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Synthesis of Macrocyclic Terpenoids by Intramolecular Carbonyl Coupling: Flexibilene and Humulene

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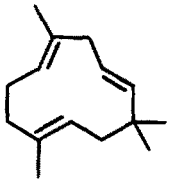
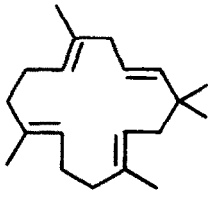
Abstract: Total syntheses of two macrocyclic sesquiterpene hydrocarbons, humulene (**1**) and flexibilene (**2**) are discussed in detail. Both were prepared in high overall yield by titanium-induced cyclization of the appropriate keto aldehyde precursors (**4** and **9**, respectively), themselves obtained by coupling of the vinylic zirconium reagent **22** with pi-allylpalladiums **26** and **23**.

Though related in structure, humulene (**1**) and flexibilene (**2**) have quite different histories in organic chemistry. Humulene, an 11-membered-ring sesquiterpene, is found abundantly in nature, most commonly in oil of hops. First isolated[1] in pure form in 1895, it was not until the advent of NMR spectroscopy more than 60 years later that the structure of humulene was determined.[2] Since that structural elucidation, three total syntheses have been recorded,[3,4,5] all which require at least 10 steps. Two[3,4] of the three use the nonstereoselective nickel-catalyzed cyclization of a bis-allylic dibromide as the key step, and the third[5] uses a palladium-catalyzed intramolecular alkylation of an allylic acetate by a β-keto ester anion. No yields are reported for the cyclization step in either of the nickel-based syntheses, but the palladium-catalyzed ring closure takes place in 45% yield.

Flexibilene, a 15-membered-ring diterpene that might be thought of as an "isoprenylogue" of humulene, is far less abundant in nature and far less well known than its smaller relative. Isolated simultaneously in the mid-1970's by two groups investigating the soft coral Simularia flexibilis,[6,7] flexibilene is the only diterpene yet known that contains a 15-membered ring. Prior to the present work, no synthesis of flexibilene had been reported.



Humulene (1)

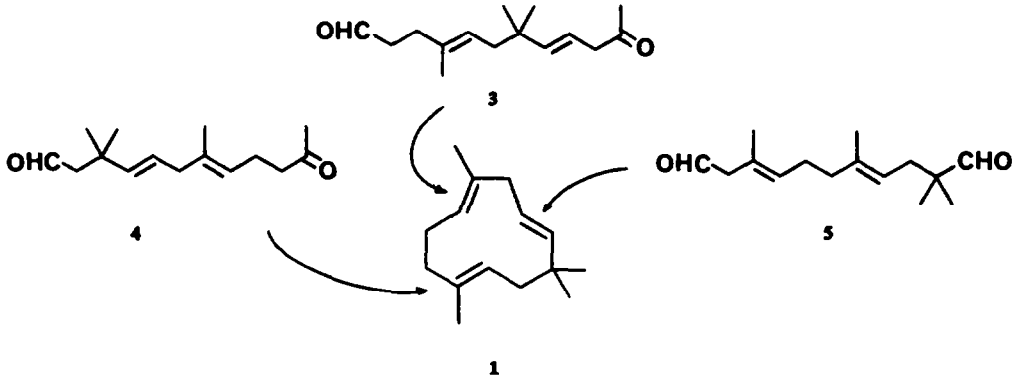


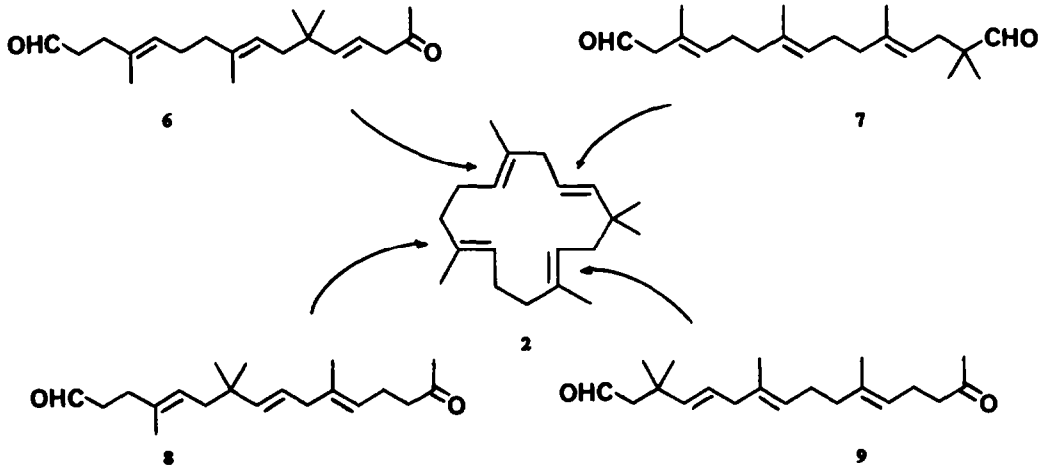
Flexibilene (2)

