needles with mp 212–215 °C dec (lit.[2] mp 215 °C for (+)-cortisone). The synthetic material was identical with an authentic (optically active) sample by 200-MHz ^{1}H NMR and 50-MHz ^{13}C NMR and TLC mobility under different conditions (50% ethyl acetate/hexane × 3, R_f = 0.29; 75% ether/hexane × 7, R_f = 0.26; 40% ethyl acetate/benzene × 3, R_f = 0.29).

Adrenosterone 49. To a stirred mixture of potassium bicarbonate (88 mg, 0.88 mmol) and mCPBA (80%, 17.2 mg, 0.080 mmol) in methylene chloride (1 mL) was added a methylene chloride solution of the enol silyl ether **47** (16.5 mg, 0.034 mmol) at 0 °C over a period of 30 min. After the solution was stirred at 0 °C for 4 h, aqueous sodium thiosulfate was added, and then the mixture was stirred at room temperature. The aqueous phase was extracted three times with methylene chloride, and the combined organic extracts were washed with brine, dried, and concentrated to obtain a crude mixture, which was purified by column chromatography on silica gel (50% ethyl acetate/hexane) to obtain

(±)-adrenosterone (**49**; 5.1 mg, 50%) as white crystals. The synthetic material was identical with authentic sample by IR, 200-MHz ^{1}H NMR, and TLC mobility (R_f = 0.40 for 50% ethyl acetate/hexane × 2; R_f = 0.28 for 30% ethyl acetate/benzene × 3).

Supplementary Material Available: General data and details of experiments for the synthesis of **3**, **51**, **52**, **57**, **58**, **60**, and **61** and the structural assignment of intermediates (15 pages). Ordering information is given on any current masthead page.

Atom Transfer Cyclization Reactions of Hex-5-ynyl Iodides: Synthetic and Mechanistic Studies[†]

Dennis P. Curran,[*,1] **Meng-Hsin Chen, and Dooseop Kim**

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260. Received January 17, 1989

Abstract: Atom transfer cyclization reactions provide a nonreductive complement to the tin hydride method for conducting radical cyclizations. Three useful sets of reaction conditions (portionwise or syringe pump addition of catalytic tributyltin hydride and photolysis with catalytic hexabutylditin) for the isomerization of hex-5-ynyl iodides to (iodomethylene)cyclopentanes have been developed. To illustrate the generality of this new reaction, a series of mono- and polycyclic derivatives (both fused and spiro) has been prepared. All evidence indicates that a two-step chain mechanism operates. In addition to the requirement for a normal initiation step, a trap for iodine must be present for the reaction to proceed. This important function is performed by the tin additive. The first-formed hexynyl radical closes in a 5-exo fashion to provide a cyclopentylidene radical. This vinyl radical then rapidly abstracts an iodine atom from the starting alkyl iodide ($k_1 \approx$ (2–5) × 10^8 M^{-1} s^{-1} at 30 °C). Stereochemical trends in the formation of (E)- and (Z)-vinyl iodides are analyzed with the aid of a Curtin–Hammett kinetic scheme. The observation of identical ratios of stereoisomers from isomeric starting iodides provides strong evidence for this mechanistic picture and demonstrates that the inversion of the intermediate radicals is more rapid than iodine atom transfer. In the formation of the spiro rings, products derived from 1,5-hydrogen atom transfer have been isolated along with the expected vinyl iodides, and a proposal that the atom-transfer reactions of intermediate vinyl radicals are faster than chair–chair interconversions of substituted cyclohexanes is considered. Cyclizations of a series of 4-*tert*-butylcyclohexane derivatives have demonstrated that hexynyl radicals have a small preference for equatorial attack, while hexenyl radicals have a small preference for axial attack.

The trialkyltin hydride mediated cyclization of hex-5-enyl and hex-5-ynyl halides (and related radical precursors) has rapidly become an important method for the formation of carbocyclic and heterocyclic rings (Figure 1).[2] Tin hydride is a valuable reagent to mediate radical chain reactions because it (1) generates radicals site-selectively, (2) provides these radicals with some solution lifetime to undergo desired reactions, and (3) traps the product radicals by hydrogen atom transfer before nonproductive radical–radical or radical–molecule reactions can occur. Inherent limitations of tin hydride reagents are well recognized and include (1) the difficulty to conduct slow cyclization or addition reactions due to competing reduction of the starting radical, (2) the difficulty to establish different lifetimes for intermediate radicals[3] due to similarities in rates for the reaction of many radicals with tin hydride, and (3) the necessity to terminate a radical sequence by hydrogen atom transfer (a net reduction always results). This last limitation is particularly troublesome if functionality is required in the cyclic product for subsequent synthetic transformations (Figure 1). Reagents that mediate the "nonreductive" cyclization and addition reactions of radicals have been the focus of recent research.[2,4]

Scheme I
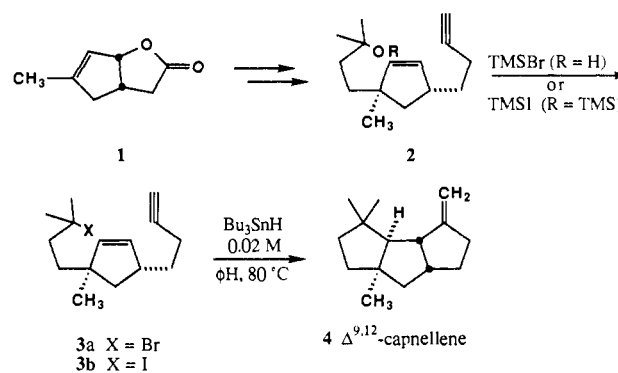
The atom transfer addition (or cyclization) of a C–X bond across a carbon–carbon multiple bond (Figure 2) is a Khar-

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Figure 1.

X-Y + ═══R → Initiator → Y⌒X⌒R

X = halogen
Y = carbon, heteroatom

Figure 2.

Scheme II

3b + Bu₃Sn· ⟶   6 + Bu₃SnI   (step 1)

6   ⟶   7   (step 2)

7 + Bu₃SnH →k_H→   4   (step 3)

7 + 3b →k_I→   (step 4)

5 + 6   (step 4)

Bu₃Sn· + 5 ⟶ 7   (step 5)
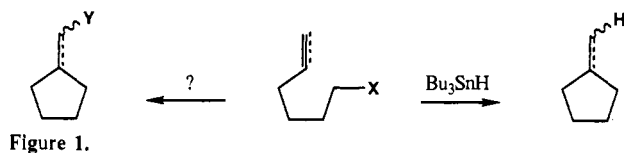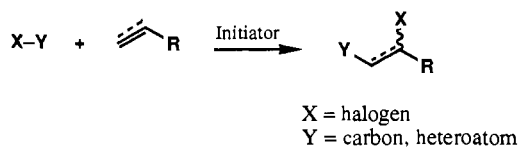
asch-type reaction, the synthetic potential of which has only re-cently begun to be tapped. Such chain isomerizations can succeed when an exothermic addition, fragmentation, or cyclization re-action generates a more reactive radical from a less reactive counterpart.[2a] Exothermic transfer of a univalent atom X from a C–X bond can then follow. We now describe in detail our synthetic and mechanistic studies on a new class of atom transfer cyclization reaction—the isomerization of hex-5-ynyl iodides to (iodomethylene)cyclopentanes.[5] These studies provide a foun-dation for application and extension of this powerful synthetic method.

Results and Discussion

Discovery. Our research on synthetic applications of atom-transfer reactions began several years ago with a series of unusual observations during a synthesis of the triquinane $\Delta^{9,12}$-capnellene (**4**) by the tandem radical cyclization strategy (Scheme I).[6,7] Readily available lactone **1** was converted to tertiary alcohol **2** by a straightforward sequence of reactions. Either tertiary bromide **3a** or tertiary iodide **3b** was readily available from **2** by using the appropriate trimethylsilyl halide (TMSBr or TMSI). Comparison of the cyclization behavior of **3a** and **3b** provided the first unusual observation: under a standard set of reaction conditions (1.1 equiv of Bu₃SnH, benzene, 1–2 h), the yield of capnellene from the reduction of bromide **3a** was higher than the yield from iodide **3b**. This is surprising because iodides are more reactive toward tin hydride than bromides.[8] For the actual synthesis, bromide **3a** was reduced to provide capnellene in good yield.

To determine the cause of the unusual behavior of iodide **3b**, its reduction was repeated and the progress of the reaction was followed over time. Iodide **3b** did indeed disappear much more
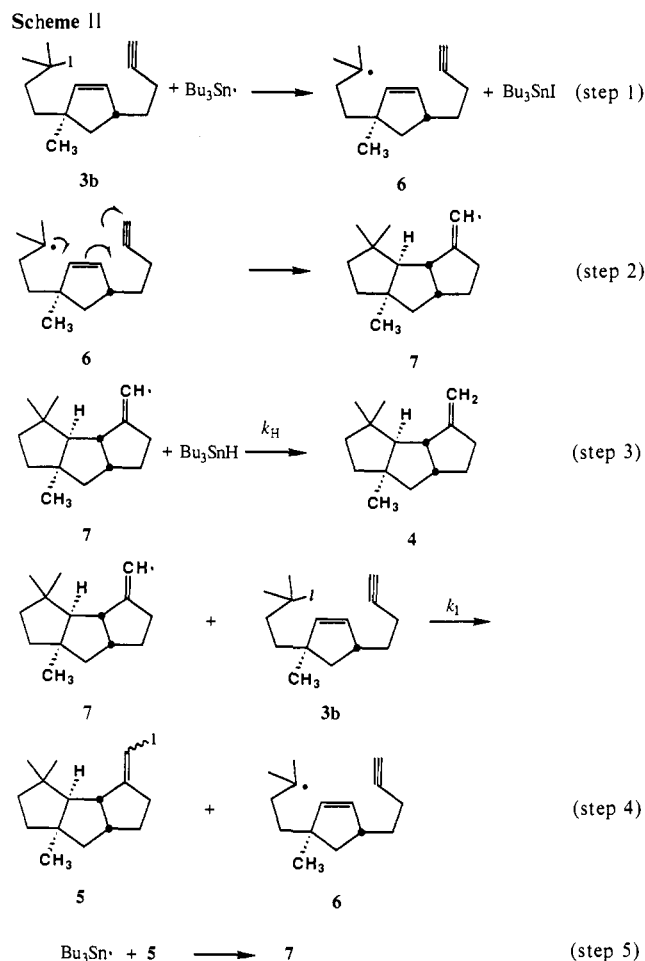
rapidly than bromide **3a**; however, the rate of appearance of final product **4** did not correspond with the rate of disappearance of **3b**. *Indeed, the yield of* **4** *continued to increase for several hours after the complete disappearance of starting iodide* **3b**! After 8 h, the GC yield of capnellene reached the same level (85%) from iodide **3b** that was attained from bromide **3a** in only 2 h. There is one explanation for these unusual observations: bromide **3a** gives **4** by the normal tin hydride mechanism, but iodide **3b** is transformed into a stable intermediate product which is subse-quently converted to capnellene in a significantly slower reaction.

To identify the suspected intermediate, we conducted a prep-arative cyclization reaction with iodide **3b** under conditions where the starting iodide was completely consumed but the yield of the final product capnellene was still at an intermediate level (1.1 equiv of Bu₃SnH, 0.03 M, reflux, 1 h). Upon careful chromatography of the reaction mixture (silica gel, 100% hexanes), the intermediate (25% isolated yield) eluted just prior to the major product cap-nellene. Once pure, it was quickly identified as the capnellene vinyl iodide (**5**, eq 1).[9] Reduction of the isomeric mixture of **5** (6/1, *E/Z*) with tributyltin hydride gave capnellene **4** as the only detectable non-tin-containing product by GC.

3b → 5 + 4   (1)

Bu₃SnH
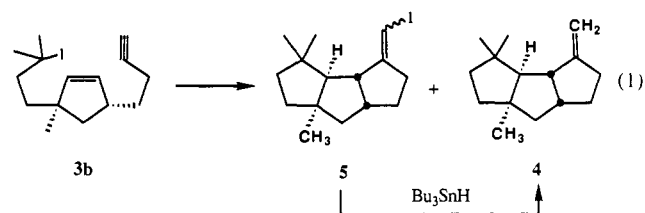
(2) (a) Curran, D. P. *Synthesis* **1988**, 417, 489. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergammon Press: Oxford, 1986. (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (d) Neumann, W. P. *Synthesis* **1987**, 665. (e) Hart, D. J. *Science* **1984**, *223*, 883.

(3) This is an important consideration in the planning of sequential radical reactions. See ref 2a, pp 435–36.

(4) For representative examples of other recent developments, see: (a) Allyl- and vinyltins: Keck, G. E.; Byers, J. H.; Tafesh, A. M. *J. Org. Chem.* **1988**, 53, 1127. Addlingtton, R. M.; Lowe, C.; O'Neil, I. A.; Sanders, G.; Schofield, C.; Sweeney, J. B.; Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1988**, 1030. Russell, G. E.; Ngoviwatchai, P.; Tashtoush, H. I. *Organometallics* **1988**, *7*, 696. (b) Acyl xanthates: Zard, S. *J. Chem. Soc., Chem. Commun.* **1988**, 308. (c) Organocobalts: Bhandal, H.; Pattenden, G. *J. Chem. Soc., Chem. Commun.* **1988**, 1111. Branchaud, B.; Meier, M. S. *Tetrahedron Lett.* **1988**, *29*, 3191. Ghosez, A.; Göbel, T.; Giese, B. *Chem. Ber.* **1988**, *121*, 1807. (d) Manganese acetate oxidation: Merritt, J. E.; Sasson, M.; Kates, S. A.; Snider, B. B. *Tetrahedron Lett.* **1988**, *29*, 5209. (e) Barton thiohydroxamates: Barton, D. H. R.; Hervè, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479. (f) Vinylcyclopropane openings: Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300.

