Synthetic Studies toward Potent Cytotoxic Agent Amphidinolide B: Synthesis of the Entire C1-C13 Moiety of the Bottom Half

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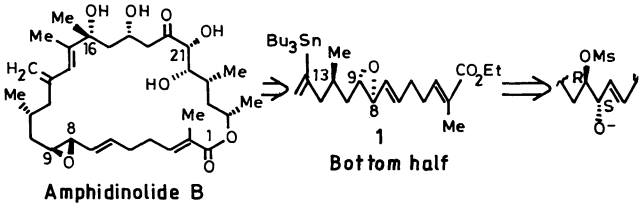
Sharpless asymmetric dihydroxylation and Nozaki-Hiyama-Kishi's Cr(II)-mediated coupling between an α-alkoxyaldehyde and a vinyl iodide are the key steps in the stereoselective synthesis of the entire C1-C13 segment of the bottom-half of amphidinolide B.

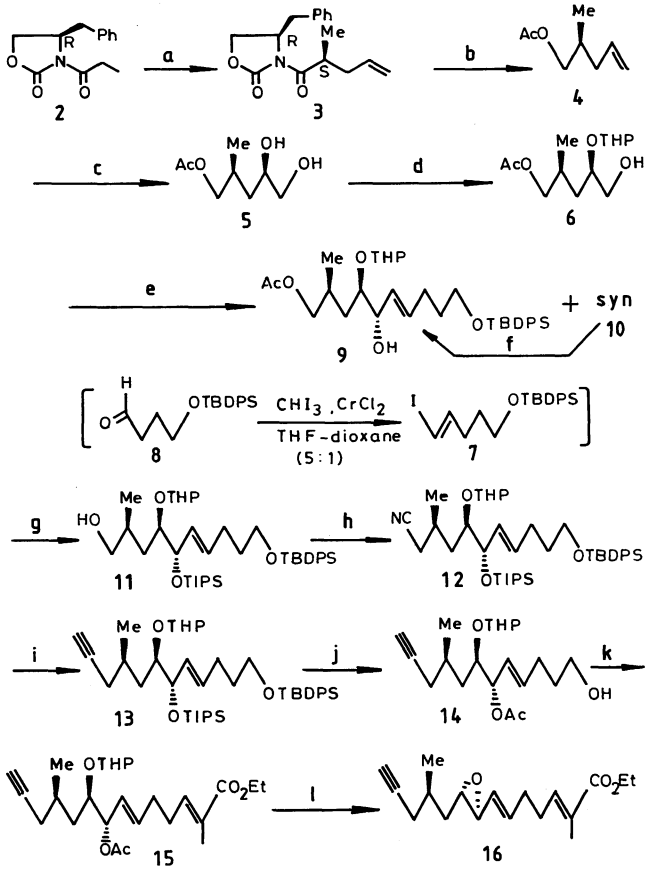
As part of our studies directed towards the syntheses of various amphidinolides,[1] we report here the synthesis of the entire C1-C13 moiety of the bottom-half (**1**), of amphidinolide B.[2] This moiety is common in many structurally related amphidinolides, like amphidinolides B, D, G, H,[3] and L.[4] The (8*S*,9*S*)-(C8-C9) epoxide moiety of this fragment is an essential structural feature of these molecules and responsible for their cytotoxic activities.[2b] The synthesis of this C1-C13 fragment will not only help to achieve the total synthesis of amphidinolide B, but also the other structurally related members of this family of polyene macrolides.[5]



Scheme 1.

All our efforts to get the *E*-double bond, next to the epoxide, starting from a suitable epoxy aldehyde precursor failed. This necessitated the synthesis of an *anti*-diol intermediate at C8-C9 position which could be converted to the requisite *E*-epoxide at a convenient stage. The difficulties encountered by us in the mesylation of allylic hydroxyl (Scheme 1) forced us to mesylate the C9-hydroxyl for epoxidation purpose making the (8*S*,9*R*)-diol as the targetted intermediate for the desired (8*S*,9*S*)-epoxide.

