Total Asymmetric Synthesis of the Aphidicolin Derivative (11*R*)-(−)-8-Epi-11-hydroxyaphidicolin Using Tandem Transannular Diels−Alder/Aldol Reactions
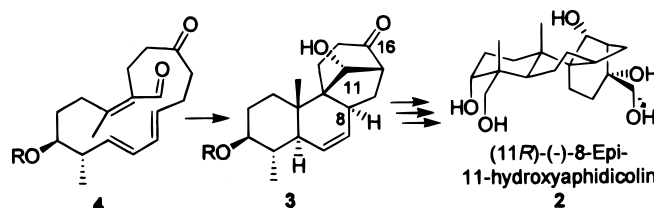
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ABSTRACT

Aphidicolin unnatural derivative (2) was synthesized using a new tandem transannular Diels−Alder/aldol methodology. The 8-epi-aphidicolane skeleton is constructed in a highly diastereoselective manner and converted into (11*R*)-(−)-8-epi-11-hydroxyaphidicolin (2). An efficient method for the difficult C16 funtionalization is presented.

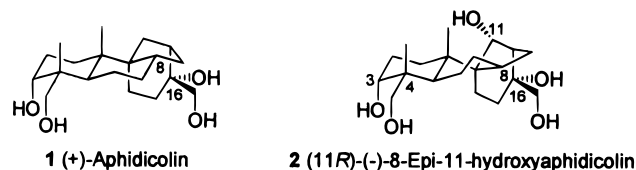The tetracyclic diterpene (+)-aphidicolin (**1**, Figure 1) was isolated from *Cephalosporium aphidicola* fungus.[1] This

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

tetraol is known to inhibit DNA polymerase α in eucaryotic cells and some viruses, such as *Herpes simplex* type 1.[2] The former property makes aphidicolin a potential agent for

cancer treatment. Since its structure elucidation by Hesp in 1972,[3] many total syntheses have been published,[4] but in most of them, introduction of the hydroxymethyl moiety at the C16 position took place with poor diastereoselectivity.[4a−i]

(1) Brundret, K. M.; Dalziel, W.; Hesp, B.; Jarvis, J. A. J.; Neidle, S. J. *J. Chem. Soc., Chem. Commun*. **1972**, 1027.
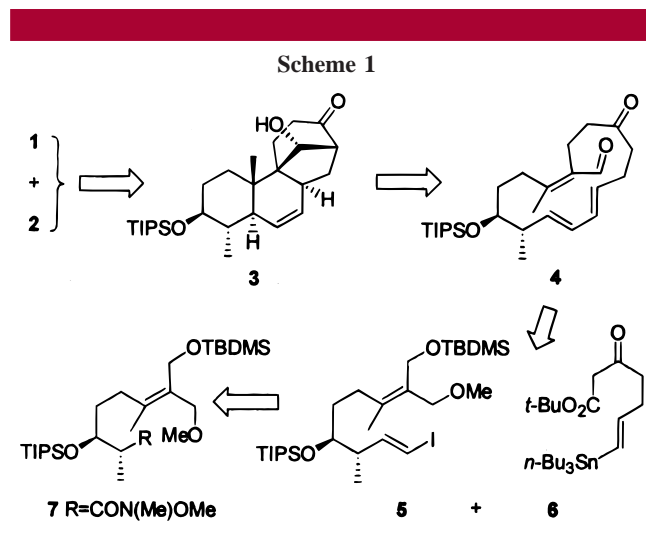
(2) Ikegami, S.; Taguchi, T.; Ohashi, M.; Oguro, M.; Nagano, H.; Mano, Y. *Nature (London)* **1978**, *275*, 458.

(3) Dalziel, W.; Hesp, B.; Stevenson, K. M.; Jarvis, J. A. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2841.