Our own interest in the chemistry of humulene and flexibilene stemmed from our discovery in the late 1970's that cycloalkenes can be prepared in high yield by treatment of dicarbonyl compounds with a titanium reagent prepared by reduction of commercially available $TiCl_3$ with Zn/Cu couple.[8] Humulene and flexibilene seemed like suitable goals for application of the titanium chemistry, and we therefore undertook their total synthesis.[9]

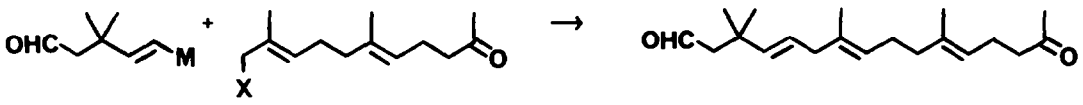
The Synthetic Plan

Humulene (**1**) could, in principle, be prepared by titanium-induced cyclization of any of the three dicarbonyl precursors **3-5**, and flexibilene (**2**) could be prepared from any of the four precursors **6-9**. In deciding which of the possibilities to pursue, we set two constraints. First, we wanted a general route that would serve with only slight modification for the synthesis of both natural products, and second, we wanted a route that would be relatively short. In other words, we wanted to be able to use a commercially available starting material that already contained much of the necessary carbon framework.





The synthesis of flexibilene appeared to be more demanding than that of humulene, and we therefore concentrated our initial efforts on that target. Of the four potential flexibilene precursors **6-9**, compounds **6** and **7** were discarded from consideration because both have β,γ-unsaturated carbonyl functions that might be difficult to prepare and that might be sensitive to acids and bases. Of the remaining two choices, **8** and **9**, compound **9** was selected as the most likely candidate for synthesis because of its resemblance to geranylacetone, a commercially available substance that contains 13 of the necessary 20 carbons. Moreover, it is well known that linear isoprenoid chains like that in geranylacetone can often be selectively oxidized on the terminal E methyl group.[18] Combination of an allylically functionalized geranylacetone derivative like **11** with a seven-carbon vinylic organometallic derivative like **10** would then lead to the desired keto aldehyde cyclization precursor **9**.



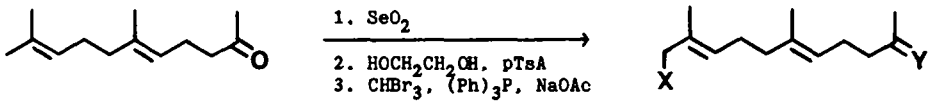
10 11 9

The advantage of this plan is that it allows us to use a starting material (geranyl acetone) that already contains two of the four double bonds in flexibilene, prepare the third from an alkyne, and prepare the fourth in the cyclization step. Thus, we should have full stereocontrol of the double bonds up to the cyclization step.

Synthesis of Flexibilene

Starting from geranylacetone (**12**),[11] our initial goal was to effect a selective allylic oxidation of the terminal E methyl group and prepare allylic bromide **13c**. Unfortunately, oxidation[10b] with SeO_2 of either geranylacetone or its corresponding ethylene acetal, gave the desired alcohol **13a** (or **13b**) in very impure form, along with substantial amounts of isomeric secondary allylic alcohols formed by oxidation at internal positions. This was a somewhat surprising result since the related oxidation of geranyl acetate has been reported to take place cleanly.[10b]

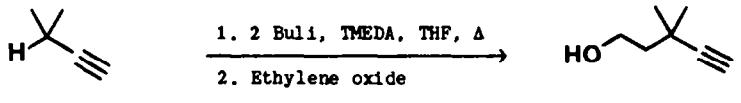
Although chromatographic purification of keto alcohol **13a** proved difficult, we discovered that acetalization with ethylene glycol and treatment of the crude hydroxy acetal **13b** with carbon tetrabromide and triphenylphosphine in the presence of a sodium acetate buffer selectively converted only the desired primary alcohol into its corresponding bromide, while leaving secondary alcohol impurities unreacted.[12] Rapid chromatography on Florisil (elution with hexane) then provided the pure bromo acetal **13c** in 32% overall yield from geranylacetone.