(5) Preliminary report: Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489. For a recent application, see: Audin, C.; Lancelin, J.-M.; Beau, J.-M. *Tetrahedron Lett.* **1988**, *29*, 3691.

(6) Curran, D. P.; Chen, M.-H. *Tetrahedron Lett.* **1985**, *26*, 4991.

(7) Review: Curran, D. P. In *Advances in Free Radical Chemistry*; Tanner, D., Ed.; JAI Press: Greenwich, CN, in press.

(8) Carlsson, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1968**, *90*, 7047. Ingold, K. U.; Lusztyk, J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 343.

(9) The ¹³C NMR spectrum was particularly informative; a highly shielded alkene resonance observed at δ 69.7 (doublet) is characteristic of an sp² carbon bearing iodine. Levy, G. C.; Lichter, R. T.; Nelson, G. L. In *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*, 2nd ed.; Wiley: New York, 1980.

Atom Transfer Cyclizations

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Table I. Cyclization of Tertiary Iodide **3b** with Bu₃SnH

entry	time, min	% **3b**	% **5**	% **4**	**4/5**
1	4	78.7	7.6	3.1	0.41
2	10	44.2	19.3	11.7	0.61
3	15	28.6	31.5	20.8	0.66
4	20	17.3	35.9	26.9	0.74
5	45	6.1	27.2	40.7	1.50
6	60	0	8.9	61.7	6.90

The isolation of vinyl iodide **5** stimulated both synthetic interest and mechanistic questions. Synthetically, a tandem radical cyclization has been terminated by transfer of an iodine atom rather than a hydrogen atom. Vinyl iodides are flexible precursors for many C–C bond-forming reactions and functional group transformations. Mechanistically, vinyl iodide **5** is an isomer of the starting iodide **3b**. Because no reduction has occurred, no tin hydride can be consumed in the formation of **5**. However, when iodide **3b** was heated in the absence of tin hydride (with or without irradiation), it rapidly decomposed without formation of **4**, **5**, or any other identifiable products. What is the source of the iodine atom in **5**, and what is the role of the tin hydride?

The mechanism outlined in Scheme II accounts for the experimental observations. Two overlapping chain reactions compete with each other for the key intermediate vinyl radical **7**. One chain is the normal tin hydride reduction. Abstraction of iodine from **3b** by Bu₃Sn• gives tertiary radical **6** (step 1). After two sequential 5-exo cyclizations, vinyl radical **7** results (step 2). Hydrogen atom abstraction by **7** from tin hydride (step 3) transfers the chain. A second reaction involving iodine atom transfer competes with step 3 for vinyl radical **7**. We propose that the source of the iodine atom in step 4 is starting iodide **3b**. Transfer of an iodine atom from **3b** to **7** is an exothermic reaction that provides vinyl iodide **5** and regenerates starting radical **6**.

This mechanism nicely accommodates the experimental observations. Because vinyl iodide **5** is much less reactive[10] toward Bu₃Sn• than tertiary iodide **3b**, many of the intermediate radicals are temporarily "sequestered" on the way to capnellene. After reactive tertiary iodide **3b** is consumed, the vinyl iodide **5** that has accumulated can react with the remaining tin hydride to produce capnellene by a normal tin hydride reduction (steps 5 and 3). If the tin hydride is consumed, or if the reaction is stopped before sufficient time elapses, then capnellene vinyl iodide is isolated. In the reduction of bromide **3a**, bromine atom transfer does not compete with hydrogen atom transfer. Thus, the normal tin hydride mechanism operates, and the rate of formation of capnellene directly corresponds to the rate of disappearance of bromide **3a**.

There are only two obvious sources of the iodine atom that is required for step 4: starting iodide **3b** and tributyltin iodide (formed in step 1). Although the abstraction of iodine from alkyl iodides by vinyl radicals has not previously been observed, it is a precedented reaction.[11] Related phenyl radicals abstract iodine very rapidly from alkyl iodides.[12] Because of the exothermicity,[13] such iodine transfers are probably not reversible.[14] Indeed, even

alkyl radicals can abstract iodine from alkyl iodides in a process that is considerably less exothermic than step 4.[15] In contrast, there is no evidence that any carbon-centered radical can abstract iodine from a tin iodide. It is the reverse of this reaction that is rapid and exothermic, as in the tin hydride chain.

Precedent not withstanding, we deemed it advisable to eliminate tributyltin iodide as a possible source of iodine. Attempts to initiate the isomerization of **3b** to **5** with tributyltin iodide (and azobis-(isobutyronitrile) (AIBN)) resulted only in decomposition. A doping experiment was also negative; the yield of vinyl iodide **5** was virtually the same when iodide **3b** was heated with hexamethylditin (0.3 equiv, 85 °C, catalytic AIBN, 2 h) in the presence or absence of 0.35 equiv of tributyltin iodide (40% and 35%, respectively). Had tributyltin iodide been a source of iodine, the former reaction should have been more efficient due to the higher tin iodide concentration. Finally, we conducted a reduction of tertiary bromide **3a** with tributyltin hydride (0.8 equiv, 0.027 M) that was doped with a large amount of tributyltin iodide (1.2 equiv). If tin iodide were the source of iodine, then this reaction should mimic the behavior of iodide **3b** since the same vinyl radical **7** is generated from the bromide. The presence of the tin iodide had no effect. At no time during the reaction could any vinyl iodide **5** (or the corresponding vinyl bromide) be detected by GC or NMR. Only the normal reduction product capnellene was formed. Thus, there is no evidence that tributyltin iodide can serve as an iodine atom donor.

A simple cyclization experiment conducted in an NMR tube provided good support for the overlapping chain mechanism proposed in Scheme II. Tertiary iodide **3b** was dissolved in benzene-d₆ (0.026 M). Tributyltin hydride (1.2 equiv) and AIBN were added, and the mixture was placed in a preheated NMR probe (80° C). The yields of starting iodide **3b**, vinyl iodide **5**, and capnellene (**4**) were measured against an internal integration standard (1,4-dimethoxybenzene). The raw data are collected in Table I.

During the first 20 min (entries 1–4), starting iodide **3b** rapidly disappears and **4** and **5** are formed. Vinyl iodide **5** is the major product at short reaction time, but capnellene (**4**) slowly "catches up" as the reaction progresses. This can be understood by comparing the two fates of vinyl radical **7** (H-atom abstraction from tin hydride versus I-atom abstraction from **3b**). At a given instant, the partitioning of **7** to **4** and **5** depends on the rate constants k_I and k_H and the concentrations of **3b** and tin hydride:

$$4/5 = k_H[Bu_3SnH]/k_I[3b]$$

At the start of the reaction, the concentrations of tin hydride and **3b** are about equal and the **4/5** ratio approximately equals the k_H/k_I ratio. As the reaction progresses, the concentration of **3b** (consumed in both chain paths) drops more rapidly than the concentration of tin hydride (consumed only in one chain path). Hence, the **4/5** ratio increases slowly. When starting iodide **3b** is nearly consumed (entries 5 and 6), the **4/5** ratio increases dramatically. This signifies the onset of the tin hydride reduction of **5** to **4**, which does not take place in the presence of iodide **3b** (because **3b** is significantly more reactive toward Bu₃Sn• than **5**). At intermediate reaction times, vinyl iodide **5** is the major reaction product, and the data in Table I indicate that more than half of the finally formed capnellene was first converted to vinyl iodide **5**.

The rate constant k_H for the reaction of vinyl radicals with tin hydride is very high ($k_H \approx 2 \times 10^8$ M⁻¹ s⁻¹ at 30 °C for the reaction of isobutenyl radical with tributyltin hydride[16]). By using

(10) We have recently determined that Bu₃Sn• abstracts iodine from related aryl iodides with $k \approx 8 \times 10^8$ M⁻¹ s⁻¹ at 80 °C (Totleben, M., unpublished results). Tertiary iodides will have $k > 5 \times 10^9$ M⁻¹ s⁻¹ (see ref 8).

(11) For reviews of halogen atom abstraction, see: (a) Danen, W. C. In *Methods in Free Radical Chemistry*; Huyser, E. S., Ed.; Marcel Dekker: New York, 1974; Vol. 5, pp 1–100. (b) Poutsma, M. L. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. II, pp 123–158. (c) Ingold, K. U. *Ibid.* Vol. 1, pp 83–88.

(12) For the reaction of phenyl radicals with 2-iodopropane, $k_I \approx 1 \times 10^9$ M⁻¹ s⁻¹ (45 °C). Kryger, R. G.; Lorand, J. P.; Stevens, N. R.; Herron, N. R. *J. Am. Chem. Soc.* **1977**, *99*, 7589.

(13) Phenyl and vinyl iodides have bond dissociation energies about 10–15 kcal/mol greater than related alkyl iodides. The following bond dissociation energies are known or can be readily calculated: iodobenzene (65 kcal/mol), iodoethene, (63 kcal/mol), iodoethane (53.5 kcal/mol), 2-iodopropane (53 kcal/mol), 2-iodo-2-methylpropane (49.5 kcal/mol). See: (a) Benson, S. W. *J. Chem. Educ.* **1965**, *42*, 502. (b) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 2nd ed.; Harper & Row: New York, 1981; pp 145–161, 681–685.

(14) For evidence that alkyl radicals cannot abstraction iodine from iodobenzene, see: (a) Cooper, R. A.; Lawler, R. G.; Ward, H. R. *J. Am. Chem. Soc.* **1972**, *94*, 545. Also see ref 15c.

(15) (a) Brace, N. O. *J. Org. Chem.* **1967**, *32*, 2711; **1966**, *31*, 2879. (b) Hiatt, R.; Benson, S. W. *J. Am. Chem. Soc.* **1972**, *94*, 25. (c) Castelhano, A. L.; Griller, D. *Ibid.* **1982**, *104*, 3655.

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Table II. Thermal Isomerization of 6-Iodo-1-hexyne (8) to (Iodomethylene)cyclopentane (9)
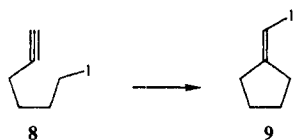
entry	additive	time, h	GC yield of 9,[a] %
1	none	24	0
2	AIBN (10%)	24	10
3	benzoyl peroxide (5%)	24	60
4	PAT (5%)	0.15	6
5	PAT (45%)	5	25
6	AIBN (10%)/Bu$_3$SnSnBu$_3$ (10%)	10	70
7	AIBN (10%)/Bu$_3$SnI (50%)	21	15
8	AIBN (6%)/Bu$_3$SnH (20%)/Bu$_3$SnI (50%)	21	19
9	AIBN (10%)/Bu$_3$SnSnBu$_3$ (20%)/Bu$_3$SnI (50%)	21	51
10	AIBN (10%)/Bu$_3$SnH (10%)/Bu$_3$SnI (100%)	8	44
11	AIBN (5%), Bu$_3$SnH (10%), 2 portions	2	67 (44)
12	AIBN (5%), Bu$_3$SnH (10%), syringe pump	10	*b* (64)

[a] Isolated yield after chromatography. [b] Not determined.

Table III. Photolytic Isomerization of 6-Iodo-1-hexyne (8) to (Iodomethylene)cyclopentane (9)

entry	light source	initiator (mol %)	reaction time	temp, °C	9, %	8, %
1	UV lamp	none	1 h	~40	0	>95
2	UV lamp	Bu$_3$SnSnBu$_3$ (2.5%)	30 min	~40	40	56
			2 h	~40	37	48
3	UV lamp	Bu$_3$SnI (20%)	1 h	~40	27	70
4	sunlamp	none	1 h	~80	0	>90
5	sunlamp	Bu$_3$SnSnBu$_3$ (2.5%)	25 min	~80	64	21
			1 h	~80	65	20
			2 h	~80	66	20
6	sunlamp	Bu$_3$SnSnBu$_3$ (5%)	30 min	~80	71	9
7	sunlamp	Bu$_3$SnSnBu$_3$ (10%)	30 min	~80	77	5
			1 h	~80	68	<1
8	sunlamp	Bu$_3$SnI (20%)	30 min	~80	44	50

this number as a model for k_H in Scheme II, by using the ratio of **4/5** at the first reaction time as an estimate for k_H/k_1, and by knowing the initial concentrations, we can estimate a minimum value for $k_1 \geq 6 \times 10^8$ M^{-1} s^{-1} at 30 °C. This rough estimate suffices to show that iodine abstraction from *tert*-alkyl iodides by vinyl radicals is a very fast reaction—within about 1 order of magnitude of the diffusion-controlled limit.

Atom Transfer Cyclization of Simple Hex-5-ynyl Iodides. The mechanism in Scheme II predicts that the isomerization of hex-5-ynyl iodides to vinyl iodides is a viable chain reaction that requires only initiation. We began the search for optimum conditions using simple substrates.

The isomerization of 6-iodo-1-hexyne (8) to the known (iodomethylene)cyclopentane (9)[17,18] was studied by using both thermal

(Table II) and photochemical (Table III) initiation methods. Unless otherwise noted, reaction mixtures containing 6-iodo-1-hexyne (8) and the indicated additive(s) were heated at 80 °C or photolyzed in benzene. Additives included azobis(isobutyronitrile) (AIBN), benzoyl peroxide,[19] phenylazotriphenylmethane (PAT),[20] tributyltin hydride, tributyltin iodide, and hexabutylditin. The yield of 9 was assayed by GC or NMR against an internal standard. Separate experiments indicated that changes in the overall concentration had relatively little effect on the yield of 9. As expected, higher concentrations of iodide 8 gave faster conversions; the reported experiments used 0.3 M 8. The starting iodide 8 was relatively stable under the reaction conditions and accounted for much of the remaining mass balance in all of the experiments shown in Tables II and III. The reduced product, methylenecyclopentane, was probably produced in small amounts in all of these reactions (see below), but it was not detected because it was inseparable from the solvent under our GC conditions.