(4) (a) Trost, B. M.; Nishimura, Y.; Yamamoto, K.; McElvain, S. S. *J. Am. Chem. Soc*. **1979**, *101*, 1328. (b) McMurry, J.; Andrus, A.; Ksander, G. M.; Musser, J. H.; Johnson, M. A. *J. Am. Chem. Soc*. **1979**, *101*, 1330. (c) Corey, E. J.; Tius, M. A.; Das, J. *J. Am. Chem. Soc*. **1980**, *102*, 1742. (d) Ireland, R. E.; Godfrey, J. D.; Thaisrivongs, S. *J. Am. Chem. Soc*. **1981**, *103*, 2446. (e) Holton, R. A.; Kennedy, R. M.; Kim, H.-B.; Kraft, M. E. *J. Am. Chem. Soc*. **1987**, *109*, 1597. (f) Toyota, M.; Nishikawa, Y.; Seishi, T.; Fukumoto, K.; *Tetrahedron* **1994**, *50*, 10183. (g) Iwata, C.; Morie, T.; Maezaki, N.; Yamashita, H.; Kuroda, T.; Inoue, T.; Kamei, K.; Imanishi, T.; Tanaka, T.; Kim, S.-W.; Murakami, K. *Abstracts of the 32nd Symposium on the Chemistry of Natural Products*; 1990. (h) van Tamelen, E. E.; Zawacky, S. R.; Russel, R. K.; Carlson, J. G. *J. Am. Chem. Soc*. **1983**, *105*, 142. (i) Bettolo, R. M.; Tagliatesta, P.; Lupi, A.; Bravetti, D. *Helv. Chim. Acta* **1983**, *66*, 1922. (j) For a review on the synthesis of aphidicolanes and stemodanes, see Toyota, M.; Ihara, M. *Tetrahedron* **1999**, *55*, 5641. (k) Rizzo, C. J.; Smith, A. B., III. *Tetrahedron Lett*. **1988**, *29*, 2793.

However, this problem was solved by Smith,[4k] who successfully accomplished this transformation using a five-step process.

We wish to report herein the total synthesis of an unnatural aphidicolin derivative, (11*R*)-(−)-8-epi-11-hydroxyaphidicolin (**2**, Figure 1). This approach presents two major advantages. First, the tetracyclic backbone is formed in a tandem two-step reaction from macrocycle **4** (Scheme 1) by

a simplified approach to **4**, as well as the completion of the synthesis. The simplification comes from a Stille coupling between vinylic iodide **5** and vinylic stannane **6** for construction of diene **10**. Synthon **5** could be prepared from our previously reported Weinreb amide **7**.[7] This was accomplished by reduction of **7** to aldehyde **8**, followed by a Takaï homologation[8] to vinylic iodide **9** and silyl ether cleavage in a 76% overall yield (Scheme 2).

Scheme 1

Scheme 2[a]

[a] (a) DIBALH, THF, −78 °C, 1 h; (b) CrCl₂, CHI₃, 1,4-dioxane/THF 2:1, rt, 1.5 h; (c) PTSA, MeOH, rt, 30 min, 76% from **7**; (d) (MeCN)₂PdCl₂, **6**, DMF, rt, 4 h, 74%; (e) HCA, PPh₃, THF, rt, 20 min; (f) Cs₂CO₃, CsI, acetone, reflux, slow addition of **11** over 15 h, final concn = 0.005 M, 79% from **10**; (g) LiI·2−3H₂O, 2,4,6-collidine, 100 °C, 15 h, 72%; (h) [i] Me₂BBr, NaI, 15-crown-5, CH₂Cl₂, 40 min, −78 °C, [ii] Et₂O, −78 °C to rt, [iii] AcONa, DMF, 50 °C, 3.5 h; (i) K₂CO₃, MeOH, rt, 15 h, 75% from **13**; (j) Dess−Martin periodinane, CH₂Cl₂, rt, 20 min, 88%; (k) Et₃N, PhMe, scealed tube, 230 °C, 24 h, 81%; (l) ClPh₃PCH₂OMe, KHMDS, THF, 0 °C, 2 h, 95%.

the transannular Diels−Alder (TADA) strategy,[5,6] and second, the (11*R*)-hydroxyl function allows specific functionalization at the C16 position. In addition, an almost perfect fit of the four hydroxyl functions of aphidicolin and its C8 epimer was observed on the AM1 minimized structures.[6a] These hydroxyls are known to be responsible for the binding in the host cavity.[6b]

