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Synthetic Studies toward Potent Cytotoxic Agents Amphidinolides: Synthesis of the C_1-C_{18} Moiety of Amphidinolides G, H and L

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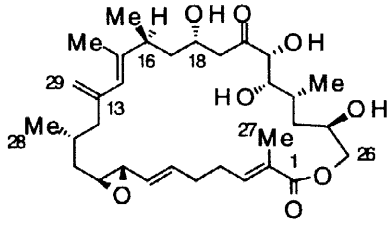
Abstract

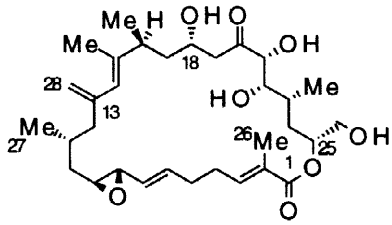
Stereoselective synthesis of the (8*S*, 9*S*, 11*R*, 16*S*)-C_1-C_{18} segment **1** of amphidinolides G, H and L, bearing the unique trisubstituted "*s-cis*-1,3-diene" moiety ($C_{28(29)}$=C_{13}–C_{14}=C_{15}), has been achieved for the first time following a highly efficient convergent strategy.

Keywords: amphidinolides; antitumor compounds; macrolides; asymmetric alkylation.

The amphidinolides constitute a family of structurally complex macrolide molecules isolated from marine sources. Many of them have potent toxicity against various tumor cell lines [1,2]. Total synthesis of none of these compounds has so far been reported [3-15]. One of the major obstacles encountered en route to the total synthesis of some of the important members of this family, like amphidinolides B, D, G, H and L, is the construction of an uncommon trisubstituted "*s-cis*-1,3-diene" moiety ($C_{28(29)}$=C_{13}–C_{14}=C_{15}), present in these molecules, in its naturally occurring configuration. We report here the first synthesis of this very important structural entity followed by its elaboration to the (8*S*, 9*S*, 11*R*, 16*S*)-C_1-C_{18} fragment of amphidinolides G, H and L.



Amphidinolide G



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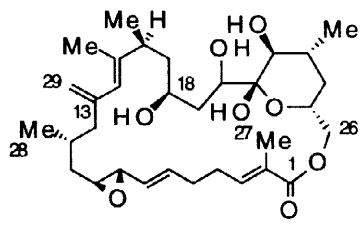

Amphidinolide L

Retrosynthetically, the C_1-C_{18} fragment **1** can be divided, as shown in Scheme 1, into two halves: the C_7-C_{18} fragment **2** bearing the diene and the epoxyaldehyde functionalities and the C_1-C_6 Wittig component **3**. The important diene moiety of **2** was planned to be constructed by coupling the *E*-α,β-unsaturated aldehyde **4** and the functionalized sulfone unit **5**.

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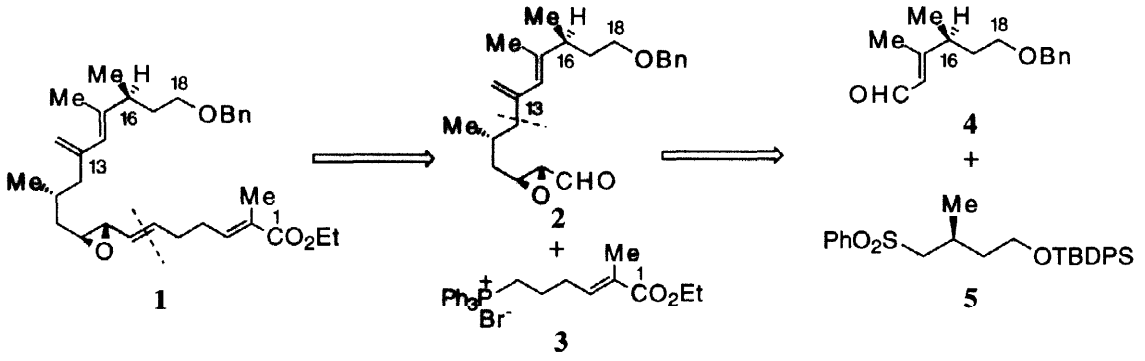
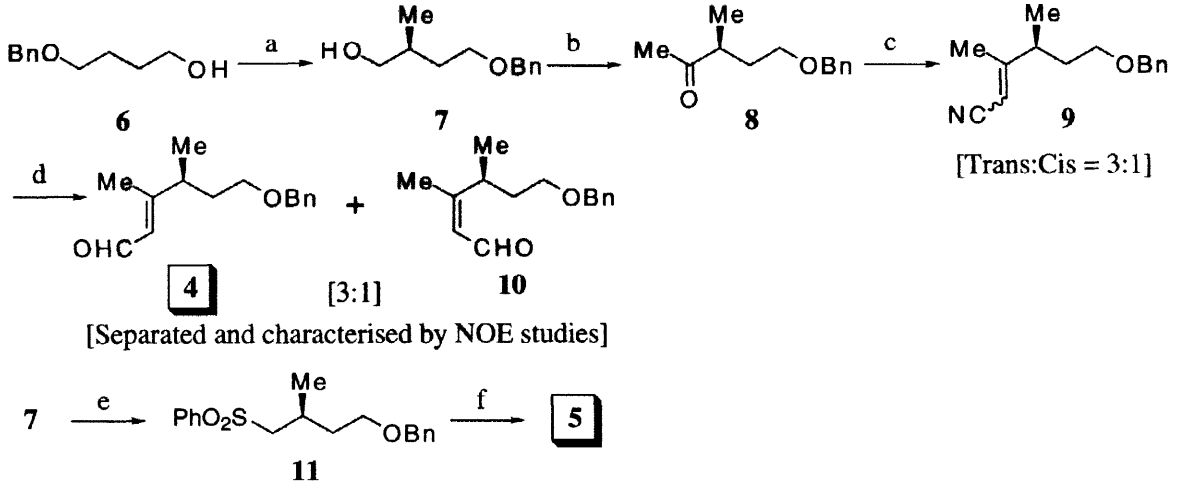


