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RADICAL CLEAVAGE OF CYCLOBUTANES: ALTERNATIVE ROUTES TO (±)-SILPHINENE

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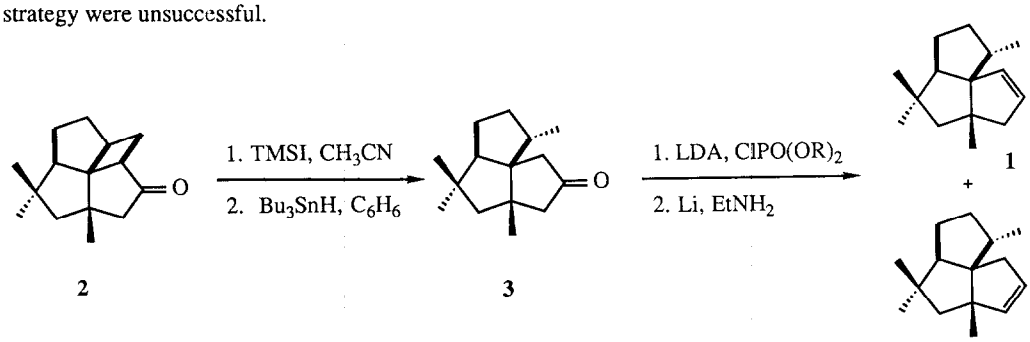
Abstract: A tributyltin hydride reduction and an atom transfer fragmentation of a iodomethyl cyclobutane have been used to complete two modified syntheses of silphinene with complete regioselectivity in the introduction of the silphinene double bond.

Recently we reported a total synthesis of (±)-silphinene **1** which relied on an intramolecular photocycloaddition to produce fenestrane **2** (41% overall in eight steps from 4,4-dimethylcyclopentenone) as the key intermediate.[2] A selective cyclobutane cleavage with trimethylsilyl iodide in refluxing acetonitrile provided ketone **3** as the precursor to silphinene. This synthesis suffered from low regioselectivity in the introduction of the double bond (4.5:1 silphinene:isosilphinene) due to the need to regioselectively enolize ketone **3** to convert it to its enolphosphate for reduction to silphinene. During the course of this synthesis, several attempts were made to couple the cyclobutane fragmentation with the introduction of the double bond to allow complete regioselectivity in the olefin introduction. Unfortunately, all attempts to implement this strategy were unsuccessful.

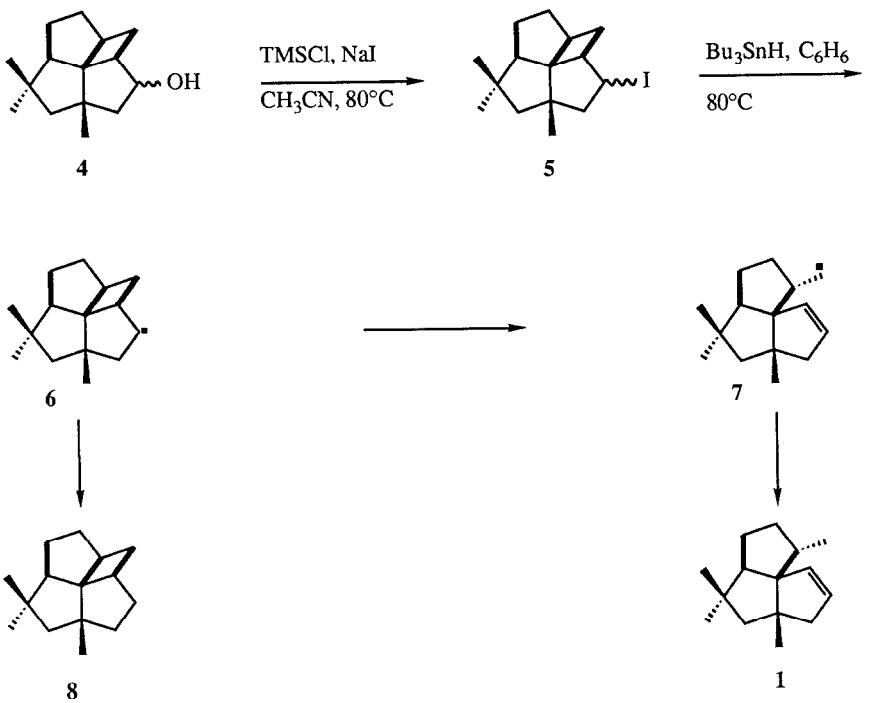


2 **3**

Subsequent to the completion of the synthesis of silphinene it occurred to us that it might be possible to accomplish the cyclobutane fragmentation concomitantly with the double bond introduction *via* a radical process if the carbonyl of **2** could be converted to a radical progenitor. To this end, ketone **2** was treated with diisobutyl aluminum hydride in ether at 25°C to produce a mixture of alcohols **4**[3] in 97% yield (Scheme 1). This mixture of alcohols could be directly converted to a mixture of iodides **5** in 98% yield by exposure to trimethylsilylchloride and sodium iodide[4] in acetonitrile at reflux for 4h. At this point it was anticipated that

exposure of the iodides **5** to tributyltin hydride in benzene at reflux would generate the radical **6** which would undergo ring opening to radical **7**. This radical would capture a hydrogen atom to produce silphinene directly from iodide **5**. When this reduction was carried out with a stoichiometric amount of tributyltin hydride in benzene at 80°C (0.01 M), a 1:1 mixture of silphinene:hydrocarbon **8** was isolated.