In many of the above reactions, the appearance of the characteristic iodine tint often seemed to coincide with the cessation of the reaction. To avoid this problem, we adopted a protocol of portionwise addition of the additive. We selected tributyltin hydride because it provided much more rapid initial conversion rates than the other additives. The addition of two portions of 10% Bu$_3$SnH/5% AIBN at 1-h intervals gave a reasonable yield of 9 (67% GC, 44% isolated) with >90% conversion of 8 (entry 11). For preparative purposes, more efficient conversions were obtained when the Bu$_3$SnH/AIBN mixture (in benzene) was added slowly by syringe pump over 10 h (isolated yield of 9, 64%). Both of these procedures are described in the Experimental Section, and throughout the paper they are referred to as the catalytic tin hydride procedure (portionwise or syringe pump).

Even better results were obtained in the photolytic experiments (Table III). Irradiation with a 275-W sunlamp through a standard Pyrex NMR tube (or test tube) gave efficient conversion of 8 to 9 provided that hexabutylditin was present. In this method, the reaction vessel was simply kept at an appropriate distance from the lamp to prevent reflux of the benzene. We estimate that the heat of the lamp rapidly warmed these reactions to 70–80 °C. The use of 10% hexabutylditin (entry 7) gave rapid and complete conversion of 8 with formation of 9 in good yield (77%). This method, subsequently referred to as the photolytic ditin procedure, is the best that we have developed to date for the atom transfer cyclization. When less than 10% ditin was used (entries 5 and 6), the initial conversion was rapid but an iodine tint soon appeared, and the conversion ceased. It was demonstrated by NMR that the appearance of this tint coincided with the disappearance of the ditin.

Preparative cyclizations of two simple substituted iodides, **10a** and **10b**, were conducted (eq 2) by the photolytic method. After irradiation with 10% hexabutylditin and chromatographic purification, vinyl iodides **11a** and **11b** were isolated in 71% and 41% yields, respectively.

10a R = Me	**11a** (71%)
10b R = SiMe$_3$	**11b** (41%)

(2)
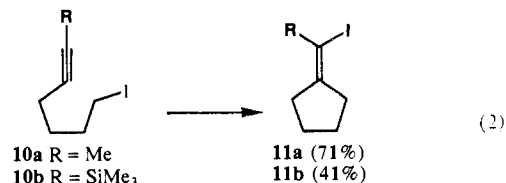
Isomerization of 6-iodo-1-heptyne (12) was also studied in some detail (eq 3). Conversion of 12 to 13 was reasonably successful with tributyltin hydride by using the syringe pump method (portionwise addition gave incomplete conversion). The inseparable vinyl iodides **13E/Z** were formed in 67% yield according to NMR integration against an internal standard and were isolated

(16) Professors A. Beckwith and K. Ingold have informed us that the originally reported rate constant is not correct (3.5 × 10^8 M^{-1} s^{-1} at 30 °C: Johnston, L. J.; Lusztyk, J.; Wayner, D. D. M.; Abeywickreyma, A. N.; Beckwith, A. L. J.; Scaiano, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1985,** *107,* 4594). Professor Beckwith estimates that the correct rate constant is about one-half of the reported value. If more accurate rate constants for the reaction of vinyl radicals with tin hydride become available, then our data can be used to provide more accurate estimates of k_1. We caution that our rate constants are only approximate because (1) the base rate constant (k_H) is not known with high precision, (2) the product ratio at short time is only an estimate of k_H/k_1 (if anything, this product ratio should overestimate the corresponding rate constant ratio, making k_1 an underestimate), and (3) a temperature dependence for k_H is not available and we have used experimental ratios determined at 80 °C to calculate rate constants at 30 °C. We are grateful to Professors Beckwith and Ingold for the unpublished information.

(17) Newman, M. S.; Beard, C. D. *J. Am. Chem. Soc.* **1970,** *92,* 4309.

(18) The structure of the vinyl iodide was further confirmed by carboxylation (a, *t*-BuLi; b, CO$_2$; c, CH$_2$N$_2$) to give the known (carboxymethylene)cyclopentane methyl ester. Khodair, A. I. *Ind. J. Chem.* **1976,** *14B,* 522.

(19) A recent paper reports similar yields in the isomerization of iodoethyl alkynoates to (iodoalkylidene)lactones in the presence of benzoyl peroxide. Haaima, G.; Weavers, R. T. *Tetrahedron Lett.* **1988,** *29,* 1085.

(20) For half-lives of these initiators, see: Walling, C. *Tetrahedron* **1985,** *41,* 3887.

$$(3)$$

conditions	yield NMR/Isolated
10% Bu₃SnH Syringe Pump	67%/44%
10% Bu₃SnSnBu₃/hv	87%/65%
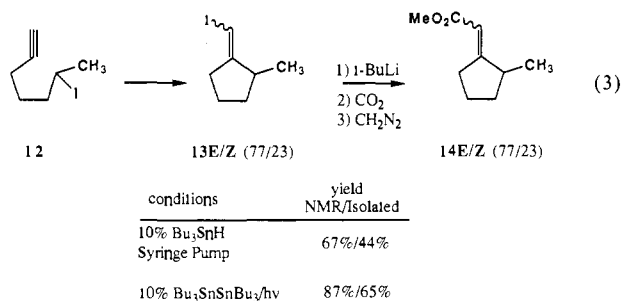
in 44% yield. Better results were obtained by the photolytic ditin procedure with 10% hexabutylditin. Vinyl iodide **13E/Z** (77/23) was formed in 87% NMR yield (65% isolated) after only 15 min of irradiation time. The stereoisomer ratio was 77/23, and the major isomer was tentatively assigned as *E* based on the de-shielding effect of iodine on cis allylic protons in the ¹H NMR spectrum.[21] This assignment was confirmed by carboxylation[22] of the vinyllithium reagent derived from **13E/Z** (eq 3). The stereochemistry of the derived methyl esters **14E/Z** was securely assigned from the chemical shifts of the allylic protons.[23]

The most reactive of the simple substrates was the tertiary iodide 6-iodo-6-methyl-1-heptyne (**15**). The isomerization of **15** was conducted under several of the conditions that were successful for primary iodide **8** (eq 4). Methods that isomerized **8** slowly


$$(4)$$
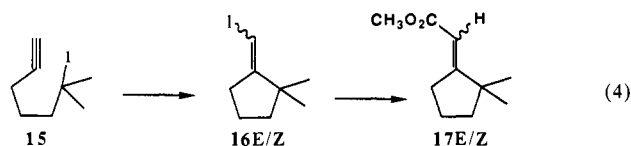
Conditions	Yield 16E/Z NMR(Isolated)
Bu₃SnSnBu₃/heat	decomposition
di-tert-butyl peroxide	decomposition
10% Bu₃SnH/portionwise	84% (47%)
Bu₃SnSnBu₃/hv	96% (60%)

were not useful because the radical chain reaction did not compete with the decomposition of the sensitive tertiary iodide **15**. Methods that promoted more rapid conversions were successful. Addition of two portions of tributyltin hydride gave complete conversion, and **16** was formed in 84% NMR yield as an inseparable 93/7 mixture of (*E*)- and (*Z*)-vinyl iodides. The reduced product, 2,2-dimethylmethylenecyclopentane (**16**, I = H), was also detected in about 5% yield.

The photolytic ditin procedure was again the most efficient. Irradiation of **15** resulted in rapid production of **16E/Z** (78% GC yield after 5 min, 96% yield after 15 min). Even though tributyltin hydride was absent, the reduced product, 2,2-dimethyl-methylenecyclopentane, was still formed in 3% GC yield. A separate preparative experiment provided **16E/Z** (93/7) in 60% isolated yield.

Preparative isomerizations of methyl- and trimethylsilyl-substituted tertiary iodides **18a/b** were also conducted under the photolytic ditin conditions (eq 5). Isomerization of **18a** provided **19a** in 54% yield as a 79/21 ratio of *E/Z* stereoisomers. Isomerization of (trimethylsilyl)alkyne **18b** provided **19b** in 45% isolated yield in a reversed stereoisomeric ratio of 18/82 (*E/Z*). A secure stereochemical assignment of **19b** was not straightforward. Reaction of a sample of **19bE/Z** (14/86) with *t*-BuLi for 1 h at −78 °C, followed by quenching with methanol, provided vinylsilanes **20E/Z** (85/15, note reverse in CIP priority relative to **19b**) in

$$(5)$$
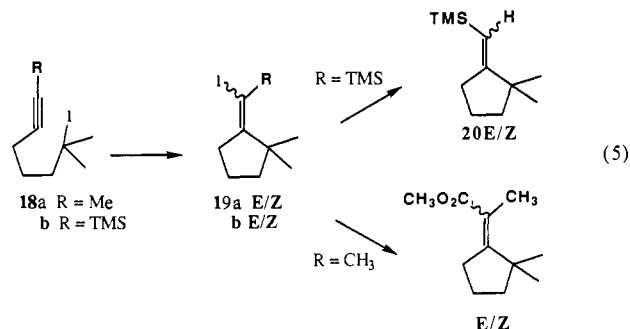
60% isolated yield. An authentic sample of **20E/Z** (97/3) was prepared by lithiation of **16E/Z** (93/7) and quenching with trimethylsilyl chloride. The uncertainty in this analysis is that silyl-substituted vinyllithiums are known to be configurationally unstable at temperatures above −40 °C.[24] That the stereoisomeric ratio of vinylsilanes **20** approximately equaled the ratio of starting iodides **19** suggests (but does not prove) that isomerization of the intermediate vinyllithium species derived from **19b** did not occur at −78 °C.

In summary, three useful procedures have been developed for the atom-transfer cyclization of hexynyl iodides to cyclic vinyl iodides: thermolysis with catalytic Bu₃SnSnBu₃/AIBN, portionwise or syringe pump addition of catalytic Bu₃SnH/AIBN, and sunlamp irradiation with catalytic hexabutylditin. The first procedure is slow but is useful for stable primary (and perhaps secondary) iodides; the one tertiary iodide that was investigated decomposed. The second procedure is useful for primary, secondary, and tertiary iodides. The problem of chain termination before complete conversion of the starting iodide decreases in the order primary > secondary > tertiary. The syringe pump method is much better than portionwise addition for the less reactive primary iodides. The photolytic ditin procedure is the best general method. It gave the fastest conversion and the highest yield in every case where a direct comparison was conducted.

Mechanistic Considerations. (a) Propagation. The propagation steps for this isomerization are cyclization and atom transfer (hence the name "atom transfer cyclization") as outlined in Scheme III. The irreversible cyclization of hexynyl radicals (step 1) is a rapid, exothermic reaction despite the loss of stability associated with the conversion of an alkyl radical to a vinyl radical counterpart. This loss in radical stabilization energy is more than offset by the very favorable conversion of a π-bond in the starting radical to a σ bond in the cyclic radical. The iodine atom-transfer reaction (step 2) is also significantly exothermic since a more stable alkyl radical is now generated from the less stable vinyl radical.[13,25] Thus, the transformation is a kind of Kharasch reaction, and such atom-transfer chains will occur whenever (1) a rapid exothermic addition, fragmentation, or cyclization reaction converts a more resonance-stabilized radical to a less resonance-stabilized counterpart and (2) halogen atom transfer from the starting halide to the product radical is sufficiently rapid to maintain the chain.[2a] Growing kinetic evidence[26] indicates that the exothermic transfer of iodine atoms is so rapid that the second condition will be met whenever an iodide is used as a radical precursor.

(b) Initiation. Despite the favorable nature of the propagation steps, the success of the reaction depends critically on the method

(21) Byrd, L. R.; Caserio, M. C. *J. Org. Chem.* **1972**, *37*, 3881.

(22) Cahiez, G.; Bernard, D.; Normant, J. F. *Synthesis* **1976**, 245.

(23) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; Pergamon: Oxford, 1969.

(24) The vinyl anion derived from (*E*)-1-iodo-1-(trimethylsilyl)-1-octene does not isomerize at −78 °C but does isomerize at a measurable rate at −40 °C. Negishi, E.; Takahashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 3402.

(25) We believe that the iodine atom transfer is not reversible under the reaction conditions and that the vinyl radicals are not in equilibrium with the product vinyl iodides. That the *E/Z* ratios were constant throughout the reaction supports this conclusion. However, the exchange of iodine atoms between phenyl radicals is a known reaction (Danen, W. C.; Saunders, D. G. *J. Am. Chem. Soc.* **1969**, *91*, 5924). From the relative rates in this paper and the absolute rate constants in ref 12, we can estimate a rate constant for this exchange: $k_1 \approx 5 \times 10^6$ M⁻¹ s⁻¹.
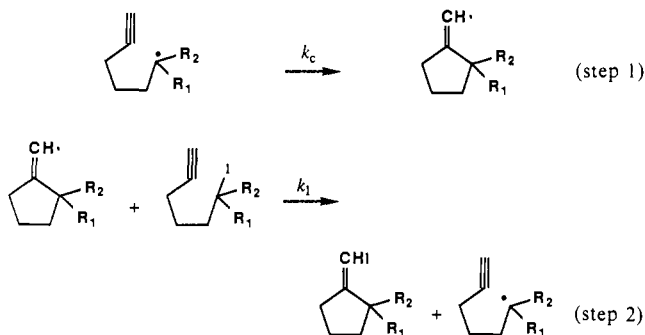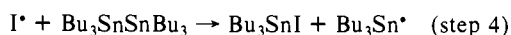
(26) (a) Newcomb, M.; Sanchez, R. M.; Kaplan, J. *J. Am. Chem. Soc.* **1987**, *109*, 1195. (b) Curran, D. P.; Bosch, E.; Kaplan, J.; Newcomb, M. *J. Org. Chem.*, in press.

