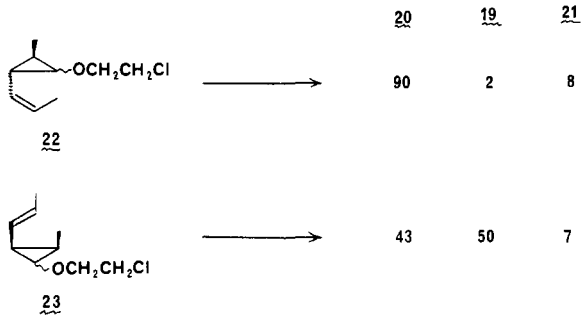
Scheme I



mechanism of this rearrangement and demonstrate the utility of this [4 + 1] annulation in the synthesis of natural products.

Acknowledgment. We thank the National Institutes of Health for generous financial support.

An Efficient, Stereoselective Total Synthesis of (±)-Aphidicolin[1]

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Contribution No. 6362 from the Chemical Laboratories California Institute of Technology Pasadena, California 91125

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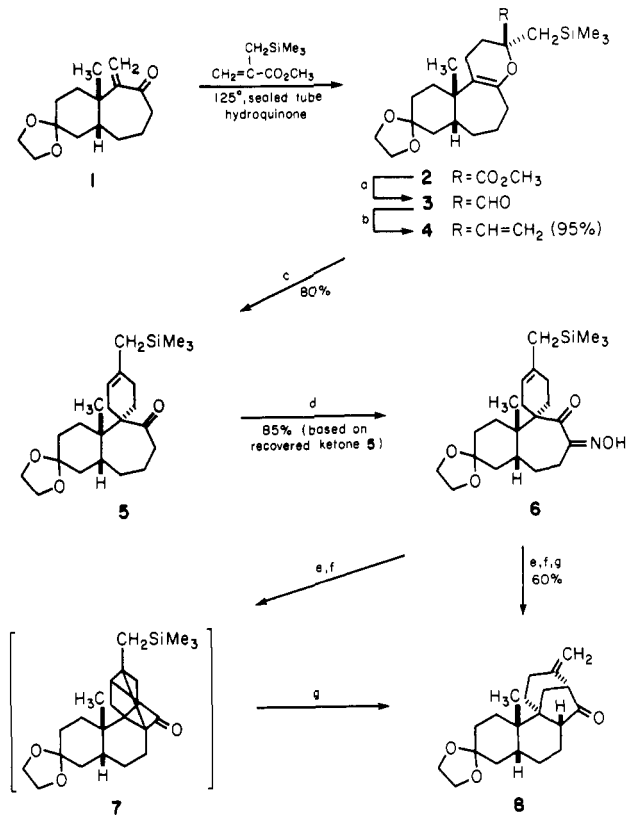
In a previous report[2] the basic principles of an approach toward the total synthesis of tetracyclic diterpenes of the aphidicolin (**15**)[3] -stemodinone[4] group was outlined, and this scheme was used to prepare the basic carbon skeleton of the aphidicolane[3] ring system. The key elements of this process were the spiroannelation of the α-methylene ketone **1**[5] and then, after B-ring contraction, a π-route solvolysis to establish the bicyclo[3.2.1]octane C/D ring structure.[2] As efficient as this general scheme was, the tetracyclic product of the solvolysis reaction was predominantly the endocyclic olefin or the tertiary alcohol, neither of which held great promise for completion of the natural product synthesis. This approach has now been modified by the propitious substitution of methyl α-(trimethylsilyl)methylacrylate[6] for methyl methacrylate in the initial hetero-Diels-Alder reaction and, with the aid of several new transformations, has resulted in a highly stereoselective total synthesis of (±)-aphidicolin (**15**).[7]

As was observed earlier[2] with methyl methacrylate, the yield and stereochemical outcome of the hetero-Diels-Alder condensation between the α-methylene ketone **1**[5] and now methyl α-(trimethylsilyl)methylacrylate was temperature dependent. When the reaction was carried out at 180 °C, the ratio of the two possible isomers favored the undesired α-carbomethoxy adduct [3:7 (NMR)], and the yield of adduct was only 36%. Lowering the reaction temperature to 125 °C gave the desired β-carbomethoxy adduct **2** as the major isomer [7:3 (NMR)] of an 89% yield of product (Scheme I). Conversion of this β-carbomethoxy adduct **2** through the aldehyde **3** to the β-vinyldihydropyran **4** followed previous[2] experience. Heat-promoted Claisen rearrangement of the vinyldihydropyran **4** established the spiroketone **5** and thus generated the allylsilane system that was proposed to result in the formation of the desired exocyclic olefin[8] after π-route solvolysis of the B-ring contracted skeleton. Such was not to be the case for on conversion of the spiroketone **5** to the α-oximino ketone **6** and thence to the corresponding α-diazo ketone, photolysis led virtually exclusively to the unstable cyclobutanone derivative **7**.[9] Even when the photolysis was conducted in methanol with a large

