

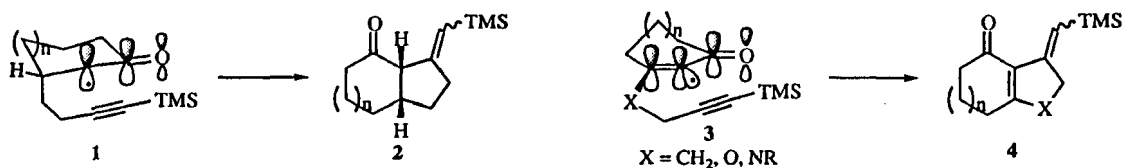
α -Carbonyl radicals for total synthesis of natural products

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Abstract: α -Carbonyl radicals, generated from the corresponding α -iodo ketones, enones, or vinylogous esters and amides, undergo intramolecular cyclization to the tethered trimethylsilylacetylenic side chain to afford the bicyclic vinylsilane ketone or enones. These radical cyclizations are applied to total syntheses of natural products.

Intramolecular radical cyclization proves useful to elaborate spiro and fused carbocyclic and heterocyclic structures. α -Carbonyl radicals **1** and **3**, generated from the corresponding α -iodo compounds, undergo intramolecular cyclization to afford bicyclic vinylsilane ketones **2** and enones **4**.¹



α -Ketone radical **1** is stabilized by the α -carbonyl π -system by resonance, whereas radical **3** that has an orbital orthogonal to the enone π -system can not be stabilized. Therefore, enone radical **3** in general is more nucleophilic than ketone radical **1** and undergoes cyclization more rapidly. We reported many instances of intramolecular cyclization of α -ketone and α -enone radicals, shown in Tables 1 and 2. In a typical reaction, the α -iodo ketone was treated with tributyltin hydride on slow addition over a period 6 h, whereas the α -iodo enone was treated with tributyltin hydride on rapid addition in one portion. Slow addition of tributyltin hydride is necessary for cyclization of α -ketone radicals because they undergo cyclization slowly. Higher concentration of tributyltin hydride causes reduction of the α -ketone radical before its cyclization.

Spirocyclization of an α -ketone radical is also facile. Ketone **52** was first transformed to its enolsilyl ether and then iodinated with sodium iodide and *m*-chloroperbenzoic acid to give α -iodo ketone **53**. Treatment of α -iodo ketone **53** with tributyltin hydride and AIBN on slow addition gave spiro ketone **54**.^{1a} Tandem radical cyclization has also been achieved. α -Iodo ketone **55** was treated with tributyltin hydride and AIBN to afford tricyclic ketone **56**.²

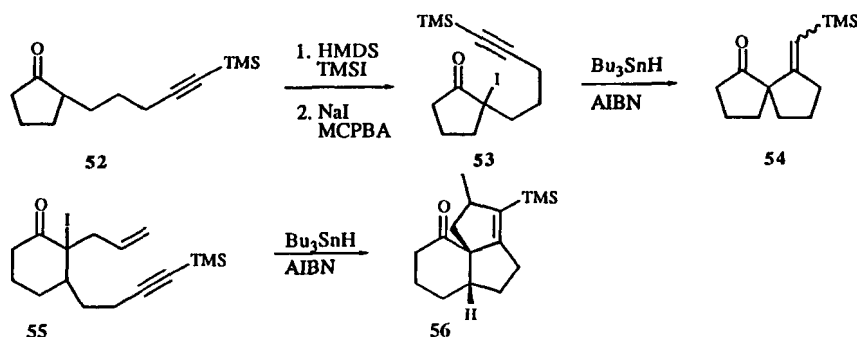


Table 1. Intramolecular Radical Cyclization of α -Carbonyl Radicals Generated from α -Iodo Ketones

Entry	Enolsilyl Ethers	α -Iodo Ketones	Cyclized Products
1			
2			
3			
4			
5			
6			

We applied this intramolecular radical cyclization to synthesize (\pm)-modhephene (**57**).^{1b} Total syntheses of enantiomerically pure (-)-5-oxosilphiperfol-6-ene (**58**)³ and (-)-dendrobine (**59**)⁴ according to this approach are currently in progress, and will be discussed in the lecture.

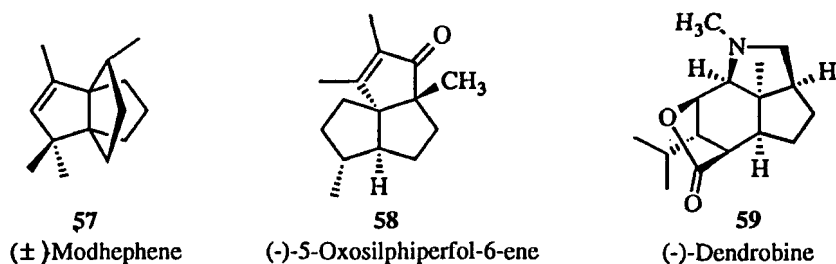


Table 2. Intramolecular Cyclization of Enone Radicals

Entry	Enone	Iodination Method and Conditions	Iodo Enone		Bicyclic Enone	
1		(A) NaN_3 , ICl CH_3CN , 24 h		52%		81% (Z:E = 8:7)
2		(A) NaN_3 , ICl CH_3CN , 24 h		50%		18%
3		(A) NaN_3 , ICl CH_3CN , 24 h		54%		70% (Z:E = 2:1)
4		(B) I_2 , DMF 2 h		88%		84% (Z:E = 2:5)
5		(B) I_2 , DMF 2.5 h		85%		81% (Z:E = 5:4)
6		(C) I_2 , CH_3CN 40 min		46 R = H 90% 47 R = <i>t</i> -Boc		89% (Z:E = 11:1)
7		(C) I_2 , CH_3CN 40 min		50 R = H 95% 51 R = <i>t</i> -Boc	—	—

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References and Notes

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