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ORGANOTIN-BASED BIFUNCTIONAL REAGENTS: 4-CHLORO-2-LITHIO-1-BUTENE AND RELATED SUBSTANCES. METHYLENECYCLOPENTANE ANNULATIONS. TOTAL SYNTHESIS OF (±)-$\Delta^{9(12)}$-CAPNELLENE

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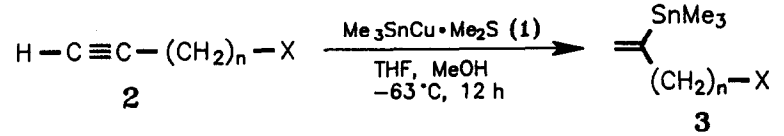
ABSTRACT - Transmetalation of 4-chloro-2-trimethylstannyl-1-butene (4) with MeLi in tetrahydrofuran (THF) at -78 °C affords 4-chloro-2-lithio-1-butene (5). At low temperatures (below approximately -50 to -60 °C), 5 functions well as a bifunctional reagent. For example, reaction of 5 with aldehydes and ketones affords, depending on reaction conditions, chloro alcohols (e.g. 11, 14 - 18) or substituted 3-methylenetetrahydrofurans (e.g. 19 - 24). Furthermore, treatment of the α,β-unsaturated N,N',N'-trimethylhydrazides 25 - 27 with reagent 5 provides smoothly the N,N',N'-trimethyl-3-methylenecyclopentanecarboxhydrazides 28 - 30, respectively. The lithio reagent 5 is readily transformed into the Grignard reagent 6 or the cuprates 7 and 8. Reagents 6 - 8 are useful for effecting methylenecyclopentane annulations, as illustrated by the conversions of 31 - 36 into 43 - 48, respectively. This novel annulation method played a key role in a total synthesis of the sesquiterpenoid (±)-$\Delta^{9(12)}$-capnellene (55).

INTRODUCTION

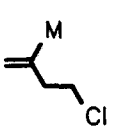
During recent years, organic reagents that possess two nucleophilic centers, two electrophilic centers, or one nucleophilic and one electrophilic site have become increasingly important in organic synthesis. Incorporation of these species into substrate molecules by simultaneous or sequential deployment of the two reactive sites often results in short, efficient conversions of structurally rather simple starting materials into significantly more complex, usefully functionalized products. Indeed, a perusal of the recent chemical literature makes it clear that an interesting variety of these "bifunctional conjunctive reagents"[1] or "multiple coupling reagents"[2] have been prepared and used effectively in organic synthesis.

In connection with ongoing studies related to the preparation and chemistry of (trialkylstannyl)copper(I) reagents,[3] we reported[4] recently that the reagent $Me_3SnCu\cdot Me_2S$ (1) adds regioselectively to ω-substituted 1-alkynes 2 (X = Cl, OH, OR) to provide the corresponding 2-trimethylstannyl-1-alkenes (3) (eq. [1]). We were intrigued by the possibility that one of

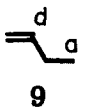


[1]

the products of this reaction, 4-chloro-2-trimethylstannyl-1-butene (4),[4] might serve as a suitable precursor for novel bifunctional reagents that would perform as synthetic equivalents to the 1-butene d^2,a^4-synthon 9.[5] For example, it seemed reasonable to expect that transmetalation of 4 with MeLi would provide the lithio reagent 5, which, if sufficiently stable, could be converted into related species such as the Grignard reagent 6 and the cuprates 7 and 8. We report herein some of the results of this study,[6] which showed that 5 - 8 are indeed viable reagents that serve well as synthetic equivalents to the donor-acceptor synthon 9.



4 M=SnMe$_3$ **7** M=CuSPh(Li)
5 M=Li **8** M=CuCN(Li)
6 M=MgBr



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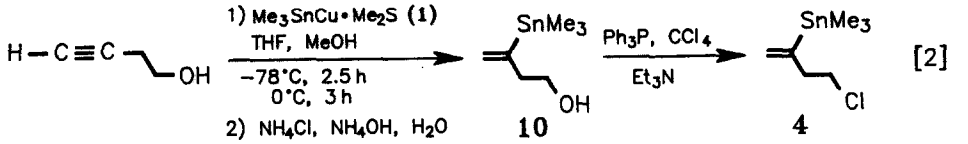
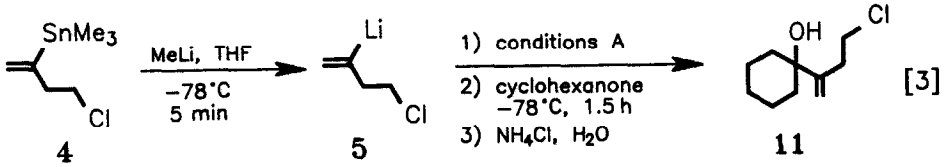
RESULTS AND DISCUSSION

(a) Preparation of 4-chloro-2-lithio-1-butene (5) and its reactions with aldehydes and ketones. The 4-chloro-2-trimethylstannyl-1-butene (4) that was employed in the present investigations was derived by reaction of the corresponding alcohol 10 with Ph_3P-CCl_4[7] in the presence of Et_3N (eq. [2]). The alcohol 10 was prepared in 69 % yield from 3-butyn-1-ol by a procedure (eq. [2]) modified from that described earlier.[4] Although the yield of 10 from this alternative procedure was somewhat lower than that reported previously (82 %),[4] the reaction was more convenient to carry out, particularly on a large scale.



[2]

Treatment of 4 with 1.1 equivalents of MeLi in THF at -78 °C for 5 minutes gave a light yellow solution of the lithio reagent 5 (eq. [3]). The fact that the latter reagent had formed and was sufficiently stable to be used in synthesis was shown as follows. Addition of cyclohexanone (1.2 equivalents) to the reaction mixture, followed by stirring at -78 °C for 1.5 hours and subsequent work-up with NH_4Cl-H_2O, gave the chloro alcohol 11 in 69 % yield (based on 4, product purified by preparative TLC and distillation). In order to acquire information regarding the stability of 5, solutions of this reagent in THF were warmed to a given temperature for 30 minutes and then were recooled to -78 °C prior to addition of cyclohexanone. On the basis of the yields of 11 obtained (see eq. [3]), it is evident that at temperatures between -78 °C and -63 °C, 5 is quite stable. On the other hand, 5 appears to decompose slowly at -48 °C and, at -20 °C for 30 minutes, it completely self-destructs.[8] The fate of 5 in the latter experiment was not determined. However, on the basis of results obtained in a subsequent related study,[10] it is highly likely that, at temperatures above approximately -50 to -60 °C, 5 cyclizes to give methylenecyclopropane.



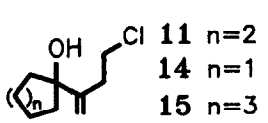
[3]

Conditions A: −78°C, 5 min; −63°C, 30 min; −48°C, 30 min; −20°C, 30 min

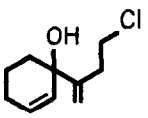
Yield of **11**: 69% 60% 42% 0%

Reaction of reagent 5 with a number of other carbonyl compounds at -78 °C in THF gave, upon workup, the corresponding 1,2-addition products 14 - 18. The results of these reactions are summarized in Table 1. Alternatively, when the cold solutions derived from reaction of 5 with the carbonyl substrates were treated with hexamethylphosphoramide (HMPA) and then were allowed to warm to room temperature, the 3-methylenetetrahydrofuran derivatives 19 - 24 were produced (Table 1). Not surprisingly, the latter substances could also be obtained by treatment of the chloro alcohols with KH in THF at room temperature, as illustrated by the efficient conversions of 11, 15, 17 and 18 into 19 (81 %), 21 (88 %), 23 (78 %), and 24 (84 %), respectively.

Table 1. Reaction of 4-chloro-2-lithio-1-butene (5) with carbonyl compounds



11 n=2
14 n=1
15 n=3



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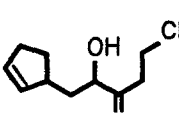

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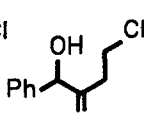
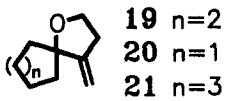
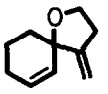


18



19 n=2
20 n=1
21 n=3



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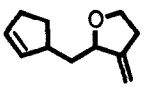

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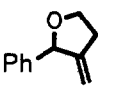


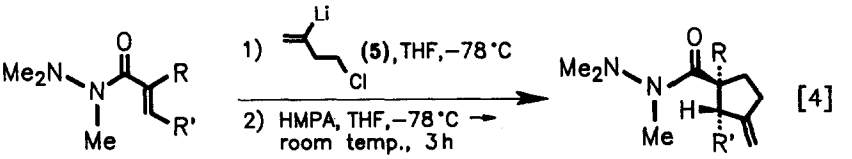
24

Carbonyl Compound	Chloro alcohol[a]	Yield (%)[b]	3-Methylene-tetrahydrofuran[c]	Yield (%)[b]
cyclohexanone	11	69	19	58
cyclopentanone	14	67	20	51
cycloheptanone	15	69	21	62
2-cyclohexen-1-one	16	72	22	62
2-(2-cyclopentenyl)ethanal	17	64	23	56
benzaldehyde	18	76	24	63

[a] (i) A solution of 0.39 mmol of 5 in THF at -78 °C was treated with 0.46 mmol of the carbonyl compound and the mixture was stirred at -78 °C for 1.5 h. (ii) The reaction mixture (-78 °C) was treated with NH_4Cl-H_2O.
[b] The yields are based on the amount of 4-chloro-2-trimethylstannyl-1-butene (4) (the precursor of 5) used and refer to purified, distilled products.
[c] (i) As in (i), above. (ii) HMPA (0.54 mmol) was added and the reaction mixture was warmed to room temperature and stirred for 3 h.

