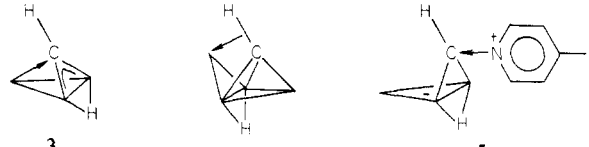
1:2:2:2:2:1 pattern. The unusual position of one of the axial carbon resonances, namely, to higher field than any of the other signals, is attributed to the distortion caused by steric interaction between this carbon (C(11)) and the bridging CH group. At higher temperatures the two axial carbonyl resonances broaden (at slightly different rates) and then coalesce (ca. −60 °C) with one of the remaining signals. These changes are due to localized 3-fold exchanges at the $Os(CO)_4$ center, as has been observed for **1**.[7b] The significantly lower activation energy for **3** ($\Delta G^{\ddagger}$ = ca. 9 kcal/mol) compared to **1** ($\Delta G^{\ddagger}$ = ca. 17 kcal/mol) can again be attributed to the distortions in **3**, in particular to the pseudo-seven-coordinate geometry around Os(1).

Although in **3** both H(1) and C(1) are close to Os(1), the interaction of the methylidyne group with this atom is fundamentally different from that found in the compound $HFe_4(CO)_{12}(\mu_4\text{-}CH)$.[4] In this latter compound the C–H bond acts as a two-electron *donor* to the adjacent unsaturated iron atom (see **4**). This is evidenced spectroscopically by a shift in the C–H ^1H NMR resonance to high field (δ −1.31) and a diminished C–H coupling constant (103 Hz).[4a] The three-center C–H–Fe bond also is acidic, since upon removal of the hydrogen atom as a proton, the electron pair remaining forms a two-center C–Fe bond.[4] However, for the CH group in **3** the ^1H NMR signal occurs at low field (δ 14.2), the coupling constant is relatively high (166 Hz, and there is no evidence of acidity (vide infra). Thus, the bonding in **3** can be regarded as two-electron donation from the formally saturated (18 electron) $Os(CO)_4$ center[19] to the nominally sp^2-hybridized carbon atom of the bridging CH moiety. In alkoxy- and aminoalkylidyne compounds related to **1**, there is crystallographic and spectroscopic evidence for π bonding between the hetero atom and the alkylidyne carbon atom.[7b,15,21] Such a resonance interaction is not available in **3**, and stabilization is achieved instead by an electrophilic interaction with the third metal atom.[22]



3 4 5

The facile reactions of **3** with various nucleophiles provide further evidence for the electrophilic nature of the methylidyne ligand. Addition of 4-methylpyridine (1 equiv) to **3** at −60 °C immediately forms the pyridinium derivative **5**.[23] The structure of **5** is evidently analogous to that of **2**; frontside attack by the base on the CH ligand displaces the Os → C donation from the backside. A similar reaction of **3** with $LiBEt_3H$ generates $[HOs_3(CO)_{10}(CH_2)]^-$ (**6**).[24] Protonation of **5** regenerates **3**, implying that the proton is added at the nitrogen atom, but protonation of **6** occurs at the Os–C bond to generate $HOs_3(CO)_{10}(CH_3)$[25] (**7**; eq 2). The conversion of **3** to **7** represents the overall hydrogenation of CH to CH_3, which, however, cannot be effected

$$\underset{\mathbf{3}}{HOs_3(CO)_{10}(CH)} \xrightarrow{H^-} \underset{\mathbf{6}}{[HOs_3(CO)_{10}(CH_2)]^-} \xrightarrow{H^+} \underset{\mathbf{7}}{HOs_3(CO)_{10}(CH_3)} \quad (2)$$

directly with H_2 due to the facile thermal rearrangement of **3** to $H_2Os_3(CO)_9(CCO)$.[26] Finally, treatment of **3** with $RHC^-\text{–}N_2^+$ (R = H, $SiMe_3$) leads to $HOs_3(CO)_{10}(CH{=}CHR)$ (R = H,[27] $SiMe_3$[13]) in high yield (>90% by NMR) presumably via nucleophilic attack followed by N_2 loss. Related coupling reactions with other carbon nucleophiles are being investigated.[28]

Acknowledgment. This research was supported at the University of Illinois by NSF Grant CHE 81-00140 (J.R.S.) and at SUNY–Buffalo by NSF Grant CHE 80-23448 (M.R.C.). Acknowledgment also is made for the use of instrumentation in the Regional NMR Center at the University of Illinois (NSF Grant CHE 79-16100).

