tables (38 pages). Ordering information is given on any current masthead page.

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(5) $R = \sum|F_o^2 - F_c^2|/\sum F_o^2$. Anomalous dispersion corrections were included for P and Rh atoms; positional and anisotropic thermal parameters were varied for all nonhydrogen atoms, while H atoms were not included. The goodness of fit, $S = [\sum w(F_o^2 - F_c^2)^2/(n - m)]^{1/2} = 1.00$, where w is the weight assigned to each reflection, n the number of observations (5837), and m the number of variable parameters (336). Weights were taken as inversely proportional to the estimated variance of each reflection where $\sigma^2(F_o^2) = \sigma_{count}^2 + (C_1 \times F_o^2)^2 + C_2$. The constants C_1 and C_2 were adjusted during the refinement process; final values are $C_1 = 0.007$ and $C_2 = 4486.0$.
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(16) The triplet is only found in samples with low (~25%) ^{13}C-isotopic enrichment; at higher levels of enrichment (~80%) the resonance becomes more complex owing to the presence of significant concentrations of isotopomers which exhibit coupling between the edge-bridging CO's in the equatorial plane.
(17) 3.16 MHz = 0 ppm for δ_{Rh} when using a magnetic field such that the protons in Me_4Si resonate at exactly 100 MHz.
(18) As has been noted above, at low temperature (−78 °C) and *P*(CO) of 1 atm, precipitation of $Rh_6(CO)_{16}$ takes place, and the equilibrium is shifted to the left.
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Received October 12, 1979

Total Synthesis of (±)-Aphidicolin

Sir:

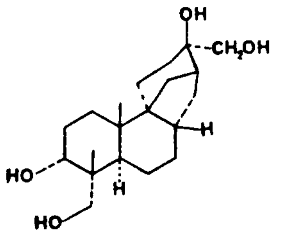
The tetracyclic diterpene aphidicolin (**1**) is noteworthy both for its intriguing molecular structure and for its biological effect as a potent antiviral and antimitotic agent.[1] We outline herein a synthesis of the racemate of **1** by an approach which includes a number of unique steps. The presently described route is based on a line of analysis which is completely different from that for two syntheses of (±)-**1** which have recently been reported.[2,3]

The oxygenated geranyl bromide **2** was prepared from geranyl acetate by the following sequence: (1) reaction with 1 equiv of selenium dioxide[4] at reflux in 95% ethanol for 1 h followed by brief treatment with sodium borohydride to form the *E,E* 8-hydroxylated derivative (61%), (2) protection of the 8-hydroxyl group as the *tert*-butyldimethylsilyl ether (*tert*-butyldimethylsilyl chloride, 4-dimethylaminopyridine, triethylamine in CH_2Cl_2 at −20 °C),[5] (3) acetate cleavage (potassium carbonate in methanol at 0 °C, 90% over two steps), and (4) conversion of the resulting hydroxy silyl ether into **2** via the mesylate (1 equiv of triethylamine, 1 equiv of CH_3SO_2Cl, in CH_2Cl_2 at −40 °C) by reaction with 2 equiv of lithium bromide in tetrahydrofuran (THF). The solution of the unstable bromide **2** was immediately added to a stirred solution of the lithio-sodio derivative of methyl acetoacetate in THF at 0 °C to give after chromatography on silica gel the keto ester **3**[6-8] (90% overall from 8-*tert*-butyldimethylsilyloxygeraniol).

Treatment of β-keto ester **3** with 1.1 equiv each of sodium hydride and diethyl chlorophosphate[9] in ether at 0 °C afforded the enol phosphate ester **4** which upon reaction with 1 equiv of mercuric trifluoroacetate[10] in nitromethane at 0 °C followed by aqueous sodium chloride produced the mercurated bicyclic keto ester **5** [mp 157–159 °C, IR max 1740, 1710 cm^{-1} ($CHCl_3$)] in 60% yield along with 20% of monocarbocyclic product. Rings A and B were thus established in a single step; the stereochemistry of the product, expected to be as shown from much literature precedent, was established by correlation with intermediates of known constitution produced as described below.