The brief study summarized above showed unambiguously that 4-chloro-2-lithio-1-butene 5 is readily prepared and, at low temperatures, functions as a viable donor-acceptor reagent. The use of this novel species in reactions involving the formation of two carbon-carbon bonds and the conversion of 5 into other useful bifunctional reagents are described in the following two sections of this paper.

(b) Reaction of 4-chloro-2-lithio-1-butene (5) with α,β-unsaturated N,N',N'-trimethylhydrazides. In 1980, Knapp and Galienni[11] reported that simple alkyllithium reagents undergo smooth conjugate addition to α,β-unsaturated N,N',N'-trimethylhydrazides. In order to demonstrate further the use of 5 as a bifunctional conjunctive reagent, we carried out a brief study of the reaction of this reagent with the three hydrazides 25 - 27.[11] Treatment of a cold (-78 °C) THF solution of 5 with a slight excess of 25, followed by stirring of the mixture for 2 hours, addition of HMPA, and warming of the solution to room temperature (3 hours), gave N,N',N'-trimethyl-3-methylenecyclopentanecarboxhydrazide (28) in 60 % yield (eq. [4]). In identical fashion, the substrates 26 and 27 were transformed into the products 29 and 30, respectively. Spectral data showed that the latter product was stereochemically homogeneous. Under the reaction conditions involved, it seems highly unlikely that the product would epimerize at the position adjacent to the carbonyl group. Since an examination of molecular models



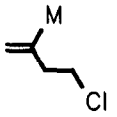
[4]

25 R=R'=H
26 R=Me, R'=H
27 R=H, R'=Me

28 R=R'=H
29 R=Me, R'=H
30 R=H, R'=Me

indicates that the transition state for cyclization leading to the trans product would be of lower energy than that leading to the corresponding cis isomer, the product derived from 27 was assigned the trans stereochemistry shown in 30.

(c) Conjugate addition of lithium phenylthio- (7) and lithium cyano[2-(4-chloro-1-butenyl)]cuprate (8) to cyclic enones. Methylenecyclopentane annulation sequences. In order to significantly enhance the synthetic utility of 4-chloro-2-trimethylstannyl-1-butene (4) as a precursor of useful bifunctional reagents, it was hoped that conjugate addition of the 2-(4-chloro-1-butenyl) group to cyclic enones could be effected conveniently and efficiently. Clearly, this type of transformation would require the conversion of 4 into reagents other than the lithio compound 5, since the latter species adds directly to the carbonyl carbon of α,β-unsaturated ketones (1,2-addition). Obviously, organocuprates were the reagents of choice. To this end, transmetalation of 4 with MeLi in THF at -78 °C, followed by addition of 1 equivalent of solid CuSPh[12] or CuCN and brief stirring of the mixtures at -63 °C, gave yellow solutions of the cuprates 7 or 8, respectively. These reagents were stable at low temperatures



4 M=SnMe$_3$ **7** M=CuSPh(Li)
5 M=Li **8** M=CuCN(Li)

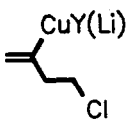
and, importantly, reacted smoothly with a variety of enones to afford the corresponding desired conjugate addition products. For example, reaction of 2-cyclohexen-1-one (31) with the phenylthiocuprate 7 (THF, -78 °C, 3 hours) or the cyanocuprate 8 (THF, -78 °C, 1 hour; -48 °C, 1.5 hours) provided, upon suitable work-up, the chloro ketone 37 (83 %, 80 %, respectively). The results obtained from reactions of reagents 7 and 8 with 2-cyclohexen-1-one (31) and other cyclic enones to provide the corresponding chloro ketones are summarized in Table 2.

Not unexpectedly, the products 38 and 40 derived from the 2-methyl-2-cycloalken-1-ones 32 and 34 consisted, in each case, of a mixture of epimers (Table 1, entries 2 and 4). On the basis of GLC and ^{1}H NMR analyses, the ratio of the two isomers in 38 and 40 were approximately 96:4 and 3:2, respectively.

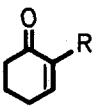
A minor difficulty arose when it was found that the reactions of 3-methyl-2-cyclopenten-1-one (35) with reagents 7 and 8 under "normal" conditions (Table 2, footnote a) failed to produce the desired conjugate addition product 41. However, it is now well known that conjugate additions of cuprates to enones are assisted by $BF_3 \cdot Et_2O$ and, indeed, when solutions of reagents 7 and 8 were treated with 1 equivalent of this Lewis acid prior to addition of the enone 35, the chloro ketone 41 was obtained in excellent yields (entry 5).

Conjugate addition of reagents 7 and 8 to the bicyclic enone 36[13] (entry 6) gave, in each case, a single product. Since it is well known[14] that conjugate additions of cuprate reagents to bicyclo[3.3.0]oct-1-en-3-ones proceed to give cis-fused products highly stereoselectively, the stereochemistry of the product 42 could be assigned with confidence.

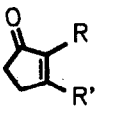
Table 2. Methylenecyclopentane annulations



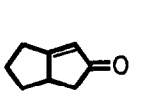
7 Y=SPh
8 Y=CN



31 R=H
32 R=Me



33 R=R'=H
34 R=Me, R'=H
35 R=H, R'=Me



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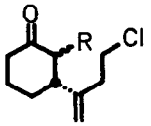
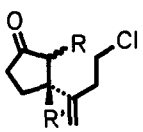
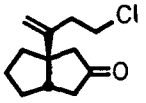


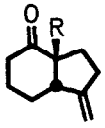
37 R=H
38 R=Me



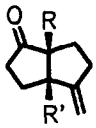
39 R=R'=H
40 R=Me, R'=H
41 R=H, R'=Me



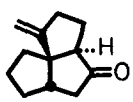
42



43 R=H
44 R=Me



45 R=R'=H
46 R=Me, R'=H
47 R=H, R'=Me



48

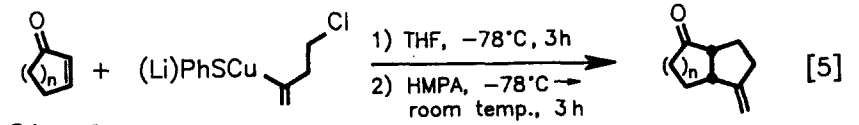
Entry	Enone	Chloro ketone[a]	Yields (%)[b]	Annulation product[c]	Yield (%)[d]
1	31	37	83, 80	43	75
2	32	38	77, 78	44	75
3	33	39	75, 77	45	68
4	34	40	77, 75	46	75
5	35[e]	41	80, 78	47	70[f]
6	36	42	70, 72	48	65

[a] The enone (0.46 mmol) was allowed to react in THF with 0.39 mmol of reagent 7 (-78 °C, 3 h) or reagent 8 (-78 °C, 1 h; -48 °C, 1.5 h).
[b] The yields are based on the amount of 4-chloro-2-trimethylstannyl-1-butene (4) (the precursor of 7 and 8) used and refer to purified, distilled products. The two numbers refer to the yields obtained from reagents 7 and 8, respectively.
[c] The chloro ketone (0.25 mmol) was allowed to react in THF with 0.75 mmol of KH (room temperature, 2.5 h).
[d] The yields are based on the amount of chloro ketones used and refer to purified, distilled products.
[e] In the reactions of 35 with 7 and 8, it was necessary, in each case, to catalyze the process with $BF_3 \cdot Et_2O$. When reagent 7 was employed, the reaction was carried out at -78 °C for 5 min, -48 °C for 1 h, and -20 °C for 1 h. With reagent 8, the reaction conditions were identical with those given in footnote a, except that $BF_3 \cdot Et_2O$ was added prior to the addition of the enone.
[f] In this case, the reaction was not complete after 2.5 h, and the mixture was therefore stirred for an additional 5 h.

Treatment of the chloro ketones 37 - 42 with KH in THF at room temperature provided cleanly the intramolecular alkylation products 43 - 48, respectively (Table 2). In each case, the product consisted of a single compound. Since it has been established that intramolecular alkylations similar to those summarized in Table 2 provide, under kinetically controlled conditions, cis-fused bicyclic products,[15] the stereochemistry of the annulation products 44 and 46 (entries 2 and 4) could be assigned with certainty. Furthermore, since highly strained trans-fused bicyclo[3.3.0]octan-2-ones are much less stable than the corresponding cis-fused isomers, the kinetically formed products 45, 47, and 48 (entries 3, 5,

and 6) would be expected to retain their stereochemistry. Finally, the initially formed, stereochemically homogeneous substance derived from cyclization of the chloro ketone 37 (entry 1) did not epimerize when stirred with base and, therefore, the isolated annulation product was also assigned the cis stereochemistry, as shown in 43. The ^{1}H NMR spectrum of 43 showed that the coupling constant between the two angular protons is 7 Hz. If these protons had been in a trans relationship, a larger coupling constant would have been expected and, consequently, the spectral data supported the stereochemical assignment.

In order to characterize all isolable synthetic intermediates, the annulation sequences described above were carried out via two distinct steps, involving conjugate addition and subsequent intramolecular alkylation. However, the annulations may be accomplished by means of a one-pot process in which the intermediate chloro ketones are not isolated. For example, reaction of the enones 31 and 33 with the phenylthiocuprate 4, followed by addition of HMPA and warming of the reaction mixtures to room temperature, afforded directly the annulation products 43 (56 %) and 45 (55 %), respectively (eq. [5]). Clearly, this one-step protocol is particularly attractive.