Scheme III

of initiation. Several standard initiation techniques were ineffective in converting 6-iodo-1-hexyne (8) to (iodomethylene)cyclopentane (9). Optimum conditions used either ditin or tin hydride additives.

What is the precise role of the hexaalkylditin additive, and why is photolysis more efficient than thermolysis? One possibility is that the di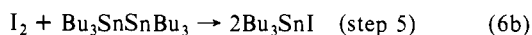tin serves as an initiator (eq 6a). Photolysis of ditins is known to produce trialkyltin radicals (step 1),[27,28] and abstraction of an iodine atom from a starting iodide (step 2) then initiates the chain. A second possibility (eq 6b) is that initiation arises

$$Bu_3SnSnBu_3 \rightarrow Bu_3Sn^{\bullet} \quad (step\ 1)$$

$$RI + Bu_3Sn^{\bullet} \rightarrow R^{\bullet} + Bu_3SnI \quad (step\ 2) \qquad (6a)$$

$$R - I \rightarrow R^{\bullet} + I^{\bullet} \quad (step\ 3)$$

$$I^{\bullet} + Bu_3SnSnBu_3 \rightarrow Bu_3SnI + Bu_3Sn^{\bullet} \quad (step\ 4)$$

or

$$I_2 + Bu_3SnSnBu_3 \rightarrow 2Bu_3SnI \quad (step\ 5) \qquad (6b)$$
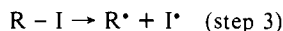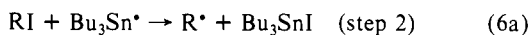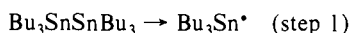
from the photolytic cleavage of the carbon–iodine bond (step 3).[29] The ditin then serves as a scavenger for either atomic iodine (step 4) or molecular iodine (step 5). The reaction of a hexaalkylditin with molecular iodine is a titration that produces a trialkyltin iodide in quantitative yield (step 5).[30] Hexaalkylditins also react rapidly with atomic iodine.[31] The scavenging of iodine is important because both atomic and molecular iodine trap carbon-centered radicals at very high rates[11] and thereby suppress chain reactions. The intense absorption of molecular iodine may also interfere with the photolytic initiation steps.

The following experimental observations are consistent with either the initiation method (eq 6a or 6b) and the two propagation steps (Scheme III):

(1) Aside from unreacted hexaalkylditin, the only other tin species that was readily detected by NMR was trialkyltin iodide.[32]

(2) The appearance of an iodine tint was coincident with the consumption of the ditin and signified a dramatic decrease (or cessation) in the rate of reaction. Upon addition of another portion of ditin, the iodine color instantly dissipated, and further conversion to product was observed on continued irradiation.

(3) Small but significant amounts of reduction products (3–5%) were always produced by H-atom transfer to the vinyl radicals. (The source of this H atom is not known.) This is because each initiation step results in the irretrievable loss of iodine; the tributyltin iodide does not return its iodine atom to the products. Because there is an insufficient number of iodine atoms for all of the cyclic radicals, some must react by other radical–molecule or radical–radical pathways. If the chain length were long enough, the amount of such products would be negligible. Thus, there is apparently still room for improvement in the method of initiation.

(4) 1-Iodobutane was detected in small amounts (2–5% yield based on starting alkyl iodide) in every reaction with either tributyltin iodide or hexabutylditin that was carefully analyzed by GC or NMR. This iodide may be formed either by the known iodinolysis of tributyltin iodide[31,33] or by the known photolytic cleavage of the carbon–tin bond of hexaalkylditins (butyl radicals so-generated might abstract iodine from the starting alkyl iodide).[27a]

Initiation by Sn–Sn cleavage (eq 6a) may be important. Ditins have no maximum in the normal UV region (hexabutylditin has no λ_{max} over 215 nm[27b]), but they do have very strong end absorption that tails to 250–260 nm. Laser-flash photolysis of hexabutylditin at 266 nm is known to produce tributyltin radicals.[34] Two lines of evidence—absorption maxima of the potential initiating species and behavior of the various initiators studied—indicate that initiation by C–I cleavage (eq 6b) is important. Alkyl iodides absorb in the near-UV ($\lambda_{max} \approx 260$ nm, $\epsilon \approx 500$), and photolysis in this region leads to efficient carbon–iodine bond cleavage.[29] Thus, the relatively small amount of light in this region that reaches the reaction by sunlamp irradiation through Pyrex[35] can be absorbed by either the ditin or the iodide.

The behavior of the various initiators can be understood by comparing their efficiencies to trap the potent radical scavenger iodine: (1) Simple photolysis (either with a sunlamp through Pyrex or with a 254-nm UV lamp through quartz) does not efficiently initiate the reaction nor does heating (or photolysis) with AIBN. While cleavage of the C–I bond may occur in these reactions, the accumulation of iodine (as indicated by the characteristic iodine tint) suppresses the chain. AIBN decomposes to relatively stable radicals that probably do not abstract iodine from alkyl iodides.[26]

(2) Phenylazotriphenylmethane (PAT) is a poor additive even though it generates reactive phenyl radicals which should readily initiate chains.[12] This is because PAT itself does not react with iodine and because unreactive trityl radicals may terminate chains.

(3) Tin hydride is a useful additive because, like ditin, it rapidly reacts with iodine.[27] However, tin hydride can competitively donate hydrogen to vinyl radicals. This step does not break the chain because a new tributyltin radical is formed, but it does consume tin hydride (the iodine scavenger), and it produces larger amounts of reduced product. Thus, a balance must be maintained: if no tin hydride is present, iodine inhibits the chain isomerization, but if the tin hydride concentration becomes too high, normal tin hydride reduction can compete with isomerization.

(4) Tributyltin iodide is only a marginally effective additive even at high concentrations because the iodinolysis of carbon–tin bonds is much slower than the iodinolysis of tin–tin bonds.[31]

(27) (a) Lehning, M.; Neumann, W.; Seifert, P. *J. Organomet. Chem.* **1978**, *162*, 145. (b) Drenth, W.; Janssen, M. J.; Van Der Kerk, G. J. M.; Vliegenthart, J. A. *J. Organomet. Chem.* **1964**, *2*, 265. (c) Sawyer, A. K. *Organotin Compounds*; Marcel Dekker: New York, 1972; Vol. 3, pp 823–879. (d) Davies, A. G.; Smith, P. J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford; 1982, Vol. 2, pp 593–599.

(28) For other synthetic methods that are based on photolysis with stoichiometric quantities of ditin, see: (a) Kuivila, H.; Pian, C. C. H. *J. Chem. Soc., Chem. Commun.* **1974**, 369. (b) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765. (c) Chenera, B.; Chuang, C.-P.; Hart, D. J.; Hsu, L.-Y. *J. Org. Chem.* **1985**, *50*, 5409. (d) Giese, B.; Rüchardt, B.; Gröninger, K. S.; Mohn, R.; Linder, H. *J. Justus Liebigs Ann. Chem.* **1988**, 987.

(29) (a) Kropp, P. J. *Acc. Chem. Res.* **1984**, *17*, 131. (b) Sammes, P. G. In *The Chemistry of the Carbon-Halogen Bond*; Patai, S., Ed.; Wiley: New York, 1973; Chapter 11. (c) Majer, J. R.; Simon, J. P. *Adv. Photochem.* **1964**, *2*, 137.

(30) (a) Tagliavini, G.; Faleschini, S.; Pilloni, G.; Plazzogna, G. *J. Organomet. Chem.* **1966**, *5*, 136. (b) Gielen, S. B. M.; Nasielski, T. *Bull. Soc. Chim. Belg.* **1964**, *73*, 864.

(31) (a) De Ryck, P. H.; Verdonck, L.; Van Der Kelen, G. P. *Bull. Soc. Chim. Belg.* **1985**, *94*, 621. (b) De Ryck, P. H.; Verdonck, L.; Van Der Kelen, G. P. *Int. J. Chem. Kinet.* **1985**, *17*(1), 95. (c) Hoste, S.; Herman, G. G.; Roelandt, F. F.; Lippens, W.; Verdonck, L.; Van Der Kelen, G. P. *Spectrochim. Acta* **1983**, *39A*, 959. (d) Verdonck, L.; Hoste, S.; Herman, G. G.; Lippens, W.; Van Der Kelen, G. P. *Spectrochim. Acta* **1984**, *40A*, 215.

(32) This was observed by using hexamethylditin in place of hexabutylditin. In benzene-d_6, the resonance of hexamethylditin (0.23 ppm) is replaced by that of trimethyltin iodide (0.49 ppm).

(33) We did not attempt to determine if Bu_2SnI_2 was present. Further iodinolysis of this species is also possible. In some cases, small amounts of a white, insoluble material were formed.

(34) Mochida, K.; Wakasa, M.; Sakaguchi, Y.; Hayashi, H. *Chem. Lett.* **1986**, 1793.

(35) A UV spectrum of a Pyrex NMR tube showed 1–2.5% transmittance at 250–260 nm (0% transmittance below 235 nm), and thus we believe that some light of the appropriate wavelength can reach the solution. No isomerization occurred when a UV filter (380-nm cut-off) was placed between the light and the reaction vessel. We thank C. M. Seong for obtaining several UV spectra.

Atom Transfer Cyclizations

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Table IV. Comparison of Hydrogen Atom Transfer with Iodine Atom Transfer

time,	% conversion (23/22)		
min	15[a]	12[b]	8[c]
2	25 (2.6)	n.d.	n.d.
5	n.d.[d]	13 (1.8)	n.d.
10	35 (2.3)	29 (1.7)	18 (1.1)
20	54 (1.8)	40 (1.6)	19 (1.0)
30	66 (1.6)	46 (1.3)	n.d.
45	82 (1.5)	51 (1.3)	28 (0.9)
60	n.d.	51 (1.2)	30 (0.8)

[a] Tertiary iodide. [b] Secondary iodide. [c] Primary iodide. [d] n.d. = not determined.

In summary, a viable initiation step is a necessary but not sufficient condition for this and related atom-transfer reactions to succeed. A potent trap for iodine should also be present. While ditin serves this function nicely, it seems likely that substitutes could be found.

(c) Rates of Iodine Atom Transfer. Knowledge of the rate constant for iodine atom transfer (k_I, Scheme III, step 2) is useful for the planning of sequences of radical reactions because one can then predict whether a specified reaction (a second cyclization, for example) can compete with the atom transfer under a given set of conditions. By conducting the cyclization reactions of these iodides in the presence of tin hydride (eq 7), one can obtain an estimate of the relative rates of hydrogen atom transfer (**21 → 22**) from tin hydride compared to iodine atom transfer from the starting vinyl iodide (**21 → 23**).
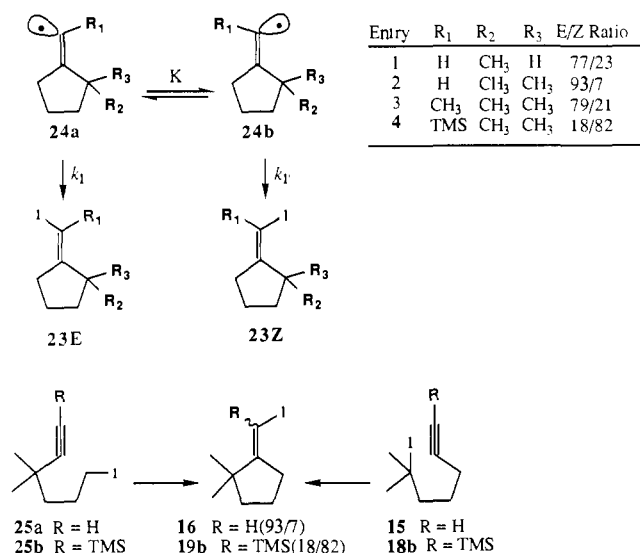

$R_1, R_2 = H$ or Me
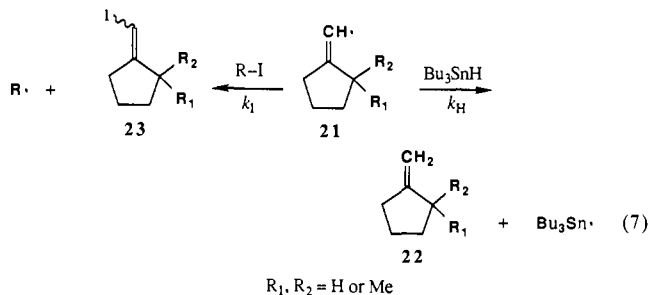
Cyclizations of tertiary iodide **15**, secondary iodide **12**, and primary iodide **8** were conducted in the presence of 1.1 equiv of tributyltin hydride (benzene-d_6, 80 °C, 0.02 M, 5% AIBN), and the ratios of the vinyl iodides (**16**, **13**, and **9**) to the reduced methylenecyclopentanes were determined by ^{1}H NMR integration of the vinyl protons. An internal standard was used to ensure that product accountability was good (>90%). The results are summarized in Table IV.

In all three cases, the vinyl iodide was the major product at short reaction time. The following expected trends were observed: (1) the ratio of vinyl iodide **23** to reduced alkene **22** decreased slowly during the reaction time (because the concentration of the iodide falls more rapidly than the concentration of the tin hydride); (2) the reactivity of the substrates (as measured by % conversion of the starting iodide) increased in the order primary < secondary < tertiary; (3) the ratio of vinyl iodide to reduced alkene at a given time interval also increased in the order primary < secondary < tertiary (because tertiary iodides are better iodine atom donors[36]).

