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AN EFFICIENT CONVERSION OF l-ABIETIC ACID TO (+)-3-DEOXYAPHIDICOLIN

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Abstract: The first total synthesis of (+)-3-deoxyaphidicolin, a selective inhibitor of eukaryotic DNA polymerase α, has been completed efficiently and stereoselectively starting from l-abietic acid.

3-Deoxyaphidicolin **1**, recently isolated as a phytotoxin from the culture broth of Phoma betae Fr. by Ichihara et al[1], has been shown to be a structural analog of aphidicolin[2] **2** and also demonstrated to be a selective inhibitor of DNA polymerase α.[3] The tetracyclic diterpene aphidicolin family has attracted a great deal of synthetic study[4] because of the interesting biological property[2] and the unique C/D ring moiety. The most severe stereochemical problem in the synthesis of **2** is located at the spiro center of C-9, and many challenges to the total synthesis were carried out[4], but none of them afforded the final product in optically active form. We describe herein the first total synthesis of optically active 3-deoxyaphidicolin **1**. Before the isolation of **1**, we became interested[5a] in the structure-activity-relationships[6] of **2** and decided to convert l-abietic acid **3** to congeners of **2** including **1**, because **3** is easily available as a main component of pine resin.[7] Cyclopentenone **4**, easily obtained in quantity[5b] by acid-catalyzed rearrangement of **3** followed by ozonolysis and esterification with CH_2N_2, was considered to be a good chiral synthon for the elaboration of aphidicolane skeleton. β-Position to the keto group of **4** is quite crowded with a quarternary center at C-10 and usual C-C bond formation at C-9 seems to be less satisfactory[4b]. However, such difficulty was remarkably overcome by using photoaddition of allene to **4**[5a]. Thus, to the ethanolic solution of **4**, allene was added in large excess and the solution was irradiated by a high-pressure mercury-lamp at -78°C for 4hr to afford a cycloadduct **5** as a main product (65% yield) along with other minor products (8% yield)[8]. The stereochemistry of **5** was unambiguously determined by X-ray analysis of the oxime derivative **5'**[9]. Therefore, the result showed that the photoaddition took place stereoselectively from α-face of

the tricyclic enone **4**, contrary to the nonstereoselective photoaddition of allene to other tricyclic enone[10]. Next, the introduction of C_3-unit at C-9 was extensively studied through fragmentation of the cyclobutane moiety of **5**. After many attempts, boron-mediated fragmentation[11] was found to be satisfactory for our purpose. Mesylate **7** was obtained in two steps (92%) from **5** ($NaBH_4$ reduction and MsCl/py). Fragmentation took place smoothly by treatment of **7** with B_2H_6 followed by aq NaOH at reflux-temperature of THF to afford a diene **8** in 65% yield. The primary alcohol selectively formed by treatment with disiamylborane (96%) and H_2O_2 was protected with TBDMSOTf to afford **9** (98%). Further hydration of the inner olefin of **9** with B_2H_6 followed by oxidation with PCC afforded cyclopentanone **10**. From our previous study[5a], it became necessary to control the direction of enolization of the ketone **10**. α-Bromoderivative (94%) was prepared through the silyl enol ether and converted to α,β-unsaturated ketone **11** with DBU (55%) and 2N-HCl (89%). The aldehyde **12** obtained by oxidation of **11** with PCC (73%) was subjected to aldol condensation with NaOEt to afford an epimeric mixture of **13** quantitatively. The catalytic hydrogenation (H_2/Pt) of the acetyl derivative (Ac_2O/Py : 73%) afforded quantitatively the saturated compound with desired stereochemistry as expected. The epimeric mixture was separated at this stage by chromatography on silica gel to afford α- and β-OAc derivatives **14**α and **14**β in a ratio of 1.2 to 1. Both epimers were separately converted to the same ketonic alcohol **15** in the following way. Successive treatment of **14**β with $LiBH_4$, TBDMSOTf, NaOMe, $COCl_2$/DMSO afforded the ketone **15** in 78% overall yields. Successive treatment of **14**α with K_2CO_3, $PhCH_2OCH_2Cl$, $LiBH_4$, TBDMSOTf, H_2/$Pd(OH)_2$, and $COCl_2$/DMSO afforded the same ketone **15** in 66% overall yields. Wittig reaction of **15** ($Ph_3\overset{+}{P}CH_3\overset{-}{B}r$/nBuLi) afforded the exomethylene derivative **16** (91%). Then, the final stage of the present synthesis was performed smoothly. Glycol-formation (90%) with OsO_4/N-methylmorpholine N-oxide, protection (95%) with 2,2-dimethoxy-propane/H^+, removal of the silyl group (quant.) with $^nBu_4\overset{+}{N}\overset{-}{F}$, Barton reaction (95%, CS_2/MeI/NaH → nBu_3SnH/AIBN), reduction (quant.) of the ester with $LiAlH_4$, and removal (quant.) of the isopropyliden group with aq HCl afforded (+)-3-deoxyaphidicolin ($[\alpha]_D^{23}$ +25.1° (c 0.750, EtOH)) identical in all respects with the natural sample[12]. Among the synthetic sequence developed here, the combination of quarternary carbon formation by photoaddition of allene to α,β-unsaturated ketone and fragmentation through boron-mediated reaction might have a great potential for natural product synthesis.

