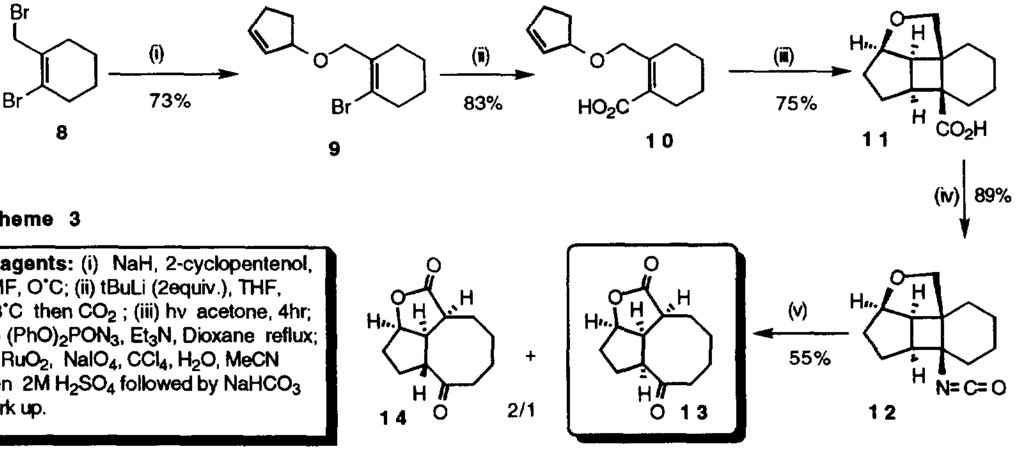
Scheme 1

We had previously found[1] that the acid-ester **5** was inert towards photolysis and none of the intramolecular photoadduct **2** was ever obtained. This failure was considered to be a consequence of the fact that esters have a conformational preference which is governed by electronic factors and that this prevents **5** from adopting a conformation necessary for intramolecular cycloaddition. This led us to consider that intramolecular [2+2] photocycloaddition of the acid-ether **6** should be more favourable in view of the fact that the carbonyl group is now absent and the sp^3 centre should allow a much greater degree of conformational mobility[3] during the cycloaddition. The lactone carbonyl could then be reintroduced, after cycloaddition, by RuO_4 oxidation of the cyclised acid-ether **7** (Scheme 2).



Scheme 2

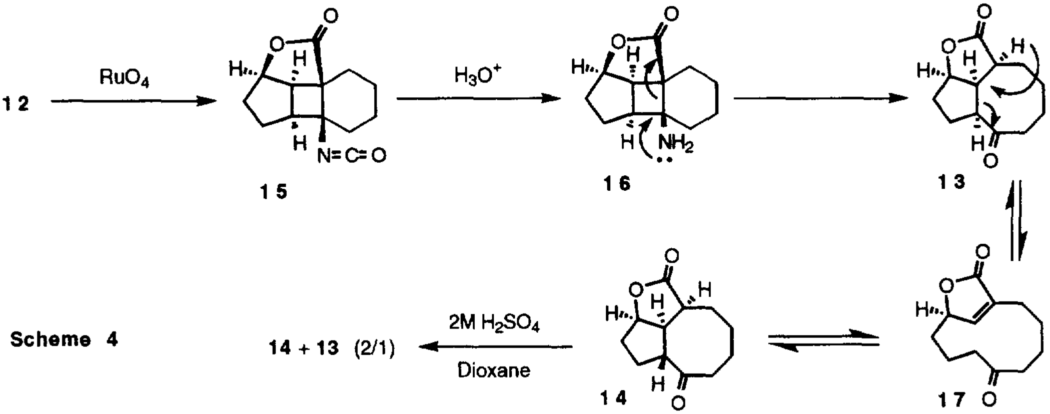
Treatment of the known[4] allylic bromide **8** with the sodium alkoxide of 2-cyclopentenol gave the ether **9** in 73% yield. Metal halogen exchange with ^tBuLi followed by quenching of the resulting vinyllithium with solid CO_2, gave the acid-ether **10** in excellent yield (83%). Photolysis[5] of **10** in acetone gave the cyclobutane **11** in good yield (75%). Curtius rearrangement[6] of **11** gave the isocyanate **12** in an 89% isolated yield. This isocyanate proved to be remarkably stable to both chromatography and acid hydrolysis and because of this we decided to use it as a rather unconventional protecting group in the subsequent ruthenium tetroxide oxidation step. Thus, oxidation[7] of **12** with RuO_4 gave a rapid (1.5hr) and clean conversion to the now labile isocyanate-lactone **15** (scheme 4) which, without purification, was immediately subjected to our aza de Mayo fragmentation by hydrolysis in aqueous acid followed by basification. This yielded the target cyclooctanone-lactone **13** and the epimeric cyclooctanone-lactone **14**, as a 1/2 mixture, in 55% overall yield from **12** (Scheme 3).



