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RADICAL-INITIATED POLYOLEFINIC CYCLIZATIONS IN LINEAR TRIQUINANE SYNTHESIS. MODEL STUDIES AND TOTAL SYNTHESIS OF (±)-HIRSUTENE

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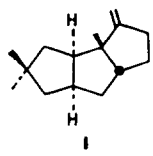
Summary: Details of a novel radical-initiated polyolefinic cyclization approach to linear condensed cyclopentanoids are reported. The strategy is executed in three stages: (1) S_n2'-anti opening of a vinyl lactone to produce a trans-3,5-disubstituted cyclopentene, (2) rapid elaboration to a cyclization precursor, and (3) single step tandem radical cyclization to produce a cis-anti-cis tricyclo[3.3.0]undecane. Model substrates 16a and 16b give high yields of tricyclic products 17 and 18, respectively. An effort to rationalize the interesting endo selectivity via the Beckwith transition state model is proposed. Cyclizations of 28 and 29 to 30 and 31 demonstrate the viability of a tandem hexenyl-hexynyl cyclization. The work culminates with a total synthesis of (±)-hirsutene. A selective approach to methyl substituted vinyl lactones by Claisen rearrangement-phenylselenolactonization-elimination of acetoxy cyclopentenols is exemplified by the synthesis of 12. Tandem cyclization of 38 produces hirsutene (1) in a single step. Alternatively, cyclization of 37 yields trimethylsilyl hirsutene.

Introduction: Until recently, condensed cyclopentanoid natural products (polyquinanes) have passed largely unnoticed with respect to their cyclohexanoid counterparts. Over the last decade or so, the existence and importance of condensed cyclopentanoids has begun to be realized.[2] Most naturally occurring polyquinanes are tricyclic sesquiterpenes which can be classed according to ring fusion as linear, angular, or propellane. These compounds come from a wide variety of natural sources and many possess significant antibiotic and/or anti-tumor activity. Not surprisingly, the above factors, coupled with the novelty and complexity of the structures, have spawned intense synthetic activity.[2]

Hirsutene (1)[3] is the naturally occurring parent member of an important class of linear triquinanes typified by the more highly oxygenated hirsutic acid (2)[4] and coriolin (3)[5], both of which possess significant antitumor activity. $\Delta^{9,12}$Capnellene (4), an isomer of hirsutene, is the parent of a second family of sesquiterpenes of marine origin.[6] Again, a variety of more highly oxygenated relatives have been isolated.[6a,b] Hirsutene and $\Delta^{9,12}$ capnellene have served as prototypes for the synthesis of linear polyquinanes and have frequently been used to illustrate new methods for construction of condensed cyclopentane rings. However, while a large number of synthetic strategies exist, generality to prepare both simple and complex cogeners[7] and flexibility to prepare isomeric relatives[8] is frequently lacking. We have embarked upon a program to develop a unified strategy for the synthesis of linear condensed cyclopentanoids employing a tandem hex-5-enyl radical cyclization as the key step.[9]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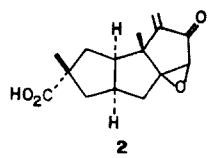
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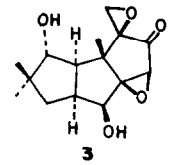
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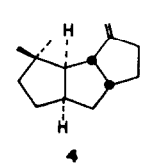
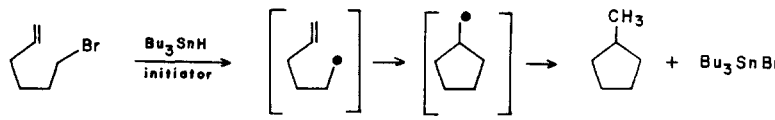
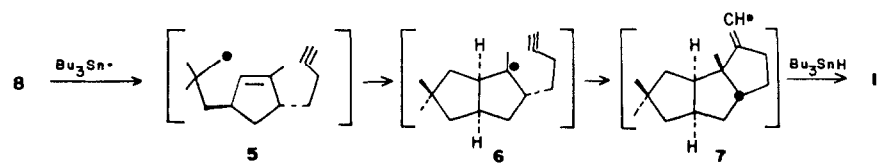

4

It is now well known that many hex-5-enyl radicals suffer rapid cyclization to cyclopentyl carbinyl radicals[10]. A vast body of mechanistic data indicates that in most cases these cyclizations are stereoelectronically controlled, irreversible, proceed regardless of the degree of substitution of starting and product radicals, and tolerate a wide variety of pendant functional groups. Factors affecting the rate of reaction and site selectivity of these radicals are also well delineated.[10] Coupled with the mild generation of radicals via trialkyltin hydride reduction of halides (or other approapriate groups) the hex-5-enyl radical cyclization provides a powerful, if infrequently utilized, synthetic method for five-membered ring formation.[10d]



Many strategies to linear cyclopentanoids involve sequential construction of each ring in the tricyclic system[12]. In such an approach, iterative annulations can be particularly valuable[2g,4,6k]. In principle, tandem construction of rings can provide an inherently more convergent approach provided that the cyclization precursors are readily available and that the necessary stereochemistry can be controlled.[13] It is readily recognized that if the initial cyclized radicals produced are again hex-5-enyl radicals, subsequent cyclizations can occur. Based on this concept, we have undertaken the development of a general radical-initiated polyolefinic cyclization approach to linear condensed cyclopentanoids. This is outlined for hirsutene in equation 1. Upon generation by treatment of an appropriate precursor (halide, xanthate, etc.) with a trialkyltin hydride, radical 5 should undergo successive hexenyl and hexynyl cyclizations to produce vinyl radical 7. In a slower step, radical 7 should then abstract hydrogen from tin hydride. Note then that hirsutene is directly produced in a single step from a relatively simple trans-3,5-disubstituted cyclopentene by construction of the two outer rings about the central ring.

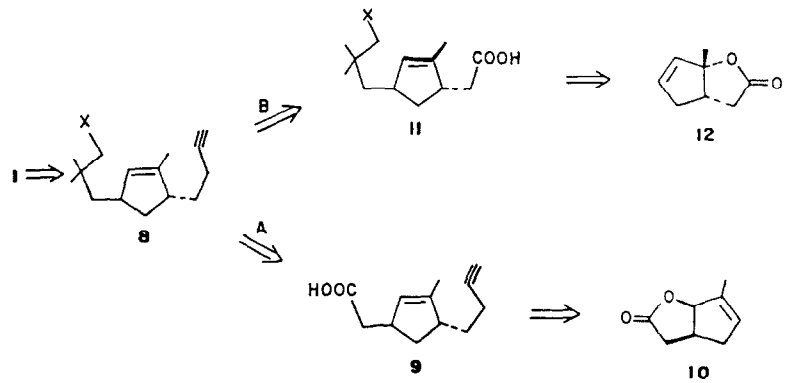
Eq 1



Since the radical cyclizations must each proceed to form a cis ring fusion, the trans disposition of the side chains effectively insures the formation of the cis-anti-cis stereochemistry present in hirsutene. Drawing analogy to the cation-initiated polyolefinic cyclization strategy for cyclohexanoids[14], we feel that this radical-initiated tandem cyclization will prove to be a powerful method for the construction of condensed cyclopentanoids. As applied to hirsutene 1, our overall strategy is outlined in Scheme 1. The synthesis is executed in three stages: 1) S_n2'-anti opening of a vinyl lactone (10 or 12) to

provide a trans-disubstituted cyclopentene (9 or 11), 2) rapid elaboration to a cyclization precusor 8, and 3) tandem radical cyclization. The generality and flexibility of the strategy are readily apparent. Note that, in principle, the two side chains are interchangeable. Depending upon which appendage is chosen as the nucleophile for the vinyl lactone opening, a different lactone (10 or 12) is required. Thus, two options for preparation of the cyclization precusor are available (in practice, route B was successful). By choice of nucleophile and subsequent reactions, unfunctionalized (for hirsutene) or highly functionalized (for coriolin or hirsutic acid) precursors might be constructed.

Scheme I



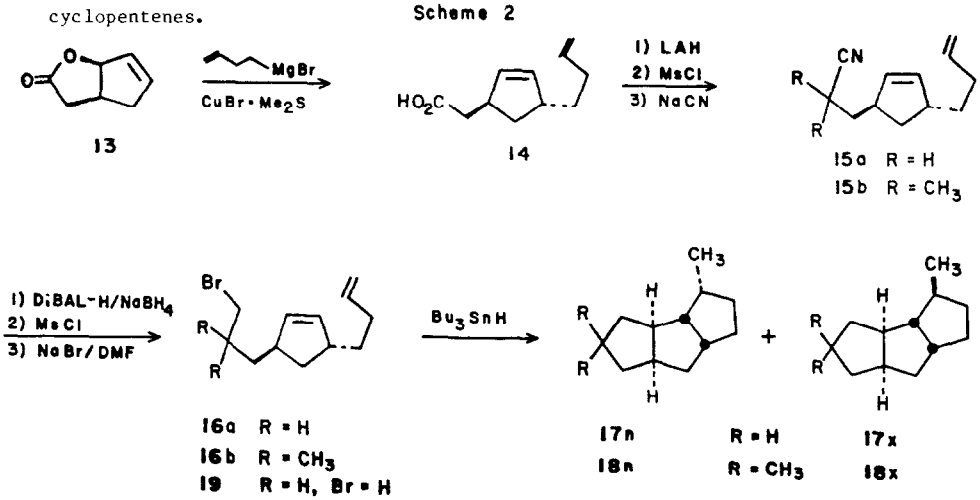
Finally, a similar retrosynthetic analysis may be readily drawn for $\Delta^{9,12}$ capnellene which delivers two lactones isomeric with 10 and 12 via the same strategy. We now wish to report complete details of our preliminary studies on the tandem radical approach to linear condensed cyclopentanoids.[9] This work has recently culminated in the total syntheses of (±)-hirsutene and sets good precedent for realization of the aforementioned goal of a unified approach to linear condensed cyclopentanoids.