According to our retrosynthetic plan, both aphidicolin (**1**) and its derivative **2** could be obtained from tetracycle **3** by functional group transformations (Scheme 1). The latter could be generated as mentioned above by tandem transannular Diels−Alder/aldol reactions on the trienic *trans-trans-cis* macrocycle **4**. The synthesis of tetracycle **3** has already been published by Hall and Deslongchamps.[6a] We report herein

The resulting alcohol **5** was subjected to Stille coupling with vinylic stannane **6**[9] to give *trans-trans* diene **10** as a single isomer in 74% yield. Chlorination[10] of allylic alcohol **10** followed by macrocyclization[11] of the acid-sensitive chloride **11** worked well to produce **12** in 83% yield. The *tert*-butyl ester moiety was removed (72%) by a modified Krapcho methodology.[12]

We then experienced some difficulties in the cleavage of methyl ether **13**. After a rigorous optimization work, we finally obtained an allylic bromide with bromodimethylborane[13] in the presence of additives[14] (sodium iodide, 15-crown-5 ether). This unstable intermediate had to be im-
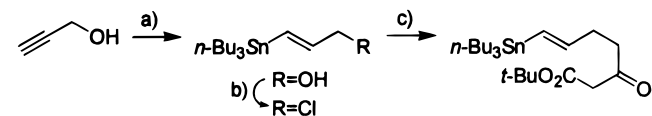
(5) (a) Deslongchamps, P. *Pure Appl. Chem.* **1991**, *24*, 23. (b) Hall, D. G.; Caillé, A.-S.; Drouin, M.; Lamothe, S.; Müller, R.; Deslongchamps, P. *Synthesis* **1995**, 1081.

(6) (a) Hall, D. G.; Deslongchamps, P. *J. Org. Chem.*, **1995**, *60*, 7796. (b) McMurry, J. E.; Webb, T. R. *J. Med. Chem.* **1984**, *27*, 1367.

(7) Toró, A.; Lemelin, C.-A.; Préville, P.; Bélanger, G.; Deslongchamps, P. *Tetrahedron* **1999**, *55*, 4655.
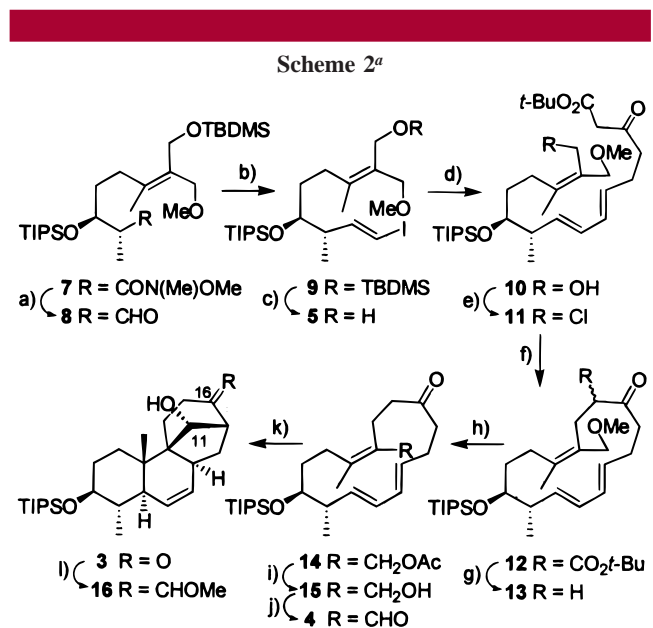
(8) Takaï, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(9) Vinylic stannane **6** was obtained in three steps from hydrostannylation of propargylic alcohol (Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851), followed by chlorination and displacement of the resulting allylic chloride by the dianion of *tert*-butylacetoacetate.