Scheme 1. Retrosynthetic analysis of **1**.

Scheme 2 outlines the syntheses of fragments **4** and **5**. Use of a common chiral precursor, (*S*)-4-benzyloxy-2-methylbutan-1-ol (**7**), for the syntheses of both the fragments is the salient feature of this scheme. The monobenzyl-protected butane-1,4-diol was transformed into **7** by Evans asymmetric alkylation method following reported procedures [16-18]. The chiral alcohol **7** was then converted to the methylketo intermediate **8** in 3 steps in 75% overall yield. Horner-Wadsworth-Emmons olefination of **8** with diethyl cyanomethylphosphonate gave a mixture of acrylonitriles **9** (3:1) in 98% yield. Reduction of this mixture of nitriles with DIBAL afforded the isomeric aldehydes **4** and **10** (3:1), in 93% yield, which could be separated easily at this stage by silica gel column chromatography. That the major isomer was the required *E*-olefin **4** was confirmed by ^{1}H NOE difference spectroscopic studies. Irradiation of the olefinic C_{14}-H signal of **10** at δ 5.87 caused significant enhancement of the 29-Me resonance at δ 1.87, indicating a *cis*-relationship between them. As expected, there was no NOE observed between the C_{14}-H and the 29-Me in the *E*-olefin **4**.