Results and Discussion: The earliest studies on radical initiated polyolefinic cyclizations emanated largely from the laboratory of Julia.[15] His use of stabilized radical intermediates led to the frequent production of thermodynamic rather than kinetic products. In this manner, condensed cyclohexanoid systems were formed. Since this pioneering work, the use of radical-initiated polyolefin cyclizations has been sparse.[16] Most recently, during our initial studies, Stork has provided elegant examples of the synthetic utility of these reactions which begin to show their potential.[17]

To determine the viability of the tandem radical cyclization approach to linear condensed cyclopentanoids, a simple model system was rapidly prepared as outlined in Scheme 2. Well known vinyl lactone 13[18] is readily available from cyclopentadiene by a sequence of 1) Diels-Alder reaction with α-chloroacrylonitrile, 2) hydrolysis, and 3) Baeyer-Villiger oxidation and acid catalysed rearrangement. Central to our strategy is the selective opening of a vinyl lactone. Addition of 3-butenyl magnesium bromide/CuBr•Me_2S to 13 produced acid 14 as a single regio- and stereoisomer in virtually quantitative yield when a stoichiometric amount of CuBr•Me_2S was employed. That this product was the result of S_n2'-anti opening of the vinyl lactone was apparent from the spectra of the derived iodolactone (see experimental). Interestingly, the use of a catalytic amount of CuBr•Me_2S provided a quantitative yield of a 1/1 mixture of

isomers.[19,20,21] Similarly, while $LiMe_2Cu$ produced a nearly 1/1 mixture of isomers[20], $CH_3MgBr/CuBr \cdot Me_2S$ produced a single S_n2'-anti product. Acid 14 was directly reduced with lithium aluminum hydride and the resulting alcohol was mesylated. Cyanide displacement then provided the homologated nitrile 15a. Sequential reduction to the aldehyde (DiBAL-H) and the alcohol ($NaBH_4$), followed by mesylation and sodium bromide displacement, produced the first cyclization precursor 16a. Alternatively, sequential methylation (LDA/CH_3I, 2X) followed by the identical sequence as above produced dimethyl derivative 16b. In this series, displacement of the neopentyl mesylate (NaBr/DMF/100°C) proceeded in only 35% yield. While not of concern in the model system, this issue would have to be addressed in the actual hirsutene synthesis. The construction of these model cyclization precursors by stereo- and regioselective vinyl lactone opening exemplifies our general strategy for the preparation of trans-3,5-disubstituted cyclopentenes.

Scheme 2



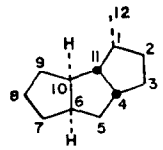
13 14 15a R = H 15b R = CH_3

16a R = H
16b R = CH_3
19 R = H, Br = H

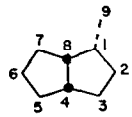
17n R = H 17x
18n R = CH_3 18x

We were most pleased to find that heating of a .02M solution of 16a and one equivalent of tri-n-butyltin hydride with a spatula tip of AIBN in benzene-d_6 for 1h showed complete disappearance of starting material and production of two major (>90%) non-tin containing products in a ratio of 8/1 as indicated by GC and ^{1}H-NMR. Due to the volatility of these tricyclic C_{12} hydrocarbons, only isolation by direct preparative GC of the reaction mixture was feasible. In this manner, an 87% yield of a mixture of 17n, x was isolated. Elemental analysis and mass spectra confirmed the expected $C_{12}H_{20}$ formula and ^{1}H-NMR showed the presence of only aliphatic protons with two methyl doublets at δ0.98 and 0.96 ($CDCl_3$). While this evidence was indicative of the general structure 17, we felt that the assignment was far from secure. The structure and stereochemistry were confirmed by ^{13}C-NMR. Table 1 lists the chemical shifts for the major isomer 17n. Adjacent to these values are a set of calculated values obtained from the data and assignments of Whitesell on endo- and exo-2-methylbicyclo-[3.3.0]octane.[22] Each carbon in 17n was assigned a model carbon from the bicyclic system. Corrections for additional β- and γ-interactions were then applied from the values of Whitesell where needed. Only significant endo γ-interactions were corrected. Indicated smaller corrections (<1.5 ppm) were not applied. The table shows an excellent correlation between the calculated and observed chemical shifts and multiplicities. This serves to confirm the structure of 17n and assign the methyl group to the endo (α) position by virtue of its upfield chemical shift. Dimethyl derivative 16b was cyclized to a similar mixture and assigned structures 18n (major) and 18x (minor) by analogy.

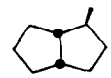
TABLE 1 C^{13}-NMR of 17n



17n



endo (N)



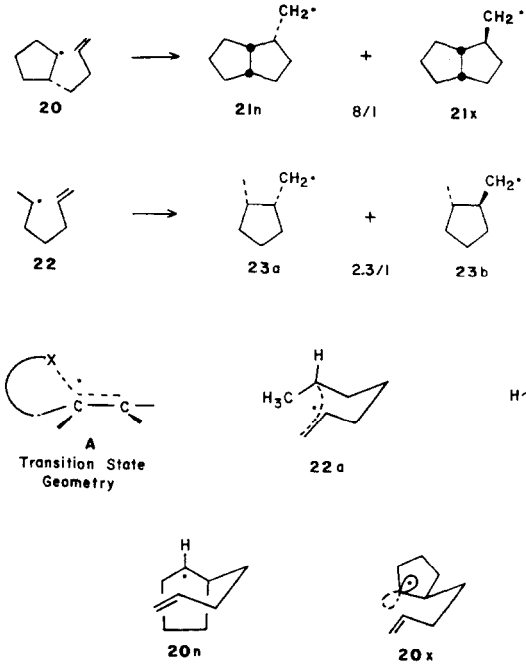
exo (X)

Carbon	Model	Chemical Shift	Correction β,γ	Calculated	Observed (67MHz, $CDCl_3$)
1	1n	37.9	0,0	37.9	38.2(d)
2	2n	33.1	0,0	33.1	33.2(t)
3	3n	32.4	0,0	32.4	32.9(t)
4	4n	43.2	0,0	43.2	44.4(d)
5	3x	33.6	+9,0	42.6	40.4(t)
6	4x	43.4	0,0	43.4	45.1(d)
7	5x	34.0	0,0	34.0	34.2(t)
8	6x	25.5	0,0	25.5	25.5(t)
9	7x	32.3	0,0	32.3	32.9(t)
10	8x	51.9	0,-6.4	45.4	46.0(d)
11	8n	47.6	+9,0	56.6	56.9(d)
12	9n	15.4	0,0	15.4	16.2(q)

The mechanism of these tandem cyclizations is analogous to that outlined in eq. 1. In support of this, the initial intermediate radical could be partially trapped as the reduced product 19 at high tri-n-butyltin hydride concentrations (2M). No evidence was obtained for trapping of the intermediate radical resulting from the first cyclization. While the stereoselectivity is not of importance for the ultimate synthesis of hirsutene, the high endo selectivity is interesting. Similar selectivity for the less stable endo isomer has been detected in related systems.[23] In particular, Wolff and Agosta have observed that cyclization of 20 produced an 8/1 mixture of 21n and 21x.[24] Such a "cis" selectivity between the C_1 substituent and the final radical is a general phenomena for carbocyclic hexenyl radical cyclizations. For example, the simple methyl substituted radical 22 provides a 2.3/1 mixture of 23a and 23b[25a]. Several interesting hypotheses have been advanced to explain this "cis" selectivty[25]; however, it seems possible that simple steric effects in the transition state might account for the observed products. Using the Beckwith transition state model[26], four transition states for the cylization of 22 can be drawn. Assuming the two boat transition states are of higher energy, the two chair transition states are 22a and 22b. The former has an equatorial-like methyl group while the later possesses an axial-like methyl. The major product 23a then results from 22a. Note that due to the stereoelectronic requirements for the cyclization (see A)[10,26], the methyl group does not severely eclipse the olefin in 22a. Recently, calculations by K. N. Houk and D. Spellmeyer have provided evidence for this rational.[26b]