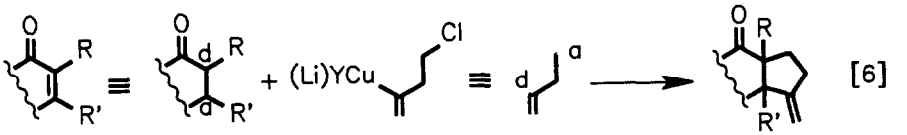
31 n=2
33 n=1

4

43 n=2
45 n=1

[5]

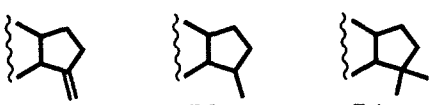
The conversions of the enones 31 - 36 into compounds 43 - 48, respectively, (Table 2 and eq. [5]) represent novel and potentially useful methylenecyclopentane annulation sequences.[16] In these transformations, the α,β-unsaturated ketones (general structure 49) serve as synthetic equivalents to the synthon 50 while the cuprates 7 and 8 are synthetically equivalent to the 1-butene d^2,a^4-synthon 9. Thus, in an overall sense, the annulation sequences can be represented by the (theoretical) combination of the two donor-acceptor synthons[5] 50 and 9, as shown in eq. [6].



49 **50** **7** Y=PhS **8** Y=CN **9** **51**

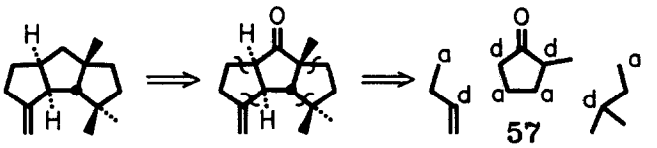
[6]

The methylenecyclopentane moiety 52 and the structurally related methylcyclopentane and gem-dimethylcyclopentane units (53, 54, respectively) are common structural features in the terpenoid family of natural products. Clearly, compounds containing the methylenecyclopentane function 52 should serve as suitable synthetic precursors to substances possessing the structural features shown in 53 and 54. Consequently, it appears that the new methylenecyclopentane annulation method described above could be very useful for the synthesis of naturally occurring substances. A specific example is given in the following section of this paper.



52 **53** **54**

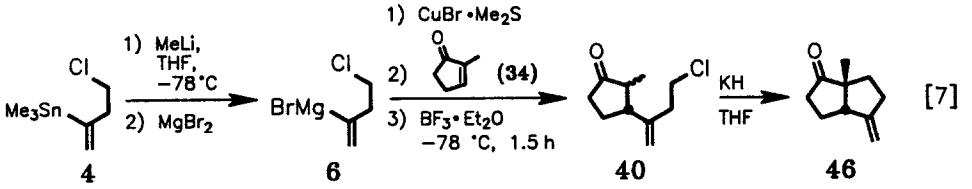
(d) Total synthesis of (±)-$\Delta^{9(12)}$-capnellene (55). The hydrocarbon (-)-$\Delta^{9(12)}$-capnellene, isolated from the soft coral Capnella imbricata, has been shown to possess the substituted cis,anti,cis-tricyclo[6.3.0.$0^{2,6}$]undecane structure 55.[17] This interesting substance is considered to be the biogenetic precursor of the capnellane family of sesquiterpenoids, which consists of a (growing) number of oxygenated derivatives of 55.[18] During the past 8 years, $\Delta^{9(12)}$-capnellene (55) has attracted considerable attention from the community of synthetic organic chemists and, indeed, a number of syntheses of (±)-55, via a variety of interesting approaches, have been reported.[19]



Scheme 1

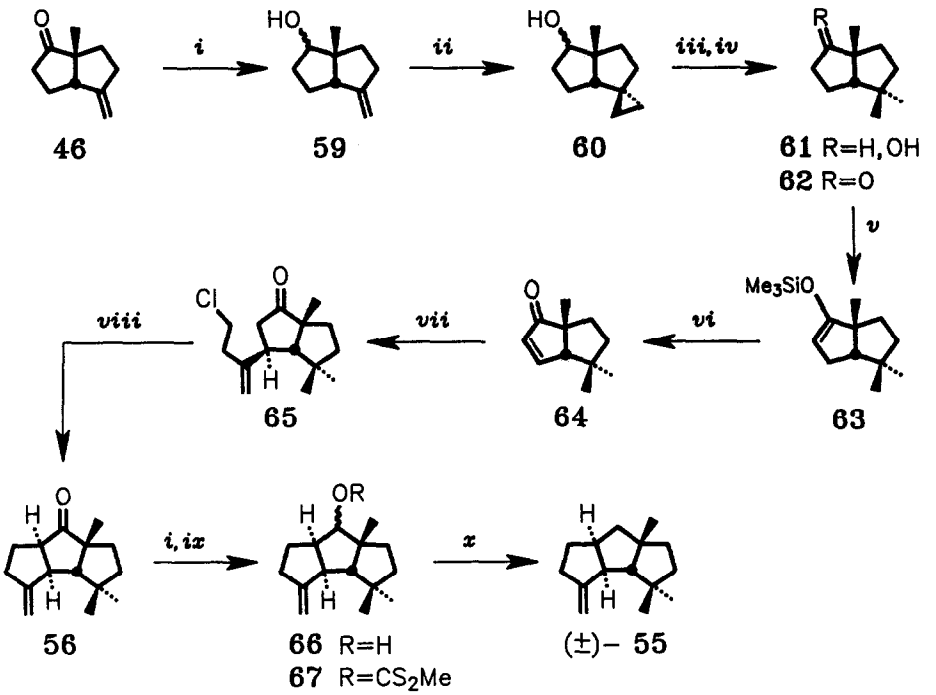
If, in a retrosynthetic sense, the target molecule 55 is "converted" into the ketone 56 and the disconnections indicated in the latter structure (Scheme 1) are carried out, the synthons 9, 57, and 58 can be produced. In the work described above, reagents (e.g. 7, 8) synthetically equivalent to the 1-butene d^2,a^4-synthon 9 were developed. As was pointed out, it appeared likely that these reagents could also be made to serve as synthetic equivalents to the 2-methylbutane d^2,a^4-synthon 58. Therefore, it was decided to attempt a total synthesis of (±)-$\Delta^{9(12)}$-capnellene (55) via a route in which both of the "outside" five-membered rings would be added to a suitably functionalized central ring. In such an approach, the two key steps would involve methylenecyclopentane annulations of the type described above.

For the "large scale" conversion of 2-methyl-2-cyclopenten-1-one (34)[20] into the methylenecyclopentane annulation product 46, it was found convenient to carry out the copper(I) catalyzed conjugate addition of the Grignard reagent 6 to the enone 34. Thus, transmetalation of the vinylstannane 4, followed by successive addition of $MgBr_2$, CuBr·Me_2S (0.25 equivalent), the enone 34, and BF_3·Et_2O afforded, after a reaction time of 1.5 hours, the chloro ketone 40 (80 %) (eq. [7]). Cyclization of 40 to 46 was carried out as described previously.



The total synthesis of (±)-$\Delta^{9(12)}$-capnellene (55) from the bicyclic ketone 46 is summarized in Scheme 2.

Attempted cyclopropanation of the carbon-carbon double bond of 46 with CH_2I_2-Et_2Zn under a variety of conditions gave poor yields (25-30 %) of the corresponding keto cyclopropane. It appeared that the presence of the carbonyl group in 46 was detrimental to the reaction and, therefore, 46 was reduced to the alcohol 59 (87:13 mixture of epimers). Cyclopropanation[21] of the latter material proceeded smoothly to provide (72 % from 46) the tricyclic alcohol 60 (88:12 mixture of epimers). Hydrogenolysis of the cyclopropane ring in 60, followed by oxidation[22] of the resultant product 61, afforded the bicyclic ketone 62 (82 % from 60). The IR (1720 cm^{-1}) and ^1H NMR (3-proton singlets at δ 0.90, 1.05, and 1.19) spectra of 62 showed clearly that the desired substituted bicyclo[3.3.0]octan-2-one had been obtained.



Reagents and conditions: i, $LiAlH_4$, Et_2O, -78 °C; ii, CH_2I_2, Et_2Zn, dry air, PhMe, 55 °C, 1.5 h; iii, H_2 (2.5 atm.), PtO_2, HOAc; iv, $C_5H_5N{\cdot}CrO_3{\cdot}HCl$, NaOAc, CH_2Cl_2; v, Me_3SiI, Et_3N, CH_2Cl_2, -78 °C; vi, $Pd(OAc)_2$, MeCN; vii, **6**, $CuBr{\cdot}Me_2S$, THF, -78 °C; viii, KH, THF; ix, NaH, CS_2, MeI, THF; x, n-Bu_3SnH, AIBN, PhMe, reflux.

Scheme 2

In order to add the second five-membered ring via our methylenecyclopentane annulation method, it was necessary to convert the ketone **62** into the enone **64**. This was conveniently accomplished by the method of Saegusa and coworkers.[23] Treatment of **62** with freshly prepared Me_3SiI[24] in the presence of Et_3N, followed by oxidation of the resultant enol silyl ether **63** with $Pd(OAc)_2$ in MeCN[23] gave the required enone **64** in 74 % yield.

On the basis of steric considerations, conjugate addition of a cuprate reagent to the enone function of **64** would be expected to take place stereoselectively, with approach of the reagent from the convex face of the substrate. Indeed, reaction of **64** with the Grignard reagent **6** in the presence of $CuBr{\cdot}Me_2S$ gave a single addition product **65**. Intramolecular alkylation of this material provided the annulation product **56** (68 % from **64**).