12

13a X = OH, Y = O
13b X = OH, Y = $-OCH_2CH_2O-$
13c X = Br, Y = $-OCH_2CH_2O-$

Acetylene **15**, the second fragment necessary for the synthesis, is a known compound that has been prepared in a fairly arduous manner from acetone.[13] Rather than repeat the published procedure, it occurred to us that a considerably more efficient route might be by the dianion alkylation of isopropylacetylene with ethylene oxide.[14] In fact, treatment of isopropylacetylene with 2 equiv BuLi and 1 equiv tetramethylethylenediamine (TMEDA) in THF at 50° for four hours, followed by addition of 1 equiv ethylene oxide, gave the desired hydroxyacetylene **15** in 80% yield. Further reaction then led either to the protected tetrahydropyranyl ether (**16**) or to the corresponding aldehyde **17**.

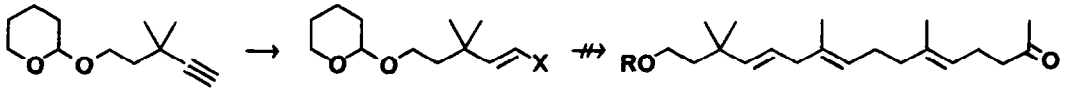


14 15

16 17

With the two pieces containing all 20 carbons of flexibilene thus available, we next attempted to join them by an alkylation reaction. Our idea was to convert acetylene **16** into a vinylic nucleophile, which we could then use in an alkylation reaction with allylic bromide **13c**. Toward this end, reaction of **16** with tributylstannane at 80°C in the presence of AIBN as a radical initiator led smoothly to vinylstannane **18a**. Surprisingly, though, **18a** resisted all attempts at transmetallation to the corresponding vinyllithium reagent, **18b**. Methyllithium, butyllithium, sec-butyllithium, and tert-butyllithium were all without effect on vinylstannane **18a** in a variety of solvents and under a variety of reaction conditions. Unable to prepare **18b** by direct transmetallation, we proceeded through the intermediate vinylic iodide **18c**. Reaction of **18a** with N-iodosuccinimide gave vinylic iodide **18c**, which could be metallated by treatment with butyllithium at -60 °C in hexane to give **18b**.

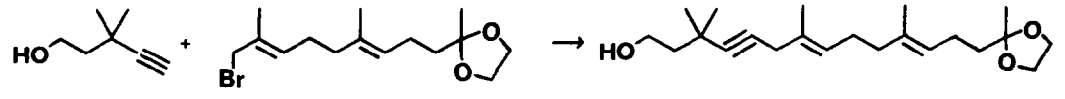
Unfortunately, all attempts to alkylate vinyllithium **18b** with allylic bromide **13c**, either directly, in the presence of CuI, in the presence of 1-hexynylcopper(I), or in the presence of Li_2CuCl_4, were unsuccessful. Similarly, all attempts to alkylate the corresponding Grignard reagent **18d**, either in the presence or absence of copper salts, were unsuccessful. Although we are at a loss to explain these results, we note that the presence of the tetrahydropyranyl ether protecting group is not responsible: A similar series of reactions carried out on the related triethylsilyl-protected vinyllithium reagent was also unsuccessful.



16 **18a** X = $SnBu_3$; **18b** X = Li; **18c** X = I; **18d** X = MgI **19**

Momentarily discouraged with vinylic anions, we next explored the possibility of alkylating **13c** with an acetylide anion. If successful, the acetylene-containing alkylation product could then be reduced with lithium in liquid ammonia to yield the necessary trans double bond. Once again, however, the coupling was unsuccessful. Treatment of allylic bromide **13c**, either with the lithium acetylide[15] prepared from protected acetylene **16**, with the dilithio dianion prepared from hydroxyacetylene **15**, or with the copper acetylide,[16] gave no useful results.

After considerable experimentation, we were able to achieve a modest measure of success by reaction of hydroxyacetylene **15** with halide **13c** in the presence of 1.1 equiv CuCl in aqueous tert-butylamine at room temperature[17] to yield **20**. Unfortunately, the reaction led to a difficultly separable mixture of alkylation products resulting both from direct displacement of the halide and from allylic displacement.