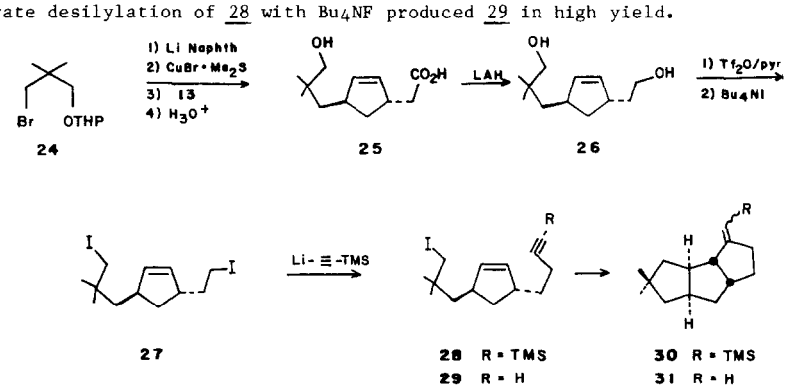
Two analogous chair transition states 20n and 20x can now be drawn for the bicyclic systems. Molecular models indicate that the strain imposed by the fused five-membered ring forces the singly occupied orbital in 20x to twist away from the olefin p-orbitals while no such problem exists with 20n. Thus, an increase in the "cis" selectivity is observed in the bicyclic system despite the fact that such endo substituents on bicyclo[3.3.0]octanes are strongly thermodynamically disfavored relative to their exo counterparts.[2] Again, due to the early transition state and the angle of attack of the radical SOMO on the olefin LUMO, the significant steric interactions present in the product 21n pass largely unnoticed in transition state 20n.

Scheme 3



Note that in this model system, the "right" side chain was introduced as a nucleophile in the vinyl lactone opening while the "left" side chain was elaborated from the resultant acid residue. As pointed out in Scheme I, these roles are potentially interconvertible. In practice, when we encountered early technical problems in the execution of route A[27] we rapidly switched to route B, requiring a "left" side chain nucleophilic equivalent and vinyl lactone 12. Bromide 24 nicely provided the intact side chain unit. While traditional methods of halogen-metal exchange failed entirely, the desired organolithium reagent could be generated from 24 by reductive lithiation with lithium naphthalenide.[28] Following addition of copper bromide-dimethyl sulfide and lactone 13, the resultant carboxylic acid (isolated by base extraction) was directly treated with pPTS to cleave the THP group. Hydroxy acid 25 could then be isolated as the single base soluble product in variable yield. This reaction proved extremely sensitive to changes in reaction conditions and, while higher yields were obtained, best conditions (see experimental) typically produced 25 in 40-50% yield. Reduction of 25 produced diol 26 which was then converted to the diiodide 27 via the intermediate ditriflate in good overall yield.[29] Employment of this procedure alleviates the problems encountered in the preparation of 16b. We could now capitalize on the difference in reactivity between the two iodides by displacement. Reaction of 27 with one equivalent of lithium trimethylsilyl acetylide[30] produced 28 along with small amounts of the desilylated product 29. As expected, the neopentyl-like iodide was unaffected. Deliberate desilylation of 28 with Bu_4NF produced 29 in high yield.

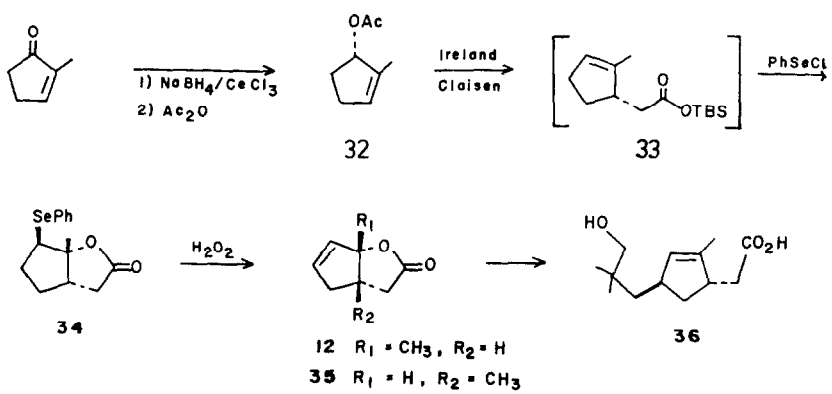
Scheme 4



The stage was now set for model reactions to incorporate the methylene group via a second hexynyl radical cyclization.[31] In the event, tri-n-butyltin hydride promoted tandem radical cyclization of 28 provided an isomeric mixture of vinyl silanes 30 as evidenced by ^{1}H-NMR (~3/1). Careful desilylation of 30 in an NMR tube (HI, C_6D_6)[32] provided the nor-methyl hirsutene 31. Similarly, direct tin hydride promoted cyclization of 29 produced 31, identical by ^{1}H-NMR to that produced by desilylation of 30. Since the synthesis of vinyl lactone 12 was completed at about this time, rather than pursue the model studies further, the knowledge gained was directly applied to the synthesis of hirsutene.

For this synthesis, a selective preparation of methyl substituted vinyl lactone 10 or 12 was required. In addition, one of two isomeric lactones is required for a proposed capnellene synthesis. Thus we desired a potentially general route to this system in which substituent regiochemistry is rigidly controlled. Interestingly, the simple Diels Alder approach employing methyl cyclopentadiene (as a mixture of 1- and 2-isomers) and chloroacrylonitrile (analogous to unsubstituted 13) would produce all four desired lactones in a single sequence. However, the lack of selectivity in the Diels-Alder reaction and the attendant separation problems strongly mitigated against this approach. Instead, a selective and potentially general approach was developed as outlined in Scheme 5. Starting from a methyl substituted cyclopentenol, Ireland-Claisen rearrangement followed by phenylselenolactonization-elimination produces a vinyl lactone in which the final position of the methyl group is rigidly dictated. Employing 2-methylcyclopentenone,[33] known Luche reduction ($NaBH_4$, $CeCl_3$)[34] and acetylation produced acetate 32. Ireland ester enolate Claisen rearrangement[35] via the t-butyldimethylsilyl ketene acetal of 32 produced crude silyl ester 33 which was directly subjected to phenylselenolactonization to produce 34.[36] Standard oxidation (H_2O_2) and elimination[36] produced vinyl lactone 12 in 62% overall yield from 32 after chromatographic purification. Via a similar sequence, 3-methylcyclopen-2-en-1-ol has recently been converted to 35 for use in the proposed capnellene synthesis.[37]

Scheme 5

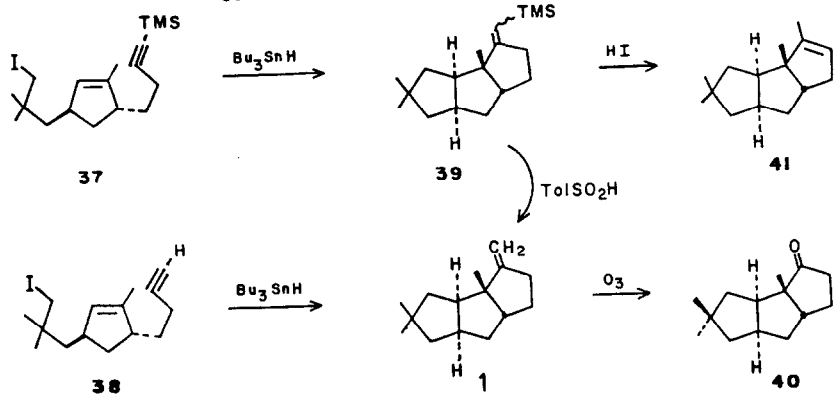


With vinyl lactone 12 in hand, the construction of the final cyclization precursors followed the model described in Scheme 4. Vinyl lactone opening produced 36 after cleavage of the THP group. Again, while yields up to 75% were realized, ~40%-50% yields were more typical. Efforts to improve the yield and reproducibility of this procedure are continuing. Reduction to the diol and conversion to the diiodide followed by displacement with lithium trimethylsilyl

acetylide, produced cyclization precursors 37 and (after desilylation) 38 in good overall yield.

The final cyclizations are outlined in Scheme 6. Standard tri-n-butyltin hydride cyclization of 38 produced hirsutene (1) directly via the tandem radical cyclization outlined in equation 1. ^{1}H-NMR and GC experiments indicated the yield of hirsutene to be ~80%. While volatility was again a problem on small scale, separation from the tin biproducts was accomplished by careful medium pressure liquid chromatography with 100% pentanes. The resultant product (65% isolated) was analysed by capillary GC (see experimental for conditions and retention times) and shown to possess four closely spaced compounds in a ratio of 6/100/2/2. The major product was clearly hirsutene while the last compound exhibited a retention time identical to tri-n-butyltin hydride. The identity of the other two minor products has not presently been ascertained. The hirsutene so produced was identical in all respects (GC, TLC, ^{1}H-NMR, ^{13}C-NMR, IR, MS) to a sample kindly provided by P. Magnus and authentic spectra provided by P. Wender and R. D. Little. In addition, ozonolysis of 1 provided the well known nor-ketone 40, identical to samples provided by R. D. Little and T. Hudlicky.

