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A FORMAL TOTAL SYNTHESIS OF (±)-APHIDICOLIN

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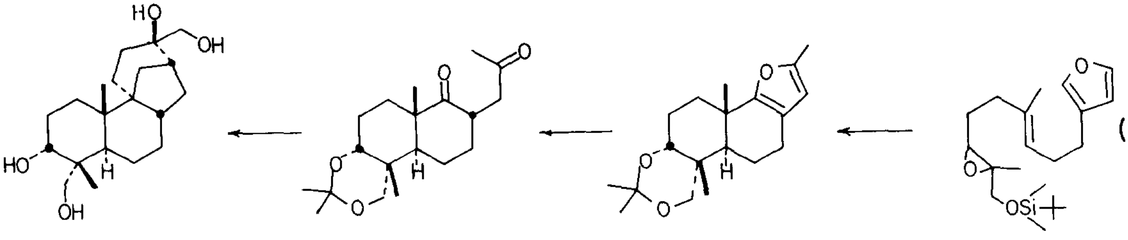
SUMMARY: *A concise formal total synthesis of (±)-1 via the furan-terminated, epoxide-initiated cationic cyclization of* **4** *is described.*

Aphidicolin **1**, a potent antiviral substance with uses in the study of DNA replication[2], has been the target of several synthetic studies.[3,4] In this letter, we report a concise formal total synthesis of (±)-**1** via diketone **2** which has previously been prepared by McMurry.[3b] As a result of our interest in furan chemistry[5] and furans as dianion equivalents in annulation sequences[5,6], we envisioned **3** (R = CH_3) as the precursor of dione **2**. Furan **3** would in turn be prepared from the product of the cationic cyclization of epoxy-furan **4**.

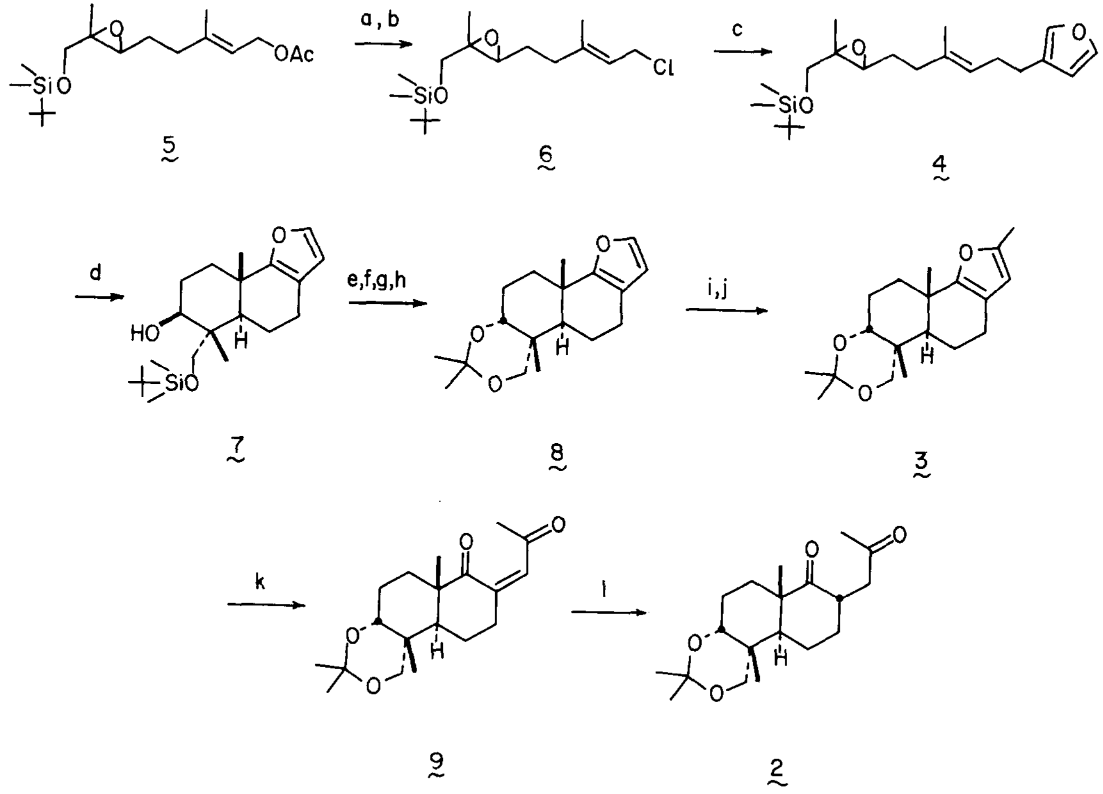


1 2 3 4 (1)

