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Diastereoselective Formal Total Synthesis of the DNA Polymerase α Inhibitor, Aphidicolin, Using Palladium-Catalyzed Cycloalkenylation and Intramolecular Diels–Alder Reactions

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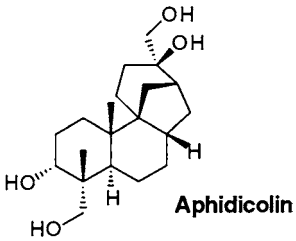
ABSTRACT



Aphidicolin

A novel diastereoselective formal synthesis of aphidicolin has been achieved by exploiting a unique characteristic of a bicyclo[3.2.1]octane prepared by employing a palladium-catalyzed cycloalkenylation process.

Palladium-promoted cycloalkenylation reactions of silyl enol ethers with olefins are key C−C bond-forming reactions utilized in organic synthesis.[1] The catalytic version of this process, developed in our laboratory, which produces bicyclic compounds, including bicyclo[3.2.1]octanes,[2] perhydro-pentalenes,[3] hydrindanes,[3] and benzo-fused bicyclo[3.3.0]-octanes,[3] has been applied to the construction of bioactive natural products, e.g., C_{20} gibberellins[4] and methyl atis-16-en-19-oate.[2,5] As part of an effort to demonstrate the versatility of the palladium-catalyzed cycloalkenylation, we have recently used this process in a novel approach to the synthesis of the molecularly complex and biologically significant target aphidicolin (**1**).

Aphidicolin (**1**)[6] is a tetracyclic terpenoid that exhibits significant antiviral and antitumor activity.[7] Following its isolation and the demonstration of its potential pharmacological uses, numerous synthetic approaches to **1** have been developed.[8] Aphidicolin (**1**) contains (1) a spiro-fused bicyclo[3.2.1]octane CD ring architecture, (2) eight stereo-

(1) (a) Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. *J. Am. Chem. Soc.* **1979**, *101*, 494−496. (b) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 5808−5810. (c) Shibasaki, M.; Mase, T.; Ikegami, S. *J. Am. Chem. Soc.* **1986**, *108*, 2090−2091.

(2) (a) Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916−4925. (b) Recent review: Toyota, M.; Ihara, M. *Synlett* **2002**, 1211−1222.

(3) Toyota, M.; Ilangovan, A.; Okamoto, R.; Masaki, T.; Arakawa, M.; Ihara, M. *Org. Lett.* **2002**, *4*, 4293−4296.

(4) Toyota, M.; Odashima, T.; Wada, T.; Ihara, M. *J. Am. Chem. Soc.* **2000**, *122*, 9036−9037.

(5) Toyota, M.; Wada, T.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 4565−4570.

(6) Brundret, K. M.; Daliziel, W.; Hesp, B.; Jarvis, J. A. J.; Neidle, S. *J. Chem. Soc., Chem. Commun.* **1972**, 1027−1028.

(7) (a) Buchnall, R. A.; Moores, H.; Simms, R.; Hesp, B. *Antimicrob. Agents Chemother.* **1973**, *4*, 294−298. (b) Ikegami, S.; Taguchi, T.; Ohashi, M.; Oguro, M.; Mano, Y. *Nature* **1978**, *275*, 458−460.

