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# A New End Game for Aphidicolin

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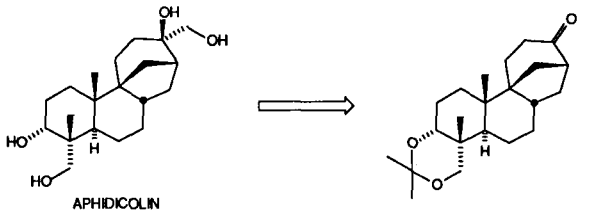
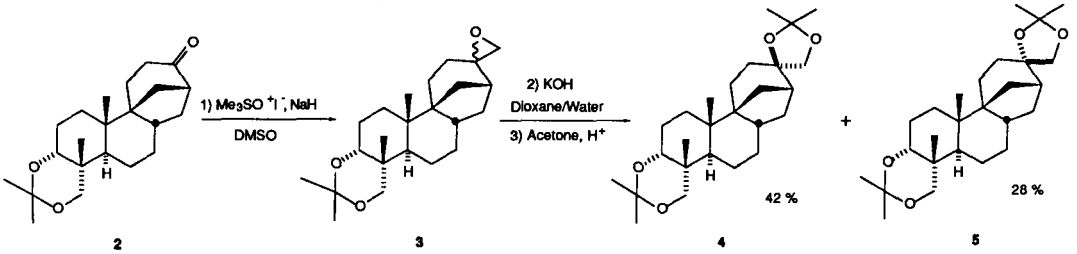
**Summary.** A highly efficient, stereocontrolled synthesis of aphidicolin from its degradation product, 3α,18-isopropylidenedioxy-17-noraphidicolan-16-one, has been achieved.

In 1972 Hesp and coworkers[2] reported the structure of aphidicolin (**1**), a novel diterpene derived from the fungus *Cephalosporium aphidicola,* which displays marked *in vitro* activity against *Herpes simplex.*[3] Given the unusual architecture, in conjunction with the aforementioned antiviral activity, it is not surprising that aphidicolin has been the subject of considerable synthetic effort. Indeed, no fewer than seven total syntheses[4] have been recorded since 1979, when Trost[4a] and McMurry[4b] concurrently announced the first total syntheses. Most recently (1987), Holton *et al.*[4i] disclosed the first enantioselective synthesis of aphidicolin, thereby unambiguously confirming the absolute stereochemistry.

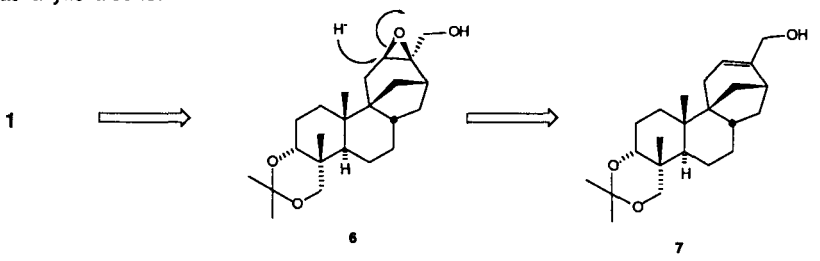



Interestingly all but the Ireland approach[4h] were based conceptually on the three step conversion of 3α,18-dihydroxy-17-noraphidicolan-16-one (**2**), or closely related derivatives thereof (i.e., acetal or ketal), to aphidicolin developed by Hesp[2b] in conjunction with the original degradation studies. This now classic end game involved treatment of **2** with dimethylsulfoxonium methylide to afford a mixture of epoxides (i.e., **3**), which upon treatment with aqueous KOH, followed by acetonide formation yields a separable mixture of **4** and **5** in 42 and 28% overall yield respectively, with the major product possessing the correct relative stereochemistry at C(16). Although moderately efficient, this scheme suffers from the lack of stereoselectivity in the initial

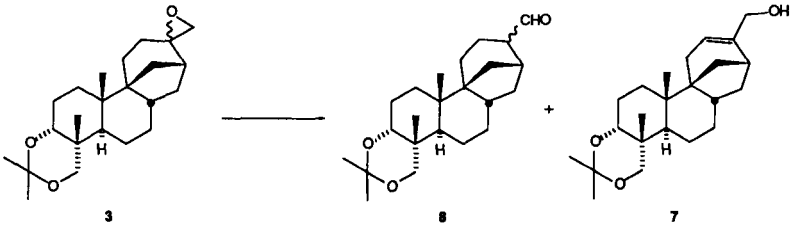
epoxidation. In connection with an ongoing aphidicolin synthesis in our laboratory, we have addressed this problem; the results of this study are reported here.[5]




Well aware that epoxidation of bicyclo[3.2.1]oct-2-ene and related systems proceeds with high *exo*-stereoselectivity,[6] we reasoned that epoxidation of an olefin such as **7**, followed by hydride opening at the least hindered end of the derived epoxide, would provide a stereoselective route to aphidicolin. Our initial target was therefore seen as allylic alcohol **7**.

