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A Conjunctive Diquinane Synthesis Using a Free-Radical Catalyzed Intramolecular [3 + 2] Methylenecyclopentane Annulation

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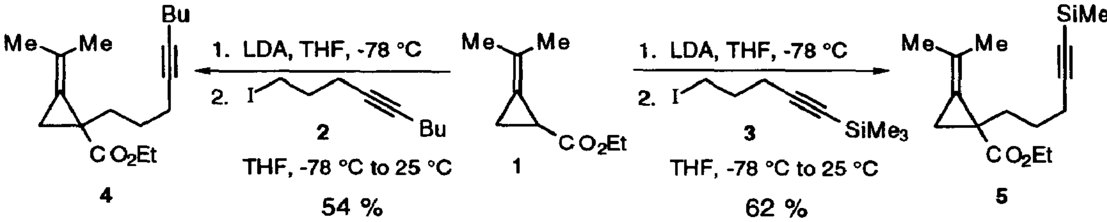
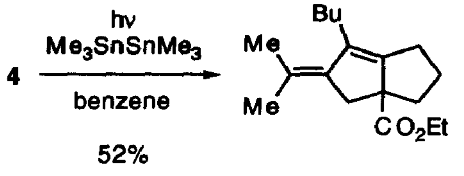
Abstract: Alkylation of the methylenecyclopropane 1 with 4-alkynyl iodides followed by a free-radical mediated intramolecular methylenecyclopentane annulation composes a quick and efficient new diquinane synthesis.

A multitude of [3-atom + 2-atom] cycloaddition-type methods for cyclopentane ring synthesis have been developed in recent years, with diverse applicability and limitations. Intramolecular cycloadditions are a powerful strategy for the synthesis of polycyclics, and intramolecular versions of the [3 + 2] cyclopentane syntheses have provided some spectacular reactions.[1] However, the intramolecular variants have only been developed for a small portion of these reactions. This is probably due to difficulties in obtaining the appropriate starting materials, a sticking point for intramolecular reactions in general.[2] We were intrigued by the likely facility of setting up intramolecular examples of our methylenecyclopentane annulations[3] through the alkylation of methylenecyclopropanecarboxylates. We report here the success of this conjunctive two-step strategy for diquinane synthesis.

Methylenecyclopropanecarboxylate **1**, readily available from the cyclopropanation of 1,1-dimethylallene with ethyl diazoacetate,[3b,4] is easily alkylated under standard conditions. Deprotonation of **1** with LDA at -78 °C in THF followed by treatment with alkynyl iodides **2** and **3**[5] afforded the alkynyl substituted methylenecyclopropanecarboxylates **4** and **5** in good yield.



All attempts to catalyze the cycloisomerization of **4** or **5** under conditions previously successful in intermolecular reactions failed. The use of both butyl disulfide/hv and phenyl disulfide/AIBN as catalysts predominantly afforded reduced products regardless of changes in concentrations and amounts of disulfide added. Early attempts to catalyze intermolecular annulations with distannanes had not worked,[3a] but our recent success in mediating allylations and vinylations with hexaalkyldistannanes/hv[6] prompted us to investigate the use of distannanes with **4** and **5**. We were encouraged to find that irradiation of a benzene solution of **4** and 20% hexabutyldistannane through pyrex (>300 nm) in a Rayonet photochemical reactor very slowly formed the desired bicyclic product **6** over the course of 10 days. Better results were obtained with hexamethyldistannane, in which case the reaction proceeded to completion in two days to afford a 52% yield of **6**.



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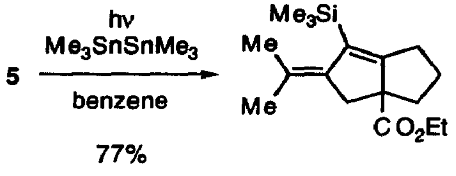

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Even better results were obtained with the silylalkyne **5**. The hexabutyldistannane catalyzed reaction of **5** afforded **7** in 57% yield after 10 days, and the hexamethyldistannane proceeded to completion in 2 days to afford a 77% yield of **7**.[7] The array of electrophilic reactions possible for the vinylsilanes[8] like **7** should make it a highly versatile intermediate for the synthesis of assorted diquinanes.

These free-radical cycloisomerizations should be complementary to other intramolecular [3 + 2] annulations. In summary, we have introduced a strategy for the rapid construction of diquinanes for which diverse applications should be possible.[9]

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2. For example, see the discussion on page 1771 of: Vandewalle, M.; De Clercq, P. *Tetrahedron* **1985**, *41*, 1767.
3. (a) Singleton, D. A.; Church, K. M. *J. Org. Chem.* **1990**, *55*, 4780-4782. (b) Singleton, D. A.; Huval, C. C.; Church, K. M.; Priestley, E. S. *Tetrahedron Lett.* **1991**, *32*, 5765-5768. (c) Singleton, D. A.; Church, K. M.; Lucero, M. J. *Tetrahedron Lett.* **1990**, *31*, 5551-5554. (d) For a full paper on this work, see: Huval, C. C.; Singleton, D. A., submitted.
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7. Example procedure: A mixture of 47.3 mg (0.16 mmol) of **5**, 56.5 mg (0.17 mmol) of hexamethyldistannane, and 1.0 mL of C_6D_6 were placed in a 5 mm pyrex tube and sealed with a septum. After bubbling nitrogen through the solution for 20 min, the tube was irradiated in a Rayonet photochemical reactor with 9 300-nm lamps for 2 d. The solution was concentrated on a rotary evaporator, and the residue was chromatographed on silica gel using 1% EtOAc in petroleum ether as eluant to afford 36.2 mg (77%) of **7**.
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9. We thank the NIH for support of this research.

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