A Concise Synthesis of the Pseudoguaianolide Skeleton

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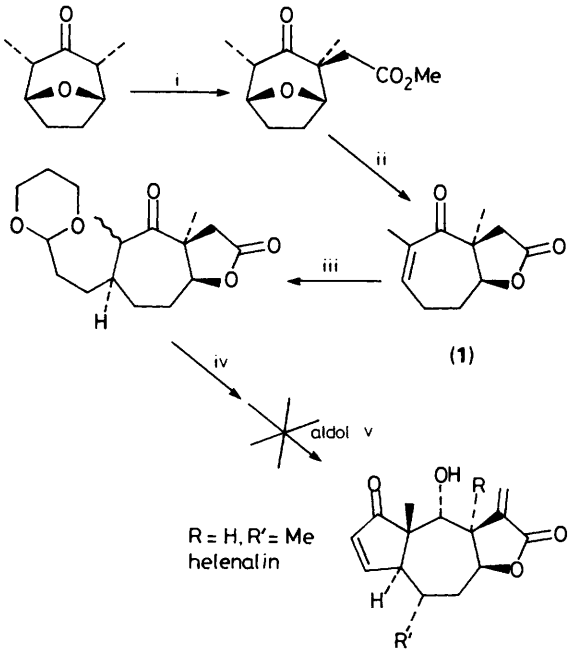
A four-stage conversion of the 8-oxabicyclo[3.2.1]octan-3-one skeleton into the pseudoguaianolide skeleton is described.

We have recently described[1] our initial attempts to effect the transformations shown in Scheme 1, where the final product has the same gross structure as a typical pseudoguaianolide sesquiterpene, *e.g.* helenalin. Our prime aim is to devise a short synthetic route that can be manipulated so as to provide gram quantities of various pseudoguaianolide-like structures for biological evaluation. In particular, we wish to probe the structural requirements (cyclopentenone, α-methylene lactone, unsaturated ester, *etc.*) for the various biological activities (anti-tumour, anti-bacterial, antifeedant, *etc.*) reported[2] for this class of isoprenoid.

The approach shown in Scheme 1 was unsuccessful because the aldol reaction failed; and to circumvent this problem, we adopted an approach that incorporates the cyclopentannelation of Demuth *et al.*[3] Thus 1,3-dimethyl-8-oxabicyclo[5.3.0]dec-3-en-2,9-dione (**1**) (prepared *via* the sequence shown in Scheme 1)[1] was irradiated for 20 hours (two 500W medium pressure mercury lamps through pyrex) in cyclohexane–THF (97:3) containing 2-trimethylsiloxybuta-1,3-diene (12 equiv.) to yield photoadduct (**2**) in 37% yield. This product crystallised directly from the reaction mixture (ν_{max} 1 784, 1 696, and 1 641 cm^{-1}); and although the stereochemistry at C-11 has not been assigned,



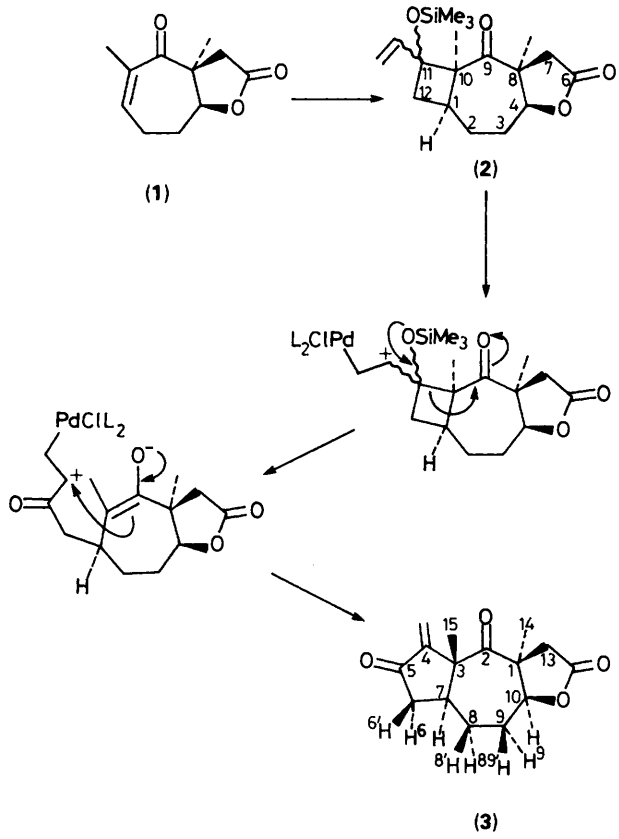
Scheme 1. *Reagents:* i, LDA, $BrCH_2CO_2Me$; ii, NaI/BF_3; iii, cuprate; iv, H^+; v, acid or base.

it was clear from a 220MHz NMR spectrum that only one regio- and stereo-isomer was present. In particular, there were discrete signals for each of the vinyl protons (dd at 5.20, *J* 10.5 and 1 Hz; dd at 5.32, *J* 17 and 1 Hz; dd at 6.00, *J* 17 and 10.5 Hz); one lone signal for the two methyl groups (s, 1.36); and the stereochemistry at C-1 (and by inference the stereochemistry at C-10) was established by NOE studies on the final product (**3**).

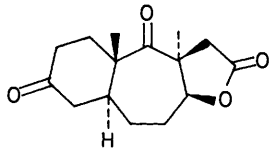
Reaction of (**2**) with bis(benzonitrile)palladium(II) chloride (3 mole %) in refluxing THF resulted in a smooth rearrangement[4] to provide the α-methylene ketone (**3**) in 95% yield (both this and the previous reaction were carried out on the one gram scale). The structure was confirmed by spectroscopic means: (ν_{max} 1 781, 1 728, 1 709, and 1 632 cm^{-1}); and key features of the NMR spectrum ($CDCl_3$, 400 MHz) included discrete singlets for the 15-Me and 14-Me (1.26 and 1.38) a multiplet for H-7 (2.59, $J_{7,6'}$ 13.0, $J_{7,6}$ 7.1, $J_{7,8}$ 4.9, $J_{7,8'}$ 13 Hz), a double doublet for H-10 (4.53, $J_{10,9'}$ 12.2, $J_{10,9}$ 1.2 Hz), and discrete singlets for the α-methylene hydrogens (5.37 and 5.97). In addition there were NOE enhancements between H-7 and H-10, and between H-10 and the 14-Me; but no effects were noted between the two methyl groups or between H-7 and the 15-Me group. In order to account for the fortuitous epimerisation at C-3, we suggest the mechanism shown in Scheme 2, whereby formation of an enolate precedes construction of the cyclopentanone ring.

The rather poor yield for the photochemical step deserves some comment. Attempts to improve the yield through the use of other solvents (THF, DME, acetonitrile) led to incomplete conversions or lower yields. In addition to the 37% yield of photoadduct (**2**), a mixture of other photoadducts (around 55% total yield) was obtained. When this crude mixture was submitted to the palladium-catalysed rearrangement procedure, a further quantity of product (**3**) was obtained, making the total yield for this compound around 45% for the two steps. However, the major product was the cyclohexanone (**4**) (*ca.* 14% yield for the two steps). The structure of this compound, in particular the *trans*-fusion of the [6,7]-ring system, was apparent from NOE studies; and its mechanism of formation is under investigation.

In conclusion, we have developed a concise and reasonably



Scheme 2.



(4)

efficient synthesis of the key tricycle (**3**). This is appropriately functionalised for conversion into analogues of helenalin, and into other more novel pseudoguaianolide-like structures, for biological evaluation.

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