The synthesis of furan **4** begins from the readily available modified geranyl acetate **5**.[7] Cleavage of the acetate (K_2CO_3,MeOH,0°, 95%) and chlorination of the resulting allylic alcohol by the procedure of Stork[8] (i. nBuLi; ii. pTsCl; iii. LiCl,HMPA; 85%) provided the highly oxidized geranyl chloride **6** in 81% yield from **5** after bulb-to-bulb distillation (oven 160°, 0.04 mm Hg). Chloride **6** was coupled with the Grignard reagent derived from 3-chloromethyl furan[9] in the presence of Li_2CuCl_4[9,10] to give the desired **4** (78%).

With **4** in hand, the cyclization sequence was then examined. In our earlier studies of epoxy-furan cyclizations[6], we discovered that ZnI_2 and $Ti(OiPr)_3Cl$ were the Lewis acids

SCHEME I



a) K_2CO_3, MeOH (95%); h) i. nBuLi, ii. pTsCl, iii. LiCl,HMPA (85%); c)  ,Li_2CuCl_4 (78%); d) ZnI_2 or Ti(OiPr)$_3$Cl,CH_2Cl_2 (0-46%) or $BF_3 \cdot OEt_2$ (3 eq.),Et_3N (1.5 eq.),CH_2Cl_2-C_6H_6-hexane (1:1:1),-78° (25-35%); e) PCC (91%); f) nBu_4NF,THF; g) LiBH $(sBu)_3$,THF,-78° (97% from **7**); h) acetone, oxalic acid, CH_2Cl_2, RT (90%); i) NBS, DMF; j) i. n,BuLi, THF, -78°, ii. CH_3I (68% from **8**); k) MCPBA (1.1 eq.) CH_2Cl_2, RT (97%); l) H_2-Pd/C (99%).

which were the most efficient at promoting cyclization without the production of unwanted side products. Exposure of **4** to ZnI_2 (3 eq. CH_2Cl_2, RT) or Ti(OiPr)$_3$Cl (3 eq. CH_2Cl_2, 0°) produced **7** in wildly variable yields (0-46%) with the bulk of the products of these cyclizations consisting of acyclic ketones. The capricious nature of the cyclization with these Lewis acids forced us to examine alternate systems in the hope of obtaining more reproducable yields. After considerable experimentation, we found that exposure of **4** to

$BF_3 \cdot OEt_2$ (3 eq.) and Et_3N (1.5 eq.) in CH_2Cl_2-benzene-hexane (1:1:1) at -78° consistently provided a 25-35% yield of **7** with acyclic ketone again comprising the bulk of the reaction product.[11]

Inversion of the C-3-OH stereochemistry was accomplished as previously described by McMurry[3b] and Corey.[3c] To that end, alcohol **7** was oxidized to provide the corresponding 3-one (PCC[12], 91%). Deprotection of the 4α-CH_2OH (nBu_4NF)[3c] and immediate reduction of the aldol with L-selectride[3b,3c,13] afforded exclusively the $3\alpha,4\alpha$-CH_2OH diol in 97% yield from **7**, which was smoothly protected as the corresponding acetonide (acetone, oxalic acid, CH_2Cl_2,RT; 90%) **8**.

Initially, we attempted to introduce a methyl at the unsubstituted furyl-α'-position by direct metallation and quenching with CH_3I. We were unable to detect any compounds arising from a lithio-furan intermediate under a variety of metallation conditions; with CH_3I or D_2O as electrophiles. In all the variations examined, we observed either no reaction or destruction of the acetonide moiety.[14] However, the methyl group was smoothly introduced by first carefully brominating the furan (NBS,DMF,0°)[15] followed by metal-halogen exchange (nBuLi, THF, -78°) and methylation (CH_3I) giving **3** (68%) and a small amount of recovered **8** (8%). The mixture was oxidized (1.1 eq. MCPBA, CH_2Cl_2)[16] and the desired ene-dione **9** (97% from **3**) was readily separated from the unoxidized disubstituted furan **8**. Reduction of **9** (H_2-Pd/C, EtOAc (1 atm)) afforded dione **2**; the identity of **2** was secured after a comparison of spectral data with spectra kindly provided by Professor J. E. McMurry.

Although the formal total synthesis of (±)-aphidicolin **1** is complete, we are continuing our studies with the intention of improving the troublesome cyclization reaction[11] and of producing optically pure materials.

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