Scheme 1



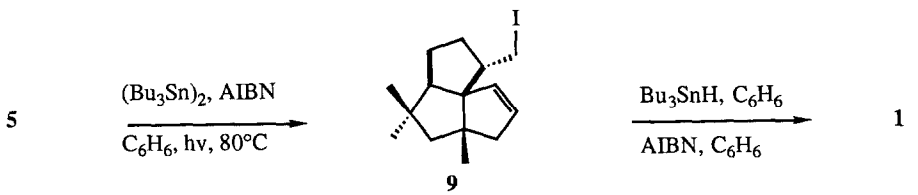
As observed in the reduction of iodide **5**, the major problem with this reaction is the competition of direct reduction (to give **8**) with ring opening followed by reduction (to produce **1**).[5-8] The obvious solution to the problem is to determine conditions which will either suppress the rate of direct reduction or increase the rate of ring opening, or both. Rate studies have been performed on reactions of this type which indicate that the rate constant for hydrogen atom abstraction for cyclobutyl carbinyl radicals is higher (9.5×10^5 $Lmol^{-1}s^{-1}$, 25°C) than that of the ring cleavage reaction (4.5×10^2 s^{-1}, 25°C) to pentenyl radical. It is also known that the rate constant for ring cleavage of the cyclobutane (5.3×10^3 s^{-1}, 60°C) increases more than does the rate of hydrogen atom abstraction (2.23×10^6 $Lmol^{-1}$ s^{-1}, 60°C) as the temperature is increased.[7] A trend toward increased amounts of ring cleavage products at higher temperatures has been observed in two studies.[8] Therefore, it would seem that higher temperatures and/or higher dilution should increase the ratio of **1**:**8** in the reduction of iodide **5**.

One convenient method for carrying out tributyltin hydride reductions at low concentration is to utilize a catyltic amount of tributyltin chloride accompanied by a stoichiometric amount of an appropriate reducing agent such as sodium borohydride.[9] When a solution of iodide **5** in absolute ethanol was treated with 0.1 equiv. of tributyltin chloride and a stoichimetric amount of sodium borohydride in a sealed tube at 150°C for two hours a >20:1 ratio of silphinene **1** : hydrocarbon **8** was obtained in quantitative yield. Alternatively, if **5** was heated to reflux in benzene followed by the very slow (syringe pump over 6h) addition of a solution of one equiv. of tributyltin hydride and a catalyic amount of AIBN in benzene, thus maintaining an extremely low concentration of tributyltin hydride at all times,[10] silphinene **1** was the only isolated product in 95% yield.

Reduction of 5	**Ratio of 1:8**
Bu_3SnH (1.0 equiv), C_6H_6, 80°, AIBN (0.01 M)	1:1
Bu_3SnCl (0.1 equiv.), $NaBH_4$ (1.0 equiv.), EtOH, 150°C	>20:1
Bu_3SnH (1.0 equiv.), C_6H_6, 80°C (syringe pump addition)	100:0

During the course of this study a publication by Curran appeared concerning atom transfer cyclizations of vinyl iodides.[11] This prompted us to investigate the possibility of executing an atom transfer fragmentation on iodide **5** as an alternate solution to minimize the problem of direct reduction of the cyclobutylcarbinyl radical. In fact Kaplan had observed a similar reaction on cyclobutylmethyl iodide nearly 20 years ago when he exposed cyclobutylmethyl iodide to 5% dibenzoyl peroxide. However, he obtained only a 2:1 mixture of 5-iodo-1-pentene:cyclobutylmethyliodide.[12] When **5** was treated according to the conditions described by Curran (10 mol % $Bu_3SnSnBu_3$, C_6H_6, hv, 80°C) for 2h, an 85% yield of iodide **9** was isolated. The absence of a source of hydrogen atom allows radical **6** to be sufficiently long-lived to open completely to **7**. Radical **7** then further propogates the chain by abstraction of an iodine atom from **5**. If **6** abstracts an iodine atom from **5** the chain is not terminated. Subsequent reduction of **9** with tributyltin hydride in benzene at 80°C provided another route to silphinene in 90% yield. A greater utility for this radical fragmentation may lie in the furhter manipulation of the resultant iodides.

Scheme 2



Thus, *via* the first route described above **1** was prepared with complete stereo and regioselectivity in 11 operations in an overall yield of 37% from 4,4-dimethylcyclopentenone. Current efforts are directed toward studying the generality of these processes in these and other related systems.

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1. Fellow of the A. P. Sloan Foundation, 1986-88.

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3. All new compounds gave satisfactory combustion analyses and consistent 250 MHz ^{1}H NMR and IR spectra. All yields are for isolated chromatographically pure material unless otherwise noted.

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