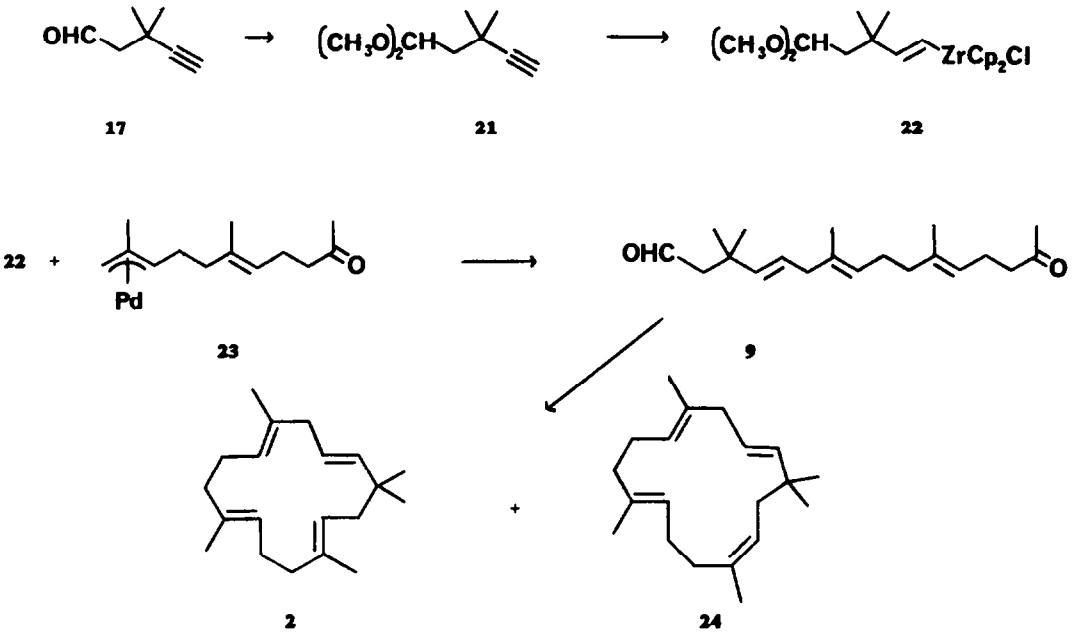
15 **13c** **20**

Although it is likely that the copper-catalyzed reaction of **15** with **13c** could ultimately have been developed into a workable synthesis, we were saved from having to do so by the well-timed appearance of a paper[18] reporting a method for effecting the stereo- and regiospecific coupling of a vinylzirconium reagent with a pi-allylpalladium species. Since vinylzirconiums

are easily prepared[19] by hydrozirconation of alkynes, there appeared to be little problem in obtaining the appropriate compound from alkyne **15**. Equally well-timed was the appearance of a second paper[20] reporting the preparation from geranylacetone of pi-allylpalladium reagent **23**, the exact species needed for a synthesis of flexibilene.

The coupling reaction did indeed work exactly as desired. Protection of aldehyde **17** as its dimethyl acetal (**21**), followed by hydrozirconation of the triple bond on reaction with bis-(cyclopentadienyl)zirconium hydridochloride, gave vinylzirconium reagent **22**. Concurrently, reaction of geranylacetone with $Pd(OCOCF_3)_2$, followed by anion exchange with tetrabutylammonium chloride, gave the necessary pi-allylpalladium complex **23**. Addition of **23** to a freshly prepared solution of **22** at -78°C in dichloromethane in the presence of maleic anhydride, followed by quenching with dilute aqueous HCl, then gave keto aldehyde **9** as a stereochemically pure substance in 76% isolated yield.

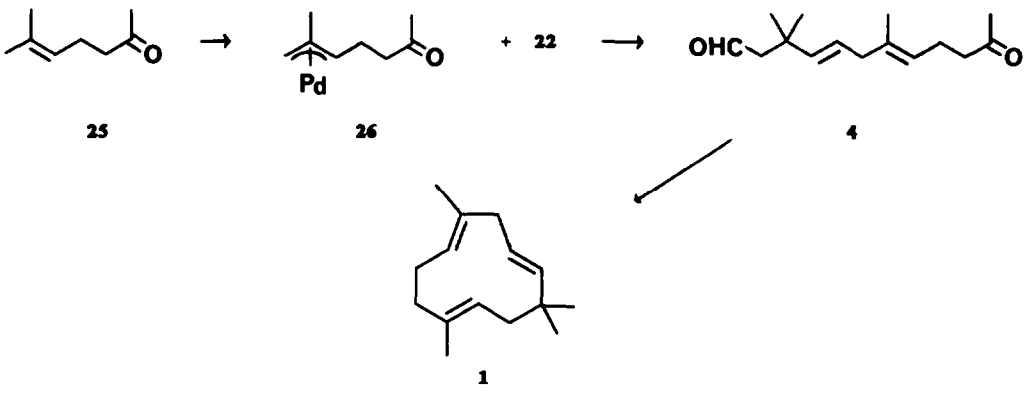
With the keto aldehyde cyclization substrate thus available, we were ready for the key titanium-induced coupling step. Preparation of the titanium coupling reagent by reduction of $TiCl_3$ with Zn/Cu in dry refluxing dimethoxyethane, followed by slow addition of keto aldehyde **9** by motor-driven syringe pump over a 32 hour period, gave a 78% isolated yield of two cyclopentadecatetraene products in a 2:1 ratio. Column chromatography followed by preparative GLC gave an analytical sample of the major component, which was spectroscopically identical with an authentic sample of natural flexibilene (**2**) by MS, IR, ^1H NMR (300 MHz) and ^{13}C NMR. The minor product differed from flexibilene only slightly in its spectral properties and was assigned the isoflexibilene structure **24**.