Completion of the synthesis of (±)-$\Delta^{9(12)}$-capnellene (**55**) required reductive removal of the carbonyl group of **56**. This was readily accomplished by the method of Barton and McCombie.[25] Reduction of **56** to the alcohol **66** (1:1 mixture of epimers), followed by reduction of the corresponding methyl xanthate **67** with n-Bu_3SnH,[25] afforded (±)-$\Delta^{9(12)}$-capnellene (**55**) (56 % from the ketone **56**). The synthetic material, a colorless oil, exhibited spectra (IR, ^1H NMR, ^{13}C NMR) identical with those of natural (-)-**55**[26] and synthetic (±)-**55**.[26]

EXPERIMENTAL

General. Distillation temperatures, which refer to bulb-to-bulb (Kugelrohr) distillations, are uncorrected. IR spectra were recorded on a Perkin-Elmer model 710B spectrophotometer and were calibrated using the 1601 cm^{-1} band of polystyrene film. ^1H NMR spectra were recorded on $CDCl_3$ solutions. Signal positions are given in ppm (δ) relative to Me_4Si. High resolution mass spectra were recorded with Kratos/AEI MS 50 or MS 902 mass spectrometers. Gas-liquid chromatography (GLC) was accomplished with Hewlett-Packard models 5832A (thermal conductivity detector, 6 ft x 0.125 in stainless steel column packed with 3-5 % OV-17 on 80-100 mesh Chromosorb W(HP)) or 5880 (flame ionization detector, 25 m x 0.21 mm fused silica column coated with cross-linked SE-54) gas chromatographs. Analytical thin-layer chromatography (TLC) was carried out with commercial silica gel plates (Eastman Chromatogram Sheet Type 13181 or E. Merck, Type 5554). Preparative TLC was done with 20 x 20 cm glass plates coated with 0.7 mm of E. Merck silica gel 60. Conventional and flash[27] column chromatography were carried out with 70-230 and 230-400 mesh silica gel (E. Merck), respectively. Reagents and solvents were purified and dried using standard methods.

Note. All compounds for which high resolution mass measurements are given exhibited clean ^1H NMR spectra and showed essentially one spot on TLC analysis and (or) one peak on GLC analysis.

Note. Unless otherwise indicated, all reactions were carried out under an atmosphere of dry argon using oven- or flame-dried glassware.

3-Trimethylstannyl-3-buten-1-ol (10). To a cold (-78 °C), stirred solution of $Me_3SnCu{\cdot}Me_2S$ (1) (49.2 mmol) in 25 mL of dry THF was added a solution of 3-butyn-1-ol (1.5 g, 21.4 mmol) in 5 mL of dry THF, followed by dry MeOH (41 mL, 1 mmol). The dark red mixture was stirred at -78 °C for 2.5 h, was warmed slowly to 0 °C, and then was stirred for an additional 3 h. Saturated aqueous NH_4Cl-NH_4OH (pH 8) (10 mL) was added and the mixture was warmed to room temperature and stirred vigorously until the aqueous phase became deep blue. The phases were separated and the aqueous layer was extracted twice with Et_2O. The combined organic extracts were washed three times with aqueous NH_4Cl-NH_4OH (pH 8), dried ($MgSO_4$), and concentrated. The crude oil contained (GLC analysis) $(Me_3Sn)_2$ and a 9:1 mixture of two products. Flash chromatography[27] (100 g silica gel, 1:3 Et_2O-petroleum ether) of this mixture, followed by distillation (~70 °C/12 Torr) of the two products thus obtained, gave 3.45 g (69 %) of the desired alcohol 10[4] and 300 mg (6 %) of the isomeric (E)-4-trimethylstannyl-3-buten-1-ol.[4]

4-Chloro-2-trimethylstannyl-1-butene (4). To a solution of Ph_3P (1.3 g, 5 mmol) in CCl_4 (15 mL) was added a solution of 0.8 g (3.4 mmol) of the alcohol 10 in CCl_4 (3 mL), followed by dry Et_3N (0.7 mL, 5 mmol). After the solution had been refluxed for 18 h, petroleum ether (30 mL) was added and the resulting white slurry was filtered through a column of Florisil (25 g) (elution with petroleum ether). Concentration of the combined eluate, followed by distillation (~60 °C/12 Torr) of the remaining oil, provided 0.6 g (70 %) of the chloride 4[4] as a colorless oil.

4-Bromo-2-trimethylstannyl-1-butene (12). To a cold (0 °C), stirred solution of Ph_3P (0.65 g, 2.5 mmol) in 10 mL of dry MeCN was added Br_2 until the solution became pale yellow. After the solution had been stirred for 5 min, Et_3N (0.7 mL, 5 mmol) and the alcohol 10 (0.4 g, 1.7 mmol) were added successively and stirring was continued for 20 min. Petroleum ether (15 mL) was added and the resulting white slurry was filtered through a column of Florisil (15 g, elution with petroleum ether). Concentration of the combined eluate and distillation (70 - 75 °C/12 Torr) afforded 332 mg (76 %) of the bromide 12 as a colorless oil that exhibited IR (neat) 915, 750 cm^{-1}; ^1H NMR (100 MHz) δ 0.18 (s, 9H, $^2J_{Sn-H}$ = 53 Hz), 2.80 (br t, 2H, J = 7 Hz, $^3J_{Sn-H}$ = 46 Hz), 2.40 (t, 2H, J = 7 Hz), 5.30, 5.75 (br s, br s, 1H each). Exact Mass calcd. for $C_6H_{12}{}^{81}Br{}^{120}Sn$ (M^+-Me): 269.0301; found: 269.0300.

General procedure I. Reaction of 4-chloro-2-lithio-1-butene (5) with carbonyl compounds. Preparation of chloro alcohols. To a cold (-78 °C), stirred solution of 4-chloro-2-trimethylstannyl-1-butene (4) (100 mg, 0.39 mmol) in 3 mL of dry THF was added a solution of MeLi (0.42 mmol) in Et_2O. After the solution had been stirred at -78 °C for 5 min, the carbonyl compound (0.46 mmol) was added and the mixture was stirred for an additional 1.5 h. Saturated aqueous NH_4Cl (0.4 mL) and Et_2O (20 mL) were added and the mixture was allowed to warm to room temperature. The organic phase was washed three times with saturated aqueous NH_4Cl (5 mL) and then was dried ($MgSO_4$) and concentrated. The remaining oil was purified by preparative TLC (5:2 petroleum ether-Et_2O, unless otherwise noted) and distillation to afford pure product.

The following alcohols were prepared via general procedure I.

4-Chloro-2-(1-hydroxycyclohexyl)-1-butene (11), from cyclohexanone; 69 %; distillation temperature 55-65 °C/0.2 Torr; IR (neat) 3375, 1060, 920 cm^{-1}; ^1H NMR (100 MHz) δ 1.50-1.76 (m, 11H), 2.62 (br t, 2H, J = 7 Hz), 3.70 (t, 2H, J = 7 Hz), 4.94 (br s, 1H), 5.24 (s, 1H). Exact Mass calcd. for $C_{10}H_{17}{}^{35}ClO$: 188.0968; found: 188.0975.

4-Chloro-2-(1-hydroxycyclopentyl)-1-butene (14), from cyclopentanone; 67 %; distillation temperature 55-60 °C/0.2 Torr; IR (neat) 3360, 920 cm^{-1}; ^1H NMR (100 MHz) δ 1.37-2.01 (m, 9H), 2.59 (br t, 2H, J = 8 Hz), 3.67 (t, 2H, J = 8 Hz), 4.88 (br s, 1H), 5.21 (s, 1H). Exact Mass calcd. for $C_9H_{15}{}^{35}ClO$: 174.0811; found: 174.0811.

4-Chloro-2-(1-hydroxycycloheptyl)-1-butene (15), from cycloheptanone; 69 %; distillation temperature 60-63 °C/0.2 Torr; IR (neat) 3375, 1610, 1440, 1015 cm^{-1}; ^1H NMR (80 MHz) δ 1.32 (s, 1H), 1.38-2.00 (m, 12H), 2.60 (br t, 2H, J = 7.5 Hz), 3.68 (t, 2H, J = 7.5 Hz), 4.80 (br s, 1H), 5.17 (s, 1H). Exact Mass calcd. for $C_{11}H_{19}{}^{35}ClO$: 202.1124; found: 202.1127.

4-Chloro-2-(1-hydroxycyclohex-2-enyl)-1-butene (16), from 2-cyclohexen-1-one; 72 %; preparative TLC 5:3 petroleum ether-Et_2O; distillation temperature 58-62 °C/0.2 Torr; IR (neat) 3380, 1620, 1160 cm^{-1}; ^1H NMR (100 MHz) δ 1.23 (s, 1H), 1.59-1.81 (m, 4H), 1.89-2.11 (m, 2H), 2.57 (br t, 2H, J = 8 Hz), 3.67 (t, 2H, J = 8 Hz), 4.94 (br s, 1H), 5.18 (s, 1H), 5.55 (dt, 1H, J = 10.5, 0.8 Hz), 5.91 (dt, 1H, J = 10.5, 4 Hz). Exact Mass calcd. for $C_{10}H_{15}{}^{35}ClO$: 186.0811; found: 186.0812.

3-(2-Chloroethyl)-1-(2-cyclopentenyl)-3-buten-2-ol (17), from 2-(2-cyclopentenyl)ethanal; 64 %; distillation temperature 60-62 °C/0.2 Torr; IR (neat) 3400, 910 cm^{-1}; ^1H NMR (100 MHz) δ 1.13-1.73 (m, 4H), 1.93-2.45 (m, 3H), 2.55 (br t, 2H, J = 7 Hz), 2.55-2.90 (m, 1H), 3.66 (t, 2H, J = 7 Hz), 4.17 (br t, 1H, J = 7 Hz), 4.93 (br s, 1H), 5.15 (s, 1H), 5.71 (m, 2H). Exact Mass calcd. for $C_{11}H_{17}{}^{35}ClO$: 200.0968; found: 200.0970.