Rough estimates for the second-order rate constants, k_I (eq 7), were made in the same manner as for iodide **3b**: tertiary iodide **15** ≈ 6 × 10^8 M^{-1} s^{-1}; secondary iodide **12** ≈ 4 × 10^8 M^{-1} s^{-1}; primary iodide **8** ≈ 2.5 × 10^8 M^{-1} s^{-1}. It is impossible to estimate error limits for these rate constants, and they should accordingly be regarded as very approximate.[16,37] Furthermore, direct comparisons between these rates constants are not strictly appropriate

Scheme IV

Entry	R_1	R_2	R_3	E/Z Ratio
1	H	CH$_3$	H	77/23
2	H	CH$_3$	CH$_3$	93/7
3	CH$_3$	CH$_3$	CH$_3$	79/21
4	TMS	CH$_3$	CH$_3$	18/82

25a R = H	16 R = H(93/7)	15 R = H
25b R = TMS	19b R = TMS(18/82)	18b R = TMS

because both the iodine donor and the abstracting radical are varied by the nature of these experiments. Nonetheless, they suffice to show that the transfer of iodine atoms from alkyl iodides to vinyl radicals is a very fast reaction!

(d) Stereochemistry. Present evidence indicates that the formation of (*E*)- and (*Z*)-vinyl iodides is kinetically controlled.[25] Two general trends concerning the *E*/*Z* ratio of the vinyl iodides emerge from this study (Scheme IV). First, the *E* selectivity increases as the size differential of the allylic substituents increases (compare entries 1 and 2 in Scheme IV). This is a very general trend (see eq 8 and 9 below). Second, although only three examples are presently available, it appears that increasing the size of the alkyne substituent (R^1) decreases the *E* selectivity (compare entries 2, 3, and 4 in Scheme IV).

In Scheme IV, we propose a Curtin–Hammett[38,39] interpretation of the stereochemical results. Simple vinyl radicals are known to be sp^2 hybridized and to invert with a very low barrier.[40] Thus, even though iodine atom transfer (a second-order reaction) is fast, the interconversion of the vinyl radicals **24a** ⇌ **24b** (a first-order reaction) is faster. Under these conditions, the ratio of **23E/23Z** is

$$23E/23Z = (k_I/k_{I'})K$$

We have no quantitative knowledge of either individual rate constant ($k_I/k_{I'}$) or the equilibrium constant (K), yet we can use the kinetic scheme as a qualitative framework to interpret the two trends. First, when $R_1 = H$, the magnitude of the equilibrium constant K probably does not depend too much on the sizes of R_2 and R_3 (because both the radical orbital and H substituent are small). As the sizes of R_2 and R_3 are increased, rate constant $k_{I'}$ is decreased relative to k_I due to the steric hindrance of the incoming iodine donor with the substituents. This results in

(36) The same trend is seen for the reactions of phenyl radicals with alkyl iodides. Danen, W. C.; Winter, R. L. *J. Am. Chem. Soc.* **1971**, *93*, 716.

(37) That these rate constants are similar to those for the reaction of phenyl radicals with alkyl iodides (ref 12) gives us confidence that they are approximately correct.

(38) (a) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111. (b) Seeman, J. I. *J. Chem. Educ.* **1986**, *63*, 42.
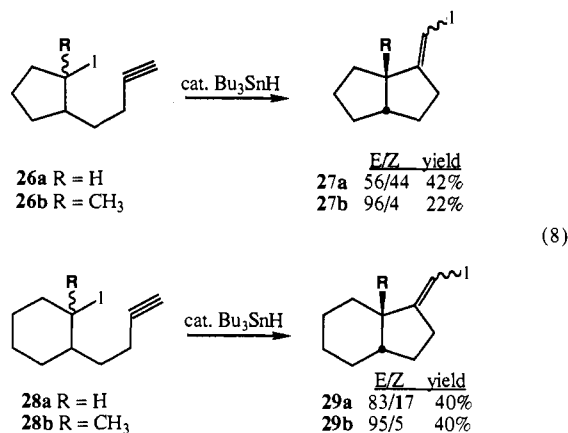
(39) The Curtin–Hammett principle has been used by Kampmeier to interpret trends in hydrogen transfer to vinyl radicals. (a) Kampmeier, J. K.; Chen, G. *J. Am. Chem. Soc.* **1965**, *87*, 2608. (b) Wedegaertner, D. K.; Kopchik, R. M.; Kampmeier, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 6890.

(40) (a) Fessenden, R. W.; Schuler, R. H. *J. Chem. Phys.* **1963**, *39*, 2147. (b) Cochran, E. I.; Adrian, F. J.; Bowers, V. A. *Ibid* **1964**, *40*, 213. (c) Whitesides observed that the tin hydride reduction of each (*E*)- and (*Z*)-2-bromo-2-butene at 25 °C gave a 2-butene mixture in the same *E*/*Z* (65/35) ratio. This was explained by postulating that vinyl radical inversion is more rapid than the hydrogen atom transfer from the tin hydride to the vinyl radical (see: Whitesides, G. M.; Casey, C. P.; Krieger, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1379). However, Kuivila obtained different ratios at -75 °C by the same method (see: Kuivila, H. G. *Acc. Chem. Res.* **1968**, *1*, 299.). Simamura reported that the vinyl radical inversion competes with the bromine atom transfer from CCl$_3$Br to a vinyl radical (see: Simamura, O.; Tokumaru, K.; Yui, H. *Tetrahedron Lett.* **1966**, 5141).

increasing E selectivity. Second, as the size of R_1 increases (now holding R_2 and R_3 constant), the equilibrium constant K shifts significantly to favor **24b** (R_1 becomes much larger than the radical). This shift in K begins to offset the rate constant bias ($k_1 > k_{1'}$) for **23E**, and the E selectivity is eroded. Restated in a more usual transition-state argument, as the size of R_1 increases, the steric interaction between R_1 and R_2/R_3 becomes greater than the steric interaction between the incoming iodine donor and R_2/R_3.[41] This is because the transition state is early and resembles the starting radicals **24a/b** more than the final products **23E/Z**.

Two experiments provided qualitative support for the Curtin–Hammett kinetics outlined in Scheme IV. Primary iodides **25a/b** are isomeric with tertiary iodides **15** and **18b**. A different E/Z ratio of vinyl iodide products from an isomeric pair of starting iodides could mean either that inversion of the vinyl radicals is not rapid relative to iodine atom transfer (that is, the Curtin–Hammett boundary conditions are not met) or that the nature of the iodine atom donor (tertiary or primary) has a significant steric or electronic influence on the stereochemistry of the iodine atom-transfer step. In the event, the result was unambiguous; isomerization of either **25a** or **25b** by the standard ditin photolysis method (Scheme IV) provided vinyl iodides **16** and **19b** in identical E/Z ratios with the products formed from the isomeric tertiary iodides **15** and **18b**. Thus, vinyl radical inversion must be more rapid than I transfer. It may seem surprising that the same E/Z ratio is obtained with a primary iodide as with a tertiary iodide. We believe this is because the transition state for iodine atom transfer is early (the forming C–I bond is very long). Thus, the vinyl radical "sees" only a relatively distant iodine atom and not the steric bulk of the substituent behind that atom.[41]

Formation of Fused and Spiro Rings by Atom Transfer Cyclization. The isomerization of a series of cyclic iodides to fused bicyclic rings was briefly studied as summarized in eq 8. In each

		E/Z	yield
26a R = H	**27a**	56/44	42%
26b R = CH₃	**27b**	96/4	22%

(8)

|		E/Z	yield
28a R = H	**29a**	83/17	40%
28b R = CH₃	**29b**	95/5	40%

case, both secondary (**26a**, **28a**) and tertiary (**26b**, **28b**) iodides were prepared. Each was isomerized by the catalytic tin hydride method (portionwise addition). The indicated yields are of purified bicyclic vinyl iodides, and all are relatively modest, in part because

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(41) Interestingly, the reaction of vinyl radicals with tin hydride (Giese, B.; Gonzalez-Gomez, J. A.; Lachhein, S.; Metzger, J. O. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 479) does not show the same trend. For example, in the normal tin hydride reduction of **18b** (see below), the stereoselectivity is op-

18b   E/Z; 24/76
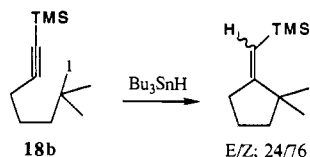
posite to that of the iodine transfer (the change in CIP priority rules reverses E/Z nomenclature compared to **19b**). Even though the reaction of vinyl radicals with tin hydride must have an early transition state, the forming and breaking of bonds to hydrogen are much shorter (compared to iodine) and thus the steric interactions of the incoming tin hydride reagent with the substituents on the vinyl radical are greater.

Scheme V

33a R = H
   b R = CH₃

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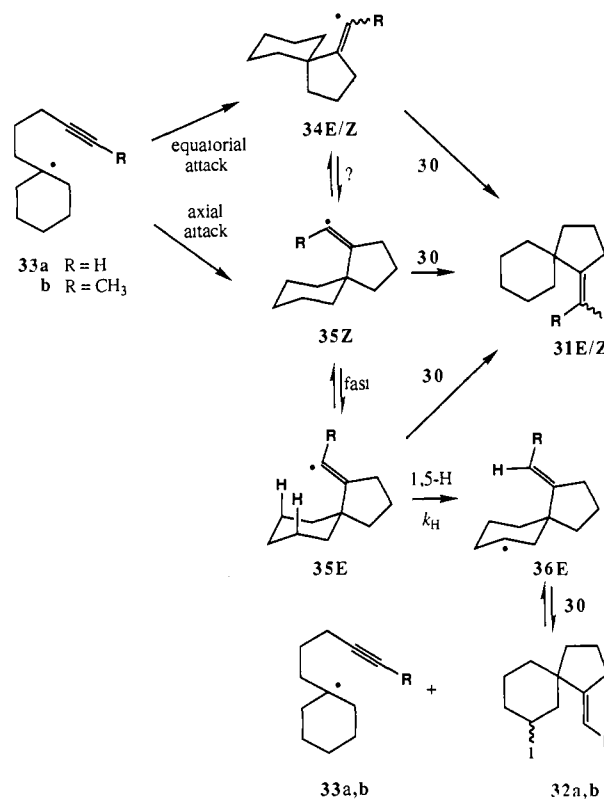
these reactions were conducted before the development of the optimum photolysis conditions.[42] Attempted thermal isomerizations of **26b** or **28b** with hexabutylditin gave only decomposition products. The E/Z stereochemistry of the vinyl iodides was assigned by spectroscopic[43] and mechanistic analogy to the simple examples. Carboxylate derivatives were not prepared for rigorous assignment, and in view of the low E/Z ratio of **27a** (56/44), this particular assignment is tentative.

Two isomerizations to form spirocyclic rings are outlined in eq 9. Unstable tertiary iodide **30a** containing a terminal alkyne was isomerized by the photolytic ditin procedure. After chroma-

(9)

		E/Z	Yield		
30a R = H	**31a**	(90/10)	40%	**32a**	7%
30b R = CH₃	**31b**	(83/17)	53%	**32b**	17%
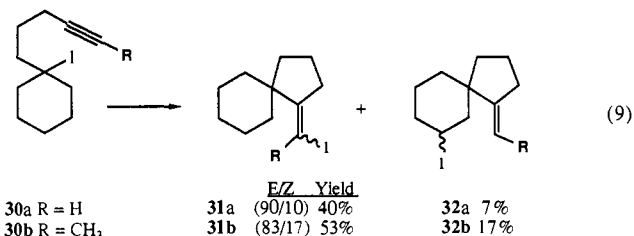
tography, the expected vinyl iodide **31a** was isolated in 40% yield (90/10 E/Z). A second isomeric compound that did not contain a vinyl iodide was isolated in 7% yield. Mechanistic considerations and chemical correlations[44] were used to assign structure **32a** to

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(42) Reaction times for the portionwise tin hydride method (2–3 h, 80 °C) caused significant decomposition of the tertiary iodides, and it was difficult to effect complete conversion of the secondary iodides. Both tertiary iodides are very unstable. They were prepared by treatment of the *tert*-trimethylsilyl ethers with TMSI and were used crude. The quoted yields of **29a/b** were calculated from the *tert*-trimethylsilyl ether precursors. Spectroscopic evidence (GC, NMR) indicated that monocyclic alkenes resulting from the (ionic?) elimination of HI were present in addition to vinyl iodides **27b** and **29b**. These volatile hydrocarbons were not isolated.