Scheme 6



Interestingly, cyclization of 37 cleanly provided 39, which was isolated in 72% yield as an isomeric mixture of vinyl silanes (3/1 ratio, isomers not assigned). Careful GC analysis showed these two products to be the only two non-tin containing compounds in the crude mixture. Unfortunately, attempted HI desilylation of the mixture 39 (C_6D_6 RT)[32] produced only endo hirsutene 41[3c,m], the result of double bond migration. Similarly, refluxing of 39 for several hours in acetic acid also gave 41.[38] Most recently, we have found that the desilylation method of Büchi employing p-toluenesulfinic acid (CH_3CN, RT)[39] does provide hirsutene as the single volatile product, free of the minor impurities detected in the direct cyclization.

In summary, the viability of this radical-initiated polyolefinic cyclization approach to linear condensed cyclopentanoids has been firmly established. Model studies have shown the utility of the tandem radical cyclization and confirmed an interesting and general endo stereoselectivity. The work has culminated with a short synthesis of (±)-hirsutene which begins to show the potential of these radical reactions in organic synthesis. Note that the final cyclization involves the conversion of a 3° radical to a vinyl radical. Despite this significant decrease in radical stability, the product is still produced in

good yield. It is also noted that while the synthesis is at present racemic, the simple modification of asymmetric reduction of 2-methylcyclopentenone (or resolution of the alcohol), will allow facile introduction of optical activity. This is significant since many synthetic approaches to condensed cyclopentanoids have not allowed for ready production of non-racemic products. Further efforts designed to show the generality and flexibility of this approach to condensed cyclopentanoids are in progress.

Experimental

General: Unless otherwise noted reactions were run under nitrogen atmosphere. Temperatures of reactions refer to bath temperatures. Solvents were dried as follows: THF, Et_2O, toluene, benzene (Na/benzophenone); dimethyl sulfide, DMSO, DMF, pyridine, HMPA (CaH_2); CH_2Cl_2 (P_2O_5).

^{1}H-NMR spectra were obtained on a Bruker model WH-300 (300 MHz), or on a Varian model EM-390 (90 MHz) spectrometer. Infrared spectra were obtained on a Beckman model Acculab 4 or a Perkin-Elmer model 247 spectrophotometer and were calibrated to a polystyrene absorption at 1601 cm^{-1}. Low resolution mass spectra were obtained on a LKB-9000 instrument. High resolution spectra were obtained by peak matching on a Varian MATCH-5DF instrument.

Flash and medium pressure (MPLC) column chromatography were performed with Kiesilgel 60 (230-400 mesh). Medium pressure chromatography was also done on pre-packed EM lobar LiChroprep Si/60 columns. Analytical gas chromatography for compounds 17 and 18 was performed on a HP-5710a instrument with a 12 ft OV-101 column. Analytical gas chromatography for all other compounds was performed on a HP-5890 instrument with a 12 ft 530 μ column. The following temperature program was used: initial temp (0 min): 100°C; temperature ramp: 15°C/min: final temp: 220°C. Preparative gas chromatography was performed on a Varian aerograph model 920 instrument with a 6 ft SE-30 packed column at 150°C.

trans-3-(Acetic acid)-5-(3-butenyl)cyclopent-1-ene (14). To a solution of freshly prepared copper bromide dimethyl sulfide complex[40] (4.1 g, 20 mmol) in dimethyl sulfide (25 mL) was added THF (50 mL). After cooling to -20°C, 3-butenyl magnesium bromide (23 mL, 20.7 mmol) was added dropwise. The resulting deep blue mixture was stirred 15 min. Lactone 13 (1.24 g, 10 mmol) was then added via syringe and the mixture was stirred at -20°C. After quenching with 10% HCl (100 mL), the acid was extracted into ether (4x). The organic layers were combined and washed with water (3x), brine (1x) and dried ($MgSO_4$). Concentration in vacuo afforded a green oil (2.00 g): ^{1}H-NMR ($CDCl_3$) δ 5.9-5.6(3H,m); 5.00(1H,dd); 4.94(1H,dd); 3.12(1H,broad t); 2.73(1H, broad t); 2.06(2H,broad q); 1.9-1.2(6H,m); IR ($CHCl_3$) 2900 (broad); 1705; 1640 cm^{-1}.

Iodolactonization of acid 14. To crude acid 14 (170 mg) in Et_2O/aq. $NaHCO_3$ was added KI and several crystals of iodine. After stirring 36h in the dark, the reaction was quenched with aqueous sodium bisulfite. The aqueous phase was extracted with ether and the combined organic phases were washed with aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The iodolactone (204 mg) was isolated as an unstable yellow oil: ^{1}H-NMR ($CDCl_3$) δ 5.80 (1H, ddt), 5.30 (1H, d, J=6.0Hz), 5.01 (2H, m), 4.53 (1H, d, J=4Hz), 3.18 (1H, m), 2.90 (1H, dd, J=7H,18Hz), 2.37 (1H, dd, J=18Hz, 2Hz); 2.1-1.2 (7H, m); IR ($CHCl_3$) 1780 cm^{-1}; MS calcd. for $C_{11}H_{15}O_2I$, 306.0117; found, 306.0112.

trans-3-(2-Hydroxyethyl)-5-(3-butenyl)cyclopent-1-ene. Lithium aluminum hydride (807 mg, 21.2 mmol) suspended in ether (25 mL) was cooled to 0°C. Crude acid 14 (2.00 g) in ether (25 mL) was slowly added and the resulting mixture was stirred 1h at 0°C. After careful standard work-up (807 μL H_2O, 807 μL 10% NaOH, 2.5 mL H_2O), the mixture was filtered through celite (ether) and dried ($MgSO_4$). Concentration and Kugelrohr distillation of the crude product (bp 85°C, 15mm) gave a clear oil (1.41 g, 85% from lactone): ^{1}H-NMR ($CDCl_3$) δ 5.83(1H,m); 5.69(2H,s); 5.02(1H,dd); 4.94(1H,dd); 3.67(2H,m); 2.80(1H,m); 2.71(1H,m); 2.08(2H,broad q); 1.8-1.2(7H,m); IR($CHCl_3$) 3450, 1640 cm^{-1}; MS m/e 166 (21%); 148 (100%); 121 (57%).

trans-3-(2-Methanesulfonyloxyethyl)-5-(3-butenyl)-cyclopent-1-ene. The above alcohol (1.37 g, 8.3 mmol) was dissolved in CH_2Cl_2 (40 mL) and Et_3N (1.7 mL, 12.3 mmol) was added. After cooling to 0°C, MsCl (850 µL, 11 mmol) was added dropwise. After 1h, the reaction mixture was poured into a separatory funnel containing water. The organic layer was separated and washed with $NaHCO_3$ and brine. Drying with Na_2SO_4 and concentration gave a yellow oil (2.25 g): ^{1}H-NMR ($CDCl_3$) δ 5.8-5.5 (3H, m); 4.95 (1H, dd); 4.89 (1H, dd); 4.20 (2H, t); 3.00 (3H, s); 2.79 (1H, m); 2.65 (1H, m); 2.02 (2H, broad q); 1.8 -1.2 (6H, m).

trans-3-(2-Cyanoethyl)-5-(3-butenyl)-cyclopent-1-ene (15a). Sodium cyanide (1.9 g, 24 mmol) was added to the above mesylate in DMSO (25 mL) and the reaction was stirred overnight at room temperature. After pouring into water, the mixture was extracted with ether (3x). Washing with water (5x) and brine (1x), followed by drying ($MgSO_4$) and concentration in vacuo gave the crude product (1.44 g). Flash column chromatography (9:1 hexanes/EtOAc) afforded 15a as a clear oil (1.017 g, 70%): ^{1}H-NMR ($CDCl_3$) δ 5.9-5.6 (3H, m); 5.01 (1H, dd); 4.96 (1H, dd); 2.85(1H, m); 2.72(1H,m); 2.35(2H, t); 2.08(2H,broad q); 1.9-1.2(6H,m); IR ($CHCl_3$) 2250, 1640 cm^{-1}; MS calcd. for $C_{12}H_{17}N$, m/e 175.1361; found, 175.1361; Anal. calcd. for $C_{12}H_{17}N$: C, 82.23; H, 9.78; found C, 82.18; H, 9.65.

trans-3-(3-Oxopropyl)-5-(3-butenyl)-cyclopent-1-ene. To a cooled (0°C) solution of 15a (532 mg, 3 mmol) in toluene (10 mL) was added slowly DIBAL (1M hexane, 3.1 mL, 3.1 mmol). The reaction mixture was warmed to room temperature and stirred overnight. Recooling to 0°C was followed by addition of 10% HCl (10 mL). The aldehyde was extracted into methylene chloride and the organic extracts were washed with water (4x), brine (1x), and dried (Na_2SO_4). Concentration gave a yellow oil (713 mg): ^{1}H-NMR ($CDCl_3$) δ 9.75 (1H, t); 5.9-5.6 (3H, m); 5.1-4.9 (2H, m); 2.70 (2H,broad q); 2.45 (2H, t); 2.10 (2H, broad q); 1.9-1.2(6H, m).