Synthesis of Humulene

With the synthesis of flexibilene accomplished and the general coupling methodology worked out, the synthesis of humulene was straightforward. Thus, treatment of commercially available 6-methyl-5-hepten-2-one (**25**) with palladium chloride gave the crystalline pi-allylpalladium complex **26** in exact analogy to the previous reaction of geranylacetone. Coupling of **26** with vinylzirconium reagent **22** in the presence maleic anhydride also proceeded exactly as before to yield 3,3,7-trimethyl-11-oxo-4*E*,7*E*-undecadienal (**4**), the substrate necessary for titanium-induced conversion into humulene. Slow addition of this keto aldehyde over an 18 hour period

to a slurry of active titanium coupling reagent in refluxing dimethoxyethane then provided pure humulene (1) as the only product in an isolated yield of 60%; no trace of an isomeric product was formed. The synthetic humulene thus produced was spectroscopically identical with an authentic sample of the natural product by IR, GLC, MS, ^{1}H NMR, and ^{13}C NMR.



25 26 4

1

Conclusion

Progress in chemistry comes slowly, and practitioners of the art of organic synthesis sometimes wonder whether their field has changed much in the last 50 years. We would like to think, however, that the work reported in this paper gives at least one small illustration of how organic synthesis advances and improves. Both the flexibilene synthesis and the humulene synthesis described herein appear short and simple, as indeed they are. But this brevity and simplicity is really just an indication of how powerful the methods now at our disposal are.

In the six or so reactions required in this work, no fewer than seven different metal-based reagents were used - Li, Cr, Zr, Pd, Ti, Zn, and Cu. Furthermore, of the six or so reactions, none were even known a decade prior to the work. The titanium-induced carbonyl coupling reaction, in particular, has proved its value as an extraordinarily effective method for preparing macrocyclic rings of all sizes, thereby allowing the "simple" and efficient synthesis of as unusual a molecule as flexibilene, and as familiar a molecule as humulene by a route less than half as long as previous ones.

Acknowledgment

This work was supported by the donors of the Petroleum Research Fund through grant 11879-AC1.

Experimental Section

General methods. All reactions were carried out under argon in glassware that had been dried at 120 °C or that had been evacuated and flamed dry prior to refilling with argon. The phrase "worked up in the usual manner" refers to extraction of the crude product with ether or dichloromethane, washing the organic layers with water and with saturated brine, drying over anhydrous sodium sulfate, filtration, and concentration by solvent removal at the rotary evaporator. Ethereal solvents were dried by double distillation under argon over molten potassium metal. NMR spectra were recorded on a Bruker WM-300 instrument.

11-Hydroxy-6,10-dimethyl-5E,9E-undecadien-2-one (13a). Geranylacetone (**12**, 0.50 g, 2.573 mmol) was added to a solution of selenium dioxide (0.115 g, 1.04 mmol) and tert-butyl hydroperoxide (0.90 mL, 90 %) in methylene chloride (2.5 mL) at 0 °C. After stirring at 0°C for 9 h, the mixture was washed successively with water, sodium bicarbonate solution, water, and brine. Workup in the usual manner gave a residue that was chromatographed on silica gel (elution with 25% ethyl acetate-hexane) to give 450 mg (46%) of allylic alcohol **13a**, which was approximately 87% pure by GC analysis: IR (film) 3400, 1700, 1360, 1015, 845; ^{1}H NMR ($CDCl_3$) δ 5.33 (t, 1 H, J = 6.8 Hz), 5.05 (t, 1 H, J = 6.8 Hz), 3.97 (d, 2 H, J = 6.2 Hz), 2.44 (t, 2 H, J = 7.4 Hz), 2.25 (m, 2 H), 2.12 (s, 3 H), 2.00 (m, 2 H), 1.63 (s, 3 H), 1.60 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.34, 135.46, 134.63, 124.67, 122.53, 67.94, 43.21, 38.80, 29.15, 25.63, 22.12, 15.44, 13.12.

