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Model Studies Towards the Total Synthesis of Asteriscanolide

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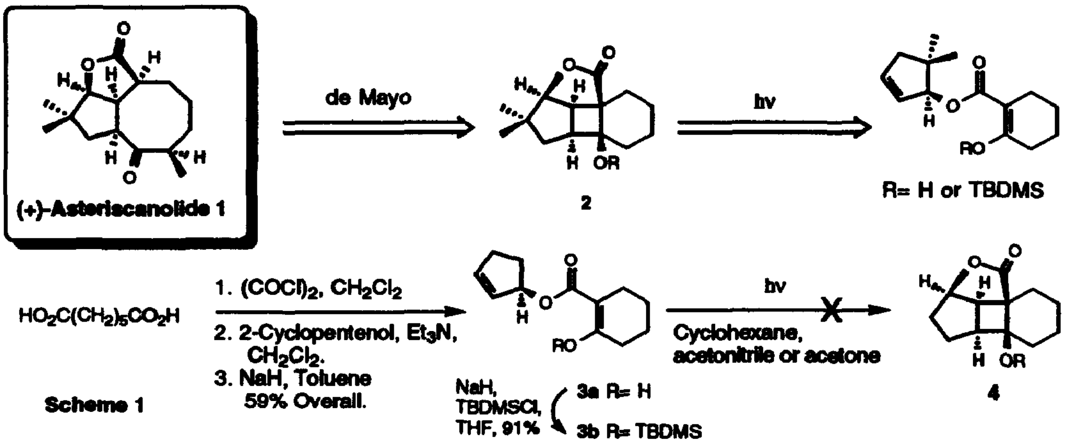
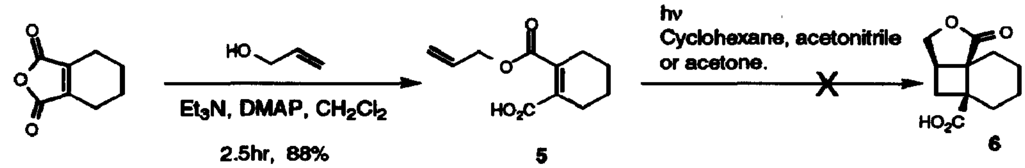
Abstract: A new route towards the Asteriscanolide skeleton is described. The key step involves a novel aza deMayo fragmentation of a cyclobutane carboxylic acid, which in turn is synthesised by an efficient [2+2] photocycloaddition involving tetrahydrophthalic anhydride.

Asteriscanolide **1** is a cyclooctane sesquiterpene isolated from *Asteriscus aquaticus* L.[1,2] and contains an interesting 5,8- fused carbocyclic system bridged by a butyrolactone ring. Our initial approach involved investigating the possibility of constructing the skeleton of **1** *via* a de Mayo[3] type fragmentation of the photoadduct **2**. However, this strategy was abandoned as we found the esters **3a** and **3b** were inert to photolysis under a variety of conditions and none of the intramolecular [2+2] photoadduct **4** was ever obtained (Scheme 1).



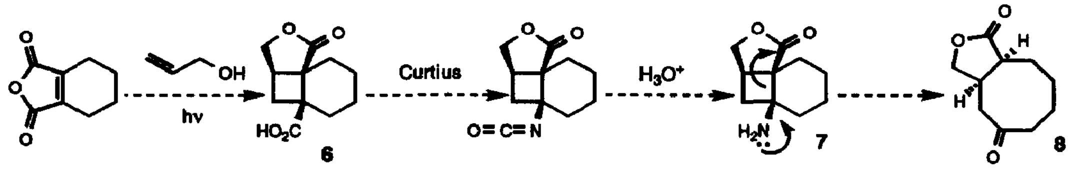
Scheme 1

The failure of **3a,b** to undergo cycloaddition was initially rationalised on the basis of electronic grounds and therefore the photochemistry of the more electron deficient acid-ester **5** was investigated. Treatment of tetrahydrophthalic anhydride (THPA) with allyl alcohol under basic conditions gave **5** in 88% yield, however, this also proved to be inert to photolysis and none of the intramolecular photoadduct **6** was ever obtained (Scheme 2). The failure of **3a,b** and **5** to undergo an intramolecular cycloaddition may be partly explained by the argument that esters have a conformational preference which is governed by electronic[4] factors and that this prevents **3a,b** and **5** from adopting a conformation necessary for intramolecular cycloaddition. Pirrung[5] experienced similar problems during an earlier study of related [2+2] photocycloadditions of allyl and propargyl esters. A similar argument has also been proposed by Boeckman[6] for the failure of certain allyl esters to undergo intramolecular Diels-Alder reactions.