Our synthesis started with the asymmetric synthesis of the C11-stereocenter (Scheme 2). Alkylation of the sodium enolate from N-acyloxazolidinone **2**[6] with allyl iodide gave the (*S*)-methyl compound **3**. Reduction of **3** with $LiBH_4$ in presence of three molar equivalents of H_2O in Et_2O[7] followed by acylation gave **4**. Sharpless asymmetric dihydroxylation with AD-mix-β[8] (1.4 g per mmol of **4**) in *t*BuOH-H_2O (1:1) at 0 °C gave the *syn*-product **5** as the major isomer (3:1 ratio). The minor isomer could be separated chromatographically. The *syn*-isomer **5** was then transformed into the primary alcohol **6** in three steps. Swern oxidation[9] of **6** followed by $CrCl_2$-mediated Nozaki-Hiyama-Kishi[10] coupling with *E*-vinyl iodide **7**, prepared from **8** with CHI_3 and $CrCl_2$, gave the *anti*-isomer **9** as the major product (**9**:**10** = 7:3). The *syn*-isomer **10** was converted back to **9**, by oxidation with Dess-Martin periodinane[11] and diastereoselective (95:5) reduction with $Zn(BH_4)_2$[12] in Et_2O at - 20 °C. Stereochemistries of **9** and **10** were confirmed by converting them to the corresponding acetonides as shown in scheme 3. The coupling constant of 6 Hz between C8-H and C9-H of the acetonide from **9** confirmed their *anti*-relationship. The same two protons of the acetonide from the *syn*-product **10** exhibited a coupling of 8.9 Hz. These coupling constants are in conformity with the values reported in the literature.[13]

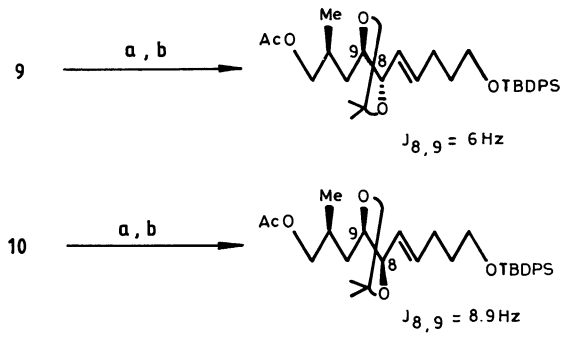


Reagents and Conditions: a) allyl iodide (3.0 eq.), NaHMDS (1.2 eq.), THF, - 78 °C, 3 h. b) (i) $LiBH_4$ (3.0 eq.), H_2O (3.0 eq.), Et_2O, 0 °C, 30 min. (ii) Ac_2O (1.2 eq.), Et_3N (2.0 eq.), DMAP (0.1 eq.), CH_2Cl_2, 0 °C, 20 min , 62% from **2**. c) AD-mix-β, *t*BuOH: H_2O (1:1), 0 °C, 6 h, 88% (*syn*: *anti* = 3:1). d) (i) TBSCl (1.0 eq.), Et_3N (1.5 eq), CH_2Cl_2, 0 °C to 25 °C, 12 h. (ii) DHP (1.1 eq.), PTSA (0.1 eq.), CH_2Cl_2, 25 °C, 2 h. (iii) TBAF (1.2 eq.), THF, 0 °C to 25 °C, 6 h, 59% from **5**. e) (i) $(COCl)_2$ (1.5 eq.), DMSO (3.2 eq.), Et_3N (5 eq.), CH_2Cl_2, - 78 °C to 0 °C, 1.5 h, 94%. (ii) **7**, $CrCl_2$ (containing 0.1% $NiCl_2$) (10.0 eq.), DMSO, 25 °C, 12 h, 80% (*syn*: *anti* = 3:7). f) (i) Dess-Martin periodinane (2.0 eq.), CH_2Cl_2, 25 °C, 1 h. (ii) $Zn(BH_4)_2$ (3.0 eq.), Et_2O, - 20 °C, 5 h, 84% from **10**. g) (i) TIPSOTf (1.1 eq.), 2,6-lutidine (2.0 eq.), CH_2Cl_2,