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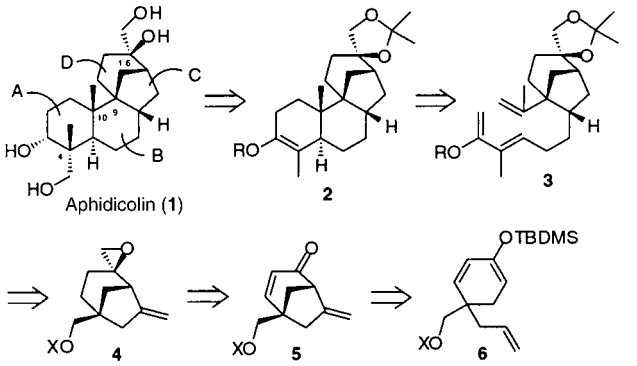
genic centers, of which five are associated with ring junctions, and (3) a sterically crowded array of two adjacent quaternary centers at C-9 and C-10. Critical problems that need to be addressed in any synthesis of aphidicolin (**1**) are (1) the construction of the tetracyclic ring system with appropriate control of stereochemistry in the CD ring system and (2) stereoselective introduction of four hydroxy groups. Previous studies in this laboratory led to the development of two formal syntheses of aphidicolin (**1**), one employing palladium-catalyzed Heck reaction[8a] and the other a cycloisomerization process[8c] in key steps. However, both approaches are problematic due to difficulties with effective functionalization of the AB ring system and the D ring. Herein, we describe an improved synthesis of aphidicolin (**1**) that features a palladium-catalyzed cycloalkenylation process, stereoselective oxirane formation to install D ring functionality, and intramolecular Diels−Alder reaction of a silyloxydiene grouping to simplify introduction of A-ring functionality.

The retrosynthetic plan guiding this synthetic approach to aphidicolin (**1**) is outlined in Scheme 1. We anticipated that

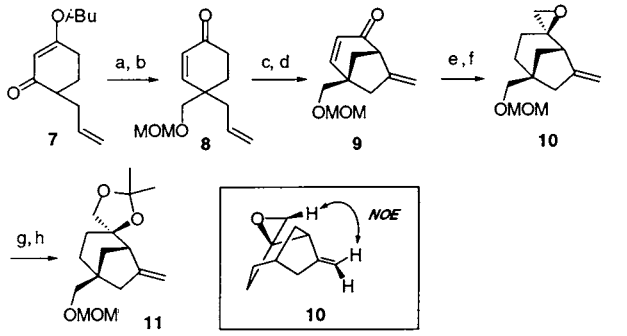
Scheme 1. Retrosynthetic Analysis of Aphidicolin



intramolecular Diels−Alder reaction of triene **3** would proceed stereoselectively to form the pentacyclic ring system in **2**, a precursor of aphidicolin (**1**). We believed that stereoselective introduction of the diene and dienophile moieties in **3** and the oxirane group in **4** could be achieved by exploiting the characteristics of the bicyclo[3.2.1]octane ring system. Finally, in a sequence based on this plan, intermediate **5** would be constructed by using palladium-catalyzed cycloalkenylation of the cross-conjugated silyl enol ether **6**.[2]

Our approach begins with the preparation of acetonide **11** by the route shown in Scheme 2. Carbomethoxylation of 6-allyl-3-isobutoxy-2-cyclohexen-1-one (**7**)[9] affords the ester, which is subjected to sequential reduction, acid treatment, and etherification. After conversion of the resulting enone **8**

Scheme 2 [a]



[a] Reagents: (a) LDA, HMPA, THF, −78 °C; $NCCO_2Me$, 93%. (b) $LiAH_4$, THF; 10% $HClO_4$, THF; MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 76%. (c) LDA, HMPA, THF, −78 °C; TBDMSCl, 91%. (d) $Pd(OAc)_2$ (5 mol %), DMSO, O_2 (1 atm), 45 °C, 89%. (e) L-Selectride, THF, −78 °C, 93%. (f) Me_2S^+ $(O)CH_2^-$, THF, 89%. (g) 1 M KOH, dioxane, 100 °C. (h) $Me_2C{=}O$, PPTS, reflux, 91% for two steps.

to the corresponding cross-conjugated silyl enol ether, cycloalkenylation[10] is performed in the presence of 5 mol % $Pd(OAc)_2$ to furnish the bicyclo[3.2.1]octenone **9** in 89% yield. Selective reduction of the conjugated double bond of **9** is then achieved by using L-Selectride. To introduce the oxirane moiety stereoselectively, we used the Corey−Chaykovsky protocol.[11] The desired oxirane **10** is obtained as the major product and is readily separated from the minor isomer by silica gel column chromatography. The proton and carbon resonances in the NMR spectra of **10** were assigned by using $^1H-^1H$ COSY and $^1H-^{13}C$ COSY techniques. The relative stereochemistry of **10** is established by employing NOESY correlations between the olefinic and methylene protons, as depicted in Scheme 2. Importantly, the stereoselectivity of the oxirane-forming reaction is in full accordance with Corey's suggestion that equatorial addition of dimethylsulfoxonium methylide to the carbonyl group of cyclohexanone derivatives is favored. Basic treatment of **10** followed by protection of the resulting diol provides the acetonide **11**.