Scheme I. Construction of the Tetracyclic Carbon Skeleton 8[a]



[a] (a) DIBAL, Et_2O, -78 °C. (b) $(C_6H_5)_3P=CH_2$, THF. (c) 150 °C, sealed tube, 7 h. (d) *n*-BuLi, *i*-AmONO, THF. (e) NH_2Cl, THF. (f) *hν*, Et_2O, -75 °C. (g) Silica gel, ether-petroleum ether.

†Postdoctoral Fellow of the National Institute of General Medical Sciences, DHEW, 1979-1980.

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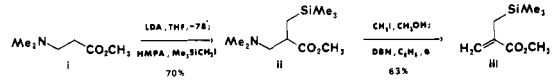

See also: Hsomi A.; Hashimoto, H.; Sakurai, H. *Tetrahedron Lett.* **1980**, 951-954.

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(9) The structure shown here for this unstable cyclobutanone **7** differs from that previously suggested[2] for the stable cyclobutanone formed in the de(trimethylsilyl) series. We are very grateful to a referee for calling to our attention this alternate structural possibility and, as a result, have extensively reexamined and refined the spectral data for both the silylated system and the previous, stable de(trimethylsilyl) compound. From this analysis—particularly, with the aid of 500-MHz NMR data on the latter compound (see supplementary material)—it has become apparent that both cyclobutanones have the structures **7** as suggested by the referee. The most diagnostic feature is the chemical shift (2.5 ppm) and splitting pattern (doublet of doublet; J = 2 and 2 Hz) of the C-12 methyne hydrogen adjacent to the ketone carbonyl that is required by structure **7** but would be absent in the alternate, previously suggested[2] arrangement. Space limitations do not allow a full elaboration of these structural analyses or the chemical and stereochemical nuances associated with the acid-catalyzed rearrangement of this system; these points together with the results from a current attempt to define the structure of the de(trimethylsilyl)cyclobutanone system by X-ray analysis will be presented in a forthcoming full paper on this and allied work.

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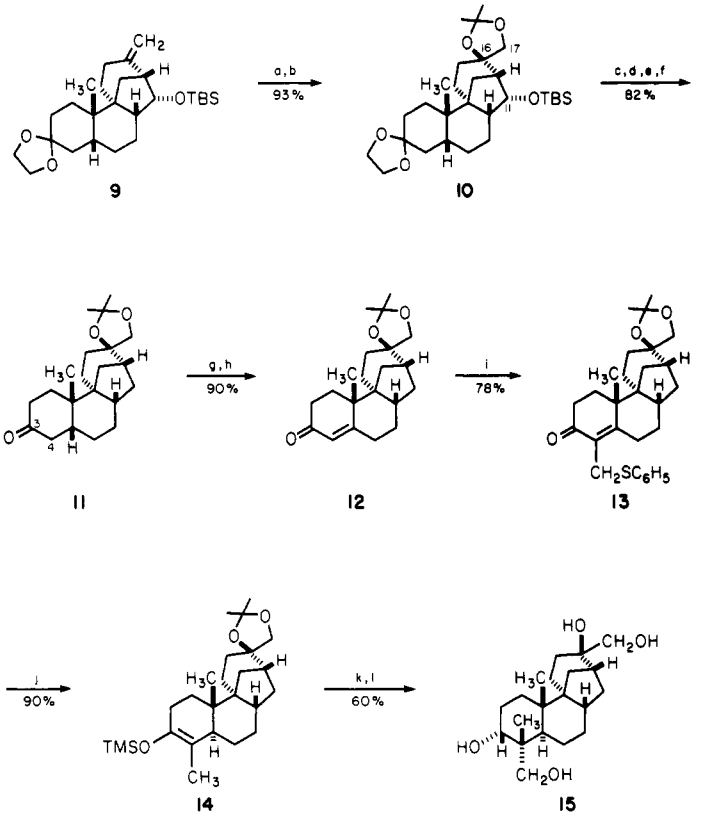
Scheme II. Completion of the Synthesis of (±)-Aphidicolin (15)[a]



