New Approach to Aphidicolin and Total Asymmetric Synthesis of Unnatural (11*R*)-(−)-8-Epi-11-hydroxyaphidicolin by Tandem Transannular Diels−Alder/Aldol Reactions

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Received May 18, 2000

The 8-epiaphidicolane skeleton (**3**) was formed in one key reaction by highly diastereoselective tandem transannular Diels−Alder (TADA)−aldol reactions from the *trans-trans-cis* trienic macrocycle (**4**). The unnatural derivative (11*R*)-(−)-8-epi-11-hydroxyaphidicolin (**2**) was thus constructed, and an original solution to the C16 functionalization problem of many aphidicolin (**1**) syntheses is presented.

Introduction

(+)-Aphidicolin (**1**, Figure 1) is a diterpenoic tetraol isolated from *Cephalosporium aphidicolia* fungus. This inhibitor of DNA polymerase α is known to act against *Herpes simplex* type I virus, as well as to slow eucaryotic cells proliferation. The latter property is quite interesting, placing aphidicolin among potential agents for cancer treatment. Its structure was elucidated by Hesp in 1972, and many total syntheses have been published since then. However, in most of them,[4a−q] functionalization at the C16 position proved to be problematic with respect to diastereoselectivity. This problem was first tackled by A. B. Smith III[4r,s] in 1988, who successfully accomplished the introduction of the hydroxymethyl moiety in a five-step process.

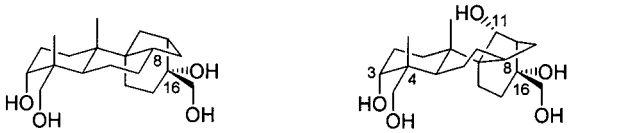

Figure 1. (+)-Aphidicolin (**1**) and unnatural derivative (**2**).

Looking more closely at aphidicolan derivative **2**, the (11*R*)-hydroxyl could be of great utility for correct functionalization at the C16 position by inducing facial selectivity. Moreover, as we reported in a previous article, a superimposition of the AM1 minimized structure of aphidicolin and of its C8 epimer showed a good overlap of the four hydroxyl functions. Knowing that aphidicolin binding in the host cavity is due to these hydroxyls, the overlap suggests a potential activity for the unnatural C8 epimer. With these two arguments, we developed an enantioselective total synthesis of (11*R*)-(−)-8-epi-11-hydroxy-aphidicolin (**2**) as reported herein.[6c]

The strategy employed uses a tandem transannular Diels−Alder (TADA)−aldol reaction as the key step, performed on *trans-trans-cis* trienic macrocycle **4** (Scheme 1). The tetracycle **3** thus produced would lead to aphidicolin **1** or its derivative **2** by further elaboration. First, macrocycle **4** could be obtained from Stille coupling between vinylic iodide **5** and vinylic stannane **6**, followed by macrocyclization. Finally, iodide **5** could be generated from our previously reported Weinreb amide **7**.[7] The synthesis of tetracycle **3** has already been published by Hall and Deslongchamps,[5] but we significantly increased the convergence and completed the synthesis from tetracyclic intermediate **3** to the end.

