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Cyclobutylcarbinyl Radical Cleavage In The Bicyclo[3.2.0]heptanone Ring System.

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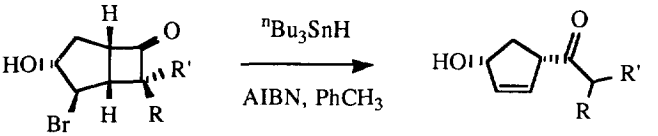
Abstract: A number of cyclobutylcarbinyl radicals were generated *via* tributyltin hydride treatment of bromohydrins derived from substituted bicyclo[3.2.0]heptenones. The radicals thus generated underwent regioselective ring-cleavage to form *cis*-disubstituted cyclopentenes.

The use of radicals in organic synthesis has greatly increased in recent years and is now an established aspect of contemporary synthetic methodology,[1] having been successfully applied in a number of elegant natural product syntheses.[2] Free radicals have also been utilised in the preparation of a variety of medium ring systems *via* ring-expansion.[3] Homolytic cleavage of a cyclobutyl ring has been a pivotal feature in several of the reported examples,[4] and current interest[5] has prompted us to disclose our own results in this area.

The bicyclo[3.2.0]heptanone ring system serves as a useful template in drug design, allowing regio- and stereoselective introduction of various functional groups.[6] We envisaged that this feature, combined with the apparent ease with which an appropriately functionalised cyclobutyl ring can undergo homolytic cleavage,[4,5]



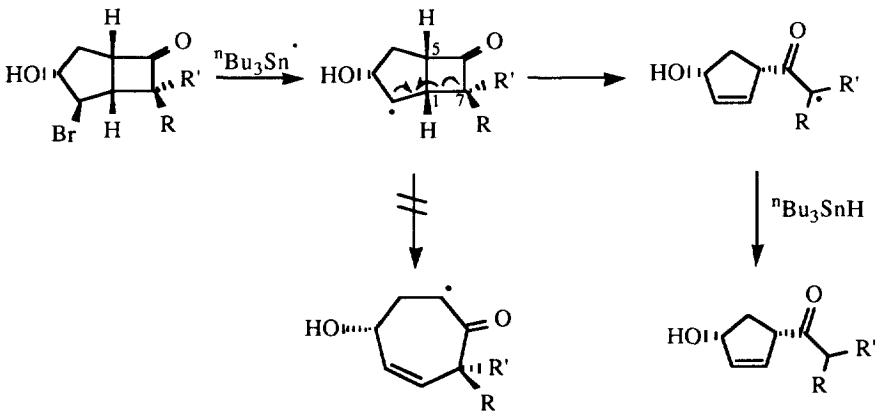
(1) R = H, R'= H
(2) R = $(CH_2)_3CO_2Me$, R'= H
(3) R = Me, R'= Me

(4) R = H, R'= H (39%)
(5) R = $(CH_2)_3CO_2Me$, R'= H (60%)
(6) R = Me, R'= Me (36%)

Scheme 1

could lead to functionalised seven membered ring templates *via* a radical ring expansion of bicyclo[3.2.0]heptanone derivatives. With peptidal side chains suitably appended, such substituted medium sized rings have the potential to serve as peptidomimetics.[7]

Treatment of the bromohydrins **1** to **3**[8] with tributyltin hydride and a catalytic amount of AIBN in refluxing toluene led not to the anticipated ring-expanded products, but to the *cis*-disubstituted cyclopentenes **4** to **6** in moderate yields[9] (Scheme 1). Of particular note is the observation that bromohydrin **1** leads to the product **4**, thus necessitating formation of a primary alkyl radical, albeit stabilised by the adjacent carbonyl group, in preference to the secondary radical that would be formed *via* cleavage of the C1-C5 bond(Scheme 2).



Scheme 2

These results may be explained as a consequence of the stereoelectronic requirement for such homolytic ring-cleavages, as outlined by Beckwith.[10] It would appear that efficient overlap of the C2 radical SOMO can only be achieved with the C1-C7 bond, presumably due to the relative rigidity of the bicyclo[3.2.0]heptanone ring system,[8] resulting in the formation of the ring opened products **4** to **6** in a highly regioselective manner.[11]

Roberts and co-workers have carried out detailed investigations into the preparation of homochiral bicyclo[3.2.0]heptanone derivatives.[12] The regioselectivity of cyclobutylcarbinyl radical cleavage in this particular ring system could therefore be extended to allow rapid access to *cis*-disubstituted cyclopentenes in an enantioselective fashion, which may in themselves serve as templates for further elaboration into novel peptidomimetics.

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