Supplementary Material Available: Listings of atomic coordinates, thermal parameters, bond lengths, and bond angles (7 pages). Ordering information is given on any current masthead page.

(19) Donation from an $Os(CO)_4$ group is seen also in the compound $HOs_3(CO)_{10}(CF_3CCHCF_3)$: Laing, M.; Sommerville, P.; Dawoodi, Z.; Mays, M. J.; Wheatley, P. J. *J. Chem. Soc., Chem. Commun.* **1978**, 1035.

(20) If in **3** the bridging hydrogen is removed as a proton and the $Os(CO)_3$ groups are replaced by isolobal CH^+ moieties, the species generated is $(CO)_4Os(C_3H_3)^+$, an 18-electron complex of the cyclopropenium ion.

(21) For aminoalkylidyne complexes $HRu_3(CO)_{10}(CNMe_2)$ and $HOs_3(CO)_{10}$(CNH-*t*-Bu) see respectively: (a) Churchill, M. R.; DeBoer, B. G.; Rotella, F. J. *Inorg. Chem.* **1976**, *15*, 1843. (b) Adams, R. D.; Golembeski, N. M. *Ibid.* **1979**, *18*, 2255.

(22) We thank a referee for suggesting that this point be mentioned explicitly.

(23) **5**: ^1H NMR (CD_2Cl_2) δ 8.48 (d, 2 H, J = 5.9 Hz), 7.84 (d, 1 H, J = 3 Hz), 7.28 (d, 2 H, J = 5.9 Hz), 2.27 (s, 3 H), −16.00 (d, 1 H, J = 3 Hz); IR (CH_2Cl_2) ν_{CO} 2110 (w), 2088 (m), 2066 (s, br), 2040 (vs), 2030 (s), 2022 (sh), 2002 (s, br), 1957 (m, br). The compound is stable at 25 °C (isolated yield 78%).

(24) Et_4N–6: ^1H NMR (CD_2Cl_2) δ 5.23 (dd, 1 H_a, J_{ab} = 5 Hz, J_{ac} = 3 Hz), 4.26 (d, 1 H_b), −17.00 (d, 1 H_c) in addition to Et_4N^+ signals.

(25) Calvert, R. B.; Shapley, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 7726. None of the tautomeric methylene compound, which would result from Os–Os bond protonation, was observed under these conditions (−40 °C).

(26) Shapley, J. R.; Strickland, D. S.; St. George, G. M.; Churchill, M. R.; Bueno, C. *Organometallics* **1983**, *2*, 185.

(27) (a) Deeming, A. J.; Hasso, S.; Underhill, M. *J. Chem. Soc., Dalton Trans.* **1975**, 1614. (b) Keister, J. B.; Shapley, J. R. *J. Organomet. Chem.* **1975**, *85*, C29.

(28) After submission of this work a paper by Casey and Fagan appeared [Casey, C. P.; Fagan, P. J. *J. Am. Chem. Soc.* **1982**, *104*, 4950] that described the 1,2-addition reaction of $[Cp_2Fe_2(\mu\text{-}CO)(\mu\text{-}CH)]^+$ with olefins, e.g., ethylene. We find that reaction of **3** with ethylene is not competitive with its intramolecular rearrangement to $H_2Os_3(CO)_9(CCO)$.[26]

Biogenetic-Type Total Synthesis of (±)-Aphidicolin

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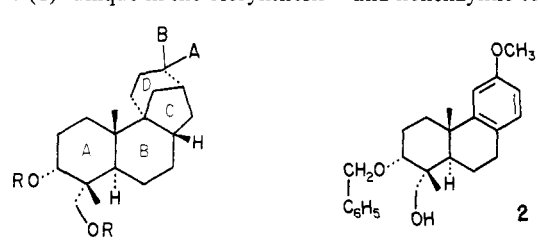
Received September 17, 1982

Aphidicolin, a potent antiviral agent and an accepted tool for the study of DNA replication,[1,2] possesses a complex diterpenoid structure (**1**)[2] unique in the biosynthesis[2,3] and nonenzymic total



1 R = H; A = α CH_2OH; B = β OH
15 R, R = $C(CH_3)_2$; A = H; B = OH
16 R, R = $C(CH_3)_2$; A, B = O

2

synthesis areas.[4,5] Herein we report a concise aphidicolin total

(1) Bucknall, R. A.; Moores, H.; Simms, R.; Hesp, B. *Antimicrob. Agents Chemother.* **1973**, *4*, 294.

