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An Expeditious and Efficient Formal Synthesis of (±)-Aphidicolin

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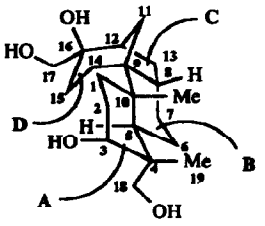
Abstract: An expeditious and efficient formal total synthesis of antiviral and antitumor tetracyclic diterpene aphidicolin has been developed. An intramolecular Heck reaction (**3**→**4**) and an intramolecular Diels-Alder reaction (**7**→**8**) were utilized for the key step of the sequence.

In 1972 Hesp and co-workers reported the isolation and structure of the tetracyclic diterpene aphidicolin (**1**), produced by the fungus *Cephalosporium aphidicolia*.[1] Aphidicolin (**1**) shows marked activity against Herpes simplex Type I virus, both *in vitro* and in the rabbit eye.[2] In addition to 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] with no discernible toxicity. Later studies elucidated the mode of action which involves highly specific competitive inhibition of DNA polymerase α; aphidicolin (**1**) thus has no effect on non-proliferating cells.[6] The development of **1** as an antitumor agent has been hampered by the poor water solubility of the parent compound, but a recent report[7] of enhanced antitumor activity associated with the more water-soluble aphidicolin glycinate ester HCl salt might revive interests in aphidicolin (**1**).



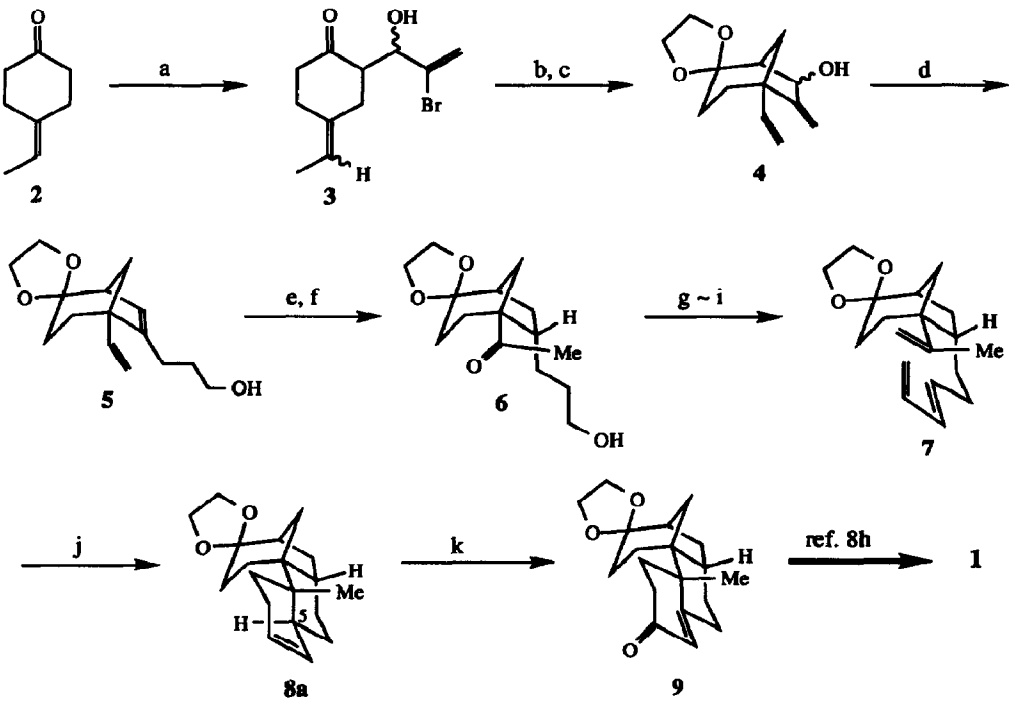
Aphidicolin (**1**)