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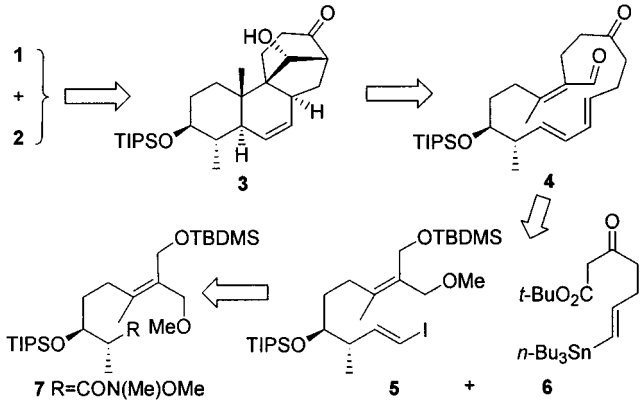
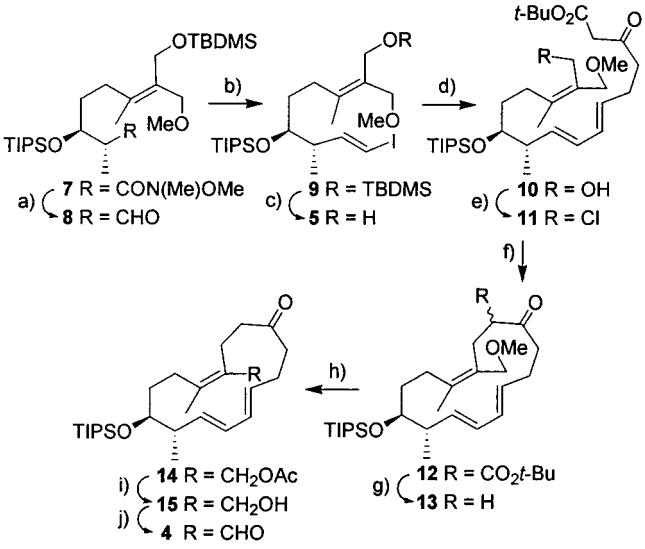
10.1021/jo0007635 CCC: $19.00 © 2000 American Chemical Society
Published on Web 09/19/2000

Scheme 1



Scheme 2[a]



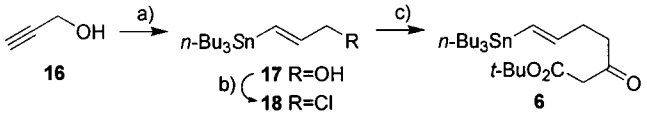
[a] (a) DIBALH, THF, −78 °C, 1 h; (b) $CrCl_2$, CHI_3, 1,4-dioxane/THF = 2:1, rt, 1.5 h; (c) PTSA, MeOH, rt, 30 min, 76% from **7**; (d) $(MeCN)_2PdCl_2$, **6**, DMF, rt, 4 h, 74%; (e) $(Cl_3C)_2CO$, PPh_3, THF, rt, 20 min; (f) $^fCs_2CO_3$, CsI, acetone, reflux, slow addn of **11** over 15 h, [Cfinal] = 0.005 M, 79% from **10**; (g) LiI.2−3H_2O, 2,4,6-collidine, 100 °C, 15 h, 72%; (h) i, Me_2BBr, NaI, 15-crown-5, CH_2Cl_2, 40 min, −78 °C; ii, Et_2O, −78 °C to rt; iii, AcONa, DMF, 50 °C, 3.5 h; (i) K_2CO_3, MeOH, rt, 15 h, 75% from **13**; (j) Dess−Martin periodinane, CH_2Cl_2, rt, 20 min, 88%.

Results and Discussion

New Approach toward the Synthesis of Macrocycle 4. According to the first generation synthesis of macrocycle **4**, some difficulties were encountered for the deprotection of macrocyclic allylic *p*-methoxybenzyl ether (PMB).[5] To circumvent this problem, we decided to change the PMB for a methyl (**13**, Scheme 2). The convergence was also significantly increased. This improvement was accomplished by synthesizing the diene using two building blocks and a Stille coupling. Part of this simplified approach has been published recently[7] up to Weinreb amide **7**.

Accordingly, the latter was reduced to aldehyde **8** (Scheme 2), followed by Takaï[8] homologation to vinylic iodide **9** and deprotection of the *tert*-butyldimethylsilyl ether to give allylic alcohol **5** in a 76% overall yield (from **7**). With this vinylic iodide, the *trans-trans* diene was formed by Stille coupling[9] on vinylic stannane **6** to yield diene **10** (74%) as a single isomer. Stannane **6** was synthesized in three steps starting with hydrostannylation[10] of propargyl alcohol **16** in 56% yield (Scheme 3), followed by chlorination of the resulting alcohol **17** to chloride **18** (96%). This acid sensitive allylic chloride **18** was used crude for the subsequent nucleophilic displacement by the *tert*-butyl acetoacetate dianion to generate the desired *β*-ketoester **6** in 85% yield.