[a] (a) OsO_4, pyr; $NaHSO_3$ (aq). (b) *p*-TsOH, $(CH_3)_2C(OCH_3)_2$. (c) *n*-Bu_4NF, THF. (d) *n*-BuLi, TMEDA-DME, Me_2NPOCl_2; Me_2NH. (e) Li, CH_3NH_2, THF, *t*-BuOH. (f) pyr, *p*-TsOH, acetone. (g) KH, THF; TMSCl, Et_3N. (h) $Pd(OAc)_2$, CH_3CN. (i) $(CH_2O)_x$, C_6H_5SH, Et_3N, EtOH. (j) Li, NH_3, *t*-BuOH-THF; Et_3N, TMSCl-THF. (k) CH_3Li, THF; HCHO (g); AcOH. (l) L-Selectride™, THF, NaOH (aq), 30% H_2O_2; 10% HCl-MeOH.

excess of sodium methoxide present to trap the presumed intermediate ketene (conditions that previously[2] obviated cyclobutanone formation), only 5–10% of the expected (carbomethoxy)cyclohexane derivative was formed and the cyclobutanone **7** still predominated. Attempted separation of this mixture by silica gel chromatography proved sufficient to effect rearrangement of the (trimethylsilyl)cyclobutanone component **7** with the fortuitious result that the desired tetracyclic exocyclic olefinic ketone **8**[10] was formed in good yield. Indeed it was not possible to isolate the cyclobutanone **7** in pure form, as even mild acid caused its rearrangement; as a result of the olefinic ketone **8** could best be prepared directly from the α-oximino ketone **6** by oxidation, photolysis at −75 °C in ether, and then chromatography on silica gel *without* isolation of any intermediate products.[10]

With the aphidicolane tetracyclic skeleton so conveniently assembled, attention was turned to the modification of the peripheral substitution pattern (Scheme II). For the stereospecific introduction of the C16,C17 diol, a transformation that has not been previously accomplished,[7b] the C13 oxygen substituent served a crucial function. Reduction (DIBAL, THF, −78 °C) of the ketone **8** led quantitatively to the C13 α-oriented alcohol which was converted into the *tert*-butyldimethylsilyl ether **9** (TBSCL, DMF, imidazole) in 95% yield. This bulky grouping served to block the α face of the 16,17 double bond, and osmylation led *stereospecifically* to the desired C16β,C17 diol, which was readily masked as its acetonide **10**.[11] The C13 alcohol function, having outlived its usefulness, was then removed through reduction[12] of the corresponding phosphorodiamidate, which was conveniently formed by the procedure of Liu.[13] Ketal exchange of the resulting ketal acetonide then formed the ketone acetonide **11** and set the stage for the incorporation of the A-ring substitution pattern.

At this juncture the A/B-cis ring fusion became important, for enolization and then trimethylsilyl chloride enolate trapping led virtually exclusively (20:1 after separation of two possible enone isomers) to the C3,C4-silyl enol ether. The enone **12** was then efficiently prepared from this silyl enol ether by the procedure of Saegusa and Ito.[14]

This enone **12** served well for both the establishment of the required A/B-trans ring fusion and the introduction of the two C4 substituents. Thus, application of the Petrow reaction[15] led to the phenyl thiomethyl enone **13**, which on lithium/ammonia reduction and then trimethylsilyl chloride enolate trapping produced the silyl enol ether **14** in good overall yield. Finally, formylation,[16] reduction,[17] and deblocking led to (±)-aphidicolin (**15**), which was identical (500-MHz NMR, IR, TLC) to a pure sample of the natural product.[18] Further refinement of this scheme and the preparation of other members of this group of diterpenes as well as analogues of aphidicolin (**15**) itself are currently under investigation.[19]

Supplementary Material Available: Infrared and proton mag-

(10) For single-crystal X-ray structural analysis, see: Mandel, N.; Mandel, C. *Acta Crystallogr.*, in press.

(11) When the C13 oxygen function of the keto olefin **8** was first removed by reduction and then the C16,C17 diol formed by osmylation, a mixture of C16 isomers was formed in which the undesired 16α-oriented hydroxyl function predominated in poor yield.

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(19) All new compounds isolated during this work have been characterized by satisfactory combustion and spectral (NMR, IR) analysis, and these data are recorded in the supplementary material.

netic resonance spectra, physical constants, thin-layer chromatographic mobility, and elemental combustion analyses of compounds **2**–**6** and **8**–**15** and isolated intermediates (6 pages). Ordering information is given on any current masthead page.

