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Radical Fragmentation of Cyclobutanes: An Approach to Medium Ring Fused Carbocycles

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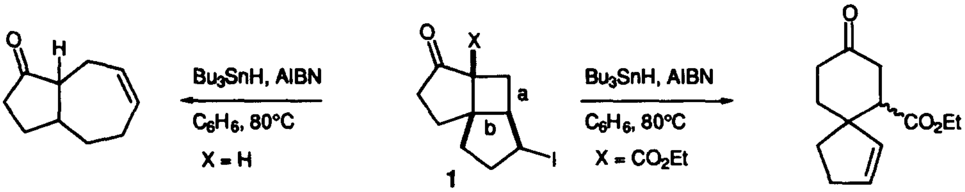
Abstract: *The combination of a zinc-copper mediated conjugate addition-cyclization, an intramolecular [2+2] photocycloaddition, and a radical fragmentation reaction provides access to a variety of medium ring fused carbocyclic systems in good overall yields.*

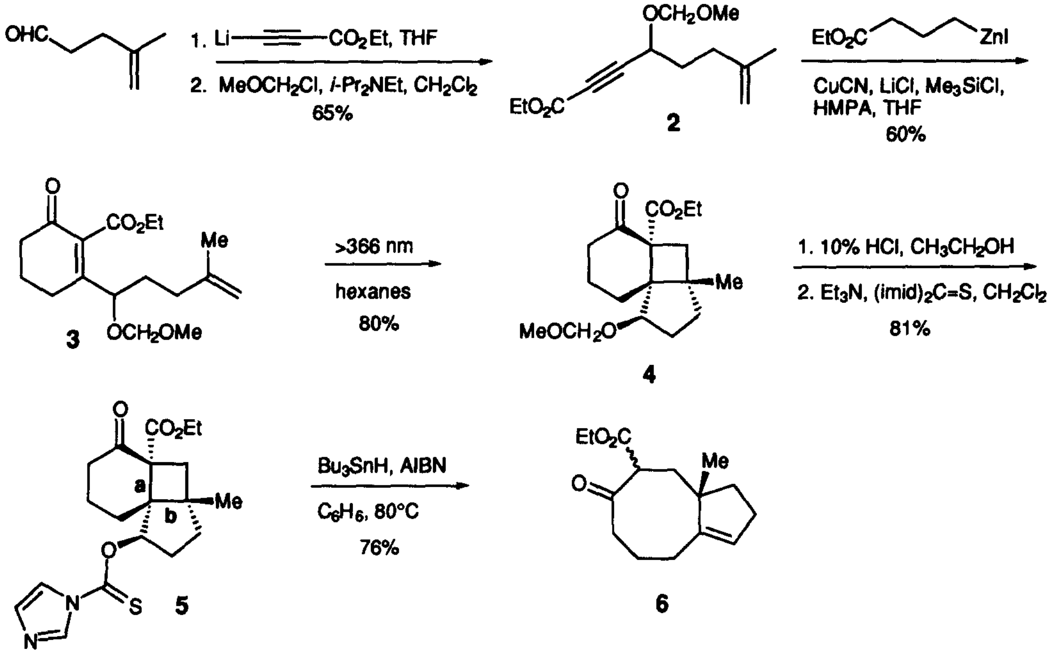
Addition of carbon radicals to pi-bonds is now a well accepted and useful method for the formation of carbon-carbon bonds in the construction of acyclic and cyclic systems.[1] In addition, radical fragmentation and rearrangement reactions, especially in the context of strained rings, have been exploited in a number of useful synthetic transformations in recent years.[2] We recently described a radical fragmentation reaction of the intramolecular [2+2] photocycloadducts **1** to construct spiro- and fused carbocycles (Scheme 1). The regioselectivity of the fragmentation of the cyclobutane of **1** (cleavage of bond a versus bond b) is sensitive to the angular substituent adjacent to the carbonyl.[3] We report here an alternative approach to medium rings which allows the rapid construction of a variety of ring sizes of fused carbocycles. The increasing interest in medium rings[4] is derived from the biological importance of a number of sesterterpenes and diterpenes, including the taxanes[5] and the ceroplastols,[6] which contain eight membered carbocyclic rings.

Scheme 1



The approach to fused medium ring carbocycles described herein relies on the combination of a zinc-copper mediated conjugate addition-cyclization reaction[7,8] with a stereoselective and regioselective intramolecular [2+2] photocycloaddition[9] followed by a radical fragmentation of the resultant cyclobutane.[3] The substrates for the radical fragmentation reaction are readily prepared in good yields as illustrated in Scheme 2. Addition of the lithium acetylide of ethyl propiolate to 4-methyl-4-pentenal followed by protection of the resultant alcohol as its methoxy methyl ether gave the acetylenic ester **2**. Treatment of the acetylenic ester **2** with the zinc copper reagent derived from ethyl 4-iodobutyrate in the presence of copper cyanide, Me_3SiCl and HMPA provided the carboethoxy cyclohexenone **3**.[8] Irradiation of a hexane solution of the cyclohexenone **3** generated a single diastereomeric photoadduct **4** in 80% yield. Hydrolysis of the methoxymethyl ether followed by acylation of the alcohol with 1,1'-thiocarbonyldiimidazole produced the radical precursor **5** in 81% yield. Slow addition of a solution of tributyltin hydride and AIBN to the thiocarbamate **5** in benzene at 80°C resulted in reductive cleavage of the cyclobutane to give a 76% yield of the fused carbocycle **6**. Selective cleavage of the cyclobutane bond exocyclic to the cyclopentane results from stabilization of the resultant radical by the two carbonyl groups and because of the excellent overlap of the SOMO with bond **a** in the intermediate radical.