2-(2-Chloroethyl)-1-phenyl-2-propen-1-ol (18), from benzaldehyde; 76 %; preparative TLC, 7:3 petroleum ether-Et_2O; distillation temperature 54-58 °C/0.2 Torr; IR (neat) 3340, 1600, 1090 cm^{-1}; ^1H NMR (80 MHz) δ 2.0 (br s, 1H), 2.40 (br t, 2H, J = 7 Hz), 3.53 (t, 2H, J = 7 Hz), 5.08 (br s, 1H), 5.20, 5.35 (br s, br s, 1H each), 7.32 (br s, 5H). Exact Mass calcd. for $C_{11}H_{13}{}^{35}ClO$: 196.0665; found: 196.0650.

General procedure II. Reaction of 4-chloro-2-lithio-1-butene (5) with carbonyl compounds. Direct preparation of 3-methylenetetrahydrofuran derivatives. To a cold (-78 °C), stirred solution of the vinyllithium reagent 5 (see general procedure I) (0.39 mmol) in 3 mL of dry THF was added 0.46 mmol of the carbonyl compound and stirring was continued for 1 h. Dry HMPA (0.54 mmol) was added, the mixture was allowed to warm to room temperature, and stirring was continued for 3 h. Saturated aqueous $CuSO_4$ (~3 mL) and Et_2O (20 mL) were added and the mixture was stirred vigorously for 10 min. The organic phase was separated, washed three times with saturated aqueous $CuSO_4$ (3 mL) and once with brine, dried ($MgSO_4$), and concentrated. The remaining oil was purified by preparative TLC (5:1 petroleum ether-Et_2O, unless otherwise noted) and distillation to afford pure product.

The following ethers were prepared via general procedure II.

4-Methylene-1-oxaspiro[4.5]decane (19), from cyclohexanone; 58 %; distillation temperature 52-58 °C/0.2 Torr; IR (neat) 1150, 760 cm^{-1}; ^1H NMR (100 MHz) δ 1.41-1.77 (m, 10H), 2.58 (ddt, 2H, J = 2, 1.5, 7 Hz), 3.79 (t, 2H, J = 7 Hz), 4.74 (t, 1H, J = 2 Hz), 4.89 (t, 1H, J = 1.5 Hz). Exact Mass calcd. for $C_{10}H_{16}O$: 152.1201; found: 152.1201.

4-Methylene-1-oxaspiro[4.4]nonane (20), from cyclopentanone; 51 %; distillation temperature 50-55 °C/0.2 Torr; IR (neat) 1220, 760 cm^{-1}; ^1H NMR (100 MHz) δ 1.44 (m, 8H), 2.60 (ddt, 2H, J = 2, 1.6, 7 Hz), 3.77 (t, 2H, J = 7 Hz), 4.83 (t, 1H, J = 2 Hz), 4.92 (t, 1H, J = 1.6 Hz). Exact Mass calcd. for $C_9H_{14}O$: 138.1045; found: 138.1045.

4-Methylene-1-oxaspiro[4.6]undecane (21), from cycloheptanone; 62 %; distillation temperature 57-60 °C/0.2 Torr; IR (neat) 920, 740 cm^{-1}; ^1H NMR (100 MHz) δ 1.43-1.81 (m, 12H), 2.59 (tt, 2H, J = 7, 2 Hz), 3.79(t, 2H, J = 7 Hz), 4.82, 4.87 (t, t, 1H each, J = 2 Hz in each case). Exact Mass calcd. for $C_{11}H_{18}O$: 166.1358; found: 166.1362.

4-Methylene-1-oxaspiro[4.5]dec-6-ene (22), from 2-cyclohexen-1-one; 62 %; preparative TLC, 5:2 petroleum ether-Et_2O; distillation temperature 55-58 °C/0.2 Torr; IR (neat) 1075, 770 cm^{-1}; ^1H NMR (100 MHz) δ 1.54-1.81 (m, 4H), 1.88-2.11 (m, 2H), 2.63 (ddt, 2H, J = 2, 1.8, 8 Hz), 3.86 (t, 2H, J = 8 Hz), 4.80 (t, 1H, J = 2 Hz), 4.97 (t, 1H, J = 1.8 Hz), 5.45 (dt, J = 10.5, 0.8 Hz), 5.89 (dt, 1H, J = 10.5, 3 Hz). Exact Mass calcd. for $C_{10}H_{14}O$: 150.1045; found: 150.1045.

2-(2-Cyclopentenylmethyl)-3-methylenetetrahydrofuran (23), from 2-(2-cyclopentenyl)-ethanal; 56 %; distillation temperature 58-60 °C/0.2 Torr; IR (neat) 890, 740 cm^{-1}; ^1H NMR (100 MHz) δ 1.25-1.61 (m, 4H), 1.83-2.32 (m, 3H), 2.32-2.63 (m, 2H), 3.49-3.96 (m, 2H), 4.03-4.33 (br signal, 1H), 4.83 (m, 1H), 4.97 (m, 1H), 5.75 (m, 2H). Exact Mass calcd. for $C_{11}H_{16}O$: 164.1201; found: 164.1206.

3-Methylene-2-phenyltetrahydrofuran (24), from benzaldehyde; 63 %; preparative TLC, 7:3 petroleum ether-Et_2O; distillation temperature 52-55 °C/0.2 Torr ; IR (neat) 1635, 1608, 760 cm^{-1}; ^1H NMR (100 MHz) δ 2.73 (br t, 2H, J = 7 Hz), 3.79-4.31 (m, 2H), 4.75 (m, 1H), 5.08 (m, 1H), 5.18 (br s, 1H), 7.25-7.38 (m, 5H). Exact Mass calcd. for $C_{11}H_{12}O$: 168.0888; found: 160.0890.

General procedure III. Cyclization of chloro alcohols to 3-methylenetetrahydrofuran derivatives. To a stirred suspension of KH (0.75 mmol) in 2 mL of dry THF was added a solution of the chloro alcohol (0.2 mmol) in 2 mL of dry THF and the mixture was stirred at room temperature for 3 h. Saturated aqueous NH_4Cl (3 mL) and Et_2O (10 mL) were added and the mixture was stirred for 10 min. The phases were separated and the aqueous layer was extracted twice with Et_2O (4 mL). The combined extracts were washed twice with brine (2 mL), dried ($MgSO_4$), and concentrated. Distillation of the remaining oil provided the cyclic ether.

The following substances were prepared via general procedure III: 4-methylene-1-oxaspiro[4.5]decane (19) from the chloro alcohol 11, 81 %; 4-methylene-1-oxaspiro[4.6]undecane (21) from the chloro alcohol 15, 88 %; 2-(2-cyclopentenylmethyl)-3-methylenetetrahydrofuran (23) from the chloro alcohol 17, 78 %; 3-methylene-2-phenyltetrahydrofuran (24) from the chloro alcohol 18, 84 %. The spectra of the products were identical with those recorded above (see general procedure II).

General procedure IV. Preparation of N,N',N'-trimethyl-3-methylenecyclopentanecarboxhydrazides. To a cold (-78 °C), stirred solution of 4-chloro-2-lithio-1-butene (5) (see general procedure I) (0.39 mmol) in 3 mL of dry THF was added the appropriate α,β-unsaturated N,N',N'-trimethylcarboxhydrazide (0.46 mmol) and the resultant solution was stirred at -78 °C for 2 h. Dry HMPA (0.54 mmol) was added, the mixture was allowed to warm to room temperature, and stirring was continued for 3 h. Saturated aqueous $CuSO_4$ (~2 mL) and Et_2O (20 mL) were added and the mixture was stirred vigorously for 10 min. The layers were separated and the aqueous phase was extracted with Et_2O. The combined extracts were washed twice with saturated aqueous $CuSO_4$ (3 mL), once with saturated aqueous NH_4Cl (3 mL), and then were dried ($MgSO_4$) and concentrated. The residual oil was chromatographed on silica gel (15 g, 2:1 petroleum ether-Et_2O). Distillation of the oil thus obtained gave the pure product.

The following substances were prepared via general procedure IV.

N,N',N'-Trimethyl-3-methylenecyclopentanecarboxhydrazide (28), from compound 25; 60 %; distillation temperature 89-92 °C/12 Torr; IR (neat) 1630, 1440, 900, 760 cm^{-1}; ^1H NMR (400 MHz) δ 1.79-1.98 (m, 2H), 2.24-2.37 (m, 1H), 2.44-2.54 (m, 3H), 2.49, 2.50, 2.88 (s, s, s, 3H each), 3.51 (m, 1H), 4.82-4.88 (m, 2H). Exact Mass calcd. for $C_{10}H_{18}N_2O$: 182.1419; found: 182.1410.