trans-3-(3-Hydroxypropyl)-5-(3-butenyl)-cyclopent-1-ene (17a). To a solution of the crude aldehyde (713 mg) in THF/EtOH (4:1) (5 mL) was added solid sodium borohydride (120 mg, 3.4 mmol). The mixture was stirred 15 minutes. The reaction mixture was poured into water. Extraction with ether (3x) was followed by washing the combined organic extracts with water (2x), brine (1x) and drying ($MgSO_4$). Concentration in vacuo and purification by Kugelrohr distillation (bp 90°C, 15mm) gave a clear oil (232 mg, 43%): ^{1}H-NMR ($CDCl_3$) δ 5.82 (1H, m); 5.63 (2H, s); 5.00 (1H, dd); 4.96 (1H, dd); 3.63 (2H, t); 2.70 (2H, broad quintet); 2.07 (2H, broad quintet); 1.8-1.2 (9H, m); IR ($CHCl_3$) 3400, 1640 cm^{-1} MS calcd. for $C_{12}H_{18}$ (M-H_2O), m/e 162.1409; found, 162.1400; MS m/e 180 (1%); 162 (3%); 121 (100%).

trans-3-(3-Methanesulfonyloxypropyl)-5-(3-butenyl)cyclopent-1-ene. The mesylate was prepared as above: ^{1}H-NMR ($CDCl_3$) δ 5.9-5.6 (3H, m); 4.99 (1H, dd); 4.95 (1H, dd); 4.22 (2H, t); 3.01 (3H, s); 2.71 (2H, m); 2.08 (2H, broad q); 1.8-1.3 (8H, m).

trans-3-(3-Bromopropyl)-5-(3-butenyl)cyclopent-1-ene (16a). To the stirred solution of the crude mesylate in DMF (3 mL) was added sodium bromide (443 mg, 4 mmol). After stirring overnight, the brown solution was poured into water. Extraction with ether (3x) was followed by washing the combined organic extracts with water (5x) and brine (1x) and drying ($MgSO_4$). Concentration in vacuo gave a brown oil which was filtered through florisil to give a pale yellow oil (178 mg, 74%). Purification by flash chromatography (hexanes) gave 16a as a clear oil: ^{1}H-NMR ($CDCl_3$) δ 5.78 (1H, m); 5.63 (2H, dd); 4.96 (1H, dd); 4.92(1H, dd); 3.37 (2H, t); 2.67 (2H, broad quintet); 2.02 (2H, broad q); 1.6 (2H, t); 1.5-1.2 (6H, m); MS m/e 242,244 (6%); 202,200 (100%); 189,187 (18%).

1-Methyltricyclo[6.3.0.0]undecane 17x,n. To a solution of 16a (58 mg, 0.239 mmol) in benzene (12 mL) was added AIBN (<.5 mg) and tri-n-butyltin hydride (84 µL, .259 mmol). The reaction mixture was placed in a preheated oil bath (80°C) and refluxed 35 min. After cooling, preparative GC of the mixture gave 17x,n (1/8) as a clear volatile liquid (34 mg, 87%): ^{1}H-NMR (of 17n) ($CDCl_3$) δ 2.6-2.35 (2H, m); 2.13 (1H, m); 1.95 (2H, m); 1.7-1.4 (8H, m); 1.4-1.2 (4H, m); 0.98 (3H, d) major isomer; 0.96 (3H, d) minor isomer; ^{13}C-NMR ($CDCl_3$) δ 56.94 (d); 46.01 (d); 44.45 (d); 40.47 (t); 38.21 (d); 34.16 (t); 33.16 (t); 32.87 (t); 31.87 (t); 25.85 (t); 16.24 (q). MS m/e 164 (100%); 122 (81%); 94 (55%); Anal. calcd. for $C_{12}H_{20}$: C, 87.73; H, 12.27; found C, 87.71; H, 12.22; GC retention time: 8.51 (minor); 8.81 (major).

trans-(2-Cyano-2,2-dimethylethyl)-5-(3-butenyl)cyclopentent-1-ene (15b). To a solution of diisopropyl amine (5.51 mL, 39.4 mmol) in THF (12 mL) at 0°C was added nBuLi (23.2 mL, 39.4 mmol). After stirring 10 minutes, one half of the LDA solution was quickly syringed into another flask at 0°C. To one of the LDA portions was added dropwise a solution of 15a (2.3 g, 13.1 mmol) in THF (5 mL). The anion was stirred 20 minutes and MeI (1.2 mL, 19.7 mmol) was added. TLC indicated monoalkylation was complete 15 min after warming to 25°C. The reaction mixture was transferred via syringe to a second LDA solution and this was stirred at 0°C for 15 minutes. MeI (3.2 mL, 52 mmol) was added and the reaction was warmed to room temperature. After 2h the cloudy solution was poured into water. Extraction with CH_2Cl_2 (3x) was followed by washing the organic fractions with water (3x), brine (1x) and drying (Na_2SO_4). Concentration in vacuo afforded the crude product. Flash column chromatography (5% EtOAc/hexanes) gave a clear oil (2.51 g, 94%): ^{1}H-NMR ($CDCl_3$) δ 5.9-5.6 (3H,m); 5.00 (1H,dd); 4.96 (1H,dd); 2.92 (1H,m); 2.7 (1H,m); 2.08 (2H, broad q); 1.9-1.3 (6H,m); 1.37 (6H,s); IR ($CHCl_3$) 2250, 1650 cm^{-1}; MS calcd. for $C_{14}H_{21}N$, m/e 203.1674; found 203.1673. MS 203 (21%); 188 (19%); 161 (100%); 148 (82%); 121 (73%).

trans-3-(3-Oxo-2-2-dimethylpropyl)-5-(3-butenyl)cyclopent-1-ene. The aldehyde was prepared as above: ^{1}H-NMR ($CDCl_3$) δ 9.47 (1H, s); 5.80 (1H, m); 5.60 (2H, dd); 4.97 (2H, m); 2.70 (1H, m); 2.05 (1H, q); 1.8-1.3 (8H, m); 1.05 (6H, s).

trans-3-(3-Hydroxy-2,2-dimethylpropyl)-5-(3-butenyl)-cyclopent-1-ene. Prepared as above: ^{1}H-NMR ($CDCl_3$) δ 5.82 (1H, m); 5.65 (2H, m); 4.98 (1H, dd); 4.95 (1H, dd); 3.33 (2H, s); 2.70 (2H, m); 2.08 (2H, broad q); 1.8-1.2 (7H; m); 0.91 (6H, s). IR ($CHCl_3$) 3400, 1640 cm^{-1}; Anal. calcd. for $C_{14}H_{24}O$ C, 80.71; H, 11.61; found C, 80.60; H, 11.44; MS calcd. for $C_{14}H_{24}O$, m/e 208.1827; found, 208.1827.

trans-3-(3-Methanesulfonyloxy-2,2-dimethylpropyl)-5-(3-butenyl)cyclopent-1-ene. Prepared as above: ^{1}H-NMR ($CDCl_3$) δ 5.80 (1H, m); 5.61 (2H, dd); 5.00 (1H, dd); 4.97 (1H, dd); 3.92 (2H, s); 3.02 (3H, s); 2.75 (2H, m); 2.09 (2H, broad q); 1.9-1.2 (6H, m); 1.02 (6H, s).

trans-3-(3-Bromo-2,2-dimethylpropyl)-5-(3-butenyl)cyclopent-1-ene (16b). The crude mesylate (1.1 g) was dissolved in DMF (15 mL) and sodium bromide (5 g, 48 mmol) was added. The mixture was refluxed 24 h followed by workup as before. Purification by flash column chromatography (100% hexanes) and Kugel Rohr distillation (105°C, 1.5 mm) afforded 16b as a clear oil (487 mg, 37%): ^{1}H-NMR ($CDCl_3$) δ 5.82 (1H, m); 5.65 (2H, m); 5.00 (1H, dd); 4.96 (1H, dd); 3.31 (2H, s); 2.71 (2H, m); 2.06 (2H, broad q); 1.8-1.2 (6H, m); 1.03 (6H, s). IR ($CHCl_3$) 1640, 1250, 700 cm^{-1}; MS m/e 270/272 (3%); 228/230 (100%); 216/218 (10%).

