Chemistry of Allene Sulphoxides: a New Methodology for the Synthesis of Spiroketals and 1,5-Dioxadecalin Ring Systems

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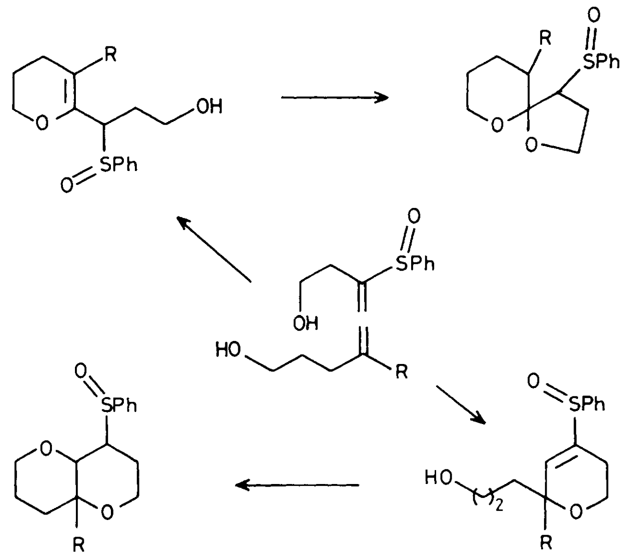
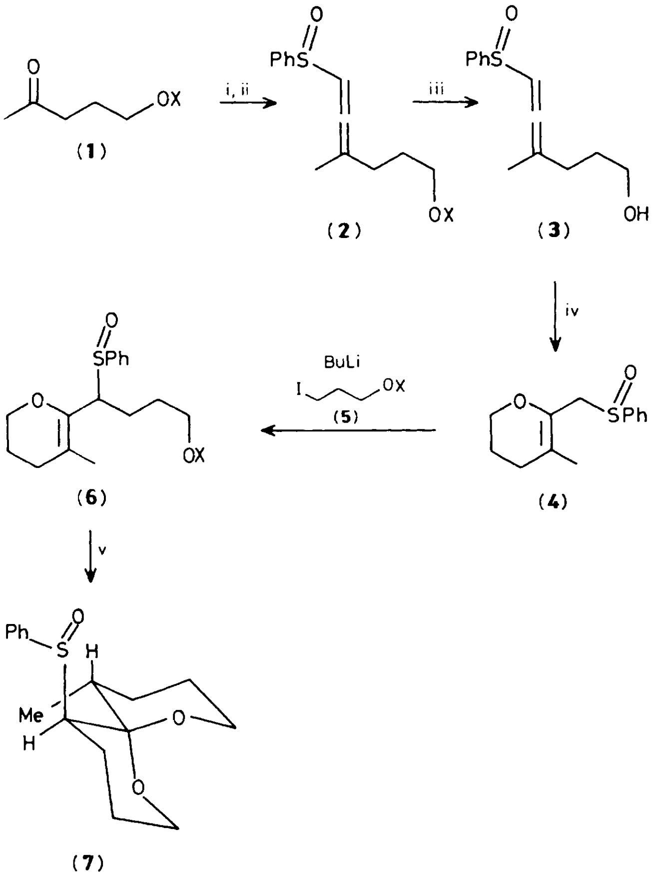
A new method for the construction of 1,5-dioxadecalins and spiroketals which utilises acid or base catalysed intramolecular additions of alcohols to allene sulphoxides is described.

Spiroketals are widely distributed in nature, and are found in molecules possessing an extremely wide range of biological activity. Examples of these include the anthelmintic avermectins and milbemycins,[1] the cytotoxic phyllanthosides[2] and calyculin A,[3] and molecules with pheromonal activity.[4] Equally the 1,5-dioxadecalins occur widely in nature and this structural unit is found, in, for example, okadaic acid[5] and brevetoxin.[6]

Although these molecules have attracted much synthetic effort[7] we became interested in the possibility of extending our