Scheme 3

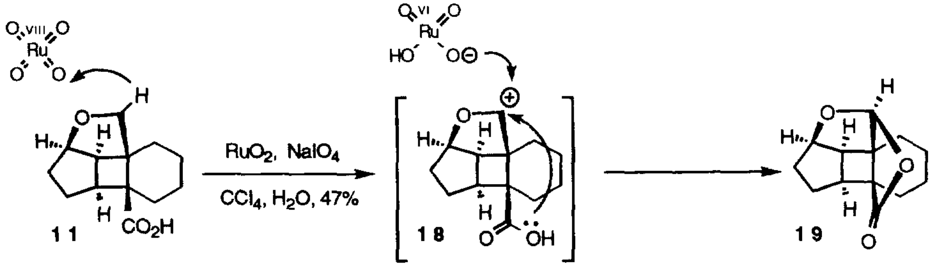
Reagents: (i) NaH, 2-cyclopentenol, DMF, 0°C; (ii) tBuLi (2equiv.), THF, -78°C then CO_2 ; (iii) hv acetone, 4hr; (iv) $(PhO)_2PON_3$, Et_3N, Dioxane reflux; (v) RuO_2, $NaIO_4$, CCl_4, H_2O, MeCN then 2M H_2SO_4 followed by $NaHCO_3$ work up.

The structure and stereochemistry of both epimers[8] was elucidated by a combination of nOe and X-ray crystallography. The conversion proceeds by hydrolysis of **15** to the amine **16** which then undergoes fragmentation *via* a retro-Mannich or aza de Mayo mechanism[9]. We believe the epimer **14** is formed by acid catalysed retro-Michael fragmentation of the initially formed **13** to yield the 11-membered keto-lactone **17** which then undergoes re-cyclisation to yield **14**. Proof of this mechanism could be obtained from hydrolysis of **15** under neutral conditions which resulted in the isolation of small amounts of **17** (22%) along with substantial amounts of the urea formed from dimerisation of **15** and **16**. Although the epimeric ratio was initially disappointing, it has been found that this interconversion is actually an equilibrium as treatment of pure **14** with 2M H_2SO_4 results in a 1/2 mixture of **13** and **14** respectively. As both **13** and **14** are quite stable to epimerisation when isolated it should be possible to maximise the formation of the desired epimer **13** by repeated epimerisation of **14** followed by chromatographic separation. Attempts to suppress the formation of **14** by using milder acid conditions in the isocyanate hydrolysis resulted in the predominant formation of the urea dimer of **15** and **16**.



Scheme 4

The reason for subjecting **11** to the Curtius rearrangement prior to oxidation was because we found that treatment of **11** with ruthenium tetroxide resulted in the exclusive formation (47%) of the rather unusual acetal-lactone **19** (Scheme 5) rather than the expected acid-lactone. We believe that this is a result of the ruthenium tetroxide abstracting hydride from **11** to give the carbocation **18** which is intercepted by the carboxylic acid group before the Ru^{VI} oxide species can react further. This would seem to provide compelling evidence that the ruthenium tetroxide oxidation of ethers does proceed[10] *via* initial hydride abstraction and carbocation formation. Further studies of this interesting cyclisation with simpler substrates are in progress, the results of which will be reported in due course.



Scheme 5

In summary, we have shown that the intramolecular [2+2] photocycloaddition/ aza de Mayo fragmentation strategy described in this letter provides rapid access to the whole asteriscanolide skeleton in five steps. Present studies are involved in the completion of this total synthesis by investigating the reaction of **8** with enantiomerically pure 5,5-dimethyl-2-cyclopentenol.

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5. All irradiations were conducted in a standard water cooled pyrex immersion well photoreactor (100ml) using a 125W medium pressure mercury discharge lamp.
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8. Selected spectral data for **13**: Colourless needles mp (EtOAc/PE) 133-136°C; ν_{max}/cm^{-1} (DCM thin film); 1751 (CO), 1683.5 (CO); δH(270MHz); 4.97 (1H, t, *J*=5.12Hz), 3.71 (1H, m), 2.88 (1H, m), 2.73 (1H, m), 2.57 (1H, m), 2.43 (1H, m), 2.21-1.38 (10H,m); δC (67.8MHz); 212.2 (Q), 178.1 (Q), 84.33 (CH), 54.46 (CH), 44.76 (CH), 43.92 (CH_2), 43.40 (CH), 30.89 (CH_2), 27.39 (CH_2), 25.28 (CH_2), 23.38 (CH_2), 22.59 (CH_2).

   Selected spectral data for **14**: Colourless, crystalline solid mp (EtOAc/PE) 60-61.5°C; ν_{max}/cm^{-1} (DCM thin film); 1764 (CO), 1696 (CO); δH(270MHz); 4.88 (1H, m), 2.86 (3H, m), 2.59-1.55 (12H, m); δC(67.8MHz); 212.3 (Q), 178.1 (Q), 84.55 (CH), 51.11 (CH), 48.91 (CH), 44.42 (CH), 41.94 (CH), 31.54 (CH_2), 27.26 (CH_2), 27.14 (CH_2), 25.77 (CH_2), 24.67 (CH_2).

   Full crystallographic details of **13** and **14** can be obtained from the author and will be reported in due course.
9. For related reactions using vinylogous amides see: (a) F.M. Schell, P.M. Cook, S.W. Hawkinson, R.E. Cassady and W.E. Thiessen, *J. Org. Chem.*, **1979**, *44*, 1380; (b) C.S. Swindell and P.B. Patel, *J. Org. Chem.*, **1990**, *55*, 3.
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