(a) AIBN, *n*-Bu₃SnH, 80°C, 48h, 56%; (b) PPh₃, CCl₄, MeCN, r.t., 2.5h, 96%; (c) CH₃COCH₂CO₂*t*-Bu, NaH, *n*-BuLi, NaI, 18-crown-6, THF, r.t., 3h, 85%.
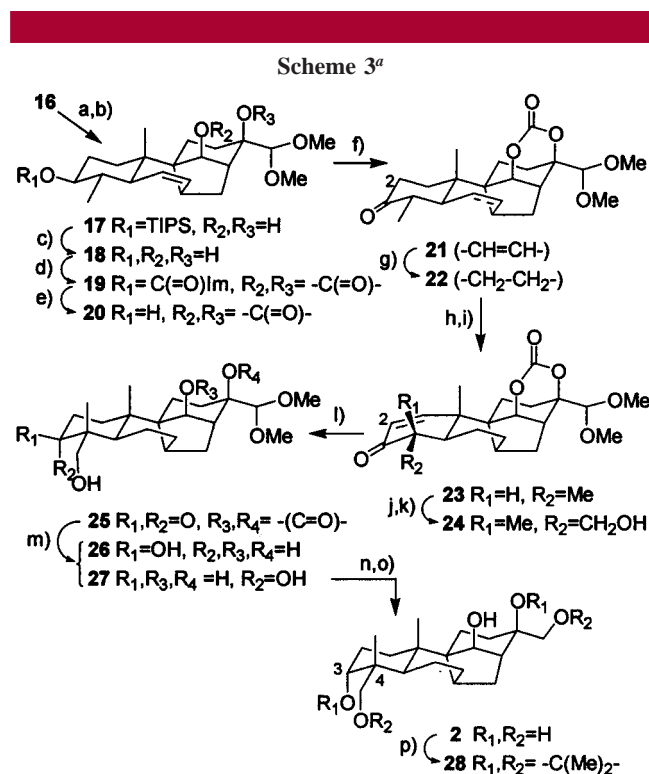
(10) (a) Magid, R. M.; Fruchey, O. S.; Johnson, W. L.; Allen, T. G. *J. Org. Chem.* **1979**, *44*, 359. (b) Schreiber, S. L.; Meyer, S. D.; Miwa, T.; Nakatsuka, M. *J. Org. Chem.* **1992**, *57*, 5058.

(11) (a) Beattig, K.; Dallaire, C.; Pitteloud, R.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5249. (b) Beattig, K.; Marinier, A.; Pitteloud, R.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5253.

(12) Elsinger, F. *Org. Synth.* **1973**, *5*, 76.

mediately displaced to give acetate **14** and then methanolyzed to the desired alcohol **15** in 75% yield from **13**. After subsequent oxidation of **15** to aldehyde **4** with Dess–Martin periodinane[15] (88%), the latter was submitted to 220 °C for 30 h in a sealed tube to produce tetracycle **3** as a sole diastereomer[16] in 81% yield (plus 8% of the isolated TADA tricyclic aldehyde intermediate).

Further transformations should lead to the introduction of hydroxymethyl functions at the C4 and C16 positions, followed by the inversion of configuration at C3. So, a Wittig olefination of ketone **3** was carried out to form an inseparable mixture of enol ethers **16** in an almost quantitative yield. This highly reactive olefin was then epoxidized and immediately methanolyzed to dimethyl acetal **18** in 70–85% yield from **16** (Scheme 3). A small quantity (5–15%) of

Scheme 3[a]

17 R$_1$=TIPS, R$_2$,R$_3$=H
18 R$_1$,R$_2$,R$_3$=H
19 R$_1$= C(=O)Im, R$_2$,R$_3$= -C(=O)-
20 R$_1$=H, R$_2$,R$_3$= -C(=O)-

21 (-CH=CH-)
22 (-CH$_2$-CH$_2$-)