Scheme 3[a]



[a] (a) AIBN, *n*-Bu_3SnH, 80 °C, 28 h, 56%; (b) PPh_3, CCl_4, MeCN, rt, 2.5 h, 96%; (c) $CH_3COCH_2CO_2t$-Bu, NaH, *n*-BuLi, NaI, 18-crown-6, THF, rt, 3 h, 85%.

The sequence continued with chlorination[11] of allylic alcohol **10** and macrocyclization performed by slow addition of chloride **11** to a suspension of cesium carbonate and cesium iodide in refluxing acetone.[12] The macrocyclic *β*-ketoester mixture **12** thus formed (79% from **10**) was de-*tert*-butoxycarbonylated (72%) to ketone **13** by a modified Krapcho methodology, using hydrated lithium iodide in hot collidine.[13] At this point, the deprotection of methyl-protected allylic alcohol **13** proved troublesome. We finally succeeded by submitting **13** to bromodimethylborane,[14] in the presence of additives such as sodium iodide and 15-crown-5 ether,[15] generating an unstable allylic bromide intermediate. Excess of Guindon's reagent was destroyed by addition of ether, and the bromide was immediately displaced with sodium acetate in warm *N*,*N*-dimethylformamide. Acetate **14** was then methanolyzed to the desired alcohol **15** in 75% yield from **13**. Dess−Martin[16] oxidation of alcohol **15** led to crystalline aldehyde **4** (88%).

Tandem Transannular Diels−Alder/Aldol Reactions. With macrocyclic aldehyde **4** in hand, we were thus ready for the key step. Under heating at 230 °C in toluene (in the presence of triethylamine as a proton scavenger) during 30 h in a sealed tube, a tandem transannular Diels−Alder/aldol reaction occurred (Scheme 4). The TADA high diastereoselectivity was induced by the preferred pseudoequatorial orientation of the silyl ether and methyl substituents in positions 3 and 4, respectively, and by an *endo* approach in the transition state.[17a] The tricyclic TADA intermediate **19** then underwent a transannular aldol reaction to generate the last of the six newly created stereocenters.[17b] In addition to the overall 81% yield of tetracycle **3** from macrocycle

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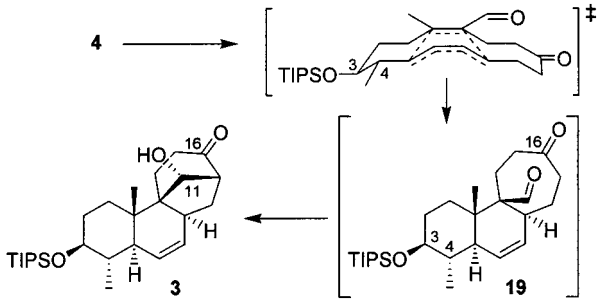
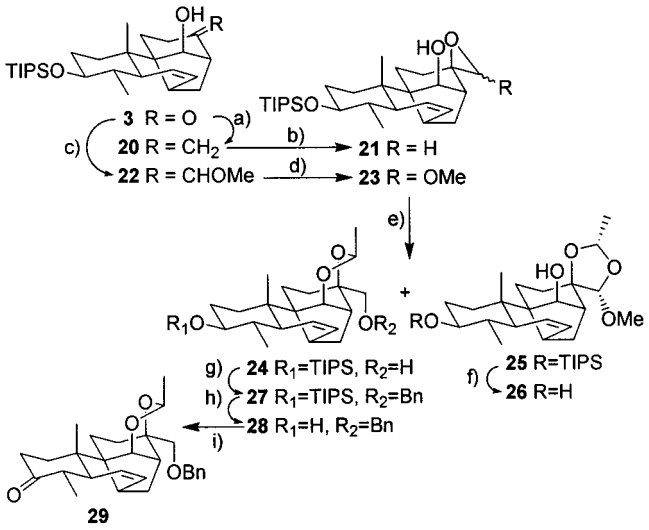
Scheme 4[a]



[a] Et_3N, PhMe, sealed tube, 230 °C, 24 h, 81% of **3** + 8% of **19**.

