the task. The successful application of the cyclopentanone annulation using the cyclopropylide reagent illustrates the utility of this method for creation of complex molecular architecture.

Acknowledgment. We thank Dr. Barrie Hesp for a generous sample of aphidicolin and related compounds and Dr. J. Calabrese for a critical X-ray structure determination. We also thank the National Science Foundation and the General Medical Sciences Institute of the National Institutes of Health for their generous support of our programs.

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(6) This compound has been fully characterized by spectral means and elemental composition determined by either high resolution mass spectroscopy and/or elementary analysis.
(7) **6:** IR 3500, 1695 cm^{-1}; 100-MHz NMR δ 0.96 (3 H, s), 1.14 (3 H, s), 3.26 and 3.58 (2 H, AB, J = 12 Hz); ^{13}C NMR δ 16.3, 16.9, 21.3, 22.7, 29.8, 30.3, 35.2, 42.5, 43.1, 52.3, 64.9, 65.2, 66.7, 112.7, 180. **9** (R = H): IR 3400 cm^{-1}; 100-MHz NMR δ 0.76 (3 H, s), 1.12 (3 H, s), 3.2–4.0 (6 H, m). **10:** IR 3400, 1710 cm^{-1}; 100-MHz NMR δ 0.85 (3 H, s), 1.14 (3 H, s), 2.96 (2 H, s), 3.61 (2 H, s), 3.85 (1 H, d, J = 3 Hz). **4:** 100-MHz NMR δ 0.82 (3 H, s), 1.16 (3 H, s), 1.32 (3 H, s), 1.36 (3 H, s), 3.18 and 3.54 (2 H, AB, J = 12 Hz), 3.58 (1 H, d, J = 3 Hz). **12** (R = H): 100-MHz NMR δ 0.76 (3 H, s), 1.22 (3 H, s), 1.28 (3 H, s), 1.34 (3 H, s), 3.16 and 3.54 (2 H, AB, J = 12 Hz), 3.60 (1 H, bs), 5.50 (1 H, t, J = 3.5 Hz). **13b:** 100-MHz NMR δ 0.13 (9 H, s), 0.60 (3 H, s), 1.00 (3 H, s), 1.28 (6 H, s), 3.04 and 3.45 (2 H, AB, J = 12 Hz), 3.50 (1 H, d, J = 3 Hz). **14:** IR 1740 cm^{-1}; 270-MHz NMR δ 0.84 (3 H, s), 1.13 (3 H, s), 1.42 (3 H, s), 1.43 (3 H, s), 2.64 (1 H, t, J = 6 Hz), 3.30 and 3.56 (2 H, AB, J = 12 Hz), 3.69 (1 H, dd, J = 3.5, 2 Hz); ^{13}C NMR (C_4D_6) δ 211.7, 97.8, 73.6, 68.0, 51.4, 48.8, 40.1, 37.9, 37.1, 36.8, 35.7, 35.6, 34.8, 30.8, 30.4, 28.4, 28.2, 24.0, 21.9, 19.7, 18.9, 18.7. **15:** IR 1700, 1635 cm^{-1}; 100-MHz NMR δ 0.76 (3 H, s), 108 (3 H, s), 1.30 (3 H, s), 1.34 (3 H, s), 3.21 and 3.58 (2 H, AB, J = 12 Hz), 3.61 (1 H, dd, J = 3.5, 2 Hz). **16:** IR 1740 cm^{-1}; 100-MHz NMR δ 0.68 (3 H, s), 1.00 (3 H, s), 1.32 (6 H, s), 3.12 and 3.53 (2 H, AB, J = 12 Hz), 3.58 (1 H, dd, J = 3.5, 2 Hz), 4.6–6.2 (3 H, m). **18:** ir 3600, 3450, 1735 cm^{-1}; 270-MHz NMR δ 0.70 (3 H, s), 1.10 (3 H, 2s), 1.41 (6 H, s), 3.22 and 3.97 (2 H, AB, J = 12 Hz), 3.98 (1 H, bd, J = 3.5 Hz), 4.03 (0.7 H, m), 4.22 (0.3 H, m). **19:** IR 3620, 3400 cm^{-1}; 270-MHz NMR δ 0.77 (3 H, s), 1.05 (3 H, s), 1.51 (6 H, s), 2.72 (1 H, ddd, J = 11.8, 8, 3 Hz), 3.43 and 3.83 (2 H, AB, J = 12 Hz), 3.8–4.0 (2 H, m). **2:** IR 1730 cm^{-1}; 270-MHz NMR δ 0.74 (3 H, s), 1.08 (3 H, d, J = 1 Hz), 1.42 (6 H, s), 3.25 and 3.61 (2 H, AB, J = 12 Hz), 3.67 (1 H, t, J = 3 Hz); ^{13}C NMR (C_6D_6) δ 211.9, 98.0, 73.6, 68.7, 49.3, 48.4, 41.5, 39.5, 34.7, 34.4, 33.4, 33.2, 31.5, 30.1, 27.2, 26.2, 24.2, 22.3, 21.6, 19.0, 17.1, 16.1.
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(13) A byproduct (~9%), presumably the hydroxy selenide, is isolated but has not been characterized; cf. ref 12b.
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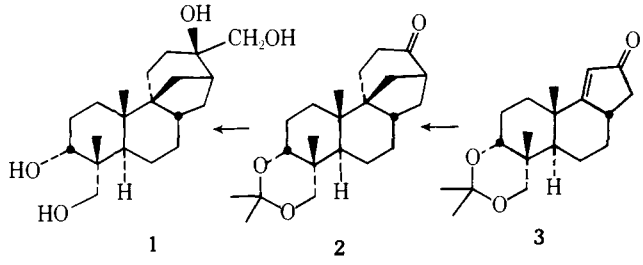
Stereospecific Total Synthesis of Aphidicolin

