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

T. K. Chakraborty* and V. R. Suresh

*Indian Institute of Chemical Technology, Hyderabad 500 007, India*

Abstract

Stereoselective synthesis of the (8S, 9S, 11R, 16S)-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. © 1998 Elsevier Science Ltd. All rights reserved.

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 (8S, 9S, 11R, 16S)-C_1-C_{18} fragment of amphidinolides G, H and L.


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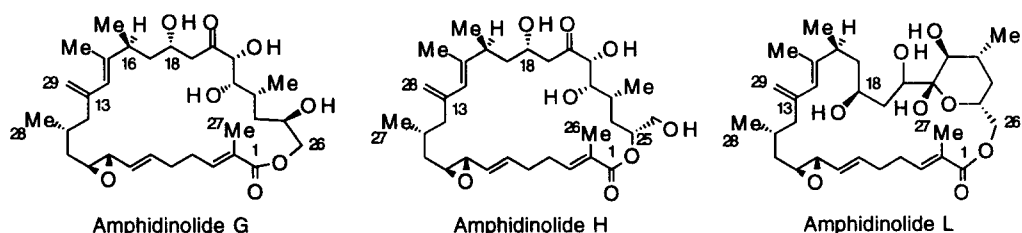
Retrosynthetically, the C_1-C_{18} fragment **1** can be divided, as shown in Scheme 1, into two halves: the C_7-C_{18} fragment **2** bearing the diene and the epoxyaldehyde functionalities and the C_1-C_6 Wittig component **3**. The important diene moiety of **2** was planned to be constructed by coupling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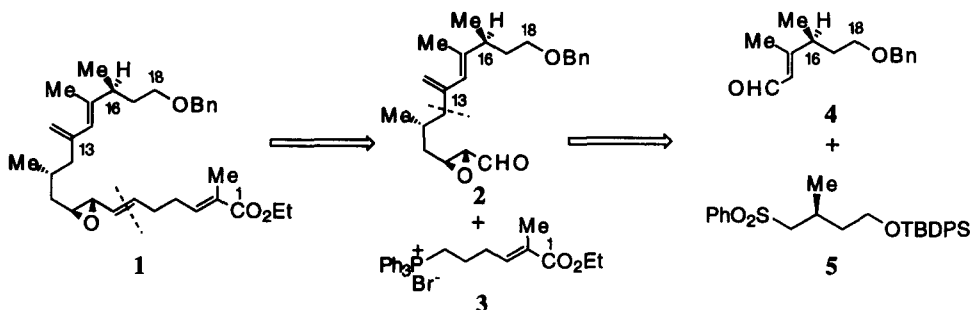
Scheme 1. Retrosynthetic analysis of 1.

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**.


[Trans:Cis = 3:1]

[Separated and characterised by NOE studies]
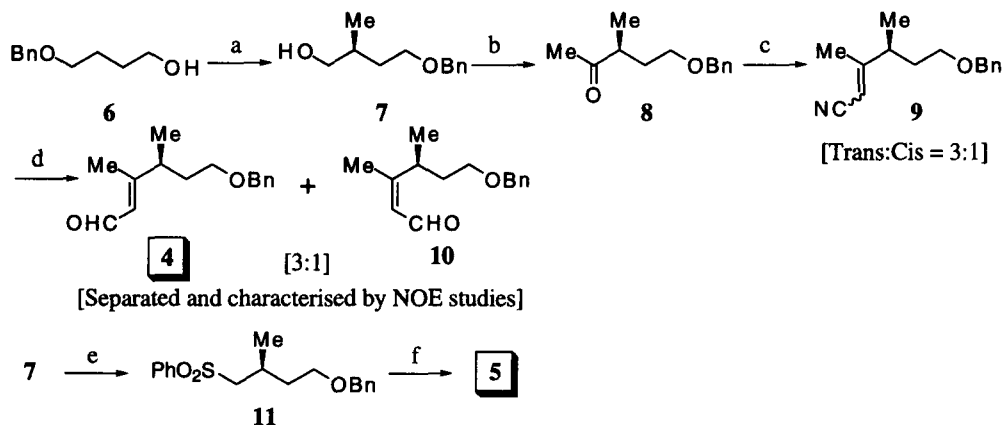
Scheme 2. Reagents and conditions. a) Ref. 16-18; b) (i) (COCl)$_2$ (1.5 eq.), DMSO (3.2 eq.), Et$_3$N (5 eq.), CH$_2$Cl$_2$, -78 to 0 °C, 1.5 h; (ii) MeMgI (2.0 M, 2 eq.), Et$_2$O, 0 to 25 °C, 1 h; (iii) same as step (i), 75% from **7**; c) (Et$_2$O)$_2$P(O)CH$_2$CN (1.5 eq.), NaH (1.5 eq.), DME, 25 °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$_2$CO$_3$ (1.5 eq.), DMF, 25 °C, 0.5 h; (iii) *m*CPBA (4 eq.), CH$_2$Cl$_2$, 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$_3$N (2 eq.), DMAP (0.1 eq.), CH$_2$Cl$_2$, 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 (8S,9S)-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**.