Scheme 5[a]



[a] (a) Ph_3PCH_3Br, KHMDS, THF, rt, 15 min, 85−95%; (b) i, $VO(acac)_2$, *t*-BuOOH, toluene, 0 °C, 40 min; ii, NaI, $Na_2S_2O_3$, H_2O, 0 °C, 30 min, 41%; (c) $ClPh_3PCH_2OMe$, KHMDS, THF, 0 °C, 2 h, 95%; (d) *m*-CPBA, CH_2Cl_2, Li_2CO_3, −78 °C, 3 h; (e) i, CH_3CHO, PTSA.H_2O, CH_2Cl_2, 0 °C, 2.75 h; ii, $NaBH_4$, EtOH, 0 °C, 3 h, 37% of **24** +17% of **25**, from **22**; (f) TBAF, THF, rt, 20 h; (g) BnBr, NaH, *n*-Bu_4NI, THF/DMF = 1:1, rt, 6 h; (h) TBAF, THF, rt, 15 h, 73% from **24**; (i) Dess−Martin periodinane, CH_2Cl_2, rt, 30 min, 71%.

4, a small amount (8%) of tricyclic intermediate **19** was also isolated.

From Tetracycle 3 to the End: First Approach. We initially had to functionalize the unmasked ketone in C16 to the corresponding diol. Our first idea was to perform an alkylation from the α face of **3**, but all attempts failed. We consequently decided to generate the exomethylene **20** by standard Wittig olefination (Scheme 5) in a variable 85−95% yield. Subsequent epoxidation of the olefin turned out to be problematic. The only reaction leading to the desired epoxide **21** was an oxidation using vanadylacetylacetonate in the presence of a large excess of *tert*-butyl hydroperoxide.[18] The latter was destroyed by addition of sodium iodide, and the iodine produced was then reduced with sodium thiosulfate. However, a low 41% yield of epoxide **21** was obtained. To form a more reactive olefin, a mixture of methyl enol ethers **22** was then prepared in 95% yield.[19] The C16 α-oxygen was then diastereospecifically introduced by treatment with *m*-chloroperbenzoic acid to yield epoxide **23**. The acid sensitive acetal **23** thus formed was treated under transacetalization conditions in the presence of acetaldehyde and *p*-toluenesulfonic acid. The crude aldehyde intermediate was immediately reduced with sodium borohydride to generate alcohol **24** in 37% yield from **22**.

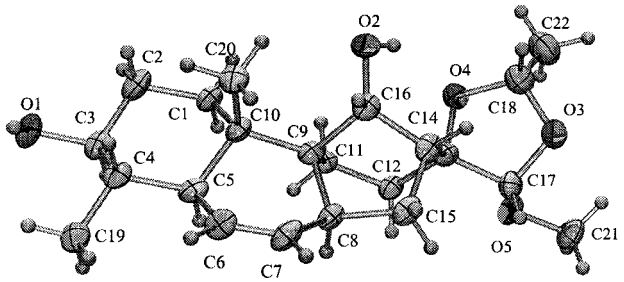
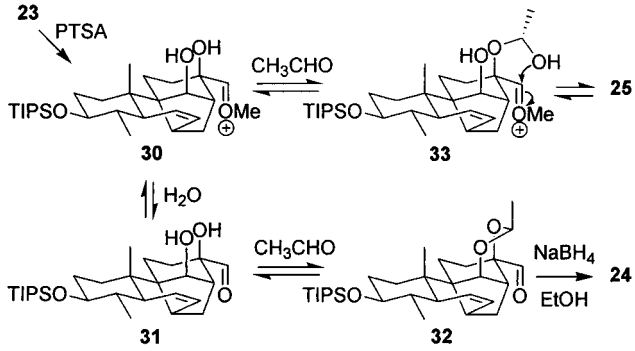


Figure 2. X-ray structure of diol **26**.