Treatment of **5** with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid in benzene at reflux gave the corresponding ethylene ketal, mp 160–161 °C (90% yield), which was converted into the keto acetal **6**, mp 127–130 °C, in 58% overall yield by the following sequence: (1) replacement of mercury by hydroxyl by addition to a solution of 2 equiv of sodium borohydride in dimethylformamide (DMF), saturated with oxygen by continuous bubbling at 23 °C, to give a mixture of C-3 epimeric alcohols, (2) oxidation to C-3 ketone using pyridinium dichromate[12] in methylene chloride at 23 °C, (3) desilylation with tetra-*n*-butylammonium fluoride[5] in THF at 0 °C for 30 min, (4) stereospecific reduction of the keto function at C-3 using lithium tri-*sec*-butylborohydride in THF at −78 °C,[13] and (5) acetalization by reaction with 1.2 equiv of pivalaldehyde and 0.15 equiv of *p*-toluenesulfonic acid in CH_2Cl_2 at 0 °C for 30 min. Reduction of **6** using lithium aluminum hydride in ether at 23 °C for 1 h, followed by oxidation of the resulting primary alcohol using 4 equiv of pyridinium chlorochromate in CH_2Cl_2 at 23 °C and deketalization (10:1:1 acetone–water–70% aqueous perchloric acid at 23 °C for 3 h), afforded keto aldehyde **7**, mp 106–108 °C, in 90% overall yield from **6**.

The keto aldehyde **7** was also synthesized by a more conventional route,[14] part of which has been used in recent syntheses of (±)-**1**.[2,3] Keto acetal **8** [made starting from 5,9-dimethyl-5(10)-octalin-1,6-dione][2,3] was converted into its trimethylsilyl enol ether with lithium diisopropylamide (LDA), followed by trimethylsilyl chloride, and epoxidized in CH_2Cl_2 with 1.1 equiv of *m*-chloroperbenzoic acid at −20 °C.[15] Treatment of the crude product with ethanolic KOH, followed by oxidation with 2 equiv of bismuth trioxide in acetic acid–acetone[16] at 135–140 °C in a pressure flask for 1.5 h, gave in quantitative yield the α diketone which was transformed into methyl enol ether **9** [IR max 1685, 1640 cm^{-1} ($CHCl_3$)] in 87–88% yield by reaction with 2.5 equiv of potassium *tert*-



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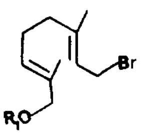

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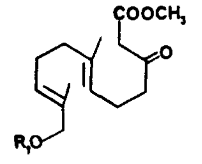

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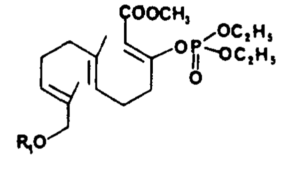

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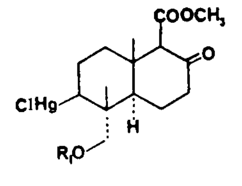

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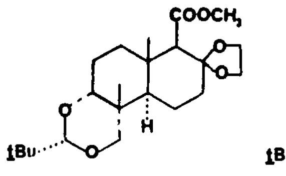

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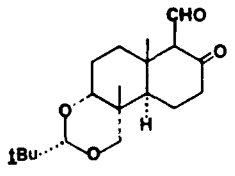

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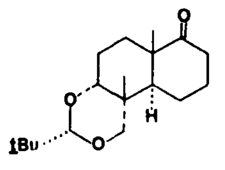

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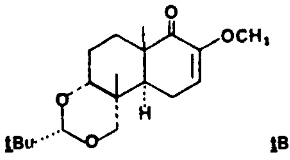

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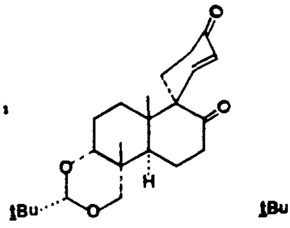

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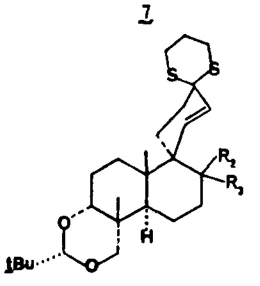


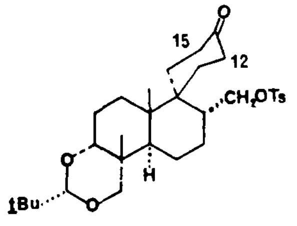
11 $R_2,R_3 = O$

12 $R_2 = CHO$, $R_3 = OSiMe_3$

13 $R_2 = CH(OSiMe_3)(SiMe_3)$, $R_3 = OH$

14 $R_2 = CHO$, $R_3 = H$

15 $R_2 = CH_2OH$, $R_3 = H$



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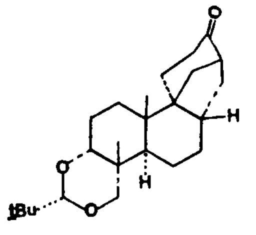

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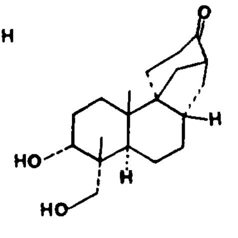
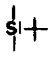