Scheme 2

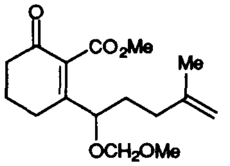
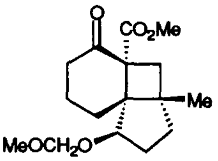
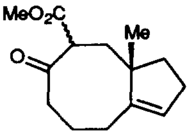
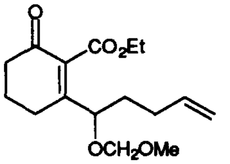
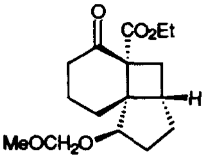
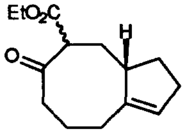
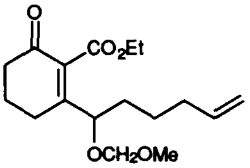
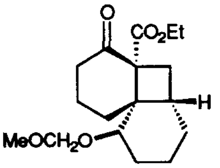
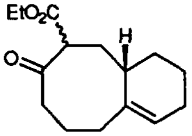
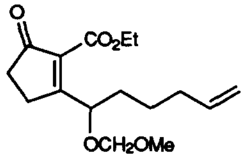
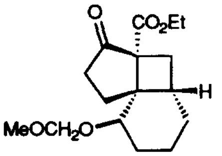
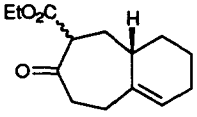
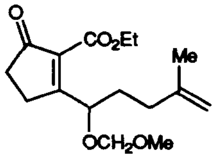
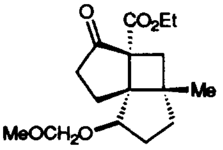
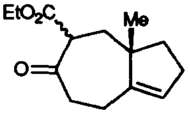


The sequence described above can be utilized to construct 5-8 fused ring systems as shown in entries 1 and 2 in the Table and to prepare 6-8 fused carbocycles as shown in entry 3 if the homologous aldehyde is used as the starting material. Use of the zinc copper reagent prepared from ethoxytrimethylsilyloxycyclopropane and zinc chloride in the conjugate addition cyclization reaction allows access to the carboethoxycyclopentenones as shown in entries 4 and 5.[7] Photocycloaddition followed by radical fragmentation as described above for the six membered ring analogs results in the preparation of the 5-7 fused carbocycles in good yields.

In a typical experimental procedure, the photosubstrate was dissolved in hexanes and irradiated with a 450W medium pressure Hanovia mercury vapor lamp for 4-12 h until the starting material was consumed (monitored by tlc). The solvent was removed in vacuo to provide the crude photoadduct which was purified by silica gel chromatography. The photoadduct was dissolved in 4:1 ethanol:10% HCl and heated to reflux for 1h.

After cooling to 25°C, the ethanol was removed in vacuo and the remaining aqueous layer was extracted 3 times with with ether. The combined ether layers were washed with sodium bicarbonate, dried and concentrated. The crude alcohol was dissolved in dichloromethane and 1.1 equiv of 1,1'-thiocarbonyldiimidazole and DMAP (10 mole %) were added. The mixture was stirred at room temperature for 4 h, washed with saturated sodium bicarbonate, dried and concentrated. The residue was purified by silica gel chromatography. The thiocarbamate was dissolved in dry, degassed benzene (0.005 M) and heated to reflux. A solution of 1.2 equiv. of tributyl tin hydride and AIBN (0.2 equiv) in benzene (0.02 M) was added over 4h by syringe pump. When the addition was complete, the benzene was removed at reduced pressure and the residue was taken up in ether and stirred overnight with saturated potassium fluoride solution. The ether layer was dried and concentrated and then purified by silica gel chromatography to provide the fused carbocyclic products.[10]

Table

Entry	Photosubstrate	Photoadduct	(yield)	Carbocycle	(yield)
1			(80)		(50)
2			(95)		(86)
3			(92)		(46)
4			(83)		(85)
5			(94)		(85)

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10. All new compounds gave consistent ^1H, ^{13}C and IR spectra as well as satisfactory C, H combustion analyses or HRMS. All yields are for homogeneous, chromatographically pure products unless otherwise indicated.

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