11-Hydroxy-6,10-dimethyl-5E,9E-undecadien-2-one ethylene acetal (13b). Alcohol **13a** (0.2337 g, 1.11 mmol) was dissolved in a mixture of ethylene glycol (3 mL), oxalic acid dihydrate (20 mg) and benzene (10 mL), and heated at reflux with azeotropic removal of water for 4 h. The mixture was diluted with ether, washed successively with sodium bicarbonate solution, water, and brine, and worked up in the usual manner to give acetal **13b** (0.279 g, 98.7%) as a pale yellow oil: IR (film) 3400, 1370, 1050, 945, 860 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.36 (t, 1 H, J = 7.3 Hz), 5.11 (t, 1 H, J = 7.3 Hz), 3.97 (s, 2 H), 3.92 (m, 4 H), 2.0-2.2 (m, 6 H), 1.64 (s, 3 H), 1.59 (s, 3 H), 1.6 (m, 2 H), 1.31 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 134.39, 125.09, 123.84, 109.6, 68.06, 64.19, 38.92, 38.62, 25.87, 23.43, 22.24, 15.56, 13.24.

11-Bromo-6,10-dimethyl-5E,9E-undecadien-2-one ethylene acetal (13c). Alcohol **13b** (0.50 g, 2.0 mmol), tetrabromomethane (0.82 g, 2.5 mmol) and sodium acetate (328 mg, 4.0 mmol) were placed in 5 mL dichloromethane and stirred at 0°C. Triphenylphosphine (655 mg, 2.5 mmol) was added in small portions, and the reaction was allowed to slowly warm to ambient temperature. After addition of petroleum ether, the reaction mixture was filtered through a short pad of Florisil and concentrated at the rotary evaporator to yield allylic bromide **13c** (270 mg, 42%), which was sufficiently pure to use without further purification: IR (film) 1450, 1105, 960 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.53 (m, 1 H), 5.10 (t, 1 H), 3.93 (s, 2 H), 3.90 (s, 4 H), 2.03 (m, 6 H), 1.66 (m, 8 H), 1.32 (s, 3 H); mass spectrum (m/z) 318 (M^+).

3,3-Dimethyl-4-pentyn-1-ol (15). 3-Methyl-1-butyne (11 mL, 0.108 mol) was dissolved in 42 mL ether at 0°C, and n-butyllithium (84 mL of 2.55 M solution in hexane, 0.214 mol) was slowly added. When addition was complete, tetramethylethylenediamine (TMEDA, 15 mL, 0.110 mol) was added, producing a white slurry. The reaction mixture was then warmed to a gentle reflux for 15 h to allow formation of the dianion, after which time a homogeneous red solution resulted. The dianion solution was next cooled to -78°C and quenched by slow addition of a solution of ethylene oxide in THF (10 mL of a 49% by weight solution, 0.095 mol). When addition was complete and the red color had disappeared, water was added to the reaction mixture and the temperature raised to ambient. Workup in the usual manner yielded a crude product that was purified by passage through a short column of silica gel to give 7.40 g (78%) of acetylenic alcohol **15**: IR (film) 3360, 3310, 2110 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.87 (t, 2 H, J = 7 Hz), 2.16 (s, 1 H), 1.72 (t, 2 H, J = 7 Hz), 1.26 (s, 6 H).

3,3-Dimethyl-4-pentynal (17). 3,3-Dimethyl-4-pentyn-1-ol (**15**, 2.26 g, 20.1 mmol) was dissolved in 30 mL dichloromethane and added rapidly to a stirred suspension of pyridinium chlorochromate (6.48 g, 30.1 mmol) in 40 mL dichloromethane at 25°C. The reaction mixture was then stirred for 2 h, ether (300 mL) was added, and the mixture was filtered through a short pad of Florisil. Concentration of the filtrate at the rotary evaporator gave a pale yellow oil that was distilled by kugelrohr to yield aldehyde **17** (1.54 g, 70%) as a colorless liquid: bp (140 mm), 75-80°C; IR (neat) 3390, 2750, 2110, 1720, 1370 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.82 (t, 1 H, J = 3 Hz), 2.41 (d, 2 H, J = 3 Hz), 2.25 (s, 1 H), 1.35 (s, 6 H).

5,5-Dimethoxy-3,3-dimethyl-1-pentyne (21). A solution of 3,3-dimethyl-4-pentynal (1.49 g, 13.5 mmol), trimethyl orthoformate (3.6 g, 34 mmol), methanol (0.2 mL), and p-toluenesulfonic acid (100 mg) in dry 20 mL benzene was stirred for 1.5 h at room temperature. Aqueous 5% $NaHCO_3$ was then added, and the resulting mixture was partitioned between ether and water. The organic phase was washed with saturated brine, dried (K_2CO_3), and concentrated at the rotary evaporator to give a yellow oil. Distillation of the oil (kugelrohr) yielded acetal **21** (1.75 g, 83%) as a colorless liquid: bp (15 mm), 75-80°C; IR (neat) 3300, 2110, 1380, 1365 cm^{-1}; ^1H NMR (CCl_4) δ 4.61 (t, 1 H, J = 5 Hz), 3.32 (s, 6 H), 2.12 (s, 1 H), 1.72 (d, 2 H, J = 5 Hz), 1.28 (s, 6 H).