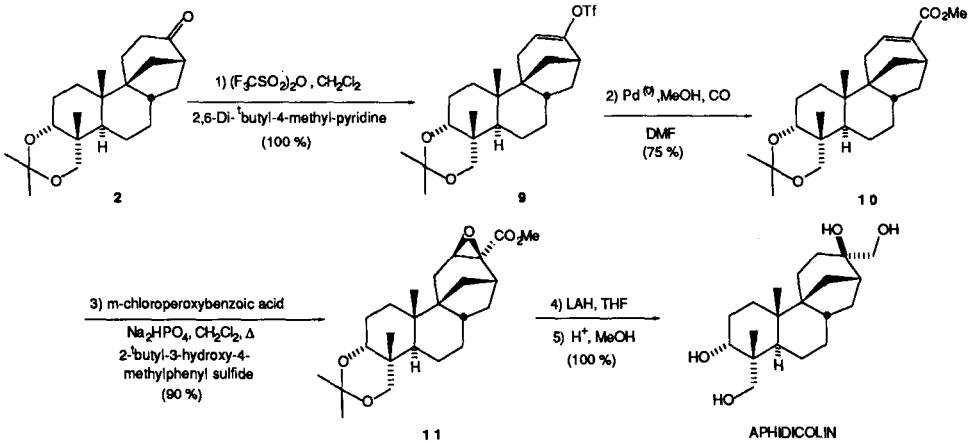



Towards this end, we subjected the readily available mixture of epoxides **3**[2] to the rearrangement conditions of Nozaki (i.e., diethylaluminium 2,2,6,6-tetramethylpiperidide, PhH, 0°C.);[7] the result was a 75% yield of aldehydes **8**,[8a] with no trace of the desired allylic alcohol. Attempts to accomplish the desired rearrangement with TMS-OTf and DBU[9] also led to aldehydes **8** in 83 % yield. In fact, the only conditions that proved at all encouraging were TMS-OTf and 2,6-lutidine ($CH_2Cl_2$; -78°C for 10 min.). Under these conditions, a mixture of the desired allylic alcohol **7** (40%)[8a] along with aldehydes **8** (45%)[8a] was obtained. In view of these difficulties, we sought an alternate route to **7** beginning with **2**.




Ideal in this regard appeared to be carbonylation of the enol triflate derived from **2**, followed by epoxidation and reduction. With this scenario in mind, ketone **2** was converted to enol triflate **9**[8] (triflic anhydride, 2,6-

di-t-butyl-4-methylpyridine, $CH_2Cl_2$)[10] in near quantitative yield. Palladium catalyzed carbonylation [$Pd(OAc)_2$, $Ph_3P$, $Et_3N$, CO, MeOH, DMF][11] then provided enoate **10** (75 %),[8] which in turn was epoxidized with *m*-chloroperoxybenzoic acid buffered with $Na_2HPO_4$ ($CH_2Cl_2$ at reflux; 8 h);[12] the result was epoxy ester **11**,[8] obtained in 90% yield. Carbon NMR analysis at 125-MHz verified that a single compound was in hand. Reduction of the latter with lithium aluminium hydride (5 mol. eq., THF, 70°C), followed by hydrolysis of the acetonide (Amberlite IR-120 $H^+$, methanol at reflux) gave synthetic aphidicolin (mp 226-228, lit.[1] 227-233) in near quantitative yield for the two steps. That synthetic aphidicolin was identical with natural aphidicolin was confirmed by careful spectral comparison [i.e., $^1H$ (500 MHz) and $^{13}C$ (125 MHz) NMR, IR and mass spectra].




In summary, we have achieved an efficient, highly stereoselective synthesis of aphidicolin from its readily available degradation product, 3α,18-isopropylidenedioxy-17-noraphidicolan-16-one. The sequence required five steps and proceeded in 67 % overall yield.

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## References and Notes

1 ) NIH Career Development Awardee, 1980-1985, and J.S. Guggenheim Foundation Fellow, 1985-1986.

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5) For previous attempts to improve this end game stategy see references 4c and 4d.