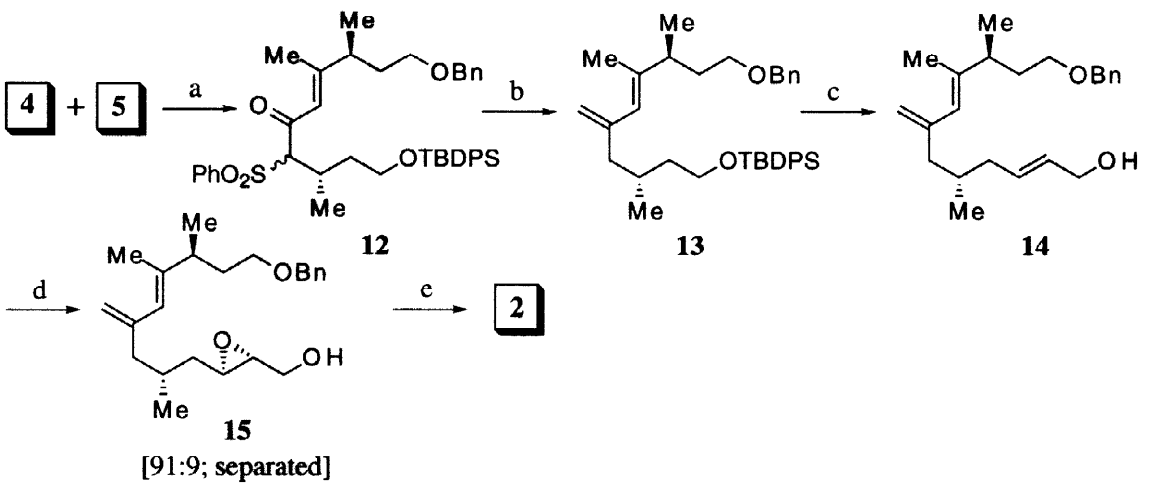


Scheme 2. Reagents and conditions. a) Ref. 16-18; b) (i) $(COCl)_2$ (1.5 eq.), DMSO (3.2 eq.), Et_3N (5 eq.), CH_2Cl_2, -78 to 0 °C, 1.5 h; (ii) MeMgI (2.0 M, 2 eq.), Et_2O, 0 to 25 °C, 1 h; (iii) same as step (i), 75% from **7**; c) $(Et_2O)_2P(O)CH_2CN$ (1.5 eq.), NaH (1.5 eq.), DME, 25 °C, 1 h, then **8** in DME, 25 °C, 3 h, 98%; d) DIBAL (1.1 eq.), toluene, - 78 °C, 1 h, 93%; e) (i) MsCl (1.2 eq.), pyridine, 25 °C, 3 h; (ii) PhSH (1.2 eq.), K_2CO_3 (1.5 eq.), DMF, 25 °C, 0.5 h; (iii) *m*CPBA (4 eq.), CH_2Cl_2, 0 to 25 °C, 3 h; 89% from **7**; f) (i) H_2, Pd/C, MeOH, 25 °C, 1 h; (ii) TBDPSCl (1.2 eq.), Et_3N (2 eq.), DMAP (0.1 eq.), CH_2Cl_2, 25 °C, 3 h; 95% from **11**.

For the synthesis of **5**, the common chiral precursor **7** (Scheme 2) was converted to the phenylsulfone **11** in 3 steps in 89% overall yield. This was followed by a change in the protective group, which was necessary to differentiate the two protective groups at a later stage, furnishing the requisite TBDPS-protected sulfone **5**.

Coupling of fragments **4** and **5** and further elaboration of the resulting coupled product to the advanced stage intermediate **2** is delineated in Scheme 3. Addition of the anion generated from **5** to the aldehyde **4** gave a diastereomeric mixture of β-hydroxysulfones which were oxidized using *O*-iodoxybenzoic acid (IBX) [19] to ketones **12** in 80% overall yield. Removal of the phenylsulfone appendage using lithium naphthalenide (LN) (60% yield) [20] and subsequent one-carbon Wittig olefination furnished the intermediate **13**[1,2] in 88% yield, thus, completing successfully the first synthesis of the targeted "*s-cis*-1,3-diene" moiety.

Routine functional group manipulations converted **13** to the allylic alcohol **14** in 4 steps in 80% overall yield. Sharpless asymmetric epoxidation [21] of **14** with natural (+)-diethyl L-tartrate gave the expected (8*S*,9*S*)-epoxy alcohol **15** as the major product (in 91:9 ratio). The minor diastereomer could be easily separated by silica gel column chromatography. The epoxyalcohol **15** was subsequently oxidized to get the intermediate **2**.



Scheme 3. Reagents and conditions. a) (i) **5** (1 eq.), ^{n}BuLi (1 eq.), THF, -78 °C, 20 min., then **4** in THF, -78 to 0 °C, 1 h; (ii) IBX (2 eq.), DMSO, 25 °C, 1 h, 80% in 2 steps; (b) (i) LN (excess), THF, -78 °C, 1 h, 60%; (ii) $Ph_3P{=}CH_2$ (2 eq.), Et_2O, 0 °C, 0.5 h, 88%; c) (i) TBAF (1.5 eq.), THF, 25 °C, 5 h; (ii) $(COCl)_2$ (1.5 eq.), DMSO (3.2 eq.), Et_3N (5 eq.), CH_2Cl_2, -78 to 0 °C, 1.5 h; (iii) $Ph_3P{=}CHCO_2Et$ (2 eq.), C_6H_6, 25 °C, 1 h; (iv) DIBAL (2.2 eq.), CH_2Cl_2, -78 °C, 1 h, 80% from **13**; d) $Ti(^iPrO)_4$ (0.2 eq.), (+)-DET (0.22 eq.), TBHP (2 eq.), CH_2Cl_2, -10 °C, 12 h, 92% (based on 40% recovered starting material); e) same as step c(ii).

Scheme 4 describes the preparation of the phosphonium salt **3** and its use in the olefination of epoxy aldehyde **2**. Mono-THP-protected butane-1,4-diol **16** was oxidized and olefination with stabilized ylide gave the α,β-unsaturated ester **17**. Deprotection of the THP-ether, bromination of the hydroxyl group and finally, treatment with Ph_3P gave the Wittig salt **3**.

