The Reaction of 1,1-Dimethoxyethylene with Bridgehead Enones. A Direct Approach to the Taxane Skeleton

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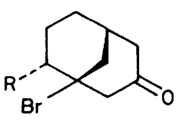
The bicyclo[5.3.1]undecene unit contained in taxanes can be constructed by a two-carbon ring expansion of a bicyclo[3.3.1]nonane using bridgehead intermediates.

Because of their high reactivity compared to simple cycloalkenones, bridgehead enones have significant potential for synthesis.[1] As House *et al.* have demonstrated, bridgehead enones can be readily prepared *in situ* from the corresponding bromoketones.[2] We now report the reaction of bridgehead enones with electron-rich alkenes.

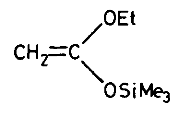
The bridgehead enones were prepared from (**1**) or (**2**) and triethylamine in methylene chloride at 0 °C in the presence of an electron-rich alkene (2—4 equiv.) as a trapping agent. The electron-rich alkenes used included the pyrrolidine enamine of cyclohexanone, ethyl vinyl ether, vinyl acetate, 1-trimethylsilyloxy-1-ethoxyethylene (**3**), the t-butyldimethylsilyl enol ether of acetaldehyde (**4**) and 1,1-dimethoxyethylene (**5**). Both the pyrrolidine enamine of cyclohexanone and vinyl acetate afforded complex mixtures of products when reacted with (**1**) and triethylamine. Ethyl vinyl ether and (**4**) did not react with (**1**). The reaction of (**3**) with the enone derived from (**1**) unexpectedly provided adduct (**6**). The reaction of (**5**) with (**1**) and triethylamine at 0 °C furnished adduct (**7**) in almost quantitative yield. Similarly, the reaction of (**5**) with (**2**) afforded (**8**). Both adducts were extremely labile on silica gel chromatography, resulting in the formation of esters (**9**) and (**10**). The cyclobutane formation is quite unusual. While cyclohexenone does not react to form cyclobutanes with electron-rich alkenes, cyclobutanes can be formed with some enones using either Lewis acid catalysis or high pressure techniques.[3]

The fragmentation of (**7**) to give (**11**) (Scheme 1) was then examined. This reaction is significant in that the bicyclo[5.3.1]undecene unit is a significant subunit in the taxane family of terpenes.[4] Several reaction conditions were examined to determine the optimal conditions for the fragmentation.[5] While most of these conditions produced some of ketone (**11**), the major product was ketone (**12**) [Li–$C_{10}H_8$ produced only (**12**), 73% yield]. The optimal conditions, Li in liquid NH_3, generated ketone (**11**) in 51% isolated yield with only 10% yield of (**12**).

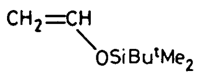
We then produced the diketone (**13**) by hydrolysis of (**11**) with pyridinium toluene-*p*-sulphonate (PPTS) in aqueous acetone. We expect that alkylation of (**13**) followed by a



(**1**; R = SPh)
(**2**; R = H)



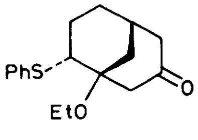
(**3**)



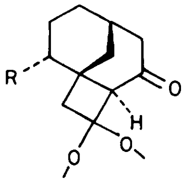
(**4**)

$(MeO)_2C = CH_2$

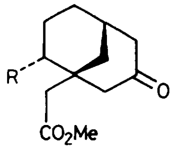
(**5**)



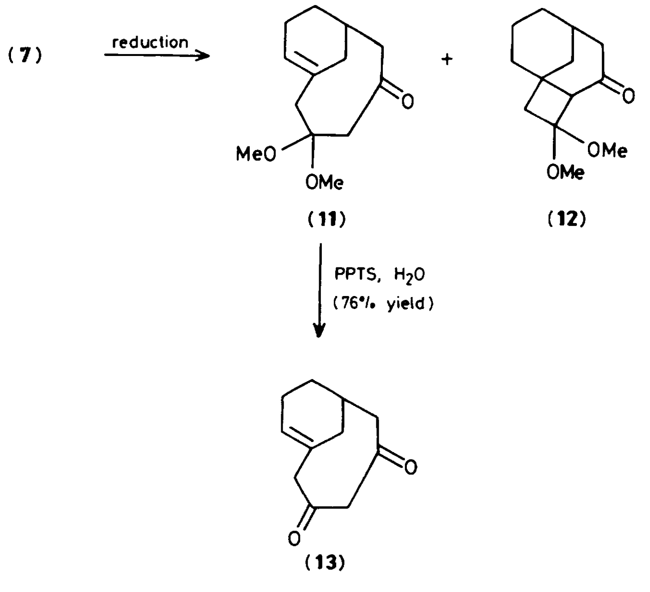
(**6**)



(**7**; R = PhS)
(**8**; R = H)



(**9**; R = PhS)
(**10**; R = H)



Robinson-type annulation will permit the completion of the taxane skeleton.

The conversion of (**1**) into (**11**) in two steps in 51% overall yield represents an unprecedented two-carbon ring expansion. Ketone (**1**) can be prepared from cyclohexenone in only three steps. This sequence represents an exceptionally direct entry to the bicyclo[5.3.1]undecene ring system.

Received, 6th July, 1987; Com. 943

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