The above-mentioned biological properties of **1**, coupled with its novel and highly unusual carbon framework present a formidable and important challenge. The novel tetracyclic carbon skeleton of **1** incorporates eight stereogenic centers and a spiro fused bicyclo[3.2.1]octane moiety which comprises the C and D rings. Not only is C9 spiro center chiral, it is also next to another quaternary center, C10. The presence of

these two adjacent chiral quaternary centers makes this region of aphidicolin quite crowded. After considerable efforts, no fewer than eight total syntheses[8] and one formal synthesis[9] have been reported to date. And recently Holton and co-workers disclosed the first enantioselective construction of **1**, unambiguously confirming the absolute stereochemistry.[8g] Although elegant, these syntheses suffer from poor overall yields due to their multi-step routes.

Herein, we describe conceptually distinct approach to **1** featuring methodologies designed to address the above-mentioned outstanding issues confronted during the total synthesis of **1**, *viz.*, (1) intramolecular Heck reaction for the construction of CD ring system, and (2) intramolecular Diels-Alder reaction affording AB *trans* ring juncture. The execution of this synthesis proceeded as summarized in Scheme I.

Scheme I



Reaction conditions: (a) LDA, THF, CH_2=CBrCHO, -78 °C (89%), (b) $Pd(OAc)_2$, P(*o*-tolyl)$_3$, K_2CO_3, MeCN, reflux (90%), (c) $HOCH_2CH_2OH$, PPTS, C_6H_6, reflux (86%), (d) CH_2=CHOEt, $Hg(OAc)_2$, reflux; Toluene, 140 °C, sealed tube; $NaBH_4$, MeOH, 0 °C (77%, 3 steps), (e) O_2, $PdCl_2$, CuCl, DMF-H_2O, 40 °C (70%), (f) H_2, 10% Pd-C, AcOEt (82%), (g) $Ph_3P^+MeBr^-$, ^{n}BuLi, THF, reflux (81%), (h) PCC, NaOAc, Florisil®, CH_2Cl_2 (92%), (i) $Ph_2P(O)CH_2CH$=CH_2, ^{n}BuLi, HMPA, THF, -78 °C → r.t. (62%), (j) Methylene blue, Toluene, 210 °C, sealed tube (67%), (k) O_2, hv, Hematoporphyrin, Pyridine; NaI, AcOH, Et_2O-EtOH; MnO_2, CH_2Cl_2 (81%, 3 steps).

The aldol reaction of α-bromoacrolein with the lithium enolate of 4-ethylidenecyclohexan-1-one (**2**) provided the allylic alcohol **3** in 89% yield. The critical Heck cyclization[10] of **3** proceeded cleanly in refluxing MeCN in the presence of 10% $Pd(OAc)_2$, 20% P(*o*-tolyl)$_3$, and 2 equiv of K_2CO_3 to give, in 90% yield, the bicyclic ketone, which was transformed into **4**[11] after ketalization (86%). The conversion of **4** to the alcohol **5** was achieved in three steps (77% overall yield), including etherification (CH_2=CHOEt, $Hg(OAc)_2$), the Claisen rearrangement of the vinyl ether (toluene, 140 °C, in sealed tube), and $NaBH_4$ reduction of the resulting aldehyde. Wacker oxidation[12] of **5** was next conducted with O_2, $PdCl_2$, and CuCl in DMF-H_2O (7 : 1) at 40 °C to give rise to the corresponding methyl ketone in 70% yield, which was then further treated with 10% Pd/C under a hydrogen atmosphere to afford the saturated ketone **6** in 82% yield. As a consequence of steric congestion on the endo surface of the bicyclo[3.2.1]octane subunit, the above hydrogenation provided solely **6**.

