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Enantioselective Total Synthetic Route to (+)-Aphidicolin

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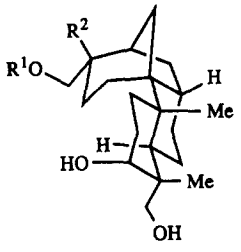
Abstract: Enantioselective total synthetic route to (+)-aphidicolin (1) has been described. Cycloisomerization reaction (**9**→**10**) and intramolecular Diels-Alder reaction (**12**→**13**) were employed for the key steps of the sequence.

In 1972, Hesp and co-workers at ICI reported the isolation of a tetracyclic diterpenoid antibiotic, aphidicolin (**1**), from the fungus *Cephalosporium aphidicola Petch*.[1] Aphidicolin (**1**) displays marked activity against Herpes simplex type I virus in cultures of human embryonic cells.[2] Apart from its antifeedant property,[3] **1** exhibits considerable antitumor activity in the C6 mouse colon and B16 mouse melanosarcoma screens[4] and has been shown to inhibit the growth of leukemic T- and B-lymphocytes.[5] The antitumor activity of aphidicolin (**1**) observed against rodent tumors has stimulated interest in clinical investigation to the effectiveness of **1** against human tumors. Although the development of **1** as an antitumor agent has been hampered by its poor water solubility, a recent report of enhanced antitumor activity associated with the more water-soluble compounds such as aphidicolin-17-glycinate HCl salt (**2**)[6] and 16-fluoroaphidicolin (**3**),[7] synthesized as pro-drugs, might revive interest in aphidicolin (**1**) and its analogues as a specific reversible inhibitor of DNA polymerase α.



R^1 = H, R^2 = OH; **Aphidicolin (1)**

R^1 = $COCH_2NH_2 \cdot HCl$, R^2 = OH; **Aphidicolin-17-glycinate HCl salt (2)**

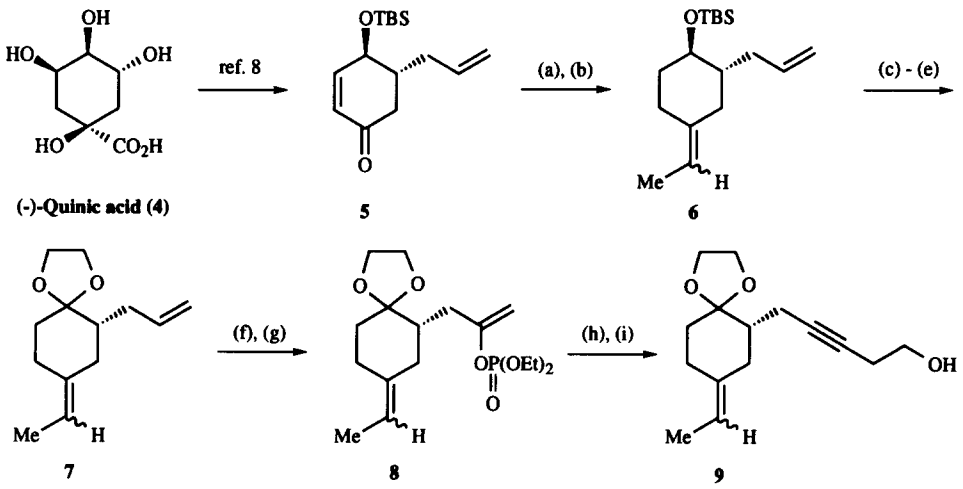
R^1 = H, R^2 = F; **16-Fluoroaphidicolin (3)**

The physiological properties coupled with its structural complexity have made aphidicolin (**1**) an attractive synthetic target. **1** incorporates three structural features which have posed long-standing synthetic problems: (i) a spiro fused bicyclo[3.2.1]octane moiety which comprises the C and D rings, (ii) adjacent quaternary stereogenic centers (C9 and C10), and A, B-*trans* ring juncture.

Herein, we describe an enantioselective total synthetic route to (+)-aphidicolin (**1**) featuring methodologies designed to address the outstanding issues confronted during the enantioselective total synthesis of (+)-**1**, *viz* (a) cycloisomerization reaction for the construction of CD ring system, and (b) intramolecular Diels-Alder reaction producing A, B-*trans* ring juncture.