(43) In these examples, the allylic protons of the minor stereoisomers were not easy to identify in the inseparable (or partially separable) mixtures. A second (less reliable) chemical shift trend was used: in benzene-d_6, the vinyl proton of the E isomers is upfield (0.05–0.02 ppm) from the Z isomer. This trend does not hold for **27a**, where these two protons are chemical shift equivalent.

this product. Isomerization of the related (and again unstable) methyl-substituted alkyne **30b** by the photolytic method gave **31b** (83/17 *E/Z*) in 53% yield and a single stereoisomer of **32b** in 17% yield.[45,46] The stereochemistry of the alkene was assigned by chemical correlation.[47]

As shown in Scheme V, we propose that **32a,b** arise from rapid intramolecular hydrogen atom transfer to the intermediate vinyl radical. Initial radical **33a,b** can close by either equatorial attack of the side chain (**33 → 34E/Z**) or axial attack (**33 → 35E/Z**). We assume that *E/Z* interconversion by inversion of vinyl radicals is very rapid relative to other processes. Equatorial isomer **34E/Z** has no proximate hydrogen for transfer and can only abstract iodine from **30** to give **31E/Z** and starting radical **33**. Axial isomer **35** can either abstract iodine (both **35E** and **35Z**) to give **31E/Z** or transfer a nearby secondary hydrogen (**35E** only) to give secondary radical **36**. Examples of this exothermic hydrogen transfer from alkyl hydrogens to vinyl radicals are known.[48] More of the 1,5-hydrogen transfer product **32b** is formed with the methyl-substituted system (even though the forming C–H bond in 32b is weaker compared to in **32a**) because the *E/Z* equilibrium is more in favor of **35E**. We propose that **36** can abstract an iodine atom from **30a,b** in a slightly exothermic but still reversible reaction.[49] Since **33** can then cyclize, this is a productive chain-transfer step.
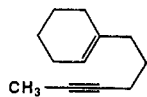
Consideration of the steps involved in the formation of the minor products **32a,b** gave impetus to three lines of research. First, it suggested that the "translocation" of a radical from vinyl to a nearby alkyl site would be a synthetically useful reaction if good iodine donors were not present to compete. Indeed, we have recently shown that 1,5-hydrogen transfer can be a very useful reaction for the indirect generation of radicals from appropriately located C–H bonds.[50] Second, it implied that reasonable chain reactions based on the transfer of iodine atoms from one alkyl radical to another could be developed even if this transfer were reversible. This is indeed the case.[51] Third, an analysis of available rate constants indicated that the subsequent hydrogen and iodine atom-transfer reactions of **34E/Z** and **35E/Z** might actually be faster than their interconversion by chair–chair flip of the cyclohexyl ring.[52]

Assuming that **34/35** abstract iodine with the same rate constant as simple tertiary iodide **15** ($k_I \approx 6 \times 10^8$ M^{-1} s^{-1}), then a *very rough* apparent first-order rate constant for H-atom transfer

can be calculated: for **34a/35a → 36a**, $k_{II} \approx 1 \times 10^7$ s^{-1}; for **35b → 36b**, $k_H \approx 6 \times 10^7$ s^{-1}.[53] The chair–chair interconversions of cyclohexane and 1,1-dimethylcyclohexane both occur with estimated rate constants of $\sim 5 \times 10^6$ s^{-1} at 80 °C, and it is known that the barrier for this interconversion is not dramatically altered by substituents.[54] If one accepts that the rate constant for the **34 ⇌ 35** interconversion is in the range of these cyclohexanes, then one concludes that this interconversion may not compete effectively with H- and 1-atom transfer.

Axial/Equatorial Selectivity in Radical Cyclizations. If **34** and **35** are not interconverting, then the kinetic partitioning of **33** between equatorial and axial attack has some effect on the final product ratio because only the product of axial attack, **35**, can transfer hydrogen. Hence, the yield of **32** could not exceed the percentage of axial attack (it can be lower because **35** may still directly abstract iodine). Despite interest in the stereoselectivity of radical cyclizations,[55] we found no evidence in the literature relating to the partitioning of radicals such as **33** between axial and equatorial attack.

We probed this partitioning with the time-honored strategy of using 4-*tert*-butylcyclohexyl derivatives as models for cyclohexane chairs with locked axial and equatorial substituents. The stereoselectivities in the standard tin hydride reductive cyclization of two simple alkynes and one alkene were determined (eq 10).

Alkynes			
37a R = H		**38 ax**	**38 eq**
37b R = CO$_2$Me		axial attack	equatorial attack
		38/62	
		32/68	
Alkene			
37c R = H		57/43	

Full details on the preparation of the precursors, cyclizations, and structure assignments (by chemical correlation[56]) of the products are given in the supplementary material. Both terminal alkyne **37a** and activated alkyne **37b** showed a slight preference to cyclize by equatorial attack, the activated alkyne being marginally more selective. Clive reported during the course of our work that the cyclization of a more complex phenyl-substituted alkyne also showed a low equatorial selectivity.[57] In contrast, the terminal alkene **37c** showed a very small preference for axial attack.

These simple systems show very little inherent bias for axial or equatorial attack, and we assume that cyclization of **33** provides **34** and **35** in a ratio not far from 1/1. Thus, although the results of eq 10 may be useful in evaluating the origins of stereoselectivity

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(44) Reduction of both **31aE/Z** and **32a** led to the same deiodinated hydrocarbon. The coupling pattern of the proton geminal to iodine indicated that it was adjacent to two vicinal pairs of protons and that it was axially oriented on the cyclohexane ring (that is, the iodide is equatorial). This eliminates C-2 as the location of the iodide. The lack of symmetry in **32a/b** eliminates C-4. Each iodide **32a** and **32b** is a single (unassigned) stereoisomer with respect to the iodine-bearing stereocenter and the spiro carbon.

(45) This isomerization was conducted at 1.0 M in alkyne **30b** and gave a 75/25 ratio of **31b/32b**. Consistent with the mechanism in Scheme V, isomerization of **30b** at 0.3 M gave a decreased ratio of **31b/32b** (67/33).

(46) The following product was also isolated in 6% yield. We do not know whether this is the result of an ionic or a radical process.

(47) The same compound was formed on reductive deiodination of **32b** (Bu$_3$SnH) and **31bZ** (a, *t*-BuLi; b, H$_2$O).

(48) (a) Gilbert, B. C.; Parry, D. J. *J. Chem. Soc., Perkin Trans. 1*, **1988**, 875, and references therein. (b) Hciba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1967**, *89*, 3772. (c) Choi, J.-K.; Hart, D. J. *Tetrahedron* **1985**, *41*, 3959. (d) Bennett, S. M.; Clive, D. L. *J. Chem. Soc., Chem. Commun.* **1986**, 878.

(49) Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206.

(50) (a) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900. (b) Lathbury, D. C.; Parsons, P. J.; Pinto, I. *J. Chem. Soc., Chem. Commun.* **1988**, 81.
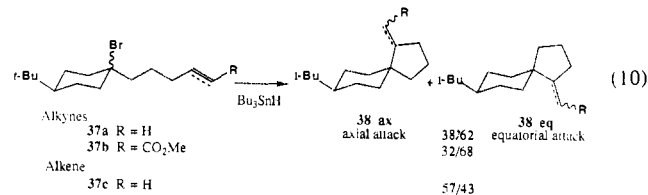
(51) (a) Curran, D. P.; Kim, D. *Tetrahedron Lett.* **1986**, *27*, 5821. (b) Fontana, F.; Minisci, F.; Vismara, E. *Tetrahedron Lett.* **1987**, *28*, 6373; **1988**, *29*, 1975. (c) Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1041.

(52) For an example where 1,5-hydrogen transfer is faster than amide bond rotation, see: Cohen, T.; Smith, K. W.; Swerdloff, M. D. *J. Am. Chem. Soc.* **1971**, *93*, 4303.

(53) If **34a** and **35a** are not in equilibrium, then k_H is actually higher: k_H for conformer **35a** $\approx 1 \times 10^7$ s^{-1}/mole fraction of axial attack.
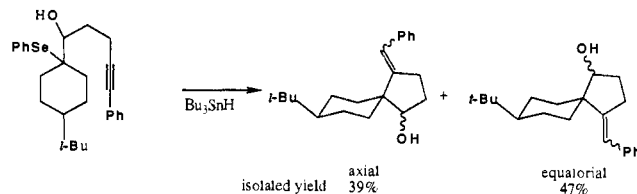
(54) These rates were calculated from the known activation parameters: (a) cyclohexane: Anet, F. A. L.; Bourn, A. J. R. *J. Am. Chem. Soc.* **1967**, *89*, 760. (b) 1,1-Dimethylcyclohexane: Dalling, D. K.; Grant, D. M.; Johnson, L. F. *J. Am. Chem. Soc.* **1971**, *93*, 3678.

(55) For leading references, see: Rajanbabu, T. V.; Fukanaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759.

(56) All of the products were correlated with the known enone i (Shimada, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759) by the following interconversions:

38a (ax/eq) $\xrightarrow{O_3}$ ...   (i)

38a (ax/eq) $\xrightarrow{H_2}$ **38c** (ax/eq)
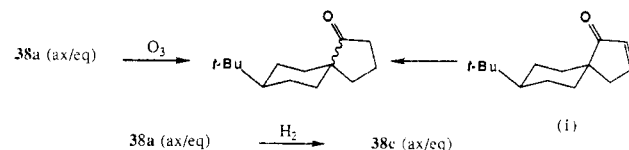
(57) Set, L.; Cheshire, D. R.; Clive, D. L. *J. Chem. Soc., Chem. Commun.* **1985**, 1205.

isolated yield   axial 39%   equatorial 47%

in certain radical cyclizations, they do not provide direct evidence that bears on the question of interconversion of **34** and **35**. The postulate that H- and I-atom transfers are faster than the chair–chair interconversion still lacks direct experimental support.

Conclusions and Recommendations

Atom transfer cyclization reactions of alkyl iodides are useful preparative procedures. The isomerization of alkynyl iodides to cyclic vinyl iodides is an efficient preparative process thanks to the rapid and irreversible abstraction of iodine by vinyl radicals. Indeed, depending on reagents and concentrations, this reaction can actually be more rapid than the reaction of vinyl radicals with tin hydride, and preisomerization of acyclic iodides to cyclic iodides prior to normal tin hydride reduction can then occur. The facility of this iodine transfer has not been widely recognized, and it can be used to rationalize past observations in which radical cyclizations of bromides (which do not efficiently propagate atom-transfer chains) gave different product distributions than from the corresponding iodides.[58] This observation, which surprised us at the outset, is now understandable.

As with other applications of radical reactions in synthesis, the knowledge of rate constants in simple systems and the understanding of substituent effects are invaluable for the planning of successful atom-transfer chains. Our work on the reaction of vinyl radicals coupled with the elegant quantitative work from the Newcomb group[26] now permits a detailed evaluation of many types of halogen atom-transfer reactions with possible competing radical reactions. The best rate constants are accurate enough to predict ratios of products at given concentrations of reactants. Thus, with a few rate constants and a knowledge of simple first- and second-order kinetics, one can not only decide whether a reaction is likely to succeed but also make an intelligent estimate of the optimum reaction conditions.

It is appropriate to compare the atom-transfer method of conducting hexenyl and hexynyl radical cyclizations with the tin hydride method. The success of the tin hydride method for a radical cyclization depends mainly on the rate of the cyclization. Rapid cyclizations are easily conducted, but competing reduction becomes a concern with slower cyclizations. Since nearly all types of radicals react with tin hydride at reasonable rates, the stabilities of the initial and final radicals are not of great concern. In the atom-transfer method, it is the rate of cyclization that is not of great concern (provided that it is sufficiently rapid relative to radical–radical and radical–solvent reactions). However, the relative stabilities of the initial and final radicals are important because the rate of iodine atom transfer roughly parallels the exothermicity of this step. Endothermic atom-transfer steps will not often be sufficiently rapid to propagate chains. Thermoneutral iodine transfers (between alkyl iodides) are tolerable; exothermic transfers are preferable.

There are at least three situations where the atom transfer cyclization may be the method of choice:

First, the tin hydride method always gives net reduction, while the atom-transfer method gives isomerization. In effect, the radical chain is terminated by an iodine atom rather than a hydrogen atom. Certain substitution patterns are not easily accommodated with reductive cyclizations. A very simple illustration of this point is given in eq 11. Tetrasubstituted olefins such as **39** are not available by the tin hydride mediated cyclizations of hexynyl radicals. In contrast, atom-transfer cyclization of **30b** gave **31b** (eq 9). Treatment of **31b** (73/27 *E/Z*) with lithium dimethyl-cuprate gave a 71/29 mixture of the desired tetrasubstituted alkene

31b E/Z 73/27   39   71/29   40

(11)
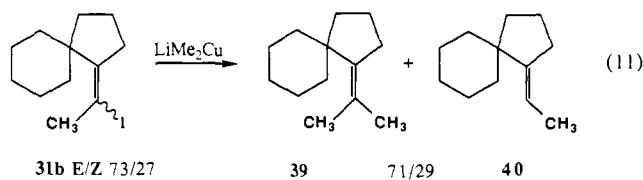
39 and **40**.[59] Of course, many other transformations of the product iodides are possible.

Second, even when net reduction is desired, there is a potential practical advantage to the atom-transfer method: relatively slow cyclizations can be conducted at high concentration because there is no tin hydride present to intercept radicals before cyclization. Since most cyclizations are not reversible, tin hydride can subsequently be added to the cyclic iodide to conduct reductive deiodination. We have provided several examples of this technique in the cyclizations of resonance stabilized radicals.[60] A very nice example in the context of alkyl iodides comes from the work of Crimmins and Mascarella.[61]

Third, selectivity becomes a serious problem when conducting certain sequential reactions by the tin hydride method because many different types of radicals react with tin hydride at the same rate. In the atom-transfer method, intermediate radicals can have significantly different lifetimes and, as a result, different selectivities. A sequence that capitalizes on this feature, atom transfer annulation, is outlined in eq 12. Reaction of electron-deficient

41   42   43   44

(12)
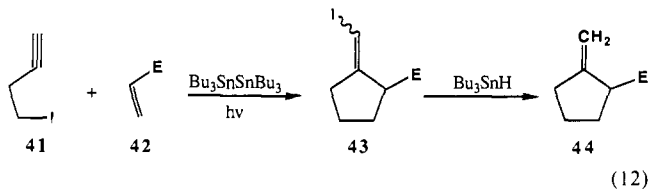
alkenes **42** with butynyl iodide **41** under the standard conditions gives reasonable yields (40–60% isolated) of annulated products **43**.[62] If desired, **44** can be produced by direct addition of tin hydride to the crude reaction mixture (0.3 M). In contrast, attempts to form **44** by the direct tin hydride reduction of mixtures of **41** and **42** were unsuccessful.