0 °C, 20 min. (ii) K_2CO_3 (1.5 eq.), MeOH, 0 °C to 25 °C, 3 h, 77% from **9**. h) (i) TsCl (1.2 eq.), Et_3N (2.0 eq.), DMAP (0.1 eq.), CH_2Cl_2, 25 °C, 3 h. (ii) NaCN (1.5 eq.), DMSO, 90 °C, 1 h, 75% from **11**. i) (i) DIBAL (1.2 eq.), toluene, - 78 °C, 30 min. (ii) Ph_3P (3.0 eq.), CBr_4 (1.5 eq.), Et_3N (1.0 eq.), CH_2Cl_2, 0 °C, 10 min. (iii) EtMgBr (3.0 eq.), THF, 0 °C to 25 °C, 30 min, 80% from **12**. j) (i) TBAF (3.0 eq.), THF, 25 °C, 12 h. (ii) TBDPSCl (1.0 eq.), imidazole (1.5 eq.), DMF, 0 °C, 30 min. (iii) Ac_2O (1.2 eq.), Et_3N (2.0 eq.), DMAP (0.1 eq.), CH_2Cl_2, 0 °C, 30 min. (iv) TBAF (1.2 eq.), THF, 25 °C, 6 h, 65% from **13**. k) (i) Same as e(i). (ii) $Ph_3P{=}C(CH_3)CO_2Et$ (2.0 eq.), benzene, 25 °C, 30 min. l) (i) PTSA (0.1 eq.), MeOH, 25 °C, 30 min. (ii) MsCl (1.5 eq.), Et_3N (3.0 eq), CH_2Cl_2, 0 °C, 2 h. (iii) K_2CO_3 (1.5 eq.), MeOH, 0 °C, 2.5 h, 71% from **15**.

Scheme 2.

Protection of the allylic alcohol was followed by a deacetylation step to get intermediate **11**. Primary hydroxyl of **11** was converted into a cyanide group in two steps to get **12**. This became necessary as our attempt for the direct alkylation of the tosylate or corresponding halides with various acetylene derivatives failed to give the desired terminal acetylene. Cyanide to terminal acetylene transformation was, thus, carried out using routine steps. All our attempts to selectively deprotect the primary hydroxyl group resulted in the formation of completely desilylated diol which was transformed into the allylic acetate



Reagents and conditions: a) PPTS (0.1 eq.), MeOH, 25 °C, 1 h. b) $(CH_3)_2C(OMe)_2$, PTSA (0.1 eq.), 25 °C, 1 h, 90% overall.

Scheme 3.

14 following standard functional group manipulations. Oxidation of the primary hydroxyl was followed by olefination with stabilized ylide to get the *E*-olefin **15**. Conversion of the homoallylic hydroxyl into a mesylate and finally mild base-catalyzed transformation into the desired *E*-epoxide furnished the targetted C1-C13 fragment **16**[14] of amphidinolide B. Further work is under progress.

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References and Notes

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14 ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.73 (t, J = 7 Hz, 1H, C3-*H*), 5.91 (dt, J = 6.5, 15.6 Hz, 1H, C6-*H*), 5.23 (dd, J = 8.1, 15.6 Hz, 1H, C7-*H*), 4.19 (q, J = 7.1 Hz, 2H, $-CO_2CH_2CH_3$), 3.08 (dd, J = 2.1, 8.1 Hz, 1H, C8-*H*), 2.84 (dt, J = 2.1, 5.6 Hz, 1H, C9-*H*), 2.30-2.20 (m, 6H, allylic and propargylic protons), 1.99 (t, J = 1.6 Hz, 1H, acetylenic), 1.94-1.91 (m, 1H, C11-*H*), 1.84 (s, 3H, C2-CH_3), 1.71-1.66 (m, 1H, C10-*H*), 1.52-1.45 (m, 1H, C10-*H*), 1.3 (t, J = 7.1 Hz, 3H, $-CO_2CH_2CH_3$), 1.08 (d, J = 6.7, 3H, C11-CH_3). MS(LSIMS): Calcd for $C_{18}H_{26}O_3$ (M^+): 290, Found m/z 291 (M^++H).