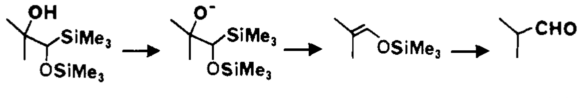
18

$R_1 =$



butoxide in THF at −50 °C, followed by treatment with 3 equiv of methyl iodide. Reaction of **9** with 3 equiv of dimethylsulfonium methylide[17] in 9:1 THF-hexamethylphosphoramide (HMPA) at 0 °C gave an epoxide which, after heating with 1 equiv of lithium perchlorate[18] in toluene at 150 °C for 0.5 h and subsequent hydrolysis with 100:1:1 acetone-water-70% perchloric acid, afforded keto aldehyde **7** in good overall yield from **9**. Samples of the keto aldehyde **7** prepared from **9** and from **6** were identical in all respects.

The next stage of the synthesis involved the addition of a spiro ring to keto aldehyde **7**. To a stirred solution of **7** in 1:1 THF-*tert*-butyl alcohol at 23 °C and 0.2 equiv each of powdered potassium carbonate and 1,5-diazabicyclo[5.4.0]-undec-5-ene (DBU) was added slowly a gaseous stream of methyl vinyl ketone[19] in argon. Extractive isolation gave the Michael adduct which upon treatment with pyrrolidinium acetate[20] in THF-methanol at 23 °C yielded the Robinson spiroannulation product **10**. The conjugated carbonyl group in **10** was selectively protected as the thioketal by reaction with bis(trimethylsilyl)propane-1,3-dithiol[21] in chloroform in the presence of zinc iodide to form **11**, mp 188–190 °C (88%). The next planned operation, replacement of the carbonyl oxygen of **11** by H and CH_2OH, proved unexpectedly difficult owing to steric inhibition of carbonyl addition relative to α deprotonation. A successful result was obtained using the following sequence: (1) conversion of **10** into the *O*-trimethylsilyl cyanohydrin (97%) using 4 equiv of trimethylsilyl cyanide and zinc iodide catalyst in chloroform at 40 °C,[22] (2) reduction of cyano to formyl using 4 equiv of diisobutylaluminum hydride in toluene at 0 °C to give **12**, mp 184–185 °C (75%), (3) reaction of **12** with 0.95 equiv of trimethylsilyllithium[23] in HMPA at −35 °C, isolation of the resulting bistrimethylsilyl compound **13** (80% after chromatography on silica gel), and treatment with 3 equiv of lithium diisopropylamide in THF containing 5% HMPA at 23 °C to give after quenching with aqueous acid the aldehyde **14**, mp 241–243 °C (~80%). This new method, which should be useful as a general solution to the problem of attaching carbon to very hindered ketonic groups,[24] was devised on the basis of the mechanistic scheme shown in eq 1.



(1)

Reduction of the aldehyde **14** with sodium borohydride in ethanol-THF at −20 °C produced the corresponding primary alcohol (**15**) quantitatively. Conversion of **15** into the keto tosylate **16** was carried out in 70% overall yield by the sequence: (1) silylation of the primary hydroxyl using *tert*-butyldimethylsilyl chloride, 4-dimethylaminopyridine, triethylamine in $CHCl_3$ at 23 °C (90%),[5] (2) thioketal cleavage to ketone by reaction with 2.2 equiv of 1,3-diiodo-5,5-dimethylhydantoin[25] at −20 °C for 30 min in 5:5:1 acetone-THF-water (86%), (3) double-bond hydrogenation at 1 atm over Pd/C catalyst, (4) desilylation,[5] (5) reaction with *p*-toluenesulfonyl chloride, 4-dimethylaminopyridine, and triethylamine in $CHCl_3$ at 23 °C.