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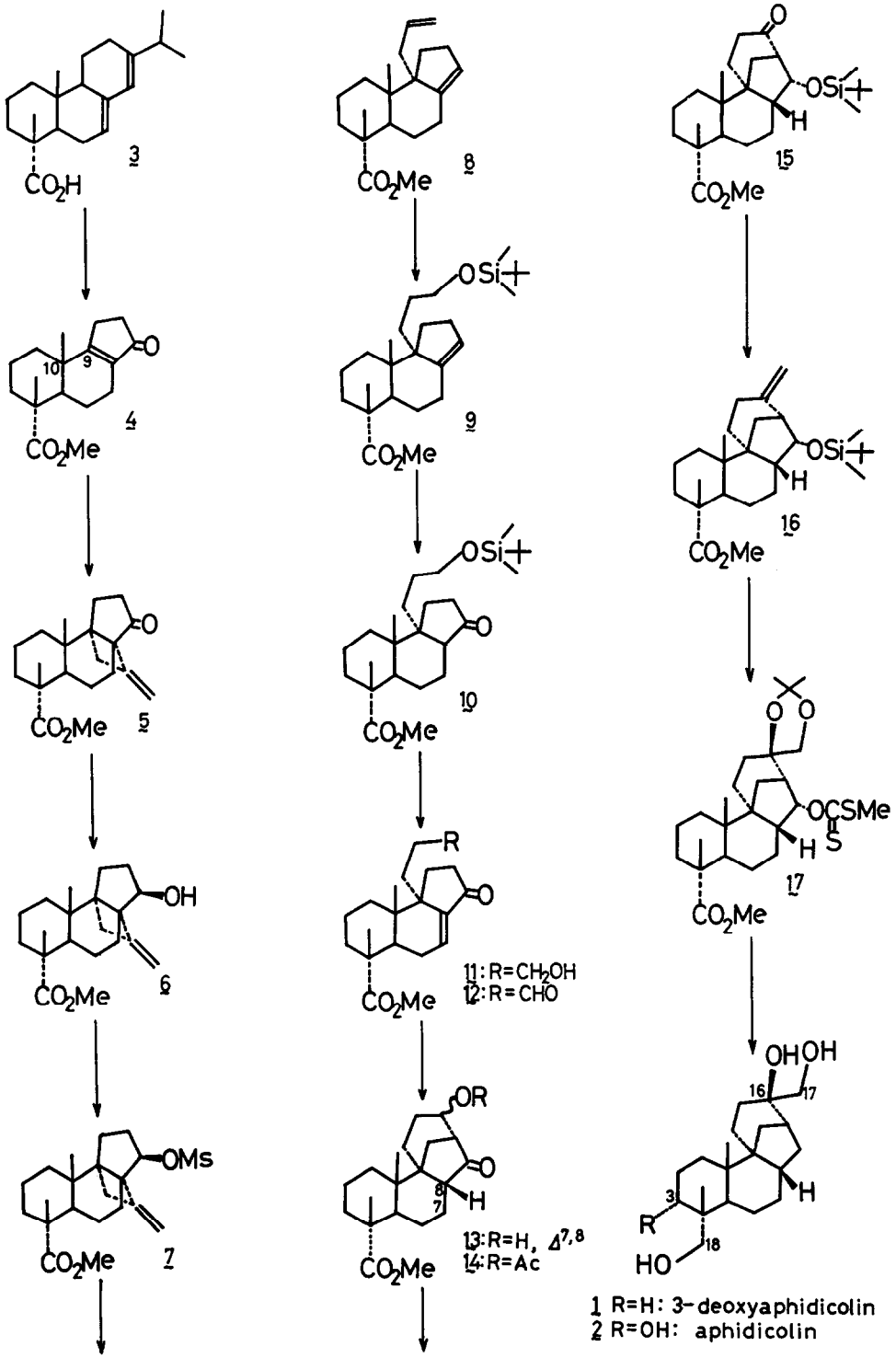
3
CO2H
4
10
9
O
CO2Me
5
CO2Me
6
OH
CO2Me
7
OMs
CO2Me
8
CO2Me
9
OSi
CO2Me
10
OSi
CO2Me
11: R=CH2OH
12: R=CHO
R
CO2Me
13: R=H, Δ7,8
14: R=Ac
OR
8
7
H
CO2Me
15
O
OSi
H
CO2Me
16
OSi
H
CO2Me
17
O
O
OCSMe
S
H
CO2Me
OH OH
16
17
3
H
R
18
HO
1 R=H: 3-deoxyaphidicolin
2 R=OH: aphidicolin

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6. (a) We were pleased to know that **1** was isolated as a secondary metabolite of a microorganism and also has very interesting biological activities kindly informed by Dr. A. Ichihara before publication. (b) We are also grateful to Dr. Hirosuke Yoshioka, the Institute of Physical and Chemical Research, for providing us with valuable information of the structure-activity relationships of aphidicolin and the homologues.
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8. Although the detail of this minor products was not investigated, the spectroscopic evidence showed that they were other allene adducts with different stereo- or regio-chemistry, and the purification of **5** was best carried out at the next reduction step.
9. Crystal data of **5'**: $C_{20}H_{29}NO_3$(MW=331.5), space group $P2_12_72_1$, a=12.068(6)A, b=20.18(10), c=7.446(4), V=1813.4A^3, Z=4, Dcal=1.215gcm^{-3}, final R factor= 0.049.
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12. All compounds developed here were purified by column chromatography on silica gel and well characterized by spectroscopic analysis.

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