Hydridometallacycloalkane Complexes of Iridium. Unassisted Intramolecular Distal C–H Bond Activation

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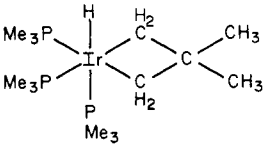
In recent years interest in transition-metal alkyl complexes has resulted in the preparation of complexes in which the well-known decomposition pathway, β-hydrogen abstraction, is obviated by substitution at the β-carbon atom.[1,2] Schrock and co-workers have demonstrated an alternative pathway, α-hydrogen transfer, in the preparation of alkylidene complexes of the early transition metals.[3] Quite recently γ- and δ-hydrogen abstractions have also been shown to be viable transformations for group 8 polyalkyl and organo f-element complexes.[4-11] Although cyclometallation involving coordinated ligands, such as $P(alkyl)_3$[12] and $P(C_6H_5)_3$ (orthometallation),[13] has long been recognized, its application to hydrocarbyl systems has been limited to a few examples. We believe that this reaction may represent a broadly applicable route to novel metallacyclic complexes and in this communication we report the facile preparation of an extensive series of hydridometallacycloalkane complexes of Ir(III) by γ- and δ-hydrogen-atom abstraction reactions of alkyl Ir(I) complexes.

A typical γ-H-atom abstraction reaction is represented by the heavy arrow in Scheme I. For group 8 complexes mechanism A, which involves initial oxidative addition to a distal C–H bond and subsequent reductive elimination of the R and H ligands, has been suggested.[7] In this reaction sequence the presence of a second alkyl or hydrido ligand may assist in driving the reaction. In the alternative mechanism B, which is related to that recently proposed for α-H abstraction,[3,14] the ligand R plays an even more fundamental role. Here an incipient radical actively abstracts a H atom in a four-centered transition state, and the metal center undergoes no formal change in oxidation state during the reaction. The reactions described below demonstrate that the oxidative addition portion of mechanism A occurs readily in Ir(I) alkyl complexes even in the absence of an "assisting" leaving group (e.g., alkyl or hydride ligand).

Reaction of $[Ir(PMe_3)_4]Cl$ (**1**)[15,16] with $LiCH_2CMe_3$ in hexane or toluene at room temperature smoothly produces *fac*-tris(trimethylphosphine)hydrido(2,2-dimethyl-1,3-propanediyl)iridium (**2**) in high yield. The complex has been characterized by IR



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and ^1H, ^{13}C, and ^{31}P NMR spectroscopies, the results of which are consistent with the structure shown.[17] Similar reactions with chloroiridium(I) complexes containing arsine ligands produce analogous products, e.g., *fac*-$IrH(CH_2CMe_2CH_2)(AsR_3)_3$, R = Me, Et,[18] and these have served to verify the spectroscopic assignments for complex **2**. Additional substantiation of the proposed formulation has been provided by an X-ray molecular structure determination of the trimethylarsine complex, details of which will be published separately. Complex **2** is remarkably stable; it is unaffected by air and moisture for short periods of time and is inert to CO and C_2H_4 at room temperature. Furthermore, a solution of complex **2** in benzene-d_6 was unchanged after 24 h at 90 °C.

We have not detected the presumed precursor to complex **2**, $Ir(CH_2CMe_3)(PMe_3)_3$, except as a transient orange solution.[19] The reaction of complex **1** with $LiCH_2SiMe_3$ does, however, yield the relatively stable initial product, $Ir(CH_2SiMe_3)(PMe_3)_3$ (**3**).[20] Only after standing for prolonged periods or upon heating does complex **3** transform into the Si congener of complex **2**, *fac*-$IrH(CH_2SiMe_2CH_2)(PMe_3)_3$ (**4**).[21] This reactivity difference may arise from the decreased steric demand of the (trimethylsilyl)methyl ligand as compared with that of the neopentyl group.[22,23] Experiments are in progress which utilize this slower