Treatment of keto tosylate **16** with base leads to internal α alkylation at either C-12 or C-15 depending on reaction conditions, the use of kinetically controlled enolate formation with a highly hindered base at low temperatures favoring the desired alkylation at C-12. Thus addition of **16** in 2-methyl-tetrahydrofuran to an excess of lithium di-*tert*-butylamide[26] in the same solvent at −120 to −130 °C, followed by gradual warming, produced the tetracarbocyclic ketone **17** in 90% yield.[27] On the other hand reaction of **16** with sodium methoxide in methanol at 0 °C led exclusively to the product of internal alkylation at C-15, probably the consequence of fast reversible enolate formation and relatively slow internal alkylation at C-12. Synthetic (±)-**17** obtained as described above was indistinguishable from an authentic sample (prepared by the acetalization of pivalaldehyde with keto diol **18** derived from 1,2-glycol cleavage of aphidicolin of natural origin[28]) by chromatographic, ^{1}H NMR, IR, and mass spectral comparison. Hydrolysis of (±)-**17** (70% aqueous perchloric acid in methanol at 80 °C for 5 days) afforded synthetic (±)-**16** which was spectroscopically and chromatographically identical with a naturally derived reference sample.[28] Reaction of (±)-**17** with 1-ethoxyethoxymethyllithium[29] afforded, after hydrolysis of the resulting C-16 carbonyl adduct with 2:2:1 acetic acid–methanol–water, a 1:1 mixture of (±)-aphidicolin and the epimer at C-16 which was not readily separable by chromatography.[30] The corresponding mixture of bisacetonides (prepared from tetraol, 10 equiv of 2-methoxypropene, and pyridinium tosylate at 23 °C for 10 min) could be separated into **1** bisacetonide and the C-16 epimer, R_f 0.22 and 0.16, respectively, on silica gel plates using three developments with 5.5% ethyl acetate in hexane. The bisacetonide of synthetic (±)-**1** was chromatographically and spectroscopically identical with the bisacetonide of natural aphidicolin.[28] Finally, acid-catalyzed hydrolysis of the synthetic bisacetonide as described previously[1] afforded (±)-aphidicolin, indistinguishable chromatographically and spectroscopically from naturally obtained aphidicolin.[28,31] The synthesis of (±)-aphidicolin described here raised a number of interesting and unexpected problems which have now been successfully overcome.[32]

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(8) Partial ^{1}H NMR data for **3** in $CDCl_3$ solution (δ): 0.85 (s, 9 H, *t*-Bu), 1.54 (br s, 6 H, $C{=}CCH_3$), 3.67 (s, 3 H, $COOCH_3$).

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(24) None of the currently used methods were successful for the transformation of ketone **11** to aldehyde **14**. The following reagents failed to add satisfactorily to the carbonyl group of **11**: (a) methoxymethylenetriphenylphosphorane (Wittig, G.; Böll, W.; Krück, K.-H. *Chem. Ber.* **1962**, *95*, 2514); (b) lithiomethoxymethyldiphenylphosphine oxide (Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Chem. Commun.* **1977**, 314); (c) phenylthiomethyllithium (Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097); (d) methylselenomethyllithium; (e) methyllithium in ether; and (f) dimethylsulfonium methylide.

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(27) The ratio of alkylation at C-12 to that at C-15 was ~10:1 in this case.

(28) We are indebted to the ICI Co. and Dr. Geraint Jones for generous samples of aphidicolin, its bisacetonide, and the keto diol **18**.

(29) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

(30) The conversion of the ketone **18** into aphidicolin via two other routes was also found to be nonstereoselective. One of these involved methylenation by the Wittig reaction and hydroxylation with osmium tetroxide (giving desired and undesired epimers in a 1.3:1 ratio) and the other addition of 2-lithio-1,3-dithiane, dithiane cleavage, and reduction of formyl to primary alcohol (giving desired and undesired epimers in a ratio of ~1:3.5).

(31) To our knowledge this is the first conversion of (±)-**18** into (±)-aphidicolin, although this step should have been a required process in previously announced syntheses of (±)-aphidicolin.[2,3]

(32) This research was assisted financially by a grant from the National Science Foundation. We are indebted to Dr. Larry C. Blasczcak for much valuable help and for providing a quantity of 5,9-dimethyl-5(10)-octalin-1,6-dione. Mr. Jay W. Ponder made helpful contributions to the experimental work.

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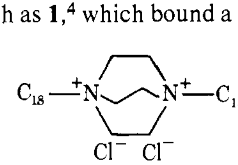
Received November 30, 1979

Carrier-Mediated Selective Transport of Nucleotides through a Liquid Membrane

Sir:

Bioenergetics is based on the interconversions among various nucleoside phosphates and other so-called high-energy phosphate compounds. This process vital to a variety of functions of living organisms requires a transmembrane movement specific for the particular phosphate involved. These phosphates should be encapsulated in an intrinsic carrier molecule such as an ionophoric protein in mitochondria[1] to facilitate the entry of otherwise highly hydrophilic phosphate anions into a lipophilic biological membrane. Although cationic transport is known to be mediated by several antibiotics and synthetic polyethers,[2] very few carrier models have been reported for the selective membrane transport of anionic species.[3]

Here we report the first successful selective transport of nucleoside phosphates through a chloroform liquid membrane. The carrier used was a lipophilic diammonium salt of diazabicyclooctane, such as **1**,[4] which bound a given nucleotide se-



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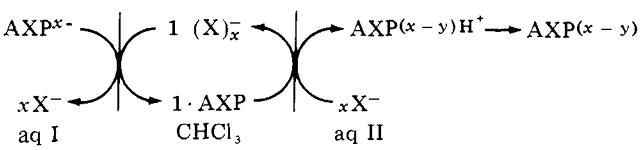

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