Sir:

The search for effective anti-viral agents has long been pursued, though with little success to date. It was therefore of interest when, in 1972, the isolation and structure determination of aphidicolin was announced.[1] Aphidicolin (**1**), a diterpenoid tetraol produced by the mold *Cephalosporium aphidicola* Petch, shows strong in vitro activity against herpesvirus, presumably through an inhibition of virus DNA synthesis.[2] We report here the stereospecific total synthesis of this interesting molecule.[3]

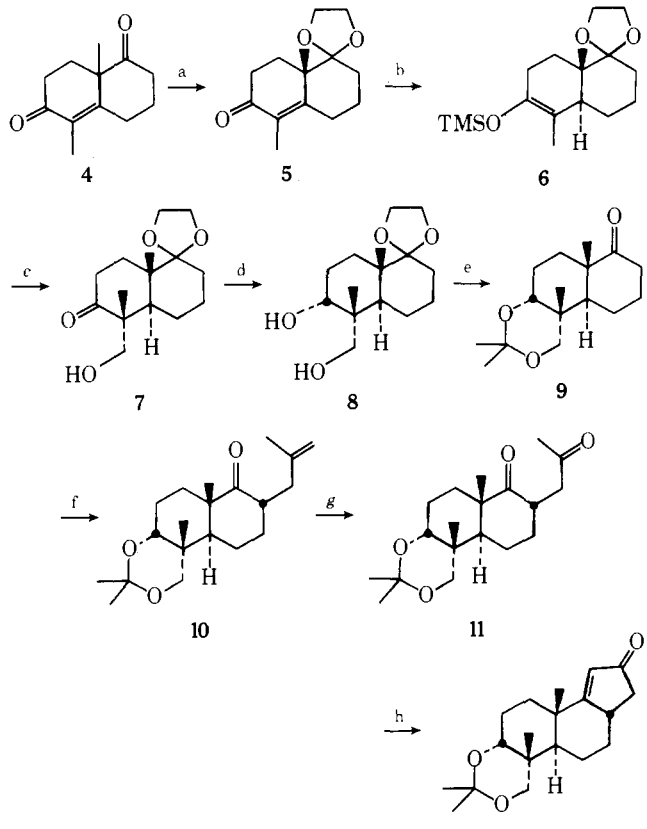
The synthetic problem is simplified to an extent by the fact that ketoacetonide **2** has been obtained from, and reconverted into, aphidicolin.[1] Compound **2** therefore became our actual synthetic goal.