23 R$_1$=H, R$_2$=Me
24 R$_1$=Me, R$_2$=CH$_2$OH

25 R$_1$,R$_2$=O, R$_3$,R$_4$= -(C=O)-
26 R$_1$=OH, R$_2$,R$_3$,R$_4$=H
27 R$_1$,R$_3$,R$_4$ =H, R$_2$=OH

2 R$_1$,R$_2$=H
28 R$_1$,R$_2$= -C(Me)$_2$-

[a] (a) *m*-CPBA, Li$_2$CO$_3$, CH$_2$Cl$_2$, −78 °C, 3 h; (b) MeOH, PTSA, rt, 15 h, 5–15% of **17** + 70–85% of **18** from **16**; (c) TBAF, THF, rt, 15 h, 67%; (d) Im$_2$CO, PhH, reflux, 2 h, 96%; (e) NaOH 0.1 N/THF 1:2, 0 °C, 1 h, 88%; (f) Dess–Martin periodinane, CH$_2$Cl$_2$, rt, 30 min, 93%; (g) H$_2$, EtOAc, Pd/C, rt, 18 h, 100%; (h) TMSCl, LDA, −78 °C, 20 min; (i) Pd(OAc)$_2$, MeCN, rt, 15 h, 80% from **22**; (j) LDA, TMSCl, THF, −78 °C, 30 min, 79%; (k) *n*-Bu$_4$NPh$_3$-SiF$_2$, HCHO$_{(g)}$, CH$_2$Cl$_2$, −78 °C to rt, 1 h, 68%; (l) H$_2$, 50 psi, Pd/C, EtOAc, rt, 4 h, 75%; (m) *t*-BuLi, DIBALH, hexanes/Et$_2$O 1:1, −78 °C to rt, 2 h, **26/27** = 1:1, 38%; (n) HCl 1 N/THF 1:1, rt, 20 h; (o) NaBH$_4$, EtOH, rt, 2.5 h, 57% from **27**; (p) Me$_2$C(OMe)$_2$, PTSA, CH$_2$Cl$_2$, rt, 5 h, 80%.

silylated compound **17** was also isolated and converted to the free alcohol **18** upon fluoride treatment. The triol was

protected as carbonate–carbamate **19** (96%) and the C3 hydroxyl function of **20** was regenerated (88%) when submitted to diluted sodium hydroxide. Upon Dess–Martin oxidation,[15] ketone **21** was prepared (93%), and the unsaturation in the B ring was quantitatively reduced by catalytic hydrogenation, leading to **22**. This step proved to be essential for enabling further oxidation of the ketone function to the enone. Otherwise, the double bond interfered with the palladium reagent used in this transformation. Accordingly, the kinetic silyl enol ether was first prepared and then submitted to palladium(II) acetate[17] to yield **23** (80%, two steps). This step was followed by an aldol condensation with gaseous formaldehyde to give **24** in 68% yield. All attempts to get an aldol adduct without blocking the C2 position failed.

Enone **24** was then reduced to ketone **25** under hydrogen pressure in the presence of palladium (75%). L-Selectride reduction of the C3 ketone, used in the literature for similar substrates,[4a–g] gave only a poor yield of the desired axial alcohol **27**. Better results, even though disappointing, were obtained with the "ate" complex of *tert*-butyllithium and diisobutylaluminum hydride,[18] to generate 38% of a separable 1:1 mixture of tetraols **26** and **27**. The completion of the synthesis was then accomplished by simple hydrolysis of dimethyl acetal **27** to the aldehyde, followed by reduction to (11*R*)-(−)-8-epi-11-hydroxyaphidicolin (**2**). The C3 proton coupling constant (doublet of multiplets, *J* = 3.5 Hz) suggested an axially oriented hydroxyl group, and the formation of acetonide **28** confirmed the C4 equatorial orientation of the hydroxymethyl[19] substituent.

With this total synthesis accomplished with an 83% average yield for 36 steps, we thus obtained a very interesting isomer of aphidicolin by the above diastereospecific tandem transannular Diels–Alder/aldol strategy. Aphidicolin can in principle be obtained from intermediate **17** by epimerization at C8 and hydrogenolysis of the C11-OH group. Work in this direction is now in progress.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds **2**–**28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem*. **1984**, *49*, 3912.
(14) (a) Niwa, H.; Hida, T.; Yamada, K. *Tetrahedron Lett*. **1981**, *42*, 4239. (b) Kuehne, M. E.; Pitner, J. B. *J. Org. Chem*. **1989**, *54*, 4553.
(15) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277.
(16) The silyl ether and methyl substituents, in positions 3 and 4, respectively, controlled perfectly the diastereoselectivity of the TADA *endo* transition state, and consequently the two other stereogenic centers formed by the transannular aldol (see ref 6a).
(17) Piers, E.; Abeysekera, B. F.; Herbert, D. J.; Suckling, I. D. *Can. J. Chem*. **1985**, *63*, 3418.
(18) Kovács, G.; Galambos, G.; Juvancz, Z. *Synthesis* **1977**, 171.
(19) With an axially oriented hydroxymethyl in C4, the acetonide formation would have inverted ring A from the chair to its boat conformation, which would not indicate the observed coupling constant for the C3 proton.