Scheme 6



To our surprise, an important byproduct, **25,** was also formed, which did not react in the reducing conditions. After cleavage of the triisopropylsilyl ether, a crystal of **26** was obtained and its structure proven by X-ray diffraction (Figure 2). Note that all the eight stereocenters have the expected stereochemistry. Moreover, we proved the C11-hydroxyl induction for the epoxidation of **23**. The proposed mechanism to explain the formation of both **24** and **25** is shown in Scheme 6.

Initial acid-catalyzed opening of acetal **23** to methylcarboxonium **30** could lead to **31** by hydrolysis with *p*-toluenesulfonic acid monohydrate. Protection of the diol to form ethylidene **32** would regenerate a molecule of water, used for the hydrolysis of **30** to **31**. With a lower water concentration, intermediate **30** could survive long enough to allow for the formation of hemiacetal **33**, which could cyclize to the observed byproduct **25**. By modifying the water concentration, a variation of the **24**/**25** ratio was expected, but it turned out to be of modest influence.

The investigations on alcohol **24** were pursued by first protecting it as benzyl ether **27** (Scheme 5), and the

(17) (a) For a detailed analysis of the outcome of the reaction, see ref 5. (b) As mentioned by one of the referees, the possibility remains that the aldol reaction occurs before the TADA step. In our opinion, this is unlikely for the following reasons: (i) a small amount (8%) of aldehyde **19** was isolated after TADA and before the aldol, which seems to indicate that the TADA step is faster than the aldol; (ii) in the case of an initial aldol followed by a TADA, it would be very surprising that the substituents in C3 and C4 are able to control the diastereoselectivity of the direct aldol on macrocycle **4**. A mixture of diastereoisomers would reasonably be expected if the aldol occurred before the TADA.

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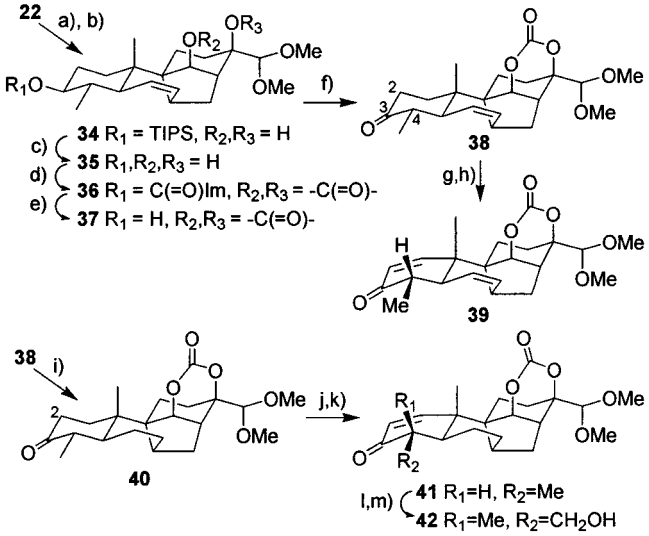
Scheme 7[a]