3,3,7,11-Tetramethyl-15-oxo-4E,7E,11E-hexadecatrienal (9). 5,5-Dimethoxy-1-pentyne (**21**, 560 mg, 4.23 mmol) was dissolved in 10 mL dry dichloromethane under an inert atmosphere at room temperature, and Cp_2ZrHCl (866 mg, 3.36 mmol) was added at once. After stirring at room temperature for 2 h, the reaction mixture was cooled to -78°C and maleic anhydride (1.11 g, 11.4 mmol) in 5 mL dichloromethane was added. Stirring was continued for an additional 0.25 h at -78°C, at which point bis[chloro(9,10,11-trihapto-6E,10-dimethyl-5,9-undecadien-2-one)-palladium (II)] (**23**, 840 mg, 2.51 equiv) in 6 mL dichloromethane was added via cannula. After stirring a further 2 h at -78°C, the reaction mixture was slowly warmed to room temperature and stirred an additional 14 h. Dilution with ether and filtration through a short pad of Florisil removed the deposited metal, after which the filtrate was concentrated at the rotary evaporator to yield a red oil. Chromatography of the crude product on silica gel (10% ethyl acetate-hexane) gave keto aldehyde **9** as a colorless oil: IR (neat) 2735, 1720, 1385, 1365, 1160, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.67 (t, 1 H, J = 2.9 Hz), 5.48 (d, 1 H, J = 15.5 Hz), 5.32 (d of t, 1 H, J_1 = 6.6 Hz, J_2 = 15.5 Hz), 5.05 (m, 2 H), 2.61 (d, 2 H, J = 6.6 Hz), 2.42 (t, 2 H, J = 7.3 Hz), 2.27 (d, 2 H, J = 2.9 Hz), 2.23 (m, 2 H), 2.10 (s, 3 H), 2.02 (m, 2 H), 1.94 (m, 2 H), 1.57 (s, 3 H), 1.51 (s, 3 H), 1.10 (s, 6 H).

2,6,6,9,13-Pentamethyl-1E,4E,8E,12E-cyclopentadecatetraene (Flexibilene, 2). A suspension of $TiCl_3$ (754 mg, 4.90 mmol) and Zn/Cu couple[21] (757 mg, 11.6 mmol) in 20 mL dry dimethoxyethane was heated at reflux for 1 h to form the active titanium coupling reagent, and 3,3,7,11-tetramethyl-11-oxo-4E,7E,11E-hexadecatrienal (**9**, 57 mg, 0.19 mmol) in 16 mL dimethoxyethane was slowly added over 32 h via motor-driven syringe pump. The reaction mixture was then heated an additional 8 h, cooled to room temperature, diluted with 50 mL hexane, and filtered through a short pad of Florisil. The filtrate was concentrated at the rotary evaporator to give a yellow oil that was purified by column chromatography on silica gel. Elution with hexane provided 41 mg (79%) of cyclized hydrocarbon product. NMR indicated the product to be a 2:1 mixture of E and Z isomers about the newly formed double bond.

A pure sample of flexibilene (**2**) was obtained by preparative GLC (10% Carbowax 20M; 5 ft x 1/4 in) and identified by comparison with an authentic[23] sample: IR (neat) 1470, 1380, 1360, 970 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.31 (m, 2 H), 5.10 (m, 3 H), 2.59 (broad s, 2 H), 2.0-2.2 (m, 12 H), 1.60 (s, 3 H), 1.58 (s, 3 H), 0.99 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 140.6, 134.6, 134.2, 133.8, 125.5, 123.9, 123.6, 121.6, 121.6, 41.5, 41.1, 39.0, 38.8, 36.4, 28.2, 24.6, 24.3, 17.6, 16.6, 15.5; anal. calc'd for $C_{20}H_{32}$: m/z = 272.2504; found: 272.2506. Isoflexibilene (**24**); ^{13}C NMR ($CDCl_3$) δ 140.9, 134.0, 133.8, 133.6, 124.8, 124.5 (2), 122.7, 42.0, 41.2, 39.1, 35.5, 30.9, 29.4, 28.0, 25.2, 22.7, 17.0, 15.9.