Synthetic organic chemists are rapidly discovering that free-radical reactions are well suited for forming many classes of functionalized molecules. This diversity notwithstanding, there remain relatively few methods by which free-radical chains can be conducted in a controlled fashion. The atom-transfer method has clearly emerged as a valuable complement to the tin hydride method.

Experimental Section[63]

The Capnellene Vinyl Iodide (5) (*E/Z* Mixture). A solution of crude iodide **3b** (35 mg, 0.106 mmol), hexamethylditin (0.2 M in benzene, 53 μL, 0.011 mmol) and AIBN (approximately 1 mg) in benzene (320 μL) was placed in a preheated oil bath (85 °C) and heated at reflux for 8 h. Concentration of the mixture and purification of the residue by medium-pressure liquid chromatography (100% pentanes) afforded **5** as a colorless oil (24.5 mg, 70%): ^{1}H NMR (CDCl$_3$) (major isomer) δ 5.82 (1 H, m), 2.70 (2 H, m), 2.41 (2 H, m), 1.91–0.98 (9 H, m), 1.14 (3 H, s), 1.04 (3 H, s), 0.96 (3 H, s); ^{13}C NMR (CDCl$_3$) δ 161.8 (s), 69.7 (d), 69.0 (d), 54.6 (d), 53.5 (s), 47.9 (d), 47.6 (t), 42.4 (s), 41.7 (t), 40.6 (t), 36.4 (t), 31.0 (q), 30.9 (q), 28.0 (t), 26.0 (q); IR (CHCl$_3$) 2970, 2900, 1635, 1475, 1385, 1215 cm^{-1}; MS, *m/e* 330, 206, 203, 147, 133, 99, 58; HRMS Calcd for C$_{15}$H$_{23}$I: 330.0845. Found: 330.0845.

(58) The reductive cyclizations of hexynyl halides (Crandall, J. K.; Michaely, W. J. *J. Org. Chem.* **1984**, *49*, 4244) provide a likely example. In the dropwise addition of a solution of CrCl$_2$ to a pair of hexynyl halides, a higher yield of a methylenecyclopentane product was consistently obtained from the iodide than from the bromide. This makes little sense if one considers only that CrCl$_2$ rapidly reduces both halides to the same radical. We speculate that CrCl$_2$ initiated the isomerization of the hexynyl iodide to the vinyl iodide at early reaction time (hence, relatively low [CrCl$_2$]) and that this intermediate was later reduced by CrCl$_2$. In reduction of the bromide, no isomerization occurred, and the competition of the initial radical between cyclization and direct reduction by CrCl$_2$ continued throughout the reaction.

(59) We suspect that **39** was formed from **31bE** and **40** from **31bZ**. We made no effort to optimize this reaction.

(60) (a) Curran, D. P.; Chang, C.-T. *J. Org. Chem.*, in press. Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1987**, *28*, 2477. (b) A potentially useful modification of our reaction conditions has recently been described: Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536.

(61) Crimmins, M. T.; Mascarella, S. W. *Tetrahedron Lett.* **1987**, *28*, 5063. See also: Kaplan, L. *J. Org. Chem.* **1968**, *33*, 2531.

(62) Curran, D. P.; Chen, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 6558.

(63) NMR spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Alkyl iodides were protected from light during preparation and storage. All reactions were conducted under a nitrogen atmosphere. For other general details, see the supplementary material.

Atom Transfer Cyclizations

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(E)- and (Z)-1-(Iodomethylene)-2,2-dimethylcyclopentane (16). Catalytic Tin Hydride Method (Portionwise). To a stirred solution of 15 (157 mg, 0.67 mmol) in degassed benzene (1 mL) was added Bu₃SnH (19.5 mg, 0.067 mmol) and AIBN (5.4 mg, 0.033 mmol) in benzene (1 mL). After the mixture was heated at reflux for 1 h, a second equal portion of Bu₃SnH/AIBN was added, and heating was continued for an additional 2 h. The crude mixture was poured into a 1:1 mixture of water (10 mL) and petroleum ether (10 mL). The aqueous layer was extracted with petroleum ether (three times), and the combined organic phase was washed with aqueous NaHCO₃ (one time) and cold brine (one time) and dried over MgSO₄. Concentration afforded vinyl iodide 16 as a 15/1 mixture of E and Z isomers as determined by ¹H NMR integration. Purification by MPLC (100% pentanes) gave an inseparable mixture of isomeric (E)- and (Z)-vinyl iodides (73.8 mg, 47%) as a clear oil: ¹H NMR (C₆D₆, E/Z mixture) E isomer δ 5.67 (1 H, t, J = 2.6 Hz), 2.26 (2 H, dt, J = 2.6, 7.1 Hz), 1.40–1.30 (4 H, m), 0.80 (6 H, s); Z isomer δ 5.58 (1 H, t, J = 2.6 Hz), 2.60 (2 H, dt, J = 2.6, 7.0 Hz), 1.40–1.30 (4 H, m, overlapped with E isomer), 1.25 (6 H, s); ¹³C NMR (CDCl₃, E/Z mixture) E isomer δ 164.6 (s), 69.2 (d), 45.2 (s), 43.4 (t), 37.7 (t), 28.2 (q), 21.4 (t); Z isomer δ 29.2, 28.7, 21.8 (difficult to assign other peaks due to a low concentration); IR (thin film, E/Z mixture) 3061, 2955, 2862, 1620, 1460, 1362, 1229, 1215, 1048, 824 cm⁻¹; MS, m/e 235 (M⁺ − H), 221 (M⁺ − CH₃), 109 (M⁺ − I). HRMS Calcd for C₈H₁₂I (M⁺ − H): 234.9984. Found: 234.9983. Anal. Calcd for C₈H₁₃I: C, 40.70; H, 5.55. Found: C, 40.45, H, 5.68.

Photolytic Ditin Method. A solution of 15 (330.8 mg, 1.40 mmol) and hexabutylditin (81.3 mg, 0.14 mmol) in degassed benzene (2 mL) in a 10-mm Pyrex NMR tube was irradiated with a 275-W GE sunlamp for 30 min. The temperature of a thermometer suspended at the same distance from the sunlamp as the tube was kept at 80–85 °C during the irradiation by adjusting the distance between the tube and the sunlamp. After evaporation of benzene, the product was purified by flash chromatography (100% hexanes) to give 16 (197.2 mg, 60%) as a clear oil.

(E)- and (Z)-1-(Iodomethylene)-2-methylcyclopentane (13). Catalytic Tin Hydride Method (Syringe Pump). To a solution of 12 (135 mg, 0.61 mmol) in benzene (1 mL) was added Bu₃SnH (35.4 mg, 0.12 mmol) and AIBN (9.9 mg, 0.06 mmol) in benzene (1 mL) by syringe pump over 4 h at 80 °C. After the addition was complete, the mixture was heated for an additional 1 h. The crude mixture was poured into a mixture of water (10 mL) and pentanes (10 mL). The aqueous layer was extracted with pentanes (three times), and the combined organic phase was washed with aqueous NaHCO₃ (one time), aqueous Na₂S₂O₃ (one time), and cold brine (one time) and dried over MgSO₄. Concentration afforded 13 as a 3.3/1 mixture of E and Z isomers as determined by ¹H NMR integration. Purification by flash chromatography (100% hexanes) gave an inseparable mixture of (E)- and (Z)-vinyl iodides (54 mg, 44%) as a clear oil: ¹H NMR (C₆D₆, E/Z mixture) E isomer δ 5.64 (1 H, m), 2.71–0.82 (7 H, m, overlapped with Z isomer), 0.77 (3 H, d, J = 6.7 Hz); Z isomer δ 5.58 (1 H, m), 2.71–0.82 (7 H, m, overlapped with E isomer), 0.77 (3 H, d, J = 6.7 Hz); ¹³C NMR (CDCl₃, E/Z mixture) E isomer δ 161.1 (s), 69.0 (d), 41.6 (d), 37.7 (t), 36.8 (t), 23.3 (t), 18.4 (q); Z isomer δ 67.4 (d), 34.7 (d), 34.2 (d), 25.3 (t), 23.5 (t) (the peaks of the other three carbons overlapped with those of the E isomer); IR (ChCl₃, E/Z mixture) 2950, 2920, 2860, 1625, 1450, 1419, 1240, 1200 cm⁻¹; MS, m/e 222 (M⁺), 95 (M⁺ − I); HRMS Calcd for C₇H₁₁I: 221.9906. Found: 221.9900. Anal. Calcd for C₇H₁₁I: C, 37.86; H, 499. Found: C, 37.90; H, 5.05.

Vinyl iodide 13 was prepared by the photolytic ditin method from 12 (59.0 mg, 0.3 mmol) and hexabutylditin (15.4 mg, 0.03 mmol) in C₆D₆ (0.9 mL). The yield of 13 was determined to be 87% by ¹H NMR integration against an internal standard (1,4-dichlorobenzene). Purification by flash chromatography (100% pentanes) afforded the vinyl iodide 13 as an inseparable 3.3/1 mixture of E and Z isomers (38.5 mg, 65%).

(1-Iodomethylene)cyclopentane (9). According to the catalytic tin hydride method (syringe pump), 9 was prepared from 8 (921.8 mg, 4.4 mmol), AIBN (72.3 mg, 0.4 mmol), and Bu₃SnH (257.9 mg, 0.9 mmol) in benzene (14 mL). Purification by flash chromatography (100% pentanes) afforded 9 as a clear oil (590 mg, 64%): ¹H NMR (CDCl₃) δ 5.87 (1 H, m), 2.33 (2 H, m), 2.24 (2 H, m), 1.83–1.74 (4 H, m); IR (thin film) 3056, 2955, 2867, 2834, 1626, 1559, 1449, 1424, 1306, 1244, 1096 cm⁻¹; MS, m/e 208 (M⁺), 81 (M⁺ − I).

According to the photolytic ditin method, 9 was prepared from 8 (52.2 mg, 0.3 mmol) and hexabutylditin (14.6 mg, 0.03 mmol) in benzene (0.8 mL). The yield of 9 as 77% by ¹H NMR integration of the vinyl proton against an internal standard (1,4-dichlorobenzene).

(1-Iodoethylidene)cyclopentane (11a). By the photolytic ditin method, 10a (146.6 mg, 0.7 mmol) was converted to vinyl iodide 11a. Purification by flash chromatography (100% pentanes) gave vinyl iodide 11a as a clear oil (104.1 mg, 71%): ¹H NMR (CDCl₃) δ 2.42 (3 H, t, J = 1.3

Hz), 2.34–2.25 (4 H, m), 1.84 (2 H, m), 1.67 (2 H, m); IR (film) 2955, 2867, 2832, 1653, 1449, 1428, 1374, 1173, 1063, 1048 cm⁻¹; MS, m/e 222 (M⁺), 95 (M⁺ − I). HRMS Calcd for C₇H₁₁I: 221.9906. Found: 221.9909.

Trimethyl[(cyclopentylidene)iodomethyl]silane (11b). According to the photolytic ditin method, 10b (60.7 mg, 0.2 mmol) was converted to vinyl iodide 11b. Purification by MPLC (100% hexanes) afforded 11b (25.1 mg, 41%) as a clear oil: ¹H NMR (CDCl₃) δ 2.43–2.41 (4 H, m), 1.88 (2 H, m), 1.67 (2 H, m), 0.25 (9 H, s); IR (thin film) 2955, 2892, 2869, 1595, 1420, 1306, 1248, 880, 839 cm⁻¹; MS, m/e 280 (M⁺), 265 (M⁺ − CH₃), 153 (M⁺ − I). HRMS Calcd for C₉H₁₇ISi: 280.0094. Found: 280.0094.

(E)- and (Z)-2,2-Dimethyl-1-(iodoethylidene)cyclopentane (19a). According to the photolytic ditin method, 18a (99.4 mg, 0.4 mmol) was converted to vinyl iodide 19a as a 3.8/1 mixture of E and Z isomers as determined by ¹H NMR integration and GC injection. Purification by flash chromatography (100% pentanes) afforded 19a (53.7 mg, 54%) as an inseparable mixture of (E)- and (Z)-vinyl iodides: ¹H NMR (C₆D₆, E/Z mixture) E isomer δ 2.49–2.40 (5 H, m), 1.40–1.16 (4 H, m), 0.94 (6 H, s); Z isomer δ 2.28 (3 H, t, J = 2.0 Hz), 2.11 (2 H, m), 1.50–1.40 (4 H, m), 1.29 (6 H, s); IR (thin film, E/Z mixture) 2952, 2865, 1653, 1456, 1362, 1034 cm⁻¹; MS, m/e 250 (M⁺), 123 (M⁺ − I). HRMS Calcd for C₉H₁₅I: 250.0219. Found: 250.0218.

(E)- and (Z)-Trimethyl[(2,2-dimethylcyclopentylidene)iodomethyl]silane (19b). According to the photolytic method, 18b (218.2 mg, 0.7 mmol) was converted to 19b as a 1/4.6 mixture of E and Z isomers as indicated by ¹H NMR integration and GC analysis. Purification by flash chromatography (100% hexanes) afforded 19b (97.8 mg, 45%) as an inseparable mixture of (E)- and (Z)-vinyl iodides: ¹H NMR (C₆D₆, E/Z mixture) E isomer δ 2.64 (2 H, t, J = 6.7 Hz), 1.70–1.12 (4 H, m, overlapped with Z isomer), 1.03 (6 H, s), 0.40 (9 H, s); Z isomer δ 2.28 (2 H, t, J = 6.8 Hz), 1.70–1.12 (4 H, overlapped with E isomer), 1.38 (6 H, s), 0.25 (9 H, s); IR (thin film, E/Z mixture) 2953, 2895, 1576, 1456, 1361, 1248, 1012, 839 cm⁻¹; MS, m/e 308 (M⁺), 181 (M⁺ − I). HRMS Calcd for C₁₁H₂₁ISi: 308.0457. Found: 308.0450.