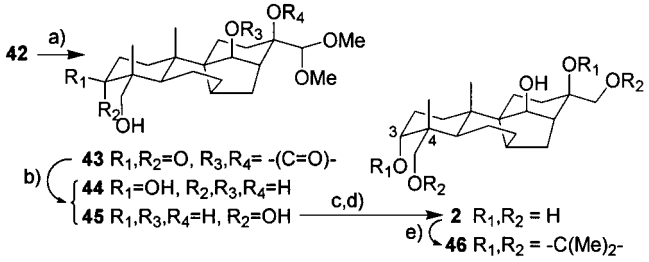
[a] (a) *m*-CPBA, Li_2CO_3, CH_2Cl_2, −78 °C, 3 h; (b) MeOH, PTSA, rt, 15 h, 5−15% of **34** + 70−85% of **35** from **22**; (c) TBAF, THF, rt, 15 h, 67%; (d) Im_2CO, PhH, reflux, 2 h, 96%; (e) NaOH 0.1N/THF = 1:2, 0 °C, 1 h, 88%; (f) Dess−Martin periodinane, CH_2Cl_2, rt, 30 min, 93%; (g) TMSCl, LiHMDS, −78 °C to rt, 8 h; (h) $Pd(OAc)_2$, MeCN, rt, 15 h, 37% from **38**; (i) H_2, EtOAc, Pd/C, rt, 18 h, 100%; (j) TMSCl, LDA, −78 °C, 20 min; (k) $Pd(OAc)_2$, MeCN, rt, 15 h, 80% from **40**; (l) LDA, TMSCl, THF, −78 °C, 30 min, 79%; (m) *n*-$Bu_4NPh_3SiF_2$, HCHO(g), CH_2Cl_2, −78 °C to rt, 1 h, 70% of **42** + 20% of **40**.

triisopropysilyl ether was cleaved to give alcohol **28** in 73% yield (two steps). Alcohol **28** was then oxidized to the corresponding ketone **29** (71%). However, due to the low yield conversion of epoxide **23** into triol **24**, this route was not pursued further and functionalization at C16 was approached in a different manner.

From Tetracycle 3 to the End: Second Approach. Accordingly, starting from enol ether **22** (Scheme 7), the epoxidation was performed as previously described, and epoxide **23** was opened in acidic methanolic medium to yield a mixture of triol **35** (major product, 70 to 85% from **22**) and diol **34** (5−15%). Silyl ether **34** was transformed (67%) into triol **35** upon fluoride treatment. The diol moiety was then protected as a cyclic carbonate. In the event, the A ring alcohol was also protected as a carbamate, giving **36** in 96% yield. The C3 hydroxyl was then regenerated with dilute sodium hydroxide in 88% yield and oxidized to ketone **38** (93%). All attempts to further introduce the desired hydroxymethyl moiety at C4 failed. A $\Delta^{3,4}$ enolate or enol ether proved to be out of reach from ketone **38**.[20] Consequently, the C2 position first had to be protected. This was accomplished by enolization to the kinetic silyl enol ether, followed by palladium(II) acetate oxidation[21] to enone **39**. The B ring double bond interfered during the latter oxidation, explaining the low 37% yield of **39** (from **38**).

To avoid this problem, olefin **38** was quantitatively reduced to **40**. The kinetic silyl enol ether was then formed using LDA and TMSCl and was taken advantage of to introduce the $\Delta^{1,2}$ unsaturation in the presence of $Pd(OAc)_2$ in 80% yield (two steps). There again, all attempts to perform the aldol reaction between enone **41** and formaldehyde failed. To explain this result, two points should be mentioned: (1) only LDA was basic enough to deprotonate ketone **41** at −78 °C; (2) the aldol reaction with gaseous formaldehyde occurred only upon warming of the solution. This gave rise to a problem of compatibility between LDA and the carbonate protecting group at temperatures higher than −78 °C. To circumvent this problem, the enolate of enone **41** was trapped as its silyl enol ether in the presence of TMSCl in 79% yield. The enolate was subsequently regenerated by treatment with a dry, nonhygroscopic fluoride source (tetra-*n*-butylammonium triphenyldifluorosilicate)[22] and treated with gaseous formaldehyde to give the desired aldol adduct **42** in 70% yield.

Scheme 8[a]



[a] (a) H_2, 50 psi, Pd/C, EtOAc, rt, 4 h, 75%; (b) *t*-BuLi, DIBALH, hexanes/Et_2O = 1:1, −78 °C to rt, 2 h, **44**/**45** = 1:1, 40%; (c) HCl, 1N/THF = 1.1, rt, 20 h; (d) $NaBH_4$, EtOH, rt, 2.5 h, 60% from **45**; (e) $Me_2C(OMe)_2$, PTSA, rt, 5 h.