N,N',N'-Trimethyl-1-methyl-3-methylenecyclopentanecarboxhydrazide (29), from compound 26; 62 %; distillation temperature 96-103 °C/12 Torr; IR (neat) 1630, 1450, 740 cm^{-1}; ^1H NMR (400 MHz) δ 1.26 (s, 3H), 1.84-1.92, 2.05-2.14 (m, m, 1H each), 2.33-2.43 (m, 2H), 2.49 (br d, 1H, J = 16 Hz), 2.74 (br d, 1H, J = 16 Hz), 2.50 (s, 6H), 2.83 (s, 3H), 4.83, 4.88 (br s, br s, 1H each). Exact Mass calcd. for $C_{11}H_{20}N_2O$: 196.1575; found: 196.1575.

trans-N,N',N'-Trimethyl-2-methyl-3-methylenecyclopentanecarboxhydrazide (30), from compound 27; 60 %; distillation temperature 93-98 °C/12 Torr; IR (neat) 1645, 1400 cm^{-1}; ^1H NMR (400 MHz) δ 1.04 (d, 3H, J = 6 Hz), 1.64 (m, 1H), 1.86-1.97 (m, 1H), 2.30-2.43, 2.50-2.60 (m, m, 1H each), 2.49, 2.51 (s, s, 3H each), 2.69-2.80 (m, 1H), 2.89 (s, 3H), 3.20 (ddd, 1H, J = 12, 10, 8 Hz), 4.88, 4.95 (d, d, 1H each, J = 2 Hz in each case). Exact Mass calcd. for $C_{11}H_{20}N_2O$: 196.1575; found: 196.1575.

General procedure V. Reaction of lithium phenylthio[2-(4-chloro-1-butenyl)]cuprate (7) with cyclic enones. To a cold (-78 °C), stirred solution of 4-chloro-2-lithio-1-butene (5) (see general procedure I) (0.39 mmol) in 3 mL of dry THF was added solid phenylthiocopper(I) (67 mg, 0.39 mmol) and the resultant slurry was stirred at -78 °C for 5 min and at -63 °C for 15 min to afford a yellow solution of the phenylthiocuprate 7. The solution was cooled to -78 °C, the appropriate cyclic enone (0.46 mmol) was added, and the mixture was stirred for 3 h. Saturated aqueous NH_4Cl (~2 mL) and Et_2O (15 mL) were added, the mixture was allowed to warm to room temperature, and the resultant slurry was filtered through a column of Florisil (10 g, elution with Et_2O). The combined eluate was dried ($MgSO_4$) and concentrated. Column chromatography of the residual material on silica gel (15 g, elution with 3:2 petroleum ether-Et_2O, unless otherwise noted), followed by distillation of the oil thus obtained, gave the product.

The following chloro ketones were prepared via general procedure V.

3-[2-(4-Chloro-1-butenyl)]cyclohexanone (37), from 2-cyclohexen-1-one (31); 83 %; distillation temperature 60-62 °C/0.2 Torr; IR (neat) 1710, 1640, 760 cm^{-1}; ^1H NMR (100 MHz) δ 1.40-1.84 (m, 2H), 1.84-2.17 (m, 2H), 2.22-2.38 (m, 5H), 2.50 (br t, 2H, J = 7 Hz), 3.60 (t, 2H, J = 7 Hz), 4.91, 4.96 (s, s, 1H each). Exact Mass calcd. for $C_{10}H_{15}{}^{35}ClO$: 186.0811; found: 186.0809.

3-[2-(4-Chloro-1-butenyl)]-2-methylcyclohexanone (38), from 2-methyl-2-cyclohexen-1-one (32); 77 %; distillation temperature 61-63 °C/0.2 Torr. GLC analysis of the distilled product indicated that it consisted of a mixture of epimers in a ratio of ~96:4. This material exhibited IR (neat) 1700, 1640, 920 cm^{-1}; ^1H NMR (400 MHz) δ 0.95, 1.00 (d, d, 3H total, ratio of signals ~95:5, J = 6 Hz in each case), 1.64-1.90 (m, 4H), 1.98-2.08 (m, 1H), 2.22-2.31 (m, 1H), 2.43 (br t, 2H, J = 7.2 Hz), 2.41-2.60 (m, 1H), 2.61 (m, 1H), 3.59 (t, 2H, J = 7.2 Hz), 4.83, 5.20 (s, s, 1H each). Exact Mass calcd. for $C_{11}H_{17}{}^{35}ClO$: 200.0968; found: 200.0968.

3-[2-(4-Chloro-1-butenyl)]cyclopentanone (39), from 2-cyclopenten-1-one (33); 75 %; column chromatography, 5:2 petroleum ether-Et_2O; distillation temperature 58-60 °C/0.2 Torr; IR (neat) 1714, 1435 cm^{-1}; ^1H NMR (80 MHz) δ 2.10-2.41 (m, 6H), 2.53 (br t, 2H, J = 7 Hz), 2.67-3.06 (m, 1H), 3.62 (t, 2H, J = 7 Hz), 4.90 (br s, 2H). Exact Mass calcd. for $C_9H_{13}{}^{35}ClO$: 172.0654; found: 172.0653.

3-[2-(4-Chloro-1-butenyl)]-2-methylcyclopentanone (40), from 2-methyl-2-cyclopenten-1-one (34); 77 %; distillation temperature 60-63 °C/0.2 Torr. GLC analysis of the distilled product showed that it consisted of a mixture of epimers (ratio 3:2). This oil exhibited IR (neat) 1725, 1625 cm^{-1}; ^1H NMR (80 MHz) δ 0.90, 1.07 (d, d, 3H total, ratio of signals ~3:2, J = 7 Hz in each case), 1.95-2.67 (m, 8H), 3.67 (t, 2H, J = 7 Hz), 4.85-5.07 (m, 2H). Exact Mass calcd. for $C_{10}H_{15}{}^{35}ClO$: 186.0811; found: 186.0810.

cis-1-[2-(4-Chloro-1-butenyl)]bicyclo[3.3.0]octan-3-one (42), from bicyclo[3.3.0]oct-1-en-3-one (36); 70 %; column chromatography, 5:2 petroleum ether-Et_2O; distillation temperature 68-72 °C/0.2 Torr; IR (neat) 1725, 1625, 1165, 900, 760 cm^{-1}; ^1H NMR (400 MHz) δ 1.45-1.55 (m, 1H), 1.66-1.93 (m, 3H), 2.01-2.16 (m, 2H), 2.22, 2.52 (d, d, 1H each, J = 18 Hz in each case), 2.50-2.59 (m, 2H), 2.52 (t, 2H, J = 8 Hz), 2.74 (m, 1H), 3.66 (t, 2H, J = 8 Hz), 4.89, 4.99 (s, s, 1H each). Exact Mass calcd. for $C_{12}H_{17}{}^{35}ClO$: 212.0968; found: 212.0968.

General procedure VI. Reaction of lithium cyano[2-(4-chloro-1-butenyl)]cuprate (8) with cyclic enones. To a cold (-78 °C), stirred solution of 4-chloro-2-lithio-1-butene (5) (see general procedure I) (0.39 mmol) in 3 mL of dry THF was added solid CuCN (34 mg, 0.39 mmol) and the mixture was stirred at -78 °C for 5 min and at -63 °C for 15 min. The yellow solution of the cyanocuprate 8 was cooled to -78 °C and the appropriate cyclic enone (0.46 mmol) was added. The mixture was stirred at -78 °C for 1 h and at -48 °C for 1.5 h. Work-up and product purification was carried out as described in general procedure V.

The following chloro ketones were prepared from the appropriate starting materials via general procedure VI: 37, 80 %; 38, 78 % (97:3 mixture of epimers); 39, 77 %; 40, 75 % (3:2 mixture of epimers); 42, 72 %.

3-[2-(4-Chloro-1-butenyl)]-3-methylcyclopentanone (41). To a cold (-78 °C), stirred solution of the phenylthiocuprate 7 (see general procedure V) (0.39 mmol) was added successively $BF_3 \cdot Et_2O$ (47 μL, 0.39 mmol) and 3-methyl-2-cyclopenten-1-one (35) (44 mg, 0.46 mmol). The deep yellow solution was stirred at -78 °C for 5 min, at -48 °C for 1 h, and at -20 °C for 1 h. Work-up and product purification as described in general procedure V gave 59 mg (80 %) of the chloro ketone 41 (distillation temperature 60-62 °C/0.2 Torr), which exhibited IR (neat) 1730, 1622, 1162, 905 cm^{-1}; ^1H NMR (80 MHz) δ 1.18 (s, 3H), 1.80-2.40 (m, 6H), 2.55 (br t, 2H, J = 7.5 Hz), 3.63 (t, 2H, J = 7.5 Hz), 4.88 (t, 1H, J = 1 Hz), 4.98 (s, 1H). Exact Mass calcd. for $C_{10}H_{15}{}^{35}ClO$: 186.0811; found: 186.0805.

The chloro ketone 41 was also prepared by reaction of 3-methyl-2-cyclopenten-1-one (35) with the cyanocuprate 8. The procedure was identical with that described in general procedure VI, except that 0.39 mmol of $BF_3 \cdot Et_2O$ was added to the reaction mixture prior to addition of the enone. The yield of 41 was 78 %.

General procedure VII. Intramolecular alkylation of chloro ketones to provide methylenecyclopentane annulation products. To a stirred suspension of KH (30 mg, 0.75 mmol) in 2 mL of dry THF was added a solution of the appropriate chloro ketone (0.25 mmol) in 1 mL of dry THF and the resultant mixture was stirred at room temperature for 2.5 h, unless otherwise noted. Saturated aqueous NH_4Cl (3 mL) and Et_2O (10 mL) were added and the mixture was stirred for 10 min. The phases were separated and the aqueous phase was extracted twice with Et_2O (4 mL). The combined extracts were washed twice with brine (2 mL), dried ($MgSO_4$), and concentrated. Column chromatography of the remaining material on silica gel (15 g, 5:1 petroleum ether-Et_2O), followed by distillation of the oil thus obtained, gave the methylenecyclopentane annulation product.