1,5,5-trimethyl-tricyclo[6.3.0.0]undecane (18x,n). Bromide 16b was cyclized by the standard conditions as described for 16a. Complete separation from tin-containing compounds was quite difficult: ^{1}H-NMR ($CDCl_3$) δ 2.55 (2H, m); 2.29 (1H, m); 2.00 (2H, m); 1.7-0.9 (10H, m); 1.04 (3H, s); 0.96 (3H, s) major isomer; 0.94 (3H, s) minor isomer; 0.92 (3H, s); ^{13}C-NMR ($CDCl_3$) δ 56.96; 49.37; 48.40; 46.55; 44.98; 44.50; 40.81; 38.00; 33.17; 30.25; 28.84; 16.43; 15.24; 13.56 cm^{-1}; MS calcd. for $C_{14}H_{24}$, m/e 192.1878; found, 192.1879; GC retention time: 4.36 min (minor); 4.52 min (major).

3-Tetrahydropyranyloxy-2,2-dimethyl-1-bromopropane (24). The known bromoalcohol[41] (1.7 g, 10 mmol), dihydropyran (1 mL, 12 mmol) and pPTS (5 mg) were stirred in CH_2Cl_2 (10 mL) for 2 h.[42] The solvent was removed in vacuo. The residue was extracted into ether and washed with half saturated brine solution. The organic solution was dried ($MgSO_4$) and concentrated to yield a clear liquid (2.4 g, 95%): ^{1}H-NMR ($CDCl_3$) δ 4.60 (1H, t); 3.86 (1H, dt); 3.58 (1H, d); 3.52 (1H, dt); 3.40 (2H, dd); 3.16 (1H, d); 1.9-1.5 (6H, m); 1.08 (3H, s); 1.03 (3H, s).

cis-6-Phenylselenyl-6a-methyl-3,3a,4-tetrahydro-2H-cyclopenta [b] furan-2-one (34). To a solution of diisopropylamine (1 mL, 7.14 mmol) in THF (10 mL), cooled to 0°C, was added nBuLi (10 mL, 6 mmol). The solution was stirred 10 min, cooled to -78°C, and a solution of acetate 32 (833 mg, 5 mmol) in THF (4 mL) was added dropwise. To the resultant anion was added t-butyldimethylsilyl chloride (964 mg, 5.4 mmol) in HMPA (5 mL). The turbid solution was stirred 1.5 h before quenching with ice cold water. Extraction with cold pentanes (2x), followed by washing with water (2x), brine (1x) and drying gave the ketenesilylacetal as a pale yellow liquid (1.589 g) after concentration in vacuo: ^{1}H-NMR ($CDCL_3$) γ 5.62 (1H, m); 4.79 (1H, m); 3.29 (1H, d); 3.10 (1H, d); 2.5-1.5 (7H, m); 0.93 (9H, s); 0.15 (6H, s).

A solution of the above ketenesilylacetal (1.589 g) in chloroform (5 mL) was refluxed 5h. Evaporation of the solvent afforded crude 33 as a yellow liquid (1.85 g): ^{1}H-NMR ($CDCl_3$) γ 5.38 (1H, m); 2.59 (1H, d); 2.54 (1H, d); 2.3-1.5 (8H, m); 0.93 (9H, s); 0.27 (6H, s). To a solution of silylester 33 (1.38 g, 5.7 mmol) in methylene chloride (40 mL) at -78°C, under argon atmosphere, was added phenylselenyl chloride (1.38 g, 6.8 mmol).[3b] After 25 min, evaporation of solvent followed by flash column chromatography (CH_2Cl_2) afforded 34 as a clear oil (1.00 g, 75% from 32). ^{1}H-NMR ($CDCl_3$) δ 7.58 (2H, m); 7.31 (3H, m); 3.90 (1H, s); 3.10 (1H, d); 3.05 (1H, d); 2.6-2.2 (5H, m); 2.0-1.5 (3H, m); MS calcd. for $C_{14}H_{16}O_2Se$, m/e 296.0316; found, 296.0319.

cis-6a-Methyl-3,3a,4-tetrahydro-2H-cyclopenta-[b]-furan-2-one (12). To a cooled (0°C) solution of 34 (950 mg, 3.22 mmol) in THF (30 mL) was added 3% hydrogen peroxide (1.5 mL).[36] After stirring overnight, extraction with ether (3x) was followed by washing with water (2x) and brine (1x), drying ($MgSO_4$), and concentration in vacuo. Flash column chromatography (CH_2Cl_2) afforded 12 as a clear oil (281 mg, 82%): ^{1}H-NMR ($CDCl_3$) δ 5.94 (1H, m); 5.79 (1H, m); 2.85-2.65 (2H, m); 2.94 (1H, dd); 2.39 (1H, dd); 2.3-2.2 (1H, dq); 1.51 (3H, s); IR ($CHCl_3$) 1760 cm^{-1}; MS calcd. for $C_8H_{10}O_2$ m/e 138.0681; found, 138.0686; Anal. calcd. for $C_8H_{10}O_2$: C, 69.53; H, 7.30; found C, 69.24; H, 7.10.

Trans-5-(Acetic Acid)-3-(3-hydroxy-2,2-dimethylpropoyl)-1-methylcyclopent-1-ene (36). A solution of lithium naphthalenide in THF (70.6 mL, 15 mmol) was transferred to a dry flask under argon.[28] After cooling to -78°C, a solution of bromide (1.5g, 6 mmol) in THF (5 mL) was added over 15 minutes and the mixture was stirred an additional 15 minutes during which time the color of the reaction changes to yellow-brown. A solution of $CuBr \cdot Me_2S$[40] (1.23 g, 6 mmol) in Me_2S (6 mL) was added to give a green solution. To this was added lactone 7 (414 mg, 3 mmol) in THF (3 mL). The reaction mixture was warmed to -20°C and stirred 5 h. The mixture was poured into a 10% NaOH solution (200 mL) and stirred a few hours or overnight. Extraction with ether (3x) removed neutral organic compounds. Acidification of the aqueous layer to pH ~3 with 40% H_2SO_4 was followed by extraction with ether (3x). The combined organic acid extracts were washed with water (3x) and brine (1x). Drying ($MgSO_4$) and concentration in vacuo afforded a slightly green oil (767 mg). This was directly dissolved in absolute ethanol (10 mL) and was heated with a spatula tip of pPTS for 4h.[42] After cooling and evaporation of the ethanol, the residue was poured into ether/50% saturated brine solution. Extraction of the aqueous layer with ether (1x) and concentration in vacuo afforded 36 as a clear oil. (512 mg, 75%): ^{1}H-NMR ($CDCl_3$) δ 5.30 (1H, s); 3.32 (2H, s); 2.90 (1H, broad m); 2.71 (1H, broad m); 2.52 (1H, dd); 2.15 (1H, dd) 1.90 (1H, m); 1.75 (1H, m); 1.67 (3H, s); 1.39 (1H, dd); 1.25 (1H, m); .90 (6H, s); IR ($CHCl_3$) 3500-2400 (broad); 1700 cm^{-1}.

trans-3-(3-Hydroxy-2,2-dimethylpropyl)-5-(2-hydroxyethyl)-1-methylcyclopent-1-ene. To a solution of 36 (254 mg, 1.12 mmol) in THF (16 mL) at -78°C was added DIBAL (6 mL, 6 mmol). This mixture was allowed to warm to 25°C and stirred 7 h. Quenching the reaction with methanol (exothermic) gave a thick suspension which dissolved upon stirring with aqueous citric acid. The mixture was extracted with ether (3x), and the combined extracts were washed with water (1x) and brine (1x). Concentration in vacuo of the dried ($MgSO_4$) extracts afforded a clear oil (197 mg, 83%). Kugelrohr distillation gave an analytical sample: ^{1}H-NMR ($CDCl_3$) δ 5.28 (1H, s); 3.70 (2H, m); 3.31 (2H, s); 2.69 (1H, m); 2.55 (1H, m); 1.85 (2H, m); 1.68 (3H, s); 1.57 (1H, m); 1.4-1.2 (5H, m); .90 (6H, s); IR ($CHCl_3$) 3200, 1260, 1040 cm^{-1}; MS calcd for $C_{13}H_{24}O_2$, m/e 212.1768; found, 212.1776; Anal. calcd. for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39; found C, 73.15, H, 11.61.

trans-3-(3-Trifluoromethanesulfonyloxy-2,2-dimethylpropyl)-5-(2-trifluromethanesulfonyloxyethyl)-1-methylcyclopent-1-ene. To a solution of pyridine (34 uL, .415 mmol) in methylene chloride (2 mL), cooled to -10°C, was added a solution of triflic anhydride (65.8 µL, .390 mmol) in methylene chloride (1 mL).[29] After stirring 10 min, a solution of the above diol (22 mg, 0.104 mmol) in CH_2Cl_2 (1 mL) was added to the thick white reaction mixture. After stirring an additional 1 h, the mixture was poured into ice water and the layers were separated. Extraction of the aqueous layer with CH_2Cl_2 (2x) was followed by drying of the combined organic extracts (Na_2SO_4). Concentration in vacuo gave a residue which, when taken up in hexanes and concentrated, afforded a relatively unstable purple oil (40 mg, 81%): ^{1}H-NMR ($CDCl_3$) δ 5.29 (1H, s); 4.57 (2H, m); 4.20 (2H, s); 2.65 (2H, m); 2.10 (1H, m); 1.85 (1H, m); 1.80-1.50 (2H, m); 1.68 (3H, s); 1.46 (1H, dd); 1.30 (1H, dd); 1.02 (6H, s).