First of all, the readily available optically pure enone (**5**), prepared from (-)-quinic acid (**4**) by using Overman's protocol,[8] was converted to the alcohol (**9**), as shown in **Scheme I**. Namely, regioselective reduction of **5** with sodium hydrosulfite[9] in the presence of Adogen 464® afforded the corresponding ketone (71%), which was subjected to Wittig reaction, furnishing the ethylidene derivative (**6**)[10] in 89% yield. Deprotection (83%) of the TBS group, followed by oxidation[11] with tetrapropylammonium perruthenate (TPAP) in the presence of N-methylmorpholin N-oxide (NMO) yielded, in 91% yield, the ketone, which was transformed into **7** after ketalization (100%). The conversion of **7** to the phosphonate (**8**) was achieved in two steps, including Wacker oxidation[12] (88%) and enolization of the resulting methyl ketone under kinetic conditions. Upon treatment of **8** with LDA, the corresponding acetylene was produced in 86% yield. Alkylation of lithium salt of the above acetylene was conducted with ethylene oxide by means of Kotsuki's procedure[13] to give rise to the alcohol (**9**) in 87% yield.

Scheme I



Reaction Conditions: (a) $Na_2S_2O_4$, $NaHCO_3$, Adogen 464®, C_6H_6-H_2O (1 : 1 v/v), reflux. (b) $Ph_3P^+EtBr^-$, ^nBuLi, THF, reflux. (c) $^nBu_4N^+F^-$, THF. (d) TPAP, NMO, 4 Å MS, CH_2Cl_2. (e) ethylene glycol, PPTS, C_6H_6, reflux. (f) O_2, $PdCl_2$, CuCl, H_2O-DMF (1 : 4 v/v), 45 °C. (g) LDA, THF, -78 °C; $ClP(O)(OEt)_2$. (h) LDA, THF, -78 °C→0 °C. (i) ^nBuLi, THF, -78 °C; ethylene oxide, BF_3·Et_2O.

With **9** in hand, the crucial cycloisomerization reaction[14] for the construction of the CD ring system of aphidicolin (**1**) was examined. As a result of testing, the cycloisomerization of **9** in C_6H_6 in the presence of $(dba)_3Pd_2$·$CHCl_3$ (2.5% mol), P(*o*-tolyl)$_3$ (5.0% mol) and AcOH (5.0% mol) proceeded quite nicely to furnish the olefinic alcohol (**10**), $[\alpha]_D^{23}$ -81.88 ° (*c* = 1.02, $CHCl_3$), in 76% yield.

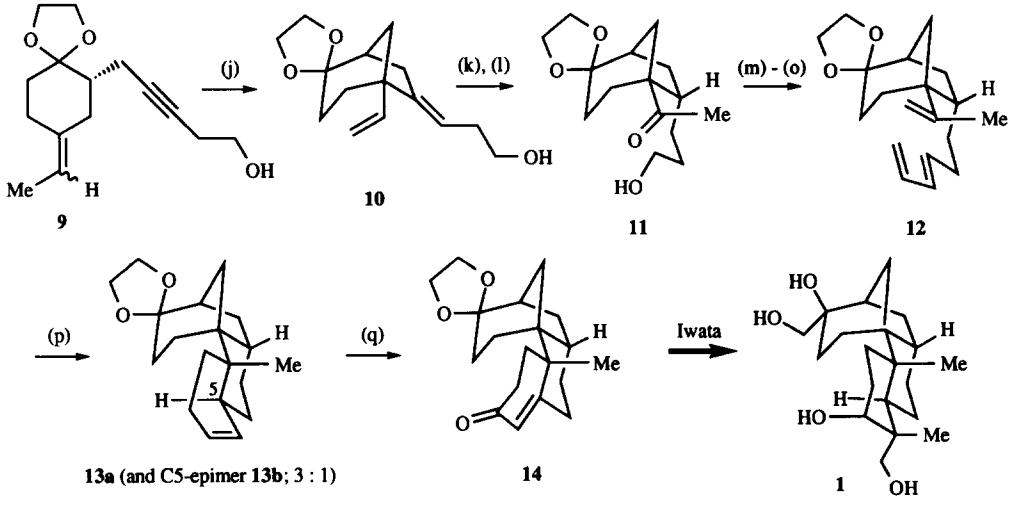
Our synthetic efforts were next focused on the introduction of diene and dienophile portions for the second key step. The requisite triene (**12**) was prepared as describe below. Wacker oxidation at 60 °C (69%)