Isomerization of 3,3-Dimethyl-6-iodo-1-hexyne (25a) to Vinyl Iodide 16. Vinyl iodide 16 was prepared according to the photolytic ditin method from 25a (169.0 mg, 0.7 mmol) and hexabutylditin (41.5 mg, 0.07 mmol) in benzene (2 mL). Purification by flash chromatography (100% hexanes) afforded vinyl iodide 16 as an inseparable 15/1 mixture of E and Z isomers (111.5 mg, 66%).

Isomerization of 25b to Vinyl Iodide 19b. According to the photolytic ditin method, 25b (72.0 mg, 0.2 mmol) was converted to 19b as a 1/4.6 mixture of E and Z isomers as determined by ¹H NMR integration and GC analysis. Purification by flash chromatography (100% hexanes) afforded 19b (33.8 mg, 47%) as an inseparable mixture of (E)- and (Z)-vinyl iodides.

2-(Iodomethylene)bicyclo[3.3.0]octane (27a) (E/Z Mixture). To a solution of the secondary iodide 26a (104.1 mg, 0.419 mmol) in benzene (1.3 mL) at 85 °C was added tributyltin hydride (11 μL, 0.063 mmol) and AIBN (22 mg, 0.134 mmol) in benzene (0.3 mL) via a syringe pump over a 3.5-h period. After refluxing 12 h, the reaction mixture was concentrated and chromatographed (100% hexanes) to afford vinyl iodide 27a and starting material 26a (27a/26a = 55/45). This mixture was resubjected to the reaction conditions [benzene (1 mL), tri-n-butyltin hydride (2.2 μL, 0.0125 mmol), and AIBN (4.1 mg, 0.025 mmol)], and after 1 h, a solution of tin hydride (2.2 μL) and AIBN (4.1 mg) in benzene (150 μL) was added via syringe pump over a 1-h period. After the mixture was refluxed 12 h, gas chromatography showed that the reaction had not gone to completion (27a/26a = 3/2). More tin hydride (2.2 μL) and AIBN (4.1 mg) were added, and this procedure was repeated after 2 h later. After refluxing for 12 h, the reaction mixture was concentrated and purified by medium-pressure liquid chromatography (100% pentanes) to afford 27a as a colorless oil (43.5 mg, 42%): ¹H NMR (CDCl₃) E isomer δ 5.80 (1 H, m), 2.95–2.11 (5 H, m), 1.94–1.24 (7 H, m); Z isomer δ 5.84 (1 H, m); IR (CHCl₃) 2925, 2860, 1450, 1220 cm⁻¹; MS, m/e 248, 121, 93, 79, 67, 55. HRMS Calcd for C₈H₁₃I: 248.0062. Found: 248.0063. Anal. Calcd for C₈H₁₃I: C, 43.57; H, 5.28. Found: C, 43.69; H, 5.40.

2-(Iodomethylene)-1-methylbicyclo[3.3.0]octane (27b) (E/Z Mixture). A solution of tertiary iodide 26b (27.3 mg, 0.104 mmol) tributyltin hydride (5.6 μL, 0.021 mmol), and AIBN (approximately 1 mg) in benzene (320 μL) was placed in a preheated oil bath (85 °C) and refluxed for 1.5 h. Evaporation of the solvent and purification of the residue by medium-pressure liquid chromatography (100% hexanes) afforded 26b as a colorless oil (6.2 mg, 23%): ¹H NMR (CDCl₃) E isomer δ 5.68 (1 H, m), 2.35 (2 H, m), 1.91–1.06 (9 H, m), 0.88 (3 H, s); Z isomer δ 5.62 (1 H, m), 1.29 (3 H, s).

2-(Iodomethylene)bicyclo[3.4.0]nonane (29a) (E/Z Mixture). To a solution of secondary iodide 28a (38.8 mg, 0.148 mmol) in benzene (0.5

mL) was added tributyltin hydride (8 μL, 0.03 mmol) and AIBN (7.7 mg, 0.04 mmol). The reaction mixture was then placed in a preheated oil bath (85 °C). After the mixture was refluxed for 12 h, the reaction was incomplete as determined by gas chromatography (29a/28a = 2/1); therefore, additional portions of tributyltin hydride (1.2 μL, 0.0045 mmol) and AIBN (1.5 mg, 0.009 mmol) were added to the solution. After 4 h at 85 °C, more tributyltin hydride (1.2 μL, 0.0045 mmol) and AIBN (1.5 mg, 0.009 mmol) were added. After refluxing 12 h, the reaction mixture was concentrated, and the residue was purified by medium-pressure liquid chromatography (100% hexanes) to give 29a as a colorless oil (15.3 mg, 40%): ^{1}H NMR (CDCl$_3$) E isomer δ 5.81 (1 H, m), 2.57–2.13, (4 H, m), 2.00–0.99 (10 H, m); Z isomer δ 5.66 (1 H, m); IR (CHCl$_3$) 2920, 2850, 1440, 1320 cm^{-1}; MS, m/e 262, 135, 95, 79, 67. HRMS Calcd for C$_{10}$H$_{15}$I: 262.0219. Found: 262.0217. Anal. Calcd for C$_{10}$H$_{15}$I: C, 45.82; H, 5.77. Found: C, 45.87; H, 5.89.

2-(Iodomethylene)-1-methylbicyclo[3.4.0]nonane (29b) (E/Z Mixture). Compound 29b was prepared following the procedure for 27b using tertiary iodide 28b (52 mg, 0.118 mmol), tributyltin hydride (5.4 μL, 0.02 mmol), and AIBN (5.9 mg, 0.036 mmol). A colorless oil (29b, 20.5 mg, 40%) was obtained after medium-pressure liquid chromatography (100% pentanes): ^{1}H NMR (CDCl$_3$) E isomer δ 5.77 (1 H, m), 2.50–2.33 (2 H, m), 1.86–1.15 (11 H, m), 1.05 (3 H, s); Z isomer δ 6.03 (1 H, m); ^{1}H NMR (benzene-d$_6$) E isomer δ 5.64 (1 H, m), 2.44–2.16 (2 H, m), 1.56–0.88 (11 H, m), 0.81 (3 H, s); Z isomer δ 5.55 (1 H, m); IR (CHCl$_3$) 2920, 2840, 1445, 1200 cm^{-1}. Anal. Calcd for C$_{11}$H$_{17}$I: C, 47.84; H, 6.21. Found: C, 47.91; H, 6.49.

2-(Iodomethylene)spiro[4.5]decane (31a) (Mixture of E and Z Isomer) and trans-2-Methylene-7-iodospiro[4.5]decane (32a). A solution of iodide 30a (33 mg, 0.12 mmol) and hexabutylditin (6 μL, 0.012 mmol) in degassed benzene (0.4 mL) was irradiated with a sunlamp (GE, 275 W, distance from tube = 10 cm) for 15 min. Evaporation of the solvent gave a crude oil which was purified by flash chromatography (100% hexanes) to afford the E and Z isomers of 31a in 40% yield (13.3 mg) and 32a in 7% yield (2.3 mg): ^{1}H NMR (CDCl$_3$) E isomer of 31a δ 5.85 (1 H, t, J = 3 Hz), 2.36 (2 H, td, J = 7, 3 Hz), 1.78 (2 H, t, J = 6 Hz),

1.69–1.25 (12 H, m); ^{1}H NMR (CDCl$_3$) 32a δ 4.89 (1 H, s), 4.80 (1 H, s), 4.26 (1 H, tt, J = 11, 4 Hz), 2.37 (2 H, m), 1.70–1.30 (10 H, m).

2-(Iodoethylene)spiro[4.5]decane (31b) (Mixture of E and Z Isomer) and trans-2-Ethylene-7-Iodospiro[4.5]decane (32b). A solution of crude iodide 30b (706 mg, 2.1 mmol) and hexamethylditin (180 μL, 0.21 mmol, 1.15 M in benzene) in degassed benzene (1.2 mL) was irradiated with a sunlamp (GE, 275 W, distance from tube = 10 cm) for 80 min. The photolysis temperature was kept at 40 °C. The resulting mixture was concentrated to give a crude brown oil. Flash chromatography (100% hexanes) afforded a pale-yellow oil which was a mixture of 32b and the E and Z isomers of 31b (432 mg, 70% overall from 30b). The undesired elimination product (4-hexynylcyclohex-1-ene) was isolated in 6% yield (20 mg): ^{1}H NMR (CDCl$_3$) E isomer of 31b δ 2.73 (3 H, t, J = 2 Hz), 2.43 (2 H, td, J = 7 Hz), 1.90 (2 H, t, J = 7 Hz), 1.80–1.18 (12 H, m); Z isomer of 31b δ 2.56 (3 H, s); ^{13}C NMR (CDCl$_3$) E isomer of 31b δ 155.2 (s), 93.1 (s), 48.1 (s), 45.9 (t), 40.4 (t), 34.5 (t), 31.4 (q), 25.9 (t), 23.3 (t), 22.7 (t); IR (thin film) 31b mixture 2928, 2857, 1636, 1446 cm^{-1}; MS 31b mixture, m/e, 290, 163, 95, 81. HRMS (31b mixture) Calcd for C$_{12}$H$_{19}$I: 290.0531. Found: 290.0531. ^{1}H NMR (CDCl$_3$) 32b δ 5.23 (1 H, m), 4.28 (1 H, tt, J = 13, 4 Hz), 2.42 (1 H, br d, J = 13 Hz), 2.27 (2 H, m), 2.18 (1 H, br d, J = 13 Hz), 1.99 (1 H, t, J = 13 Hz), 1.87 (1 H, m), 1.66–1.25 (8 H, m), 1.60 (3 H, d, J = 1 Hz); IR (thin film) 32b 2020, 2953, 1670, 1447 cm^{-1}; MS 32b, m/e, 290, 240, 197, 163. HRMS (32b) Calcd for C$_{12}$H$_{19}$I: 290.0531. Found: 290.0533.

Supplementary Material Available: Full details on the general aspects of the work, the preparation of all cyclization precursors, and the characterization of products by syntheses of authentic samples and by chemical transformations (38 pages). Ordering information is given on any current masthead page.

Xestovanin A and Secoxestovanin A, Triterpenoid Glycosides with New Carbon Skeletons from the Sponge *Xestospongia vanilla*

Peter T. Northcote and Raymond J. Andersen*

Contribution from the Departments of Chemistry and Oceanography, University of British Columbia, Vancouver, British Columbia, Canada V6T 1W5. Received January 18, 1989

Abstract: Xestovanin A (1) and secoxestovanin A (2), two new triterpenoid glycosides, have been isolated from extracts of the Northeastern Pacific marine sponge *Xestospongia vanilla*. The structures of 1 and 2 were solved by extensive spectroscopic analysis and chemical transformations. Xestovanin A (1) gave the hexaacetate 5 on treatment with acetic anhydride and pyridine. Reaction of 1 with hot aqueous potassium hydroxide gave the organic soluble elimination product 6. Acidic hydrolysis of the water soluble material from the elimination reaction gave D-fucose and L-rhamnose. Secoxestovanin A (2) gave the same elimination product 6 on treatment with hydroxide. *X. vanilla* is only the second sponge known to contain triterpenoid glycosides. The aglycones of 1 and 2 both have new triterpenoid carbon skeletons. Xestovanin A (1) shows antifungal activity against *Pythium ultimum*.

Marine sponges are an extremely rich source of sesqui-, di-, and sesterterpenoids.[1] The reported occurrence of squalene-derived triterpenoids in sponges is, by contrast, currently limited to a relatively small number of compounds in only a few different species. The first examples were a family of isomalabaricane triterpenoids isolated from the Pacific Ocean sponge *Jaspis stellifera*[2a] and the Indian Ocean sponge *Stelletta* sp.[2b] Subse-

quently, a Red Sea sponge, *Siphonochalina siphonella*, yielded triterpenoids representing three new carbon skeletons all formed by novel modes of squalene cyclization.[3] Recently, sarsinosides A$_1$, B$_1$, and C$_1$, a family of norlanostane oligoglycosides,[4] and

(1) (a) Minale, L. In *Marine Natural Products, Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol 1, Chapter 5. (b) Faulkner, D. J. *Natural Product Reports* **1987**, 4, 539. (c) Faulkner, D. J. *Ibid.* **1986**, 3, 1. (d) Faulkner, D. J. *Ibid.* **1984**, 1, 551.

(2) (a) Ravi, B. N.; Wells, R. J.; Croft, K. D. *J. Org. Chem.* **1981**, 46, 1998. (b) McCabe, T.; Clardy, J.; Minale, L.; Pizza, C.; Zollo, F.; Riccio, R. *Tetrahedron Lett.* **1982**, 23, 3307.

(3) Carmely, S.; Kashman, Y. *J. Org. Chem.* **1986**, 51, 784 and references therein.

(4) (a) Kitagawa, I.; Kobayashi, M.; Okamoto, Y.; Yoshikawa, M.; Hamamoto, Y. *Chem. Pharm. Bull.* **1987**, 35, 5036. (b) Schmitz, F. J.; Ksebati, M. B.; Gunasekera, S. P.; Agarwal, S. *J. Org. Chem.* **1988**, 53, 5941.