trans-3-(3-Iodo-2,2-dimethylpropyl)-5-(2-iodoethyl)-1-methylcyclopent-1-ene. To a solution of the above ditriflate (40 mg, .084 mmol) in benzene (4 mL) was added tetrabutylammonium iodide (155 mg, .46 mmol).[29] This mixture was refluxed 2 h, and concentrated in vacuo. The residue was taken up in hexanes, filtered through florisil (100% hexanes) and concentrated to give a clear liquid (26 mg, 75%): ^{1}H-NMR ($CDCl_3$) δ 5.27 (1H, s); 3.30-3.00 (2H, m); 3.18 (2H, s); 2.60 (2H, m); 2.10 (1H, m); 1.85 (1H, M); 1.8-1.4 (2H, m); 1.68 (3H, s); 1.30 (1H, M); 1.02 (6H, s); ^{13}C-NMR ($CDCl_3$) δ 141.3 (s); 130.9 (d); 48.9 (t); 47.4 (t); 40.0 (d); 37.8 (t); 34.0 (s); 27.5 (q); 25.0 (t); 14.7 (q); 4.2 (t); IR ($CHCl_3$) 1150 cm^{-1}; MS calcd. for $C_{13}H_{21}I_2$, m/e 431.9811; found 431.9809; GC Retention time: 6.78 min.

trans-3-(4-Trimethylsilyl-3-butynyl)-5-(3-iodo-2,2-dimethylpropyl)-1-methylcyclopent-1-ene (37). A .25M solution of lithium trimethylsilyl acetylide[30] was generated by addition of n-BuLi to trimethylsilylacetylene in THF. A portion of the anion solution (856 uL, .214 mmol) was transferred to a cooled (0°C), dry flask and a solution of diiodide 41 (84 mg, .194 mmol) in HMPA (2 mL) was added. After 20 min, the dark solution was poured into hexanes/water. The aqueous phase was extracted with hexanes (3x) and the combined organic fractions were washed with water (3x) and brine (1x) and dried (Na_2SO_4). Evaporation of solvent afforded a clear liquid (65 mg) which was a mixture of silylated (37) and desilylated (38) acetylenic products (approx. 85:15). MPLC (hexanes) gave pure 37: ^{1}H-NMR ($CDCl_3$) δ 5.24 (1H, m); 3.18 (2H, s); 2.55 (2H, m); 2.20 (2H, m); 1.9-1.2 (6H, m); 1.66 (3H, s); 1.02 (6H,s); 0.18 (9H, s); IR ($CHCl_3$) 2160, 1200 cm^{-1}; MS calcd. for $C_{18}H_{31}SiI$: m/e 402.1240; found, 402.1242. GC Retention time: 7.00 min.

trans-3-(3-Butynyl)-5-(3-iodo-2,2-dimethylpropyl)-1-methylcyclopent-1-ene (38). To a solution of the acetylenic mixture (65 mg) in THF (5 mL) was added tetrabutylammonium fluoride (30 mg). The mixture was stirred 2h. Extraction with hexanes (3x) gave fractions which were combined, washed with water (1x), brine (1x) and dried (Na_2SO_4). Evaporation of solvent gave a yellow liquid which could be purified by MPLC (hexanes) (48 mg, 75%): ^{1}H-NMR ($CDCl_3$) δ 5.25 (1H, s); 3.19 (2H, s); 2.60 (2H, m); 2.3-2.0 (2H, m); 1.96 (1H, t); 1.9-1.2 (6H, m); 1.68 (3H, s); 1.05 (6H, s); ^{13}C-NMR ($CDCl_3$) δ 142.1 (s); 130.6 (d); 84.7 (s); 68.2 (d); 47.6 (t); 47.0 (d); 40.0 (d); 39.2 (t); 34.1 (s); 32.1 (t); 27.5 (q); 25.1 (t); 16.6 (t); 14.8 (q); IR ($CHCl_3$) 3320, 2120, 1650 cm^{-1}; MS calcd. for $C_{15}H_{23}I$: m/e 330.0845; found, 330.0845; GC Retention time: 5.09 min.

Hirsutene (1). A solution of 38 (37.5 mg, .113 mmol), tri-n-butyltin hydride (40 µL, .147 mmol) and AIBN (approx. 1 mg) in benzene (5.6 mL) was placed in a preheated oil bath (85°C) and refluxed 1 h. Ethyl bromide (500 µL, excess) and AIBN (approx. 1 mg) were added and the mixture was heated an additional 1h to destroy excess tri-n-butyltin hydride. Evaporation of solvent gave a residue which afforded 3 upon purification by MPLC (pentanes) (14.7 mg, 64%): ^{1}H-NMR ($CDCl_3$) δ 4.84 (1H, s); 4.78 (1H, s); 2.7-2.4 (4H, m); 2.16 (1H, q), 1.8-0.8 (8H, m); 1.05 (3H, s); 0.95 (3H, s); 0.92 (3H, s). ^{13}C-NMR ($CDCl_3$) δ 163.0; 103.4; 53.8, 50.4; 49.1; 44.3: 42.1; 41.0; 38.8; 31.1; 29.8; 27.4; 27.0; 23.3. One quarternary carbon not visible due to low concentration. GC Retention time: 2.01 min.

Trimethylsilylhirsutene (39). Iodide 37 was cyclized as above. (31 mg, .077 mmol); Bu_3SnH (31 uL, .116 mmol); AIBN (1 mg); benzene (3.9 mmol); A clear liquid was obtained after MPLC (hexanes) (15.3 mg, 72%): ^{1}H-NMR ($CDCl_3$) δ 5.28 (1H, s); 2.83 (1H, q); 2.52 (3H, m); 2.18 (1H, q); 1.8-1.1 (8H, m); 1.03 (3H, s); 0.96 (3H, s); 0.90 (3H, s); 0.14 (9H, s). IR ($CHCl_3$) 1610, 1225, 840 cm^{-1}. MS calcd. for $C_{18}H_{32}Si$, m/e 276.2773; found, 276.2775. GC Retention time: 3.94 min (major isomer); 4.18 min (minor isomer).

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References:

1) Recipient of a Dreyfus Young Investigator Award, 1981-86. Eli Lilly Grantee, 1985-86. A fellow of the Alfred P. Sloan Foundation, 1985-87.

2) Reviews: a) Paquette, L. A., Top. Curr. Chem. (1983), 119, 1. Ibid (1979), 79, 41. b) Trost, B. M. Chem. Soc. Rev. (1982), 11, 141.

3) Isolation and synthesis: a) Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S. Tetrahedron Lett. (1976), 195. Biosynthesis and synthesis from biogenetic intermediates. b) Shirahama, H.; Osawa, E.; Matsumoto, T. J. Am. Chem. Soc. (1980), 102, 3208. c) Ohfune, Y.; Shirahama, H.; Matsumoto, Tetrahedron Lett. (1976), 2695., d) Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. Ibid. (1978), 1991; Helv. Chim. Acta. (1981), 64, 1347. e) Misumi, S.; Matsushima, H.; Shirahama, H.; Matsumoto, T. Chemistry Lett. (1982), 855. Synthesis. f) Tatsuta, K.; Akimoto, K.; Kinoshita, M.; J. Am. Chem. Soc. (1979), 101, 6116. g) Greene, A. E. Tetrahedron Lett. (1980), 21, 3059. h) Hudlicky, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T. J. Am. Chem. Soc. (1980), 102, 6351. Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P., J. Org. Chem. (1980), 45, 5020. i) Mehta, G.; Reddy, A. V.; J. Chem. Soc. Chem. Commun. (1981), 756. j) Little, R. D.; Muller, G. W.; Venegas, M. G.; Carroll, G. L.; Bukhari, A; Patton, L.; Stone, K. Tetrahedron (1981), 37, 4371. Little, R. D.; Higby, R. G.; Moeller, K. D. J. Org. Chem. (1983), 48, 3139. k) Wender, P. A.; Howbert, J. J. Tetrahedron Lett. (1982), 23, 3983. l) Ley, S. V.; Murray, P. J. J. Chem. Soc. Chem. Commun. (1982), 1252. m) Magnus, P.; Quagliato, P. A. Organometal (1982), 1, 1243. n) Dawson, B. A.; Ghosh, A. K.; Jurlina, J. L.; Stothers, J. B., J. Chem. Soc. Chem. Commun. (1983), 204. o) Funk, R. L.; Bolton, G. L. J. Org. Chem. (1984), 49, 502.

4) For a recent hirsutic acid synthesis and leading references see: Greene, A. E.; Luche, M.-J.; Depres, J.-P. J. Am. Chem. Soc. (1983), 105, 2435.

5) For recent syntheses of coriolin and leading references see: a) Schuda, P. F.; Heinemann, M. R. Tetrahedron (1984), 40, 2365. b) Demuth, M; Ritterskamp, P.; Schalfmen, K. Helv. Chim. Acta. (1984), 67, 2023. c) Wender, P. A.; Howbert, J. J. Tetrahedron Lett. (1983), 24, 5325.