1 2 3

After considering a number of possible synthetic paths to **2**, we settled on cyclopentenone **3** as our key intermediate. Addition of a three-carbon piece across the ends of the enone system of **3** would then construct the bicyclo[3.2.1]octane

Scheme I[a]



4 5 6 7 8 9 10 11 3

[a] (a) $HOCH_2CH_2OH$, *p*-TsA, benzene, 80%. (b) Li, NH_3, THF, and then $(CH_3)_3SiCl$, $(CH_3CH_2)_3N$, 97%. (c) CH_3Li, THF, and then CH_2O. (d) Li(*sec*-Bu)$_3$BH, THF. (e) CH_3COCH_3, *p*-TsA, CH_2Cl_2, 85% from **6**. (f) 1.2 equiv of LDA, THF, and then methallyl iodide, 89%. (g) Trace of OsO_4, $NaIO_4$, H_2O, dioxane, 86%. (h) NaH, trace of *tert*-amyl alcohol, benzene, reflux, 95%.

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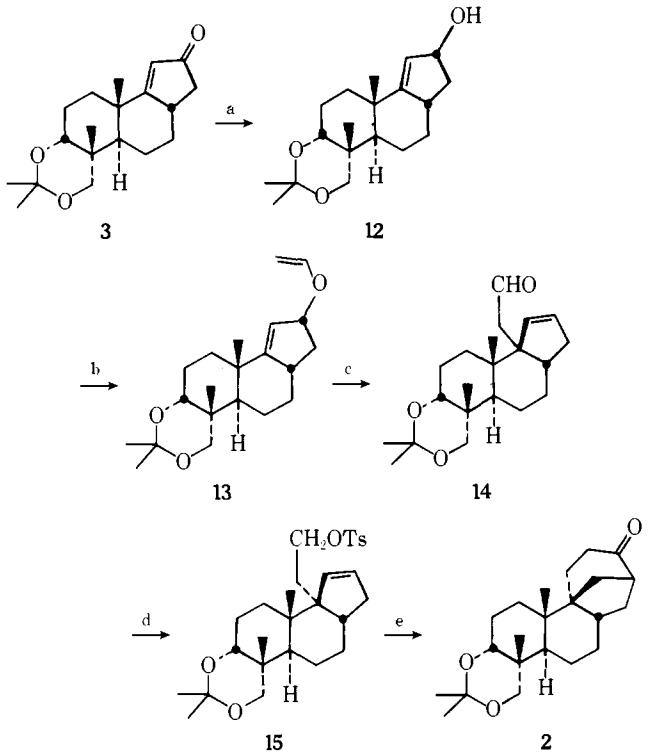
Scheme II[a]



[a] (a) $LiAlH_4$, ether, 95%. (b) $CH_3CH_2OCH{=}CH_2$, $Hg(OAc)_2$, reflux, 90%. (c) 360 °C, quartz tube, 20%. (d) $LiAlH_4$, THF, and then *p*-TsCl, pyridine, 60%. (e) $Na_2Fe(CO)_4$, *N*-methylpiperidone, 50 °C, 30%.

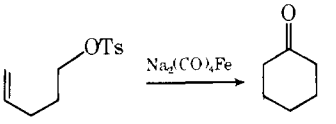
portion of aphidicolin. Enone **3** was synthesized as shown in Scheme I.

Selective ketalization of enedione **4**[4] at the saturated carbonyl[5] gave the product **5,** mp 57–59 °C, which was then reductively hydroxymethylated. This was accomplished by the general procedure of Stork[6] in which **5** was reduced with lithium in liquid ammonia and the resultant enolate was trapped with chlorotrimethylsilane. Regeneration of the enolate by treatment of **6** with methyllithium, followed by addition of gaseous formaldehyde, gave keto alcohol **7.** The stereochemistry of this hydroxymethylation was remarkably clean in that only one stereoisomer was produced. We expected the major product to be the isomer indicated but had no proof at this stage. Ketone **7** was immediately reduced with lithium tri-*sec*-butylborohydride[7] (L-Selectride™) to yield diol **8.** The stereochemistry of reduction was assigned as shown because of the known propensity of L-Selectride to produce axial alcohols.[8] Deketalization and concomitant acetonide formation were accomplished in a single step by subjecting **8** to treatment with acetone in methylene chloride containing a catalytic amount of *p*-toluenesulfonic acid. Keto acetonide **9,** mp 103–104 °C, could be prepared in 83% overall yield from enone **5.** Although not definitive at this point, we viewed the ready acetonide formation as good evidence that the stereochemistry of **9** is as shown. Had the hydroxymethylation proceeded with different stereochemistry, acetonide formation should be quite difficult.[9] Alkylation of the enolate of **9** with methallyl iodide gave **10,** mp 94–96 °C, whose stereochemistry was assigned on the basis of equilibration experiments (equatorial side chain). The olefinic bond of **10** could be readily cleaved to give dione **11,** mp 104–105 °C, which underwent internal aldol cyclization.