Bis[chloro(5,6,7-trihapto-6-methyl-5-hepten-2-one)palladium(II)] (26). A solution of 110 mL acetic acid, 8.5 mL acetic anhydride, 10.7 g sodium acetate, 10.1 g sodium chloride, 8.8 g anhydrous cupric sulfate, and 1.78 g (10.0 mmol) palladium chloride was heated at 90°C for 1 h and then cooled to 60°C. 6-Methyl-5-hepten-2-one (2.85 g, 22.6 mmol) in 10 mL acetic acid was then added, and the solution was maintained at 60 °C for 4 h. After cooling to room temperature, the reaction mixture was poured into 250 mL water, extracted with a 1:1 mixture of ethyl

acetate/benzene, and worked up in the usual manner to give a yellow oil that solidified on standing. Column chromatography on silica gel (elution with 50% ethyl acetate in hexane) gave 1.53 g (57%) **26** as a yellow solid that was used in the next step without further purification.

3,3,7-Trimethyl-11-oxo-4E,7E-dodecadienal (4). 5,5-Dimethoxy-1-pentyne (**21**, 406 mg, 2.60 mmol) was dissolved in 8 mL dichloromethane, and Cp_2ZrHCl (420 mg, 1.63 mmol) was added in one portion. After stirring for 1 h at room temperature, the solution was cooled to -78°C and maleic anhydride (502 mg, 5.12 mmol) was added in 3 mL of dichloromethane. Stirring was continued an additional 0.25 h, at which point a solution of bis[chloro(5,6,7-trihapto-6-methyl-5-hepten-2-one)palladium (II)] (**26**, 271 mg, 1.01 equiv) in 3 mL dichloromethane was added via cannula. The resulting solution was stirred for 2 h at -78°C, then slowly warmed to room temperature and stirred an additional 15 h. Dilution of the reaction mixture with ether, filtration through a short pad of Florisil to remove deposited metal, and concentration at the rotary evaporator then gave a red oil. Since hydrolysis of the dimethyl acetal function was incomplete at this point, the red oil was dissolved in 10 mL THF and treated for 2 h with 5 mL 2.5% aqueous $HClO_4$. Workup in the usual manner gave an oil that was purified by column chromatography on silica gel (elution with 10% ethyl acetate in hexane) to provide keto aldehyde **4** (201 mg, 84%) as a colorless oil: IR (neat) 2740, 1720, 1385, 1365 1160, 1045, 975 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.71 (t, 1 H, J = 3.4 Hz), 5.53 (d, 1 H, J = 15.9 Hz), 5.35 (d of t, 1 H, J_1 = 6.8, J_2 = 15.9 Hz), 5.08 (t, 1 H, J = 4.8 Hz), 2.65 (d, 2 H, J = 6.8 Hz), 2.47 (t, 2 H, J = 7.3 Hz), 2.32, (d, 2 H, J = 3.4 Hz), 2.25 (m, 2 H), 2.14 (s, 3 H), 1.57 (s, 3 H), 1.14 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 208.4, 203.2, 139.6, 135.1, 125.6, 123.4, 55.1, 43.5, 42.6, 35.2, 29.8, 27.9, 22.4, 15.9.

2,6,6,9-Tetramethyl-1E,4E,8E-cycloundecatriene, (Humulene, 1). A suspension of $TiCl_3$ (480 mg, 3.11 mmol) and Zn/Cu couple (570 mg, 8.78 mmol) in 25 mL dry dimethoxyethane was refluxed for 1 h to form the active titanium coupling reagent, and a solution of 3,3,7-trimethyl-11-oxo-4E,7E-dodecadienal (**4**, 90 mg, 0.38 mmol) in 12 mL dimethoxyethane was added over 18 h by motor-driven syringe pump. After refluxing an additional 4 h, the reaction mixture was diluted with hexane, filtered through a short pad of Florisil, and concentrated by solvent removal at the rotary evaporator. Kugelrohr distillation of the crude oil gave pure humulene (45 mg, 58%) as a colorless liquid that was identified by comparison with an authentic sample: bp (0.4 mm) 85-90°C; IR (neat), 1660, 1385, 1365, 967 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.59 (d of t, 1 H, J_1 = 7.3, J_2 = 15.8 Hz), 5.15 (d, 1 H, J = 15.8 Hz), 4.95 (broad t, 1 H), 4.87 (broad t, 1 H), 2.51 (d, 2 H, J = 7.3 Hz), 2.08 (m, 4 H), 1.91 (d, 2 H, J = 7.7 Hz), 1.63 (d, 3 H, J = 1.1 Hz), 1.43 (d, 3 H, J = 0.7 Hz), 1.06 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 141.0, 139.1, 133.1, 127.7, 125.9, 125.0, 42.1, 40.4, 39.8, 37.3, 27.1, 23.4, 17.9, 15.1.

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21. The preparation of the Zn/Cu couple needed for titanium-induced carbonyl couplings is detailed in ref. 8b, page 3264.
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