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1,5 Allylic Abstraction, Cyclisation : A New Route To Five Membered Carbocycles[1]

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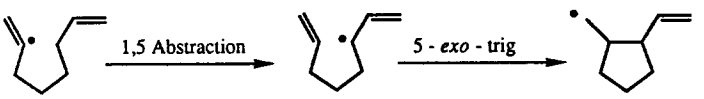
Abstract: A new 1,5 allylic abstraction cyclisation sequence has been developed. The method is based upon a novel radical rearrangement and is applicable to the construction of highly functionalised cyclopentanoid ring systems.

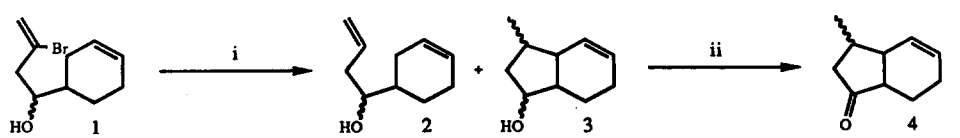
Previous reports have shown that free radical hydrogen atom abstraction followed by cyclisation may serve as a useful route to five and six membered carbocycles.[3,4,5] We envisaged that a 1,5 allylic abstraction, cyclisation strategy would provide an interesting new route to a variety of ring systems (scheme 1). In this letter we disclose our preliminary results, which show that such a strategy may be employed to generate a wide variety of functionalised carbocycles.

SCHEME 1



Our initial investigations were based upon the cyclisation of the vinyl bromide (1).[6] We believed that the alkenyl side chain in (1) would prefer to adopt a pseudo-equatorial position in the transition state[7] and consequently the only cyclised material observed would be (3). In the event, when the vinyl radical was generated from (1) using the "catalytic tin" conditions[8] we were delighted to find that the desired bicycle (3) was isolated *as the only cyclised product* (43%). Reduction product (2) was the only other material isolated from the reaction mixture (20%) (scheme 2). Oxidation of (3) using either Swern or PDC conditions gave the ketone (4) as a 1:1 inseparable mixture of diastereoisomers in moderate yield (scheme 2).

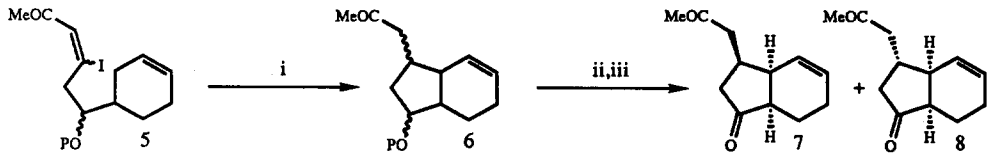
SCHEME 2



Reagents and Conditions; (i) Bu_3SnCl, $NaCNBH_3$, AIBN, t-BuOH, Δ, 3 days (63%) , (ii) PDC or Swern (40-50%)

In an attempt to enhance the abstraction pathway we decided to "activate" the acceptor olefin with an electron withdrawing group; the desired precursor (5) was constructed from commercially available 1,2,5,6-tetrahydrobenzaldehyde. We were pleased to find that treatment of either of the isomeric vinyl iodides[9] under standard "tin hydride" conditions led us to isolate the highly functionalised bicyclic ring system (6) *as the only product*, in good to excellent yield (61-78%). It is interesting to note that the reaction times were far shorter (one hour) than the three days required for the conversion of (1) to (3). We found that vinyl bromides could also be used for these reactions but longer reaction times and poorer yields (53-65%) were obtained. Deprotection and subsequent oxidation of (6) gave a chromatographically separable mixture of two diastereoisomeric ketones (7) and (8), in good yield (scheme 3). We believe that the electron withdrawing group is responsible for the marked improvement in the rate of the desired cyclisation.

SCHEME 3

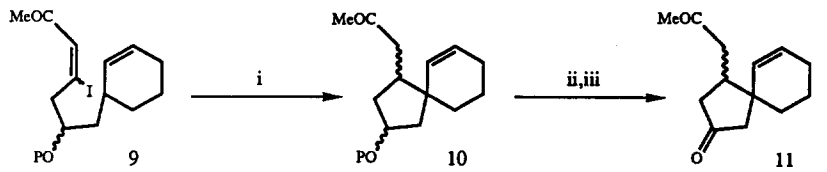


P = $Si(Me)_2$ (t-Butyl)

Reagents and Conditions: (i) Bu_3SnH, AIBN, Benzene, Δ, (61-78%) (ii) HF, MeCN, r.t., (73%) (iii) PDC, (62%)

Our attention next focused upon the synthesis of spirocyclic systems utilising this method; precursor (9) was synthesised from cyclohexenyl-acetaldehyde.[10] Successful cyclisation under the standard "tin hydride" conditions gave the desired spirocyclic product (10) as the only product.[11] Deprotection and oxidation of (10) gave (11) as an inseparable mixture of two diastereoisomeric ketones in good yield (scheme 4).

SCHEME 4



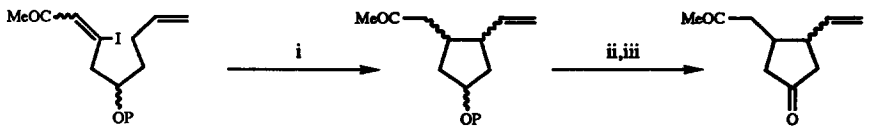
P = $Si(Me)_2$ (t-Butyl)

Reagents and Conditions: (i) Bu_3SnH, AIBN, Benzene, Δ, (45%) (ii) HF, MeCN, r.t., (97%) (iii) PDC, (62%)

In order to ascertain whether a 1,5 allylic abstraction, cyclisation process would compete with 6-*exo*-trig cyclisation a final experiment was required.[12] Precursor (12) was constructed from 4-pentenal[13] and then

subjected to the standard cyclisation conditions. We were once more delighted to find that the desired cyclised material (13) was isolated as the major product. Standard deprotection and oxidation of (13) gave the 3,4 disubstituted cyclopentanone (14) in moderate yield (scheme 5). We also isolated two minor products from the reaction which resulted from 6-*exo*-trig cyclisation and "reduction" (16% yield combined).[14]

SCHEME 5



12 13 14

P = $Si(Me)_2$ (t-Butyl)

Reagents and Conditions; (i) Bu_3SnH, AIBN, Benzene, Δ, (78%) (ii) HF, MeCN, r.t., (98%) (iii) PDC, (50%)

The isolation of (13) as the major product from this final experiment shows that even in a flexible molecule a 1,5 allylic abstraction, cyclisation can be the favoured reaction pathway in preference to a 6-*exo*-trig cyclisation. In addition it shows that cyclopentane systems can be constructed in synthetically useful reactions from acyclic precursors. We believe that our preliminary investigations show that this sequence should provide a powerful new method for the synthesis of highly functionalised five membered ring systems. Further applications of this method in natural product synthesis are ongoing and will be disclosed in due course.

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References and Notes:

1. This work was presented in part at the Society of the Chemical Industry Symposium symposium "Free Radicals in Organic Synthesis", 28th March 1989, London. For a full account of this work see S. Caddick PhD Thesis, University of Southampton (1989).
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