[91:9; separated]
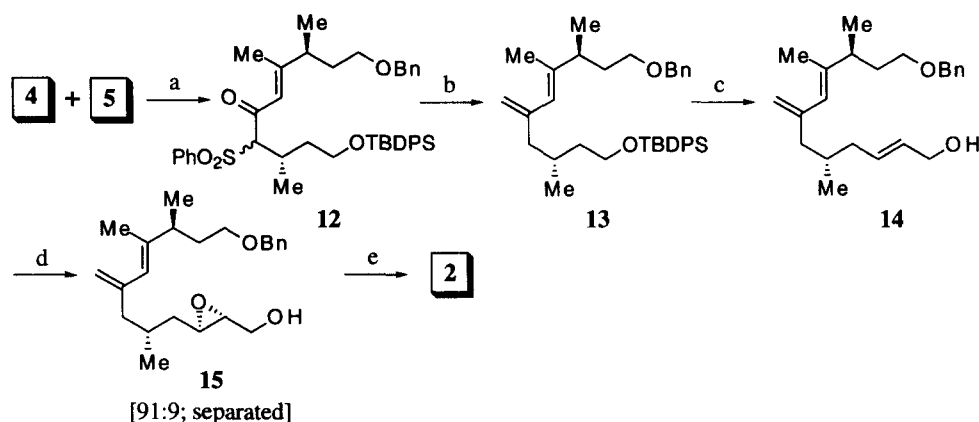
Scheme 3. Reagents and conditions. a) (i) **5** (1 eq.), "BuLi (1 eq.), THF, -78 °C, 20 min., then **4** in THF, -78 to 0 °C, 1 h; (ii) IBX (2 eq.), DMSO, 25 °C, 1 h, 80% in 2 steps; (b) (i) LN (excess), THF, -78 °C, 1 h, 60%; (ii) Ph₃P=CH₂ (2 eq.), Et₂O, 0 °C, 0.5 h, 88%; c) (i) TBAF (1.5 eq.), THF, 25 °C, 5 h; (ii) (COCl)₂ (1.5 eq.), DMSO (3.2 eq.), Et₃N (5 eq.), CH₂Cl₂, -78 to 0 °C, 1.5 h; (iii) Ph₃P=CHCO₂Et (2 eq.), C₆H₆, 25 °C, 1 h; (iv) DIBAL (2.2 eq.), CH₂Cl₂, -78 °C, 1 h, 80% from **13**; d) Ti(ⁱPrO)₄ (0.2 eq.), (+)-DET (0.22 eq.), TBHP (2 eq.), CH₂Cl₂, -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 Ph₃P 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 C₁-C₁₈ 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, CHCl₃); ¹H NMR (CDCl₃, 200 MHz): δ 7.7-7.2 (m, 15 H, aromatic), 5.54 (s, 1 H, C₁₄-H), 4.91 and 4.75 (two s, 2 H, C=CH₂), 4.42 (s, 2 H, CH₂Ph), 3.67 (t, J = 6.8 Hz, 2 H, CH₂OTBDPS), 3.35 (t, J = 6.8 Hz, 2 H, CH₂OBn), 2.32 (m, 1 H, C₁₆-H), 2.06 (dd, J = 14.8, 5.6 Hz, 1 H, C₁₂-H), 1.88-1.52 (m, 4 H, C₁₁-H, C₁₂-H, C₁₇-H₂), 1.68 (s, 3 H, C₁₅-CH₃), 1.3 (m, 2 H, C₁₀-H₂), 1.04 (s, 9 H, SiPh₂ᵗBu), 1.0 (d, J = 6.7 Hz, 3 H, C₁₆-CH₃), 0.78 (d, J = 6.3 Hz, 3 H, C₁₁-CH₃).