6) Isolation: a) Sheikh, Y. M.; Djerassi, C.; Braekman, J. C.; Daloze, D.; Kaisin, M; Tusch, B.; Karlsson, R. Tetrahedron (1977), 33, 2115. b) Ayanoglu, E.; Gebreyesus, T.; Beechan, C. M.; Djerassi, C.; Kaisin, M. Tetrahedron Lett. (1978), 1671. Synthesis. c) Little, R. D.; Carroll, G. L., Peterson, J. L. Ibid. (1981) 22, 4389. J. Am. Chem. Soc. (1893), 105, 928. d) Stevens, K. E.; Paquette, L. A. Tetrahedron Lett. (1981) 22, 4393. e) Birch, A. M.; Pattenden, G. Ibid. (1982), 23, 991 J. Chem. Soc. Perkin I (1983) 1913. f) Oppolzer, W.; Battig, K. Ibid. (1982) 23, 4669. g) Pattenden, G.; Teague, S. J. Ibid. (1982), 23 5471. h) Karpf, M.; Dreiding, A.S. Helv. Chim. Acta. (1982), 65, 2413. i) Mehta, G.; Reddy, D. S.; Mehta, A. M. J. Chem. Soc. Commun. (1983), 824, j) Piers, E. C. Cand. J. Chem. (1984), 62, 631. k) Crisp, G. T.; Scott, W. J.; Stille, J. K. J. Am. Chem. Soc. (1984), 106, 7500.

7) Some exceptions include the approaches of Wender (refs. 2k, 5c) and Greene (refs. 2g, 4).

8) Some exceptions include the approaches of Little (refs. 2j, 6c) and Mehta (refs 2i, 6i).

9) For a preliminary communication outlining the synthesis of hirsutene, see: Curran, D. P.; Rakiewicz, D. M. J. Am. Chem. Soc. (1985), 107, 1448.

10) For recent reviews see: a) Beckwith, A. L. J.; Ingold, K. U. in "Rearrangements in Ground and Excited States" deMayo, P., ed.; Academic Press, NY, (1980), pp. 162-283. b) Beckwith, A. L. J., Tetrahedron (1981), 37, 3073. c) Surzur, J. M. in "Reactive Intermediates" Abramovitch, R. A., ed., Vol. 2, Chapt. 3, Plenum Press, NY (1981). d) Hart, D. J. Science (1984), 223 , 883.

11) For use of a related reductive cyclization , see ref. 6g.

12) For a summary of basic strategies of ring construction which have been employed, see ref. 30.

13) The elegant routes of Little (2j, 6c), Wender (2k, 5c), and Mehta (2i, 6i) also involve multiple ring construction. Professor K. N. Houk and T.-C. Wu have also recently developed an elegant intramolecular [6 + 2] cycloaddition approach to linear triquinanes (in press).

14) Johnson, W. S. Biorg. Chem. (1976), 5, 51.

15) Julia, M. Pure Appl. Chem. (1974), 40, 553; Acc. Chem. Res. (1971), 4, 386.

16) a) Beckwith, A. L. J.; Phillipou, G.; Serelis, A. K. Tetrahedron Lett. (1981), 22, 2811. b) Beckwith, A. L. J.; Moad, G. J. Chem. Soc. Perkin Trans. I (1975), 1726. c) Chatzopouloulis, M.; Montheard, J.-P. C. R. Hebd. Sceance Acad. Sci. Ser. C (1975), 280, 29. d) Breslow, R.; Olin, S. S.; Groves, J. T. Tetrahedron Lett. (1968), 1837. e) Stella, L. Ang. Chem. Int. Ed. English (1983), 22, 337.

17) Stork, G.; Mook, R. J. Am. Chem. Soc. (1983) 105, 3720. Stork, G.; Mook, R.; Biller, S. A.; Rychnovsky, S. D. Ibid. (1983), 105, 3741.

18) a) Meinwald, J.; Seidel, M. C.; Cadoff, B. C. J. Am. Chem. Soc. (1958), 80, 6303. b) Freeman, P. K.; Ballo, D. M.; Brown, D. J. J. Org. Chem. (1968), 33, 2211.

19) For a review of the regiochemistry of allylic displacements, see Magid, R. M. Tetrahedron (1980), 36, 1901.

20) The second isomer is thought to be the result of S_n2-anti substitution.

21) Interesting contrasts are available for cuprate openings of related vinyl lactones, see: Grieco, P. A.; Srinivasan, C. V. J. Org. Chem. (1981), 46, 2591. Corey, E. J.; Mann, J. J. Am. Chem. Soc. (1973), 95, 6832. For mechanistic studies, see: Goering, H.; Singleton, V. D.; J. Org. Chem. (1983), 48, 1561, and references therein.

22) Whitesell, J. K.; Matthews, R. S. J. Org. Chem. (1977), 42, 3878. Also; Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. Ibid. (1980), 45, 5020.

23) Hart, D. J.; Tsai, Y.-M. J. Am. Chem. Soc. (1982) 104, 1430. Ibid. (1984) 106, 8209.

24) Wolff, S.; Agosta, W. C. J. Chem. Res. Synop. (1981), 78.

25) a) Beckwith, A. L. J.; Blair, I.; Phillipou, G. J. Am. Chem. Soc. (1974); 96, 1613. b) Corey, E. J.; Shimoji, K.; Shih, C. Ibid. (1984), 106, 6425. See also ref. 10a, b.

26) a) The Beckwith TS model assumes a cyclohexane like conformation since the length of the forming C-C bond in the transition state is similar to the C_1-C_3 distance in cyclohexane. Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. Aust. J. Chem. (1983), 36, 545. b) Calculations by Prof. K. N. Houk and D. Spellmeyer (in press) have revealed a transition state strikingly similar to the Beckwith model. We are grateful to K. N. H. and D. S. for providing us this information prior to publication. Since the submission of this manuscript, a similar computational analysis by Beckwith has appeared. Beckwith, A. L. J.; Schiesser, C. H. Tetrahedron Lett. (1985), 26, 373.

27) Difficulties in preparing the required Grignard reagent from 1-trimethylsilyl-4-bromobutyne and handling the sensitive 1-methyl-cyclopent-2-en-1-ol lead us to abandon route A; however, with proper modifications, we do feel that this would be a viable approach.

28) Freeman, P. K.; Hutchison, L. L. J. Org. Chem. (1980), 45, 1924. Screttas, C. G.; Micha-Screttas, M. Ibid. (1979), 44, 713. Cohen, T.; Matz, J. R.; J. Am. Chem. Soc. (1980), 102, 6900. We thank Prof. T. Cohen for helpful advice on the reductive lithiation.

29) Binkley, R. W.; Ambrose, M. G.; Hehemann, D. G. J. Org. Chem. (1980), 45, 4387.

30) Hansen, R. T.; Carr, D. B.; Schwartz, J. J. Am. Chem. Soc. (1978), 100 2244. Verboom, W.; Meijer, J.; Brandsma, L. Synthesis (1978), 577.

31) Hex-5-ynyl radicals are useful for cyclizations. See refs. 10 and 17 also: Clive, D. L.; Beaulieu, P. L.; Set, L. J. Org. Chem. (1984), 49, 1313 and references therein. Corey, E. J.; Pyne, S. G. Tetrahedron Lett. (1983), 24, 2821.

32) Utimoto, K.; Kitai, M.; Nozaki, H. Tetrahedron Lett. (1975), 2825.

33) While many methods are available for the synthesis of 2-methylcyclopentenone (see: Funk, R. L.; Vollhardt, K.P.C. Synthesis (1980), 118), we found the method of Smith to be far superior to several others. Smith, A. B., III: Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N. J. Am. Chem. Soc. (1982), 104, 4015. We thank Prof. Smith for detailed experimental procedure. See also: Fischli, A.; Klaus, M.; Mayer, P.; Schönholzer, P.; Rüegg, R. Helv. Chim. Acta. (1975), 58, 564.

34) Luche, J.-L. J. Am. Chem. Soc. (1978), 100, 2226.

35) Ireland, R. E.; Mueller, R. H.; Willard, A. K. J. Am. Chem. Soc. (1976), 98, 2868.

36) Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. J. Am. Chem. Soc. (1979), 101, 3884.

37) W. Lin, unpublished results from these laboratories.

38) Dunogues, J.; Bourgeois, P.; Pillot, J. P.; Merault, G.; Calas, R. J. Organometal. Chem. (1975), 87, 169.

39) Büchi, G.; Wuest, H. Tetrahedron Lett. (1977), 4305.

40) Townsend, C. A.; Theis, A. B. Syn. Commun. (1981), 11, 157.

41) Searles, S.; Nickerson, R. G.; Witsiepe, W. K. J. Org. Chem. (1960), 1839.

42) Grieco, P. A.; Miyashita, N.; Yoshikoshi, A. Ibid., (1977), 42, 3772.