The synthesis of cyclopentenone **3,** mp 136 °C, was accomplished in 73% yield from enone **9** thus giving us ready access to our key intermediate.

It was our intention initially to effect some manner of conjugate addition to the enone **3,** but this proved impossible. The β carbon of the cyclopentenone is extraordinarily hindered and, in consequence, even organocuprate reagents give only direct carbonyl addition rather than conjugate addition. Thus stymied in all attempts to effect *inter*molecular addition to C(9) of enone **3,** we turned to attempts at *intra*molecular addition. Models show clearly that the top face of the carbonyl is less hindered to nucleophilic attack than the bottom face, and we were not surprised to find that a single alcohol **12,** mp 140–142 °C, resulted on reduction of **3** with $LiAlH_4$. This alcohol was converted to its vinyl ether **13,** in the usual way, and vapor phase pyrolysis of **13** at 360 °C in a nitrogen swept quartz pyrolysis tube[10] then provided the Claisen rearrangement product **14,** mp 127 °C. This rearrangement is a delicate one which proceeds in only modest yields and which requires carefully controlled conditions. The major byproduct is the cyclopentadiene resulting from simple elimination of the vinyl alcohol. Such modifications of the normal Claisen reaction as the ester enolate,[11] ketene acetal,[12] and ketene silyl acetal[13] variants have thus far not proven successful in improving the yield of rearrangement product though we are continuing our studies.

With the Claisen reaction successfully carried out, the crucial stereochemistry of aphidicolin had been established and it remained only to knit the final ring together. Although one can imagine multistep sequences that will accomplish the transformation of **14** to **2,** we chose to use an extremely direct carbonylation procedure. Both Collman[14] and Merour[15] have reported that, when a five-carbon unsaturated tosylate is treated with disodium tetracarbonylferrate, cyclohexanone is produced.



Application of this reaction to the synthesis of aphidicolin occurred in the exact manner desired. Reduction of **14,** followed by tosylation, gave unsaturated tosylate **15,** mp 123–125 °C. Treatment of this tosylate with disodium tetracarbonylferrate then produced keto acetonide **2,** mp 138–139 °C, which had previously been transformed into aphidicolin.[1] The synthetic **2** was identical with an authentic sample by TLC, gas chromatography, mass spectroscopy, IR, and ^1H NMR. The transformations from cyclopentenone **3** are summarized in Scheme II.

Although the total synthesis of aphidicolin is complete in a formal sense, we are continuing our work with the intention of improving the overall yield and producing the natural material.[16]

Acknowledgment. We thank Dr. Barrie Hesp, Imperial Chemical Industries, Ltd., for his help in supplying a comparison sample of aphidicolin and derived materials. This work was supported by the National Institutes of Health through Grant AI 14127. The NMR and GC/MS instruments used in this work were partially funded by grants from the National Science Foundation.

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Cleavage of Alkanes by Transition Metal Ions in the Gas Phase

Sir:

Oxidative addition of covalent bonds to metals is common in the chemistry of transition metals in lower oxidation states. There is little evidence in the literature, other than a recent report by Davis and Klabunde,[1] that suggests that carbon–carbon bonds of alkanes add oxidatively to transition metals. We report here observation of gas-phase ion–molecule reactions in which transition metal ions cleave alkanes. Reaction 1, for example, is observed between Fe^+ generated by electron

$$Fe^+ + i\text{-}C_4H_{10} \xrightarrow{85\%} FeC_3H_6^+ + CH_4 \qquad (1)$$
$$\xrightarrow{15\%} FeC_4H_8^+ + H_2$$

impact on $Fe(CO)_5$ and i-C_4H_{10}. The extent of conversion to products observed in our ion cyclotron resonance spectrometer can only be accounted for by a rapid ($k \geq 10^{-10}$ cm^3 molecule^{-1} s^{-1}) bimolecular process.[2] Double resonance unambiguously identifies the Fe^+ as the source of the product ions. The branching ratio and stoichiometry of the products is confirmed by the reactions of i-C_4D_{10}.

Several mechanisms might be postulated to account for the observed products. The reaction of 2-deuterio-2-methylpropane, however, eliminates some possibilities (see eq 2). The

$$Fe^+ + \text{(2-deuterio-2-methylpropane)} \rightarrow FeC_3H_5D^+ + CH_4 \qquad (2)$$
$$\rightarrow FeC_4H_{10}^+ + HD$$

indicated isotopic variants of the products are the only ones observed indicating they account for at least 90% of the products in each case.