Our synthetic efforts were next focused on the introduction of diene and dienophile portions for the intramolecular Diels-Alder reaction. The requisite triene **7** was readily prepared as described below. Namely, Wittig olefination ($Ph_3P^+MeBr^-$, ^{n}BuLi, THF, reflux, 81%) of **6** followed by oxidation with PCC in the presence of NaOAc of the resulting alcohol led to the corresponding aldehyde (92%), which was allowed to Yamamoto reaction[13] ($Ph_2P(O)CH_2CH$=CH_2, ^{n}BuLi, HMPA, THF, -78 °C → r.t., 62%) to furnish **7**.[14]

With the efficient synthesis of the triene **7** realized, the stage was now set for the construction of aphidicolane-type ring system. An intramolecular Diels-Alder reaction was performed in the presence of methylene blue[15] in toluene at 210 °C for 120 h in a sealed tube to produce the desired tetracyclic compound **8** in 67% yield as a 4 : 1 diastereomeric mixture at C5.[16]

Finally, consecutive irradiation[17] of **8** in the presence of hematoporphyrin under oxygen atmosphere with a halogen lamp, reductive work-up (NaI, AcOH, Et_2O-EtOH) and MnO_2 oxidation (81% overall yield) provided the enone **9**, which displayed spectral properties identical with those reported by Iwata and co-workers in a total synthesis of aphidicolin (**1**),[8h] thus completing a formal total synthesis of **1**.

In conclusion, we have established expeditious and highly stereocontrolled methodology for the formal total synthesis of aphidicolin based on Heck cyclization reaction and intramolecular Diels-Alder reaction. The success of the above procedure rests on the extremely high regio- and stereoselectivities observed through the overall sequences.

Acknowledgment: We are very grateful to Professor C. Iwata for sending us copies of the spectral data of **9**.

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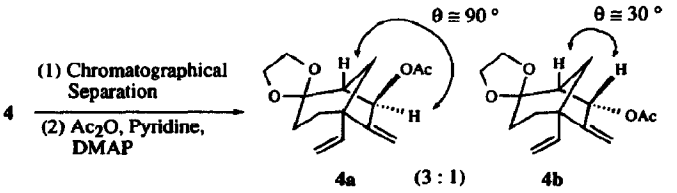
11. Although the stereochemical assignment of **4** was not possible at this stage, successful elaboration of **4** to **4a** and **4b** definitely confirmed their stereochemistry as shown below.



4a: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.05 (3H, s), 3.90 - 4.04 (4H, m), 5.06 (1H, dd, *J* = 11.0 and 1.0 Hz), 5.07 (1H, dd, *J* = 17.5 and 1.0 Hz), 5.13 (1H, br d, *J* = 1.0 Hz), 5.37 (1H, br s, C*H*OAc), 5.57 (1H, br d, *J* = 1.0 Hz), and 5.91 (1H, dd, *J* = 17.5 and 11.0 Hz). **4b**: ^{1}H-NHR (300 MHz, $CDCl_3$): δ 2.10 (3H, s), 3.75 - 4.00 (4H, m), 5.00 (1H, br d, *J* = 2.5 Hz), 5.09 (1H, dd, *J* = 17.5 and 1.0 Hz), 5.10 (1H, dd, *J* = 11.0 and 1.0 Hz), 5.17 (1H, br d, *J* = 2.5 Hz), 5.35 (1H, dt, *J* = 6.0 and 2.5 Hz, C*H*OAc), 5.87 (1H, br dd, *J* = 17.5 and 11.0 Hz).
The stereoselectivity of the aldol process (**2** → **3**) is consistent with the rule, based on the Zimmerman-Traxler cyclization state model, that *E*-enolates should selectively produce *threo* aldol products.
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14. E/Z ratio (22 : 1) was determined by integration of the resonances due to the olefinic proton in the nmr spectra of reaction mixture.
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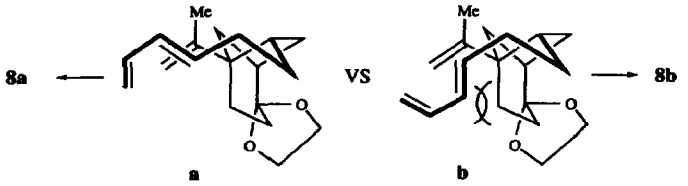
16. The steric congestion in the trasition state **b** makes it less favorable than the alternative transition state **a** which gives rise to **8a**.



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