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(15) Abbreviations: Me, CH_3; Et, C_2H_5; Ph, C_6H_5; Cp, η^5-C_5H_5; THF, tetrahydrofuran.
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(17) Complex **2**: IR (Nujol mull) ν_{Ir-H} 2018 (s) cm^{-1}; ^1H NMR (C_6D_6, 220 MHz) δ −9.81 (dt, $^2J_{HP_{trans}}$ = 167 Hz, $^2J_{HP_{cis}}$ = 21 Hz, IrH), 1.37 (18, d, $^2J_{HP}$ = 7 Hz, PCH_3 (basal)), 1.40 (dd, $^2J_{HP}$ = 7 Hz, $^4J_{Hhydride}$ = 1 Hz, PCH_3 (axial)), 1.46 (3, s, CCH_3), 1.77 (3, s, CCH_3); $^1H\{^{31}P\}$ NMR (C_6D_6, 100 MHz) (m), (s), (d), (s), (s), δ 0.55 (2, d, $^2J_{AB}$ = 8 Hz, $IrCH_2$), 1.02 (2, dd, $^2J_{AB}$, $^3J_{Hhydride}$ = 2 Hz, $IrCH_2$); $^{13}C\{^1H\}$ NMR (C_6D_6, 22.63 MHz) δ −17.87 (d, $^2J_{CP_{trans}}$ = 65 Hz, $IrCH_2$), 18.23 (d, $^1J_{CP}$ = 19 Hz, PCH_3 (axial)), 22.84 (d, $^1J_{CP}$ = 28 Hz, PCH_3 (basal)), 31.72 (s, CCH_3), 38.60 (s, CCH_3), 45.75 (s, CH_2CCH_3); $^{13}C\{^1H$ single-frequency off-resonance decoupled$\}$ NMR (dt plus long range J_{CH}), (dq), (dq), (q), (q), (s); $^{31}P\{^1H\}$ NMR C_6D_6, 29.94 MHz) AB_2 pattern, centered at −60.3 ppm relative to 85% H_3PO_4 (external). Anal. Calcd for $C_{14}H_{38}IrP_3$: C, 34.21; H, 7.79. Found: C, 34.30; H, 7.81.
(18) *fac*-$IrH(CH_2CMe_2CH_2)(AsR_3)_3$: R = Me; IR ν_{Ir-H} 2044 cm^{-1}; ^1H NMR δ −12.4 (1, s, IrH), 1.25 (18, s, $AsCH_3$(basal)), 1.30 (9, s, $AsCH_3$ (axial)), 1.38 (3, s, CCH_3), 1.70 (3, s, CCH_3), 0.92 (2, d, $^2J_{AB}$ = 8 Hz, $IrCH_2$), 1.45 (2, dd, $^2J_{AB}$, $J_{Hhydride}$ = 2 Hz); $^{13}C\{^1H\}$ NMR δ −20.96 ($IrCH_2$), 12.25 ($AsCH_3$ (axial)), 16.96 ($AsCH_3$ (basal)), 31.62 (CCH_3), 36.75 (CCH_3), 47.28 (CH_2CCH_3); $^{13}C\{^1H$ SFORD$\}$ NMR (t), (q), (q), (q), (q), (s). R = Et; IR ν_{Ir-H} 2010 cm^{-1}; ^1H NMR δ −13.3 (1, s, IrH), overlapping aliphatic region. Anal. Calcd for $C_{23}H_{56}As_3Ir$: C, 36.85; H, 7.53. Found: C, 37.01; H, 7.56.
(19) Note that under these conditions the analogous rhodium(I) neopentyl complex is isolated, unpublished results.
(20) Complex **3**: ^1H NMR δ 0.38 (9, s, $SiCH_3$), 0.65 (2, dt, $^3J_{HP_{trans}}$ = 8 Hz, $^3J_{HP_{cis}}$ = 13 Hz, $IrCH_2Si$), 1.24 (9, d, $^2J_{HP}$ = 8 Hz, PCH_3 (unique)), 1.31 (18, t (virtual), $^2J_{HP}$ + $^4J_{HP}$ = 6 Hz, PCH_3 (mutually trans)).
(21) Complex **4**: IR ν_{Ir-H} 2005 (m) cm^{-1}; ^1H NMR δ −10.93 (1, dt, $^2J_{HP_{trans}}$ = 168 Hz, $^2J_{HP_{cis}}$ = 22 Hz, IrH), −1.01 (2, br m, $IrCH_2Si$), −0.40 (2, br m, $IrCH_2Si$ (wings of AB quartet with superimposed J_{HP} and J_{HH})), 0.36 (3, s, $SiCH_3$), 0.63 (3, s, $SiCH_3$), 1.13 (9, d, $^2J_{HP}$ = 7 Hz, PCH_3 (axial)), 1.20 (18, d, $^2J_{HP}$ = 7 Hz, PCH_3 (basal)); $^{31}P\{^1H\}$ NMR AB_2 pattern centered at δ −58.35 and −60.72. Anal. Calcd for $C_{13}H_{38}IrP_3Si$: C, 30.76; H, 7.55. Found: C, 30.80; H, 7.71.
(22) Compare: the complex $(\eta^5$-$C_5Me_5)_2Zr(CH_2SiMe_3)_2$ is readily prepared whereas we have been unable to prepare the analogous bis(neopentyl) complex. Tulip, T. H., unpublished results.

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