Triene **19**, required for the intramolecular Diels−Alder reaction, is synthesized by the pathway shown in Scheme 3. Allylation of the ketone, resulting from ozonolysis of olefin **11**, affords olefin **12** as a single diastereomer. This substance is stereoselectively transformed to α-alcohol **13** by hydroboration−oxidation, followed by protection and hydride reduction. Direct dehydration of **13**, by using either the Martin or Burgess reagent, is not successful. However, **13** can be converted to the corresponding olefin **14** by syn elimination of its thioimidazolide derivative.

We anticipated that hydrogenation of the resulting olefin would occur preferentially from the convex face. In the event, catalytic hydrogenation of the olefinic alcohol, obtained by

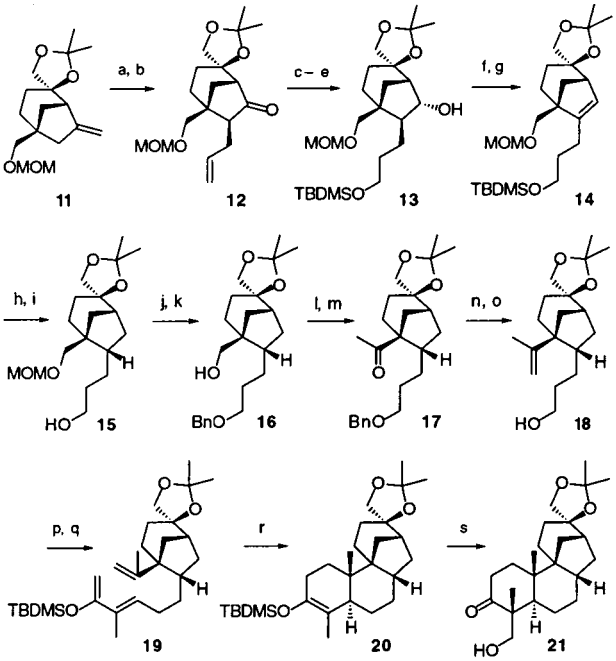
(8) Recent review: Toyota, M.; Ihara, M. *Tetrahedron* **1999**, *55*, 5641−5679. Our previous work: (a) Toyota, M.; Nishikawa, Y.; Fukumoto, K. *Tetrahedron Lett*. **1994**, *35*, 6495−6498. (b) Toyota, M.; Nishikawa, Y.; Seishi, T.; Fukumoto, K. *Tetrahedron* **1994**, *50*, 10183−10192. (c) Toyota, M.; Nishikawa, Y.; Fukumoto, K. *Tetrahedron Lett*. **1995**, *36*, 5379−5382. (d) Toyota, M.; Nishikawa, Y.; Fukumoto, K. *Tetrahedron* **1996**, *52*, 10347−10362.

(9) Stork, G.; Danheiser, R. L. *J. Org. Chem*. **1973**, *38*, 1775−1776.

(10) Toyota, M.; Rudyanto, M.; Ihara, M. *J. Org. Chem*. **2002**, *67*, 3374−3386.

(11) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc*. **1965**, *87*, 1353−1364.