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8) a) The structure assigned to each new compound is in accord with its infrared, 500-MHz $^1H$ and 125-MHz $^{13}C$ NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry. (b) In addition, an analytical sample of this new compound gave satisfactory C and H combustion analysis (i.e., 0.4%). (c) Spectral data for representative intermediates are given below: **9**: $[\alpha]_D^{24}$= -12.4 (c=1.3, $CHCl_3$); IR ($CHCl_3$): 2990 (m), 2950 (m), 2870 (m), 1690 (w), 1415 (s), 1390 (m), 1370 (m), 1240 (s), 1200 (s), 1140 (s), 1080 (m), 1060 (s), 865 (m), 845 (m) $cm^{-1}$; $^1H$ nmr (500 MHz, $CDCl_3$): δ 5.42 (m, 1H), 3.65 (dd, J=2.8, 2.5 Hz, 1H), 3.60 (d, $J_{ab}$=12.2, 1H), 3.24 (d, $J_{ab}$= 12.2, 1H), 2.60 (dd, $J_{ab}$=18.83, J= 4.73, 1H) 2.53-2.41 (m, 3H), 2.89 (m, 1H), 1.75-1.68 (m, 2H), 1.60-1.50 (m, 4H), 1.42 (s, 6H), 1.42-1.26 (m, 2H), 1.08 (s, 3H), 0.94 (ddd, J=12.7, 3.5, 2.9, 1H), 0.71 (s, 3H); $^{13}C$ nmr (125 MHz, $CDCl_3$): δ 158.4, 118.6 (q, $J_{C-F}$=320 Hz), 114.4, 100.0, 73.4, 68.4, 49.2, 41.8, 39.4, 38.5, 38.0, 36.5, 34.5, 34.6, 31.9, 29.9, 26.6, 25.3, 25.0, 24.0, 21.4, 18.9, 17.0, 16.7; **10**: $[\alpha]_D^{24}$= -12.6 (c=1.6, $CHCl_3$); IR ($CHCl_3$): 3100 (s), 2950 (s), 2870 (s), 1690 (s), 1650 (s), 1455 (s), 1435 (s), 1390 (s), 1360 (s), 1250 (s), 1220 (s), 1160 (m), 1070 (s), 1050 (m), 995 (m) $cm^{-1}$; $^1H$ nmr (500 MHz, $CDCl_3$): δ 6.71 (m, 1H), 3.71 (s, 3H), 3.65 (t, J=2.9, 1H), 3.64 (d, $J_{ab}$=12.1, 1H), 3.24 (d, $J_{ab}$=12.1, 1H), 2.98 (dd, J= 6.0, 7.3, 1H), 2.71 (ddd, $J_{ab}$=20.7, J= 4.8, 1.5, 1H), 2.56 (dd, $J_{ab}$=20.8, J= 3.1, 1H), 2.43 (dd, J=12.8, 2.8, 1H), 2.16-2.00 (m, 3H), 1.89 (tdd, J=11.8, 4.1, 2.4, 1H), 1.70 (m, 1H), 1.63 (dd, J=5.7, 10.7, 1H), 1.53-1.46 (m, 4H), 1.46 (s, 3H), 1.44 (s, 3H), 1.29 (m, 1H), 1.19 (d, J=10.7, 1H), 1.07 (s, 3H), 1.00-0.72 (m, 3H), 0.67 (s, 3H); $^{13}C$ nmr (125 MHz, $CDCl_3$): δ 166.5, 142.9, 139.5, 97.9, 73.5, 68.4, 51.3, 49.0, 42.3, 39.2, 39.0, 35.5, 34.6, 32.8, 31.9, 29.8, 29.0, 26.4, 25.3, 24.0, 21.5, 18.9, 17.0, 16.5; **11**: mp=168-170°C; $[\alpha]_D^{24}$= -1.90 (c=0.95, $CHCl_3$); IR ($CHCl_3$): 2990 (s), 2935 (s), 2870 (s), 1740 (s), 1435 (m), 1385 (m), 1370 (m), 1280 (m), 1255 (m), 1205 (s), 1195 (s), 1090 (s), 1075 (m) $cm^{-1}$; $^1H$ nmr (500 MHz, $CDCl_3$): δ 3.73 (s, 3H), 3.63 (t, J=2.92, 1H), 3.58 (d, J=12.1, 1H), 3.35 (d, J=3.9, 1H), 3.23, (d, J=12.2, 1H), 2.75 (t, J=6.5, 1H), 2.41 (d, $J_{ab}$=16.4, 1H), 2.30 (dd, J=13.0, 3.0, 1H), 2.20-1.98 (m, 4H), 1.85 (tdd, J=11.7, 4.1, 2.4,1H), 1.72 (m, 1H), 1.65 (d, J=11.54, 1H), 1.54-1.43, (m, 2H), 1.43 (s, 3H), 1.41, (s, 3H), 1.30-1.20 (m, 2H), 1.10 (dd, J=13.4, 9.9, 1H), 0.96 (s, 3H), 0.90 (dt, J=13.1, 2.7, 1H), 0.68 (s, 3H); $^{13}C$ nmr (125 MHz, $CDCl_3$): δ 171.0, 97.9, 73.4, 68.4, 62.7, 57.3, 52.3, 47.8, 41.0, 39.3, 34.6, 33.9, 33.3, 32.1, 29.8, 29.1, 26.4, 26.2, 24.2, 24.0, 21.3, 18.9, 17.0, 15.3.

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