Finally, the ylide generated from **3** was reacted with the aldehyde **2**, following the procedure reported by Kobayashi *etal* [13], giving a mixture of olefins (*trans:cis* = 55:45) which were separated by preparative TLC to furnish the desired C_1-C_{18} fragment **1**.[1,3]

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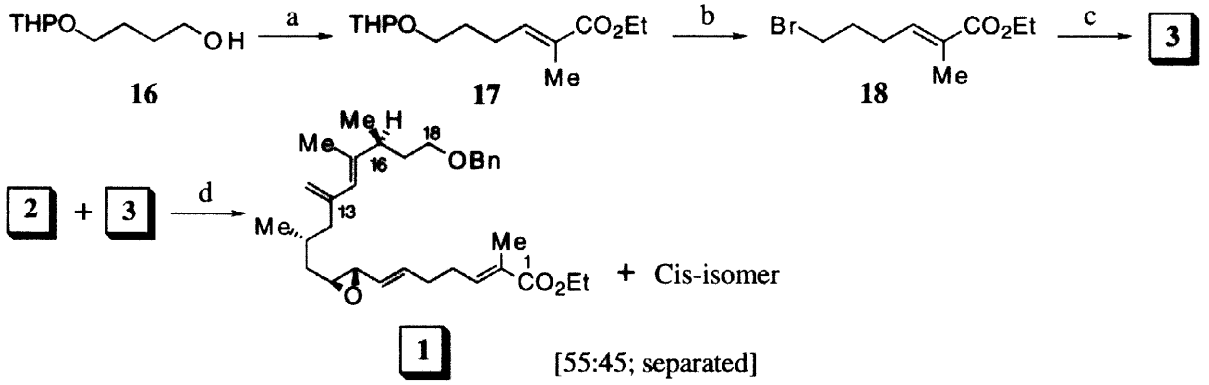
[1] Satisfactory NMR, IR and mass spectra were obtained for this compound.

[2] **13**: $[\alpha]_D^{22}$ = -10.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.7-7.2 (m, 15 H, aromatic), 5.54 (s, 1 H, C_{14}-*H*), 4.91 and 4.75 (two s, 2 H, C=C*H*$_2$), 4.42 (s, 2 H, C*H*$_2$Ph), 3.67 (t, *J* = 6.8 Hz, 2 H, C*H*$_2$OTBDPS), 3.35 (t, *J* = 6.8 Hz, 2 H, C*H*$_2$OBn), 2.32 (m, 1 H, C_{16}-*H*), 2.06 (dd, *J* = 14.8, 5.6 Hz, 1 H, C_{12}-*H*), 1.88-1.52 (m, 4 H, C_{11}-*H*, C_{12}-*H*, C_{17}-*H*$_2$), 1.68 (s, 3 H, C_{15}-C*H*$_3$), 1.3 (m, 2 H, C_{10}-*H*$_2$), 1.04 (s, 9 H, $SiPh_2{}^tBu$), 1.0 (d, *J* = 6.7 Hz, 3 H, C_{16}-C*H*$_3$), 0.78 (d, *J* = 6.3 Hz, 3 H, C_{11}-C*H*$_3$).

[3] **1**: $[\alpha]_D^{22}$ = 14.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32 (m, 5 H, aromatic), 6.74 (t, *J* = 7 Hz, 1 H, C_5-*H*), 5.69 (dt, *J* = 15.2, 7.7 Hz, 1 H, C_6-*H*), 5.57 (s, 1 H, C_{14}-*H*), 5.08 (dd, *J* = 15.2, 8.1 Hz, 1 H, C_7-*H*), 4.96 and 4.81 (two s, 2 H, C_{13}=C*H*$_2$), 4.48 (s, 2 H, C*H*$_2$Ph), 4.19 (q, *J* = 7 Hz, 2 H, $CO_2CH_2CH_3$), 3.4 (t, *J* = 7 Hz, 2 H, C*H*$_2$OBn), 3.29 (dd, *J* = 8.1, 2.1 Hz, 1 H, C_8-*H*), 2.8 (dt, *J* = 7, 2.1 Hz, 1 H, C_9-*H*), 2.45-1.88 (m, 8 H, allylic, C_{11}-*H*, C_{16}-*H*), 1.84 (s, 3 H, C_2-C*H*$_3$), 1.8-1.58 (m, 4 H, C_{10}-*H*$_2$, C_{17}-*H*$_2$), 1.7 (s, 3 H, C_{15}-C*H*$_3$), 1.28 (t, *J* = 7 Hz, $CO_2CH_2CH_3$), 1.03 (d, *J* = 6.8 Hz, 3 H, C_{16}-C*H*$_3$), 0.9 (d, *J* = 6.7 Hz, C_{11}-C*H*$_3$).



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In conclusion, an efficient convergent route presented here led to the first stereoselective synthesis of the (8*S*, 9*S*, 11*R*, 16*S*)-C_1-C_{18} segment of amphidinolides G, H, and L which will help to achieve the total synthesis of these molecules. Further work is under progress.

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