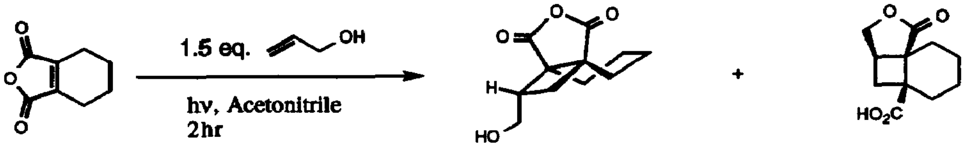
Scheme 2

During the synthesis of the acid ester **5** it was observed that there was no ester formation between THPA and allyl alcohol under neutral conditions. It was therefore decided to investigate the intermolecular [2+2] cycloaddition between THPA and allyl alcohol as a strategy towards the acid lactone **6**. It was conceived that subjecting **6** to a Curtius rearrangement followed by hydrolysis of the isocyanate would yield the cyclooctanone-lactone **8** by a new aza de Mayo fragmentation of the cyclobutylamine **7**, thus providing a suitable model for the total synthesis of Asteriscanolide (Scheme 3).



Scheme 3

Irradiation[7] of a 0.08 M acetonitrile solution of THPA with 1.5 equivalents of allyl alcohol for 2hrs gave a quantitative yield of a mixture of the hydroxy anhydride **10** and the desired acid lactone **6** in a ratio of 85:15 respectively. The anhydride **10** could be isolated pure in 80% yield by recrystallisation from ether. Interestingly irradiation in benzene changed the ratio to 69:31, although a longer reaction time (10hr) was necessary in order to drive the reaction to completion. Further studies in a variety of other solvents will be required in order to see if the selectivity can be increased in favour of **6** (Scheme 4).



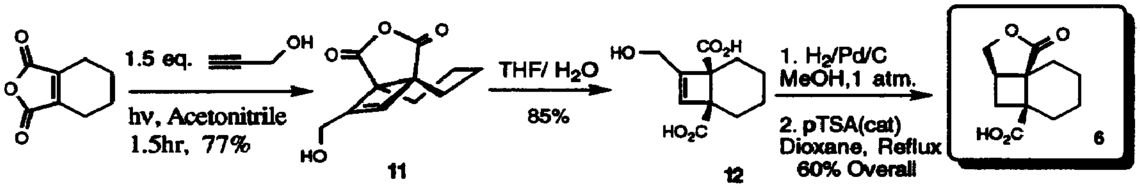
10 (80% isolated yield)

6

Solvent	Ratio
Acetonitrile	85:15
Benzene	69:31

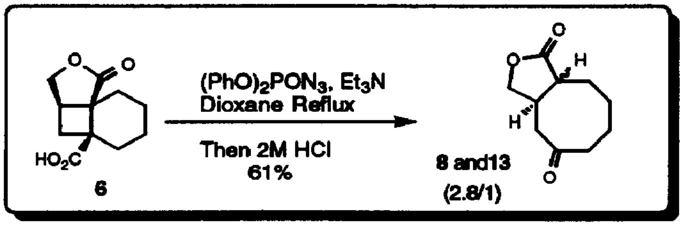
Scheme 4

A more efficient route to the acid ester **6** involved irradiation of a 0.08M solution of THPA with propargyl alcohol (1.5 eq.) for 1.5hr which yielded the slightly unstable cyclobutene anhydride **11** which could be isolated pure by rapid flash chromatography (77%). Hydrolysis in aqueous THF gave the stable crystalline diacid **12**. Hydrogenation followed by acid catalysed cyclisation of the resulting crude hydroxy diacid gave **6** in 60% overall yield from **12** (Scheme 5).