(2) Dalziel, W.; Hesp, B.; Stevenson, K. M.; Jarvis, J. A. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2841.

(3) Adams, M. R.; Bu lock, J. D. *J. Chem. Soc., Chem. Commun.* **1975**, 389.

(4) For the first syntheses of (±)-17-noraphidicolin-16-one, see: (a) McMurry, J. E.; Andrus, A.; Ksander, G. M.; Musser, G. H.; Johnson, M. A. *J. Am. Chem. Soc.* **1979**, *101*, 1330. (b) Trost, B. M.; Nishimura, Y.; Yamamoto, K. *Ibid.* **1979**, *101*, 1328. For the reconstitution of aphidicolin from optically active 17-noraphidicolin-16-one gotten by degradation of the natural product, see ref 2.

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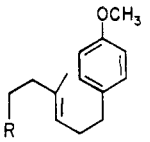
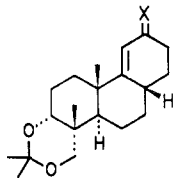
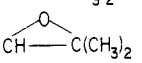
synthesis which, paralleling in important respects the likely biolgenesis, features direct formation of the A–B ring system in a key intermediate (**2**) having the exact functionality and relative stereochemistry characteristic of the A ring in the natural product.

Treatment of phenylgeranyl thioether[6] anion with *p*-methoxybenzyl chloride (THF, −78 °C) provided (86%) the expected alkylation product, which was reduced (Li/NH_3, −78 °C; 47%) to diene **3**. Selective oxidation[7] to the terminal bromohydrin (1.1

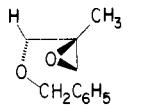




3 R = $CH{=}C(CH_3)_2$

4 R = 

5 R = $CH(OH)C(CH_3){=}CH_2$

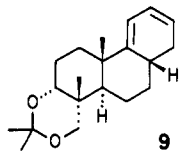
6 R = 

7 X = O

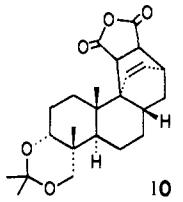
8 X = $NNHC_6H_2(iPr)_3$

equiv of NBS in $THF–H_2O$, 0 °C) followed by exposure to K_2CO_3 in MeOH afforded the 2,3-oxide **4** (33%). Elimination induced by $LiN(Et)_2$ (refluxing Et_2O, 57%) led to allyl alcohol **5**, which on $VO(acac)_2$-catalyzed oxidation with *t*-BuO_2H[8] in benzene[9] was converted (80%) to a single racemate, the erythro glycidol, readily O-alkylated with benzyl iodide (NaH, THF, 90%)[9] to the glycidyl benzyl ether **6**.

In an adaptation of the normal enzymic cyclization process,[10] intermediate **6** was transformed ($FeCl_3$, toluene)[9] to the hydrophenanthrene **2** (OAc, mp 102–103 °C).[11] Simultaneous de-O-benzylation and Birch-type reduction (Li, EtOH–THF, −78 °C) was followed by hydrolysis (0.5 M HCl–EtOH)[9] of the intermediary enol ether and ketalization of the released diol moiety (acetone; TsOH, 100%),[9] yielding (55%) the cyclohexenone **7** (mp 186–188 °C). After formation of the trisylhydrazone (**8**) (70%) (trisylhydrazine, TsOH, THF)[9] a Bamford–Stevens-type reaction (*n*-BuLi, TMEDA, hexane, −78 °C)[12] produced the cyclohexadiene (**9**) needed for elaboration of a fourth carbocyclic ring (82%).