[3] **1**: $[\alpha]_D^{22}$ = 14.5 (c 0.2, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ 7.32 (m, 5 H, aromatic), 6.74 (t, J = 7 Hz, 1 H, C₃-H), 5.69 (dt, J = 15.2, 7.7 Hz, 1 H, C₆-H), 5.57 (s, 1 H, C₁₄-H), 5.08 (dd, J = 15.2, 8.1 Hz, 1 H, C₇-H), 4.96 and 4.81 (two s, 2 H, C₁₃=CH₂), 4.48 (s, 2 H, CH₂Ph), 4.19 (q, J = 7 Hz, 2 H, CO₂CH₂CH₃), 3.4 (t, J = 7 Hz, 2 H, CH₂OBn), 3.29 (dd, J = 8.1, 2.1 Hz, 1 H, C₈-H), 2.8 (dt, J = 7, 2.1 Hz, 1 H, C₉-H), 2.45-1.88 (m, 8 H, allylic, C₁₁-H, C₁₆-H), 1.84 (s, 3 H, C₂-CH₃), 1.8-1.58 (m, 4 H, C₁₀-H₂, C₁₇-H₂), 1.7 (s, 3 H, C₁₅-CH₃), 1.28 (t, J = 7 Hz, CO₂CH₂CH₃), 1.03 (d, J = 6.8 Hz, 3 H, C₁₆-CH₃), 0.9 (d, J = 6.7 Hz, C₁₁-CH₃).
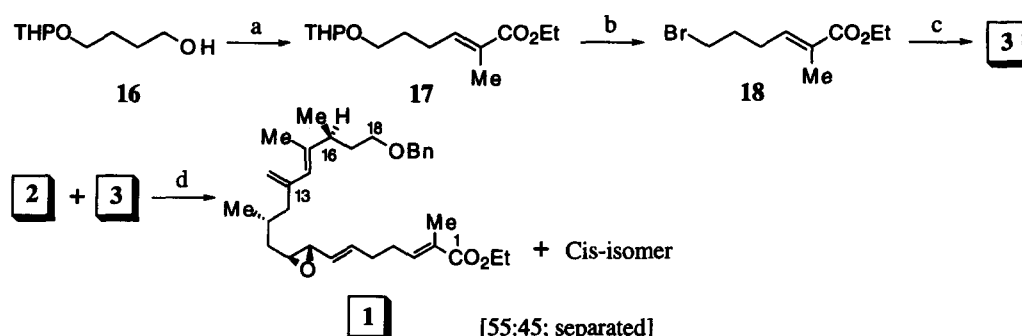
Scheme 4. Reagents and conditions. a) (i) $(COCl)_2$ (1.5 eq.), DMSO (3.2 eq.), Et_3N (5 eq.), CH_2Cl_2, -78 to 0 °C, 1.5 h; (ii) $Ph_3P=C(CH_3)CO_2Et$ (2 eq.), C_6H_6, 25 °C, 1 h, 90% from **16**; b) (i) PTSA (cat.), MeOH, 25 °C, 2 h; (ii) CBr_4 (2.5 eq.), Ph_3P (2.5 eq.), CH_2Cl_2, 0 to 25 °C, 2 h, 92% from **17**; c) Ph_3P (1.2 eq.), CH_3CN, reflux, 12 h, 85%; d) **3** (2 eq.), "BuLi (2 eq.), THF, -78 °C, 2 h, then **2** in THF, -78 to 25 °C, 12 h, 80%.

In conclusion, an efficient convergent route presented here led to the first stereoselective synthesis of the (8S, 9S, 11R, 16S)-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.

Acknowledgements

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