followed by catalytic hydrogenation of the resulting olefinic ketone gave the keto alcohol (**11**), $[\alpha]_D^{25}$ -19.25 ° (c = 0.267, $CHCl_3$), in 52% yield. Wittig olefination (62%) of **11** followed by oxidation with PCC in the presence of NaOAc of the resulting alcohol led to the corresponding aldehyde (85%), which was subjected to Yamamoto reaction[15] (73%) to give **12** {$[\alpha]_D^{25}$ -7.96 ° (c = 0.470, $CHCl_3$)}.

With the efficient synthesis of the triene (**12**) realized, the stage was now step for the construction of aphidicolane-type ring system. An intramolecular Diels-Alder reaction of **12** was performed in toluene at 220 °C for 11 days in a sealed tube to provide the tetracyclic compounds (**13**), in 70% yield as a 3 : 1 diastereomeric mixture at C5,[16] which was used directly in next step without separation.

Finally the pivotal transformation of **13** into the enone (**14**), $[\alpha]_D^{25}$ +91.57 ° (c = 0.375, $CHCl_3$), was conducted, 55% overall yield for 3 steps, under standard conditions[17] (**Scheme II**).

Scheme II



Reaction Conditions: (j) $(dba)_3Pd_2{\cdot}CHCl_3$, P(*o*-tolyl)$_3$, AcOH, C_6H_6, 60 °C, reflux, tube. (k) O_2, $PdCl_2$, CuCl, H_2O-DMF (1 : 4 v/v), 60 °C. (l) H_2, PtO_2, EtOH. (m) $Ph_3P^+MeBr^-$, ^nBuLi, DME, reflux. (n) PCC, NaOAc, Florisil®, CH_2Cl_2. (o) $Ph_2P(O)CH_2CH{=}CH_2$, ^nBuLi, HMPA, THF, -78 °C→room temperature. (p) 220 °C, toluene, sealed tube. (q) O_2, hv, pyridine, hematoporphyrin; NaI, AcOH, EtOH, Et_2O; TPAP, NMO, 4 Å MS, CH_2Cl_2.

An important advantage of the present synthetic strategy is that each diastereoisomer (**13a** and **13b**), isomeric only at C5 position, affords the same enone (**14**),[18] which displays the same spectra with those provided by Iwata and co-workers in a total synthesis of (±)-aphidicolin (**1**). Thus, the present enantioselective synthesis of **14** gives rise to the formal total synthetic route to (+)-aphidicolin (**1**).

In conclusion, we have demonstrated enantioselective formal total synthetic route to (+)-aphidicolin (**1**) based on cycloisomerization reaction and intramolecular Diels-Alder reaction.

Acknowledgment

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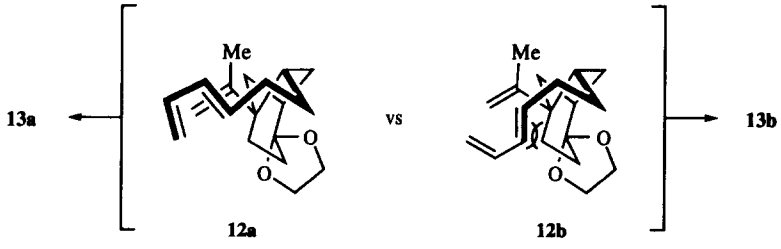

12a MMX rel = 0.0 kcal/mol **12b** MMX rel = 1.0 kcal/mol

These calculations suggested that the transition state (**12a**) is considerably lower in energy than the alternative one (**12b**). Thus, this analysis supports the tentative assignment of **13a** as the major product of the intramolecular Diels-Alder reaction of **12**.

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