In addition to reacting with isobutane, Fe^+ undergoes reaction 3 with n-butane. Determination of the branching ratio

$$Fe^+ + n\text{-}C_4H_{10} \rightarrow FeC_3H_6^+ + CH_4 \qquad (3)$$
$$\rightarrow FeC_4H_6^+ + 2H_2$$

is complicated in this instance by the presence of several ions in the mass spectrum of $Fe(CO)_5$ with the same masses as possible product ions. The first channel is four or five times as fast as the second. The possibility of $FeC_2H_4^+$ and $FeC_4H_8^+$ products cannot be completely eliminated. Co^+ and Ni^+, formed by electron impact on $Co(NO)(CO)_3$ and $Ni(CO)_4$, react with n-C_4H_{10} to form products analogous to those of eq 3. Ti^+ formed by electron impact on $TiCl_4$ reacts with n-C_4H_{10} to form only $TiC_4H_8^+$ and $TiC_4H_6^+$ products.

A mechanism for the cleavage reaction consistent with our observations is outlined in reaction 4. This mechanism is

$$Fe^+ + \text{(alkane)} \rightarrow CH_3\text{–}Fe^+\text{(H, alkyl)} \rightarrow \qquad (4)$$
$$\mathbf{1}$$
$$\text{(H, CH}_3\text{, Fe}^+\text{ allyl)} \rightarrow \text{(Fe}^+\text{ allyl)} + CH_4$$
$$\mathbf{2}$$

analogous to that for dehydrohalogenation of alkyl and aromatic halides by Fe^+ [3-5] and accounts for the elimination of methane and the retention of the label in reaction 2. It does not account for the H_2 loss channel. A mechanism such as reaction 5 beginning with attack on the C–H bond is required to account for H_2 loss. It is possible that a methyl group in **3** could migrate

$$Fe^+ + \text{(alkane)} \rightarrow H\text{–}Fe^+\text{(H, alkyl)} \rightarrow \qquad (5)$$
$$\mathbf{3}$$
$$\text{(H, H, Fe}^+\text{ allyl)} \rightarrow \text{(Fe}^+\text{ allyl)} + H_2$$

to the metal forming **2** which could then lose methane. Hence both reaction channels could pass through **3** and **1** could be unimportant. In either case, at some point in the mechanism carbon–carbon bond cleavage must be dominant over carbon–hydrogen bond cleavage to give the observed product distribution.

We have previously reported the reaction of Fe^+ with CH_3I to form $FeCH_3^+$ from which we deduce that $D(Fe^+\text{-}CH_3) > 56$ kcal/mol.[3] This result combined with $D(CH_3\text{-}i\text{-}C_3H_7) = 84$ kcal/mol[6] indicates that formation of **1** is exothermic if $D(CH_3Fe^+\text{-}i\text{-}C_3H_7) > 28$ kcal/mol, well within the range of measured metal–alkyl radical bond strengths.[3] If we assume that $D(Fe^+\text{-}CH_3) \simeq D(Fe^+\text{-}i\text{-}C_4H_9)$, then (noting that $D(H\text{-}i\text{-}C_4H_9) = 98$ kcal/mol[6]) formation of **3** will be exothermic if $D(i\text{-}C_4H_9Fe^+\text{-}H) > 42$ kcal/mol. This is certainly a reasonable possibility since it has been reported that $D(Fe(CO)_5^+\text{-}H) = 74$ kcal/mol.[7] Hence formation of either **1** or **3** seems thermodynamically feasible.

We note that either proposed mechanism (initial C–C insertion or initial C–H insertion) can account for the cleavage of n-C_4H_{10} by the metal ions. The $FeC_4H_6^+$ product is readily accounted for by initial formation of $FeC_4H_8^+$ in a process analogous to reaction 5 followed by a second metal insertion into an allylic carbon–hydrogen bond as indicated in reaction 6.

$$\text{(Fe}^+\text{ allyl)} \rightarrow H\text{–}Fe^+\text{(alkene)} \rightarrow \qquad (6)$$
$$\text{(H, H, Fe}^+\text{ allyl)} \rightarrow \text{(Fe}^+\text{ allyl)} + H_2$$

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