Scheme 3 [a]



[a] Reagents: (a) O_3, MeOH, −78 °C; Me_2S, 96%. (b) LDA, HMPA, THF, −78 °C; $CH_2{=}CHCH_2I$, −78 to rt, 92%. (c) Dicyclohexylborane, THF; NaOH, H_2O_2, 0 °C. (d) TBDMSCl, imidazole, DMF, 0 °C. (e) $NaBH_4$, MeOH, 86%. (f) $(Imid)_2C{=}S$, CH_2Cl_2, reflux, 96%. (g) 250 °C, toluene, in stainless autoclave, 77%. (h) Bu_4NF, THF, 100%. (i) H_2, PtO_2, MeOH, 100%. (j) NaH, BnBr, DMF, 75%. (k) 10% $HClO_4$, THF, 45 °C; Me_2CO, *p*-TsOH, 53%. (l) $SO_3{\cdot}Py$, DMSO, Et_3N; MeLi, Et_2O, −78 °C. (m) TPAP, NMO, 4 Å molecular sieves, CH_2Cl_2, 50% for three steps. (n) $Ph_3P^+MeBr^-$, BuLi, toluene, 85%. (o) Li, liquid NH_3; NH_4Cl, 96%. (p) $SO_3{\cdot}Py$, DMSO, Et_3N, 83%; $(EtO)_2P(O)CH(Me)COMe$, NaH, THF, 95%. (q) TBDMSOTf, *i*-Pr_2NEt, CH_2Cl_2, 93%. (r) 230 °C, toluene, in stainless autoclave, 75%. (s) CH_2O, anhydrous Bu_4NF, THF, 44%.

removal of the TBDMS group from **14**, produces the corresponding alcohol **15** as a single stereoisomer. Sequential benzylation of **15**, acid treatment, and reprotection of the partially generated 1,2-diol results in the formation of alcohol **16**. Formation of the dienophile moiety is achieved by successive functional group manipulations of **16**. Accordingly, Parikh oxidation of **16** followed by methyllithium addition and TPAP oxidation provides methyl ketone **17**, which is converted to **18** by Wittig olefination and reductive debenzylation. Assembly of the diene part of the alcohol **18** involves Parikh oxidation followed by Emmons olefination and silyl enol ether formation.

Intramolecular Diels−Alder reaction of **19**, conducted in toluene at 230 °C in a stainless steel autoclave, yields the desired cycloadduct **20** (75%) as a single stereoisomer. Finally, the requisite C-4 hydroxymethyl group is introduced by reaction with formaldehyde in the presence of anhydrous tetrabutylammonium fluoride in THF. The NMR spectroscopic data of **21**, the key synthetic intermediate formed in this process, were identical to those previously reported.[12]

The high degree of stereoselectivity observed in the intramolecular Diels−Alder reaction of **19** is attributed to the strong conformational bias favoring transition state **A**, in which 1,3-allylic strain between the olefinic hydrogen of the isopropenyl group and a ring proton is minimized, and the absence of a nonbonded interaction between the equatorial hydrogen and the methyl group on the diene portion that is present in transition state **B** (Figure 1). The conversion of **21** to aphidicolin (**1**) was reported earlier by Ireland.[12]

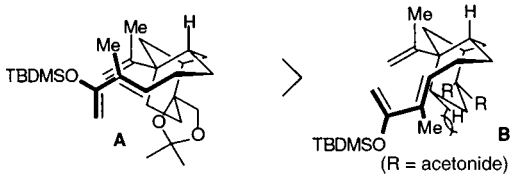


Figure 1. Plausible conformations for the intramolecular Diels−Alder reaction.

In conclusion, a novel and improved diastereoselective formal total synthesis of aphidicolin has been achieved by exploiting the characteristics of a bicyclo[3.2.1]octane ring system that was poduced by employment of a palladium-catalyzed cycloalkenylation process. In this sequence, highly diastereoselective oxirane formation was employed to install C-16 functionality. The strategy used in this aphidicolin synthesis, relying on the combined use of palladium-catalyzed cycloalkenylation and intramolecular Diels−Alder reactions for diastereoselective polycyclic ring system formation, should be broadly applicable to the preparation of targets with related structural features.

Acknowledgment. This work is supported by a Grant-in-Aid (No. 14571994) from the Ministry of Education, Science, Sports and Culture, Japan.

Supporting Information Available: Full experimental details and spectral data for **8**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Ireland, R. E.; Dow, W. C.; Godfrey, J. D.; Thaisrivongs, S. *J. Org. Chem.* **1984**, *49*, 1001−1013.