

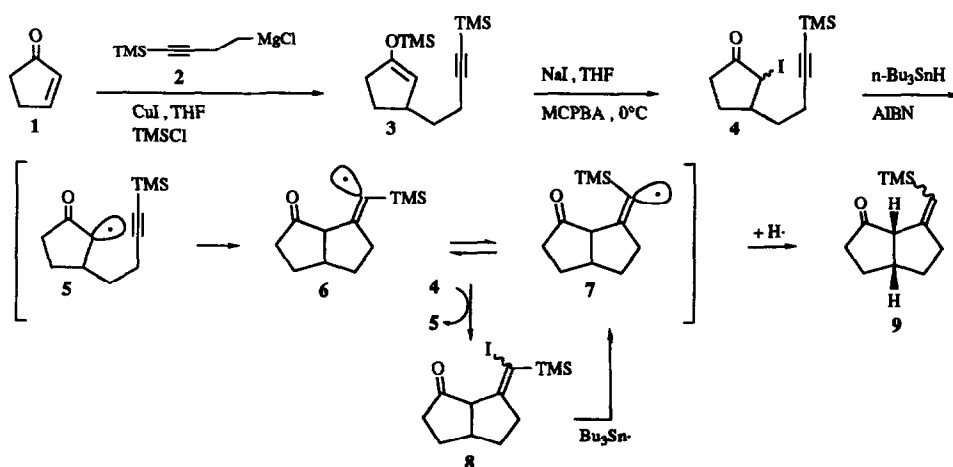
INTRAMOLECULAR RADICAL CYCLIZATION OF SILYLACETYLENIC OR OLEFINIC α -IODO KETONES: APPLICATION TO THE TOTAL SYNTHESIS OF (\pm)-MODHEPHENE

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Summary: Silylacetylenic or olefinic α -iodo ketones were treated with tributyltin hydride and AIBN to give bicyclic ketones by an intramolecular α -carbonyl radical cyclization reaction. As an application of this radical cyclization reaction, the total synthesis of (\pm)-modhephene has been accomplished efficiently.

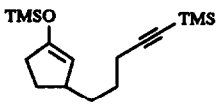
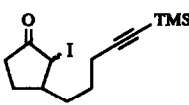
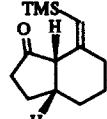
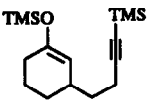
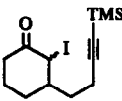
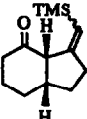
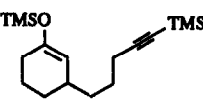
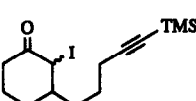
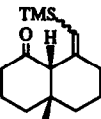
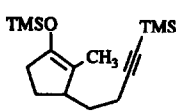
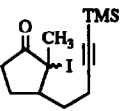
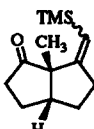
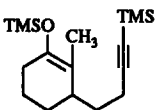
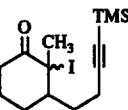
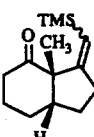
Intramolecular radical cyclization reactions have been proven synthetically useful to elaborate spiro and fused carbocyclic and heterocyclic structures.¹ Many applications for the total synthesis of natural products have further demonstrated the generality and utility of this reaction.² Since we recently discovered a facile and regioselective method for the synthesis of α -iodo ketones,³ we decided to investigate the intramolecular cyclization reaction of α -carbonyl radicals generated from α -iodo ketones.⁴ We here report the preliminary results of this investigation which lead to a new synthesis of bicyclic vinylsilane ketones and an efficient total synthesis of (\pm)-modhephene.⁵

Conjugate addition of Grignard reagent **2** to cyclopentenone **1** mediated by cuprous iodide, followed by trapping enolate with trimethylsilyl chloride, yielded trimethylsilyl enol ether **3**. Treatment of **3** with sodium iodide and *m*-chloroperbenzoic acid afforded α -iodo ketone **4** regioselectively (*trans* : *cis* = 3 : 1).³ When α -iodo ketone **4** bearing the silylacetylenic chain β to the carbonyl group was treated with tributyltin hydride and AIBN (azobisisobutyronitrile), an intramolecular radical cyclization occurred smoothly to afford the bicyclic vinylsilane ketones **9** (81%, *Z* : *E* = 7 : 3).⁶



Presumably, the reaction of α -iodo ketone **4** with tributyltin radical produces the α -carbonyl radical **5**. Intramolecular cyclization of radical **5** gives the vinylsilyl radicals **6** and **7** which are in equilibrium. Preferential abstraction of a hydrogen atom from tributyltin hydride by **7** affords a mixture of the *Z* and *E* isomers of **9** in 7 : 3

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

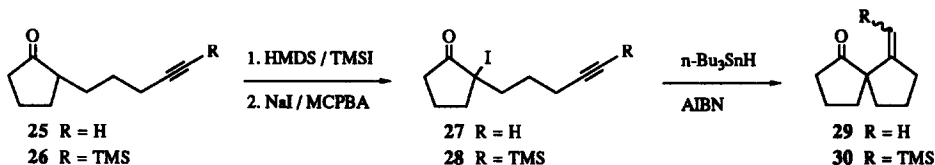
entry	enol silyl ethers	α -iodo ketones ^b	cyclized products ^{b,c}
1			 12 43% (Z)
2			 15 73% (Z:E = 6:1) ^d
3			 18 40% (Z:E = 9:1) ^d
4			 21 75% (Z:E = 4:1) ^f
5			 24 65% (Z:E = 5:1) ^f

a. The reactions were performed by the slow addition (6 h) of a solution of Bu_3SnH (0.08 M, 1.1 eq) and AIBN (0.05 eq) in benzene to a solution of the substrate (0.02 M) in benzene at 80°C . b. Isolated yields. c. The uncyclized reduction products were 40% for entry 1, 0% for entry 2, 45% for entry 3, 10% for entry 4, and 15% for entry 5. d. The ratios were determined by ^1H NMR spectra integration. e. The *trans* to *cis* ratio was not determined. f. The Z:E ratios were based on the isolated yield.