Hydrogenation of enone **42** gave ketone **43** (75% yield, Scheme 8). However, the reported L-Selectride reduction (ref 4a−n) of the ketone to the axial alcohol proved troublesome and led to a poor yield of alcohol **45** (ref 23). Instead, an "ate" complex of *tert*-butyllithium and diisobutylaluminum hydride (refs 4a and 24) was used, giving a 1:1 mixture of tetraols **44** and **45** in a disappointing 40% combined yield.

Hydrochloric acid hydrolysis of dimethylacetal **45**, followed by ethanolic sodium borohydride reduction of the resulting aldehyde, finally yielded (11*R*)-(−)-8-epi-11-hydroxyaphidicolin (**2**). The relative stereochemistry at the C3 and C4 positions was established by chemical proof when pentaol **2** was protected as its bisacetonide **46**. In fact, the low coupling constant for the C3 proton (δ = 3.40 ppm, doublet of multiplet, J = 3.5 Hz) indicated an axially oriented C3-hydroxyl, and the formation of acetonide **46** confirmed the C4 equatorial position of the hydroxymethyl. Had the latter been axially oriented, the acetonide formation would have inverted the chair ring

(20) This problem would have been difficult to predict. On the basis of previous work in the aphidicolane series, many of the authors made use of a $\Delta^{4,5}$ unsaturation to introduce the C4 substituents and thus did not have to tackle this enolization. In addition, on a bicyclic model containing rings A and B of aphidicolin, a 5:1 mixture of $\Delta^{3,4}$ and $\Delta^{2,3}$ enol acetates could be easily generated in 92% yield using Ac_2O and catalytic $HClO_4$ in refluxing CCl_4. These conditions turned out to be incompatible with ketones **38** and **40**.

(21) Piers, E.; Abeysekera, B. F.; Herbert, D. J.; Suckling, I. D. *Can. J. Chem.* **1985**, *63*, 3418.

(22) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166.

(23) This problem has been reported several times. For example, Trost and co-workers had to use the same "ate" complex before they could obtain decent results (ref 4a). Tanis and co-workers had to try out a combination of reducing agent and several Lewis acids to obtain satisfactory result (see Tanis, S. P.; Chuang, Y.-M.; Head, D. B. *J. Org. Chem.* **1988**, *53*, 4929). Fukumoto and co-workers obtained a modest 50% yield for the same transformation (see ref 4l). In addition, we did not have enough materials to search for optimal conditions.

(24) Kovács, G.; Galambos, G.; Juvancz, Z. *Synthesis* **1977**, 171.

A to its boat conformation, which would not indicate the observed coupling constant for the C3 proton.

Conclusion

The total enantioselective synthesis of (11*R*)-(−)-8-epi-11-hydroxyaphidicolin (**2**) was completed in 37 steps. In this work, the key step gave perfect stereocontrol of the six newly created asymmetric centers. Moreover, the C11-hydroxyl group produced during the transannular aldol induced the expected highly diastereoselective functionalization of the C16 ketone into the desired diol, solving the long lasting problem of stereoselective C16 elaboration. However, in light of our experience with ring A transformations, a modified approach is under investigation. The synthesis described herein thus constitutes an interesting entry to aphidicolin and potentially active derivatives via an efficient tandem transannular Diels−Alder/aldol strategy. Finally, aphidicolin could be, in principle, obtained from C8-epimerization of intermediate **34** and hydrogenolysis of the C11-OH group. Work in this direction is also in progress.

Acknowledgment. A basic research Chair in organic chemistry granted to Professor P. Deslongchamps from BioChem Pharma Inc. is deeply appreciated. Fellowships from FCAR-Quebec, Bio-Mega/Boehringer Ingelheim Inc., and NSERC-Canada to G. Bélanger are highly appreciated. The authors wish to thank Mrs M.-M. Leroux and Dr. E. Marsault for editorial assistance.

Supporting Information Available: Experimental procedures and characterization data for compounds **2**−**6**, **8**−**15**, **17**−**29**, and **34**−**46**, including copies of representative ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0007635