The following substances were prepared via general procedure VII.

cis-7-Methylenebicyclo[4.3.0]nonan-2-one (43), from the chloro ketone 37; 75 %; distillation temperature 57-59 °C/0.2 Torr; IR (neat) 1700, 890 cm^{-1}; ^1H NMR (400 MHz) δ 1.60-1.70 (m, 1H), 1.74-1.96 (m, 4H), 2.14-2.24 (m, 1H), 2.27-2.41 (m, 4H), 2.73 (q, 1H, J = 7 Hz), 2.97 (br signal, 1H, $w_{1/2} \approx 16$ Hz), 4.83, 4.91 (m, m, 1H each). Exact Mass calcd. for $C_{10}H_{14}O$: 150.1044; found: 150.1044.

cis-1-Methyl-7-methylenebicyclo[4.3.0]nonan-2-one (44), from the chloro ketone 38; 75 %; distillation temperature 58-61 °C/0.2 Torr; IR (neat) 1700, 1640, 890 cm^{-1}; ^1H NMR (400 MHz) δ 1.21-1.31 (m, 1H), 1.22 (s, 3H), 1.74-2.00 (m, 4H), 2.24-2.48 (m, 5H), 2.54 (br s, 1H), 4.82, 4.92 (m, m, 1H each). Exact Mass calcd. for $C_{11}H_{16}O$: 164.1201; found: 164.1206.

cis-6-Methylenebicyclo[3.3.0]octan-2-one (45), from the chloro ketone 39; 68 %; distillation temperature 53-55 °C/0.2 Torr; IR (neat) 1712, 740 cm^{-1}; ^1H NMR (80 MHz) δ 1.85-2.46 (m, 8H), 2.50-2.82, 3.02-3.37 (m, m, 1H each), 4.86-5.01 (m, 2H). Exact Mass calcd. for $C_9H_{12}O$: 136.0888; found: 136.0888.

cis-1-Methyl-6-methylenebicyclo[3.3.0]octan-2-one (46), from the chloro ketone 40; 75 %; distillation temperature 58-60 °C/0.2 Torr; IR (neat) 1730, 1460, 890 cm^{-1}; ^1H NMR (400 MHz) δ 1.12 (s, 3H), 1.50-1.60, 1.80-1.90, 1.95-2.03, 2.09-2.21 (m, m, m, m, 1H each), 2.23-2.34, 2.38-2.48 (m, m, 2H each), 2.75 (br s, 1H), 4.95 (br s, 2H). Exact Mass calcd. for $C_{10}H_{14}O$: 150.1044; found: 150.1039.

cis-5-Methyl-6-methylenebicyclo[3.3.0]octan-2-one (47), from the chloro ketone 41; reaction time 7.5 h; 70 %; distillation temperature 58-60 °C/0.2 Torr; IR (neat) 1712, 890 cm^{-1}; ^1H NMR (400 MHz) δ 1.27 (s, 3H), 1.83-1.99 (m, 3H), 2.06-2.39 (m, 5H), 2.45-2.56 (m, 1H), 4.90-4.98 (m, 2H). Exact Mass calcd. for $C_{10}H_{14}O$: 150.1044; found: 150.1040.

The tricyclic ketone 48, from the bicyclic chloro ketone 42; 65 %; distillation temperature 64-67 °C/0.2 Torr; IR (neat) 1712, 1620, 900 cm^{-1}; ^1H NMR (400 MHz) δ 1.39-1.48 (m, 1H), 1.67-2.32 (series of m, 9H), 2.34-2.48 (m, 3H), 2.52 (t, 1H, J = 9 Hz), 4.92 (br s, 2H). Exact Mass calcd. for $C_{12}H_{16}O$: 176.1201; found: 176.1199.

Direct methylenecyclopentane annulations of 2-cyclohexen-1-one (31) and 2-cyclopenten-1-one (33) with the phenylthiocuprate 7. To a cold (-78 °C), stirred solution of the phenylthiocuprate 7 (see general procedure V) (0.39 mmol) in 3 mL of dry THF was added 0.46 mmol of the enone. After the yellow solution had been stirred at -78 °C for 3 h, dry HMPA (0.64 mmol) was added, the mixture was allowed to warm to room temperature, and then was stirred for an additional 3 h. Et_2O (15 mL) was added and the mixture was filtered through a column of Florisil (10 g, elution with Et_2O). The combined eluate was dried ($MgSO_4$) and concentrated. Column chromatography (15 g silica gel, 5:1 petroleum ether-Et_2O) and distillation of the resultant oil gave the product. The yields of the annulation products 43 and 45 were 56 and 55 %, respectively.

Large scale preparation of cis-1-methyl-6-methylenebicyclo[3.3.0]octan-2-one (46). To a cold (-78 °C), stirred solution of 4-chloro-2-lithio-1-butene (5) (see general procedure I) (1.9 mmol) in 10 mL of dry THF was added 386 mg (2.1 mmol) of dry $MgBr_2$. After the mixture had been stirred at -78 °C for 15 min, CuBr·Me_2S (110 mg, 0.54 mmol), $BF_3 \cdot Et_2O$ (232 μL, 1.9 mmol), and 2-methyl-2-cyclopenten-1-one (34) (153 mg, 1.6 mmol) were added successively. The deep yellow solution was stirred at -78 °C for 1.5 h. Saturated aqueous NH_4Cl-NH_4OH (pH 8) (5 mL) and Et_2O (30 mL) were added, the mixture was warmed to room temperature, and vigorous stirring was maintained until the aqueous phase became deep blue. The organic phase was separated, washed with saturated aqueous NH_4Cl-NH_4OH (pH 8), dried ($MgSO_4$), and concentrated. Distillation (60-63 °C/0.2 Torr) of the remaining oil gave 238 mg (80 %) of the chloro ketone 40 (3:2 mixture of epimers). Following general procedure VII, this material was converted into 145 mg (75 %) of the bicyclic ketone 46 (distillation temperature 58-63 °C/0.2 Torr) as a clear, colorless oil.

cis-1-Methyl-6-methylenebicyclo[3.3.0]octan-2-ol (59). To a cold (-78 °C), stirred solution-suspension of $LiAlH_4$ (0.19 g, 5.0 mmol) in 15 mL of dry Et_2O was added a solution of the ketone 46 (1.5 g, 10.0 mmol) in 4 mL of dry Et_2O. The mixture was stirred at -78 °C for 1.5 h. Saturated aqueous NH_4Cl (3 mL) and Et_2O (20 mL) were added, the mixture was warmed to room temperature, and the white slurry was filtered through a column of Florisil (20 g, elution with Et_2O). The eluate was dried ($MgSO_4$) and concentrated. Distillation (54-57 °C/0.4 Torr) of the remaining oil provided 1.45 g (95 %) of the alcohol 59, GLC analysis of which showed that it consisted of an 87:13 mixture of epimers. This material exhibited IR (neat) 3320, 3035, 1625, 1090, 890 cm^{-1}; ^1H NMR (400 MHz) δ 1.03 (s, 3H), 1.31 (m, 1H), 1.40-1.50 (m, 1H), 1.50-1.64 (m, 2H), 1.76-1.92 (m, 3H), 2.33-2.43 (m, 3H), 3.78-3.86 (m, 1H), 4.73, 4.83 (br s, br s, 1H each). Exact Mass calcd. for $C_{10}H_{16}O$: 152.1201; found: 152.1198.

Preparation of the tricyclic alcohol 60. To a stirred solution of the alcohol 59 (1.35 g, 8.8 mmol) in 2 mL of dry toluene at 55 °C was added successively 9.9 mL (12.3 mmol) of a 15 % solution of Et_2Zn in toluene and 1.02 mL (12.3 mmol) of CH_2I_2. Dry air was slowly passed through this mixture for 1.5 h. The mixture was cooled to room temperature and 5 mL of 5 % hydrochloric acid was added. The phases were separated and the aqueous layer was extracted twice with Et_2O (10 mL). The combined organic extracts were washed twice with 5 % hydrochloric acid (3 mL) and twice with brine (2 mL) and then were dried ($MgSO_4$) and concentrated. Column chromatography (65 g silica gel, 3:2 petroleum ether-Et_2O) of the residual material and distillation (55-60 °C/0.4 Torr) of the oil thus obtained afforded 1.12 g (76 %) of the alcohol 60.

GLC analysis of this material showed that it was an 88:12 mixture of two components. This oil exhibited IR (neat) 3350, 1445, 1090 cm^{-1}; ^1H NMR (400 MHz) δ 0.28-0.48 (m, 4H), 1.19 (s, 3H), 1.30-1.46 (m, 3H), 1.46-1.62 (m, 4H), 1.67-1.76 (m, 1H), 1.78-1.86 (m, 1H), 1.90-1.98 (m, 1H), 3.80 (br t, 1H, J = 6 Hz). Exact Mass calcd. for $C_{11}H_{18}O$: 166.1358; found: 166.1344.

cis-1,6,6-Trimethylbicyclo[3.3.0]octan-2-ol (61). To a solution of the tricyclic alcohol 60 (1.07 g, 6.4 mmol) in 10 mL of HOAc was added 0.14 g (0.64 mmol) of PtO_2 and the resultant suspension was shaken mechanically under an atmosphere of hydrogen (2.5 atm.) at room temperature for 8 h. The mixture was filtered, saturated aqueous $NaHCO_3$ was added to the filtrate until it was basic, and the resultant mixture was extracted twice with Et_2O (20 mL). The ether extracts were washed twice with brine (3 mL), dried ($MgSO_4$), and concentrated. Distillation (52-55 °C/0.4 Torr) of the remaining material gave 1.028 g (95 %) of the alcohol 61, GLC analysis of which showed that it was an 87:13 mixture of epimers. This oil exhibited IR (neat) 3360 cm^{-1}; ^1H NMR (80 MHz) δ 0.92, 1.00, 1.12 (s, s, s, 3H each), 1.16-2.06 (m, 9H), 3.70 (br t, 1H, J = 8 Hz). Exact Mass calcd. for $C_{11}H_{20}O$: 168.1514; found: 168.1514.