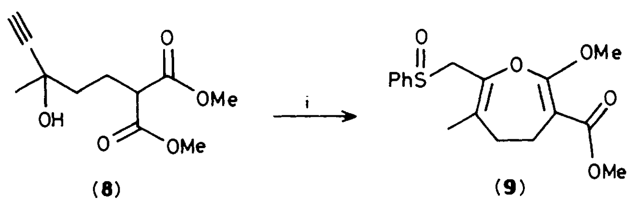


Scheme 1

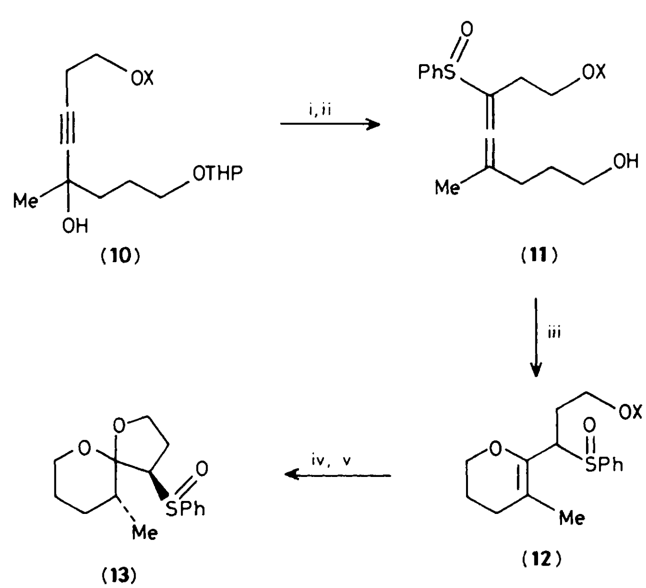


Scheme 2. *Reagents:* i, NaC≡CH; ii, PhSCl, Et_3N; iii, HF–MeCN; iv, NaH–THF; v, CSA–MeOH; X = $SiBu^tMe_2$.

allene sulphoxide chemistry to the synthesis of spiroketals and dioxadecalins. We have shown[8] that nucleophilic addition to allene sulphoxides can give usefully functionalised aldehydes and we now demonstrate the possibility of inducing a similar but intramolecular process, which can be used for the construction of spiroketals and 1,5-dioxadecalins (Scheme 1).



Scheme 3. *Reagents:* i, $PhSCl–Et_3N–Et_2O$.



Scheme 4. *Reagents:* i, $PhSCl–Et_3N$; ii, $MgBr_2–Et_2O$; iii, NaH–THF; iv, HF–MeOH; v, $CSA–CH_2Cl_2$; X = $SiBu^tMe_2$; THP = tetrahydropyran-2-yl.

Our initial experiments explored the possibility of using base catalysed cyclisations for the formation of oxygenated rings. Thus, treatment of the silylated ketone (**1**) (Scheme 2) with lithium acetylide in tetrahydrofuran (THF) gave an acetylenic alcohol, which was then converted into the allenyl sulphoxide (**2**).[8] Removal of the silyl protecting group with HF in wet (**3**) acetonitrile[9] gave the key alcohol (**3**). When the allene sulphoxide (**3**) was added to 5 mol % NaH in THF at room temp. the dihydropyran (**4**) was obtained in 97% yield. Metallation of (**4**) with BuLi in THF followed by alkylation with the iodide (**5**) gave the silyl ether (**6**). Removal of the silyl protecting group in (**6**) as before, followed by reaction of the resulting alcohol with a catalytic quantity of camphorsulphonic acid (CSA) in methanol, gave the spiroketal (**7**).†

Similarly, treatment of the acetylenic alcohol (**8**) with benzenesulphenyl chloride and triethylamine resulted in the formation of the seven-membered ring (**9**) (Scheme 3).

Encouraged by these results we prepared the spiroketal (**13**) using the route shown in Scheme 4. When the alcohol (**11**) was treated with sodium hydride (1 equiv. in ether) cyclisation occurred. After treatment of the resulting dihydropyran (**12**) with HF in methanol, the crude product was dissolved in dichloromethane containing a catalytic amount of CSA and from this mixture was isolated the spiroketal (**15**).† When the fully deprotected diol (**14**) (Scheme 5) was treated with

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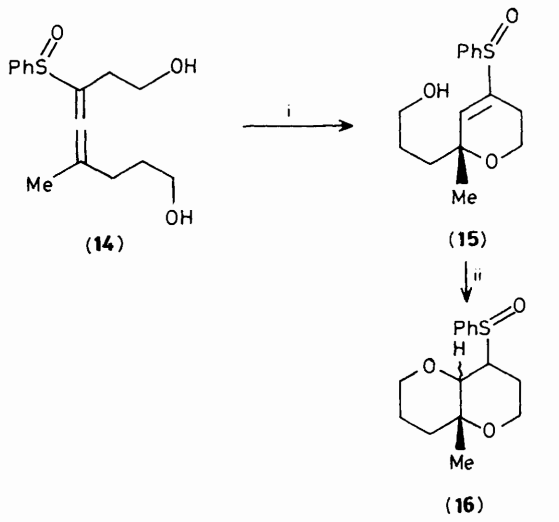
† Stereoisomeric mixture at S.



Scheme 5. *Reagents:* i, PTSA–C_6H_6; ii, NaH–THF.

toluene-*p*-sulphonic acid (PTSA) in boiling THF, the dihydropyran (**15**) was formed in 88% yield. Stirring (**15**) with a trace of NaH in dry THF gave the 1,5-dioxadecalins (**16**) which were isolated in 50% yield as a mixture of diastereoisomers.

This chemistry offers new routes to biologically important oxygen heterocycles.

Financial support by the S.E.R.C. is gratefully acknowledged.

Received, 6th July 1987; Com. 936

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