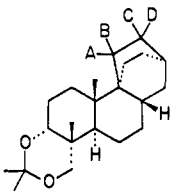


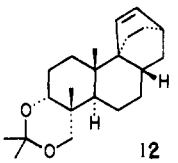
9



10

Rigidly stereocontrolled by the bulk of the two α-substituents at C-3 and C-4, the reaction of diene **9** with maleic anhydride (benzene, 80 °C, 86%) gave rise to adduct **10**. Catalytic reduction of the corresponding diacid (Pt black, H_2O–EtOH, 90%)[9] to **11** followed by $Pb(OAc)_4$-induced decarboxylation (O_2-saturated pyridine, 28%)[13] produced olefin **12** (mp 113–115 °C). All attempts to functionalize appropriately the bicyclooctene unit failed, except for epoxidation (*m*-$ClC_6H_4CO_3H$, CH_2Cl_2, $NaHCO_3$, 100%)[9] followed by Na metal reduction in refluxing benzene,[14] which yielded (20%) only the alcoholic regio- and stereoisomer (**13**) needed for effecting the biomimetic skeletal isomerization to the aphidicolane ring system.





12

11 A = D = H; B = C = CO_2H

13 A = B = C = H; D = α OH

14 A = B = C = H; D = αOSO_2CH_3

Solvolytic rearrangement of the derived mesylate **14** (refluxing acetone–H_2O, $CaCO_3$) generated the desired bicyclo[3.2.1]octanol **15** (60% overall from **12**), readily oxidized (CrO_3–py, CH_2Cl_2, 90%)[9] to the corresponding (±)-ketone **16** (mp 137–139 °C).[4,5] NMR, IR, and mass spectral as well as GC behavior of our synthetic **16** was indistinguishable from that of corresponding material derived from the natural product. In view of the known conversion of the norketone to the natural product system[4,5] the work described herein constitutes a total synthesis of (±)-aphidicolin.

Acknowledgment. National Science Foundation for financial support (CHE-8002661), Dr. B. Hesp for an aphidicolin sample, NSF (GP28142) for provision of XL-100-FT NMR facility are thanked.

Supplementary Material Available: NMR as well as certain IR and mass spectra, corroborated structures assigned to all intermediates (3 pages). Ordering information is given on any current masthead page.

(5) For total syntheses of (±)-aphidicolin, see: (a) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc.* **1980**, *102*, 1742. (b) Ireland, R. E.; Godfrey, J. D.; Thaisrivongs, S. *Ibid.* **1981**, *103*, 2446.

(6) Altman, L. J.; Ash, L.; Marson, S. *Synthesis* **1974**, 129.

(7) van Tamelen, E. E.; Curphey, T. J. *Tetrahedron Lett.* **1962**, 121.

(8) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(9) Reaction carried out at room temperature.

(10) For the related cyclization of 1,6-diene 1,2-oxides see, e.g.: (a) Goldsmith, D. J.; Clark, B. C., Jr. *Tetrahedron Lett.* **1967**, 1215. (b) van Tamelen, E. E.; Pedlar, A. D.; Li, E.; James, D. R. *J. Am. Chem. Soc.* **1977**, *99*, 6778.

(11) Although the actual yield is estimated at 25–30%, repeated tedious HPLC separations provide only 12% of isolated pure **2**.

(12) Chamberlin, A. R.; Stemke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.

(13) Yield reflects recovery of starting material as the cyclic anhydride.

(14) Mousseron, M.; Richard, R.; Granger, R.; Winternitz, F.; Combes, G.; Canals, E.; Souche, L.; Froger, P. *Bull. Soc. Chim. Fr.* **1946**, 629.

^1H NMR Studies of Nitrogen-15-Labeled *Escherichia coli* $tRNA_f^{Met}$. Assignments of Imino Resonances for Uridine-Related Bases by ^1H–^{15}N Heteronuclear Double Resonance Difference Spectroscopy

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Received July 16, 1982

We recently reported that the imino protons of uridine and bases derived from uridine biosynthetically in *E. coli* $tRNA_f^{Met1}$ can be identified in a ^1H NMR spectrum by ^1H–^{15}N couplings.[2,3] On the basis of the X-ray structure of the molecule,[4] we expected to

(1) Abbreviations used are tRNA, transfer ribonucleic acid; ppm, parts per million; NOE, nuclear Overhausen effect; ψ, pseudouridine; rT, ribothymidine; s^4U, 4-thiouridine; EDTA, ethylenediaminetetraacetic acid; P, phosphate.

(2) Griffey, R. H.; Poulter, C. D.; Yamaizumi, Z.; Nishimura, S.; Hurd, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5810–5811.

(3) Griffey, R. H.; Poulter, C. D.; Yamaizumi, Z.; Nishimura, S.; Hurd, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5811–5813.

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