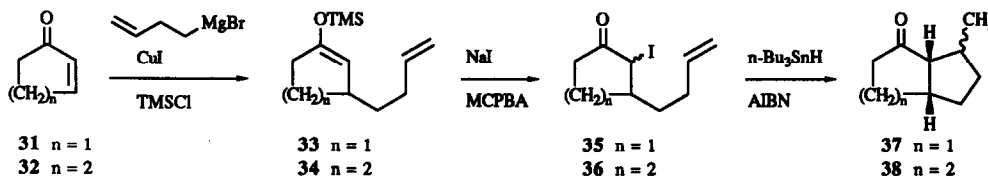
ratio. However when a reaction was carried out in an NMR tube and carefully monitored by ^1H NMR spectroscopy, we observed the formation of vinyl iodide **8** via a second reaction pathway. Apparently, vinyl radicals **6** and **7** can also react with α -iodo ketone **4** in a radical chain transfer step to give **8** and regenerate **5**; subsequently vinyl iodide **8** reacts with new tributyltin radical to go back to **6** and **7** which finally lead to product **9**. The radical chain transfer pathway observed in this reaction is in accord with Curran's iodine atom transfer

mechanism.^{2c} Other examples of this intramolecular radical cyclization reaction are summarized in Table 1. As we expected, the cyclizations leading to five-membered rings gave products in good yields, such as entries 2, 4, and 5. The major side products resulted from the direct reduction of α -iodo groups by tributyltin hydride.

On the other hand, acetylenic ketone **25**⁷ was treated with trimethylsilyl iodide and hexamethyldisilazane, followed by sodium iodide and *m*-chloroperbenzoic acid, to give the α -iodo ketone **27**. Treatment of **27** with tributyltin hydride and AIBN produced the spiro ketone **29** (47%). The same sequence of reactions starting from ketone **26**⁷ but with a 2-silylacetylenic side chain gave spiro vinylsilane ketone **30** (78%).

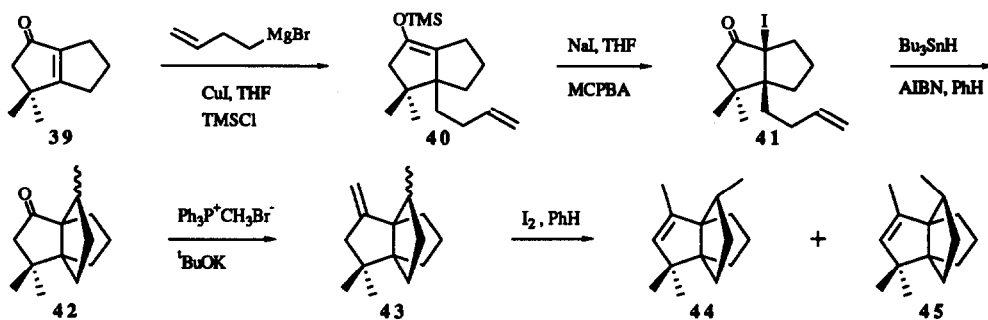


Furthermore, upon the treatment of tributyltin hydride and AIBN, iodo ketones **35** and **36**⁸ with an olefinic side chain were also cyclized to give bicyclic ketones **37** (60%) and **38** (25%) respectively.



Finally, application of this reaction sequence to the total synthesis of (\pm)-modhephene was carried out as shown in scheme 1. Conjugate addition of 3-butenylmagnesium bromide to enone **39** mediated by cuprous iodide, followed by the trapping of the enolate with trimethylsilyl chloride, afforded the trimethylsilyl enol ether **40** (80%). Treatment of **40** with sodium iodide and *m*-chloroperbenzoic acid gave α -iodo ketone **41** (67%). Treatment of **41** with tributyltin hydride and AIBN produced the tricyclic ketone **42** (85%, *anti* : *syn* = 4 : 1).⁹ It is notable that the same transformation employing intramolecular ene reaction afforded only the undesired isomer with a *syn* methyl group.^{5b} Wittig reaction of the mixture **42** with triphenylmethylphosphonium bromide and potassium *tert*-butoxide gave **43** (72%). Treatment of **43** with iodine gave a mixture of (\pm)-modhephene **44** and epi-(\pm)-modhephene **45** (81%, **44** : **45** = 4 : 1).¹⁰

In conclusion, we have demonstrated that α -iodo ketones can be prepared regioselectively and used to generate α -carbonyl radicals to effect an intramolecular radical cyclization reaction. This reaction sequence is synthetically practical and under very mild reaction conditions. The corresponding transformation involving the intramolecular ene reaction needs high temperature conditions, which commonly cause the thermal rearrangement of the products.¹¹ The application of this methodology for the total synthesis of (\pm)-modhephene further proves the usefulness of this radical cyclization reaction. Other applications of this reaction sequence are under current investigation.



Scheme 1

ACKNOWLEDGEMENT: Financial support by the National Science Council of the Republic of China is gratefully acknowledged.

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(Received in Japan 7 May 1990)