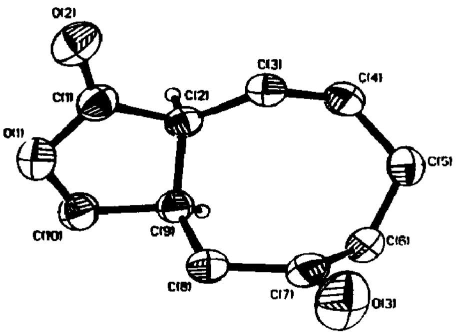


Scheme 5

We were now at a stage where we could investigate the novel aza de Mayo fragmentation by subjecting **6** to a Curtius rearrangement. This was conveniently achieved with diphenylphosphoryl azide[8] which smoothly converted **6** to the corresponding isocyanate (ν_{max} 2265cm^{-1}), this was not isolated but hydrolysed *in situ* to give the fragmented cyclooctanone-lactones **8** and **13** as a 2.8/1 mixture of *cis/trans* isomers[9] in 61% yield. X-ray analysis[10] of a single crystal of **8** confirmed the *cis* -stereochemical relationship at the ring junction (Scheme 6).



Scheme 6



Molecular structure of 8 (*Cis*)

The results of these successful model studies are currently been applied to the total synthesis of Asteriscanolide by investigating the intermolecular [2+2] photocycloaddition between THPA and 5,5-dimethyl-2-cyclopentenol and will be reported in due course.

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References and Notes

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7. All irradiations were conducted in a standard water cooled immersion well photoreactor (100ml) using a 125W mercury lamp.
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9. Selected spectral data for **8** (*cis*): ν_{max} 1765 and 1695 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 4.34 (dd,1H, Jgem= 9.23, Jvic= 5.94 Hz), 4.01(dd,1H, Jgem= 9.22, Jvic= 3.2 Hz), 3.3-3.12 (m, 1H), 2.9-2.27 (m, 5H), 2.23-1.9 (m, 3H), 1.88-1.67 (m, 1H), 1.52-1.18 (m, 2H); ^{13}C NMR (75.47 MHz) δ 212.91 (C=O), 177.63 (C=O), 71.03 (CH_2), 44.92 (CH), 42.82 (CH_2), 41.38 (CH_2), 36.24 (CH), 27.17 (CH_2), 26.83 (CH_2), 23.67 (CH_2); HRMS (CI) found: $M^+(+NH_4)$ 200.1291, $C_{10}H_{14}O_3NH_4$ requires 200.1287.

   13 (*trans*): ν_{max} 1770 and 1695 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ 4.38 (t, 1H, J= 7.86Hz), 3.74 (t, 1H, J= 9.46), 2.68-2.38 (m, 4H), 2.39-2.26 (dquin.,1H), 2.23-2.12 (dq,1H), 2.05-1.72 (m, 3H), 1.61-1.44 (m, 2H), 1.39-1.2 (m, 1H); ^{13}C NMR (75.47 MHz) δ 212.47 (C=O), 177.95 (C=O), 69.93 (CH_2), 45.19 (CH), 44.08 (CH_2), 41.95 (CH), 41.13 (CH_2), 26.51 (CH_2), 26.17 (CH_2), 24.77 (CH_2); HRMS (CI) found: $M^+(+NH_4)$ 200.1285, $C_{10}H_{14}O_3NH_4$ requires 200.1287.
10. Crystal data for **8** (*cis*): $C_{10}H_{14}O_3$, M=182.2, mpt=75-77°C, D_c= 1.367 gcm^{-1}. Crystal size 0.5 x 0.3 x 0.25mm from ethyl acetate/pet. ether (40-60°C). Triclinic $\bar{P}1$, Z=2, a = 6.390 (2), b = 8.385(2), c = 8.703 (3) Å, α= 78.57 (2), β= 85.51 (3), γ= 75.78° (2), V=442.8 (2) $Å^3$.T= 293 K, 2804 reflections collected, R = 4.87%, wR = 6.10% ($w^{-1} = \sigma^2(F) + 0.0006F^2$). Full crystallographic data deposited at the Cambridge Crystallographic Data Centre.

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