cis-1,6,6-Trimethylbicyclo[3.3.0]octan-2-one (62). To a stirred slurry of pyridinium chlorochromate (1.80 g, 0.84 mmol) and NaOAc (137 mg, 1.68 mmol) in 15 mL of dry CH_2Cl_2 was added a solution of the alcohol 61 (0.95 g, 5.6 mmol) in 2 mL of dry CH_2Cl_2. The reaction mixture was stirred at room temperature for 2 h. Et_2O (20 mL) was added and the mixture was filtered through a column of Florisil (15 g, elution with Et_2O). Concentration of the eluate and distillation (52-56 °C/0.4 Torr) of the remaining oil gave 0.807 g (86 %) of the bicyclic ketone 62, which exhibited IR (neat) 1720, 1450 cm^{-1}; ^1H NMR (400 MHz) δ 0.90, 1.05, 1.19 (s, s, s, 3H each), 1.34-1.50 (m, 2H), 1.55-1.71 (m, 2H), 1.89-2.00 (m, 3H), 2.14-2.24 (m, 1H), 2.31-2.41 (m, 1H); Exact Mass calcd. for $C_{11}H_{18}O$: 166.1358; found: 166.1358.

cis-1,6,6-Trimethylbicyclo[3.3.0]oct-3-en-2-one (64). To a cold (-78 °C), stirred solution of the ketone 62 (0.7 g, 4.2 mmol) and dry Et_3N (3.5 mL, 25 mmol) in 20 mL of dry CH_2Cl_2 was added dropwise 4.3 mL (21 mmol) of freshly prepared Me_3SiI. The orange slurry was stirred at -78 °C for 15 min. Saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was warmed to room temperature. The phases were separated and the aqueous layer was washed 3 times with Et_2O (10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give the enol silyl ether 63 (Exact Mass calcd. for $C_{14}H_{26}OSi$: 238.1753; found: 238.1756). This material was dissolved in 15 mL of dry MeCN, $Pd(OAc)_2$ (1.12 g, 5.0 mmol) was added, the mixture was stirred at room temperature for 3 h, and then was filtered through a short column of silica gel (15 g, elution with Et_2O). Removal of the solvent from the eluate gave a viscous brown oil that was chromatographed on silica gel (100 g, 1:1 petroleum ether-Et_2O). Distillation (57-61 °C/0.4 Torr) of the oil thus obtained produced 0.511 g (74 %) of the bicyclic enone 64, an oil that exhibited IR (neat) 1675, 1580, 900 cm^{-1}; ^1H NMR (400 MHz) δ 1.03, 1.12, 1.22 (s, s, s, 3H each), 1.25 (partially obscured ddd, 1H, J = 14, 7, 7 Hz), 1.35 (ddd, 1H, J = 14, 7, 3 Hz), 1.65 (ddd, 1H, J = 14, 7, 7 Hz), 1.89 (ddd, 1H, J = 14, 7, 3 Hz), 2.49 (br s, 1H), 6.13 (dd, 1H, J = 6, 2.5 Hz), 7.13 (dd, 1H, J = 6, 3.5 Hz). Exact Mass calcd. for $C_{11}H_{16}O$: 164.1201; found: 164.1206.

Preparation of the bicyclic chloro ketone 65. To a cold (-78 °C), stirred solution of 4-chloro-2-lithio-1-butene (5) (see general procedure I) (1.9 mmol) in 10 mL of dry THF was added 386 mg (2.1 mmol) of dry $MgBr_2$, and the mixture was stirred at -78 °C for 15 min. $CuBr \cdot Me_2S$ (110 mg, 0.54 mmol) and the enone 64 (262 mg, 1.6 mmol) were added successively and the deep yellow solution was stirred at -78 °C for 1.5 h. Saturated aqueous NH_4Cl-NH_4OH (pH 8) (5 mL) and Et_2O (30 mL) were added, the mixture was warmed to room temperature, and vigorous stirring was continued until the aqueous phase became deep blue. The organic layer was separated, washed with saturated aqueous NH_4Cl-NH_4OH (pH 8), dried ($MgSO_4$), and concentrated. Distillation (65-70 °C/0.4 Torr) of the remaining material gave 320 mg (79 %) of the chloro ketone 65, an oil that exhibited IR (neat) 1715, 1640 cm^{-1}; ^1H NMR (80 MHz) δ 0.97, 1.10, 1.25 (s, s, s, 3H each), 1.38-1.77 (m, 5H), 1.85-2.08 (m, 2H), 2.37-2.55 (partially obscured m, 1H), 2.53 (partially obscured br t, 2H, J = 7 Hz), 3.66 (t, 2H, J = 7 Hz), 4.93, 4.97 (s, s, 1H each). Exact Mass calcd. for $C_{15}H_{23}{}^{35}ClO$: 254.1438; found: 254.1432.

Preparation of the tricyclic ketone 56. Following general procedure VII (vide supra), the chloro ketone 65 (300 mg, 1.18 mmol) was allowed to react with 116 mg (2.9 mmol) of KH in 8 mL of dry THF. Distillation (62-67 °C/0.4 Torr) of the crude product afforded 221 mg (86 %) of the tricyclic ketone 56, a clear oil that exhibited IR (neat) 1720, 890 cm^{-1}; ^1H NMR (400 MHz) δ 0.96, 1.14, 1.15 (s, s, s, 3H each), 1.33-1.43 (m, 1H), 1.46-1.68 (m, 2H), 1.81-1.95 (m, 3H), 1.98-2.07 (m, 1H), 2.15-2.26, 2.30-2.40 (m, m, 1H each), 2.74 (ddd, 1H, J = 10, 8, 4 Hz), 2.92 (br d, 1H, J = 10 Hz), 4.91, 4.99 (m, m, 1H each). Exact Mass calcd. for $C_{15}H_{22}O$: 218.1670; found: 218.1667.

(±)-$\Delta^{9(12)}$-Capnellene (55). To a cold (-78 °C), stirred solution-suspension of $LiAlH_4$ (16 mg, 0.42 mmol) in 8 mL of dry Et_2O was added a solution of the tricyclic ketone 56 (190 mg, 0.87 mmol) in 2 mL of dry Et_2O, and the mixture was stirred at -78 °C for 1.5 h. Saturated aqueous NH_4Cl (1 mL) and Et_2O (15 mL) were added, the mixture was allowed to warm to room temperature, and the slurry was filtered through a column of Florisil (10 g, elution with Et_2O). The eluate was dried ($MgSO_4$) and concentrated. Distillation (62-67 °C/0.4 Torr) of the remaining oil gave 168 mg (88 %) of the alcohol 66, GLC analysis of which showed that it was a 1:1 mixture of epimers [IR (neat) 3350 cm^{-1}; Exact Mass calcd. for $C_{15}H_{24}O$: 220.1827; found: 220.1824].

To a stirred suspension of NaH (12 mg, 0.54 mmol) in 3 mL of dry THF was added a solution of the alcohol **66** (40 mg, 0.18 mmol) in 1 mL of dry THF and the mixture was stirred at room temperature for 2 h. CS_2 (271 μL, 4.5 mmol) and MeI (89 μL, 1.4 mmol) were added consecutively and the mixture was stirred for 18 h. Saturated aqueous NH_4Cl (5 mL) and Et_2O (30 mL) were added and the mixture was stirred for 10 min. The phases were separated and the aqueous layer was washed twice with Et_2O (10 mL). The combined extracts were washed with brine (3 mL), dried ($MgSO_4$), and concentrated to provide the crude xanthate **67** as a yellow oil. To a solution of this material in 2 mL of dry PhMe was added 78 mg (2.7 mmol) of n-Bu_3SnH and 4 mg of 2,2'-azobisisobutyronitrile and the mixture was refluxed for 4 h. Removal of most of the toluene, followed by column chromatography of the remaining material on silica gel (15 g, petroleum ether) and distillation (58-60 °C/0.4 Torr) of the oil thus obtained, provided 24 mg (64 %) of (±)-$\Delta^{9(12)}$-capnellene (**55**) as a clear colorless oil that exhibited IR (neat) 3045, 1640, 1450, 1369, 1361, 870 cm^{-1}; ^1H NMR (400 MHz) δ 0.98, 1.07, 1.15 (s, s, s, 3H each), 1.42-1.78 (series of m, 9H), 2.30-2.68 (m, 4H), 4.78, 4.89 (br s, br s, 1H each); ^{13}C NMR (100 MHz) δ 26.08, 29.22, 30.84, 31.69, 31.79, 40.65, 41.77, 42.37, 46.07, 48.13, 52.36, 53.59, 69.27, 104.90, 150.75. Exact Mass calcd. for $C_{15}H_{24}$: 204.1878; found: 204.1882. This synthetic material exhibited spectra identical with those of natural (-)-55[26] and synthetic (±)-55.[26] The chromatographic (TLC, GLC) behavior of our (±)-55 was identical with that of the same material prepared by Professor R. D. Little.[26]

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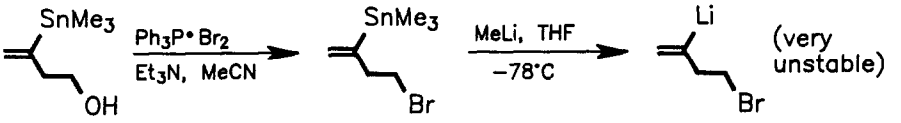

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