Synthetic Studies toward Potent Cytotoxic Agent Amphidinolide B : Synthesis of the Entire C14-C26 Moiety of the Top Half

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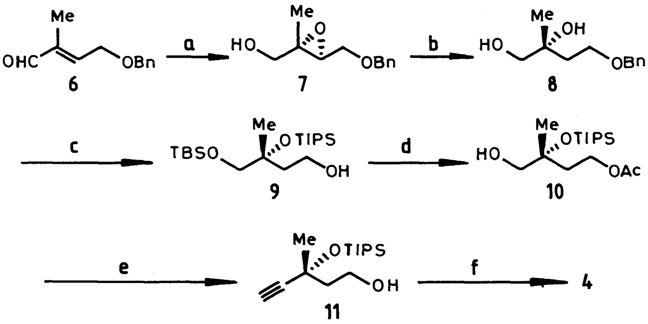
Regioselective hydroboration of a 4-methyl-2-alkene, oxidation of the resulting mixture of isomeric alcohols, and finally diastereoselective reduction of the ketone are the key steps in the stereoselective synthesis of C19-C26 fragment of amphidinolide B which was coupled with the C14-C18 fragment leading to the first synthesis of the entire C14-C26 moiety of this important molecule.

Amphidinolides isolated from marine dinoflagellate of the genus *Amphidinium* have potent toxicity against various tumor cell lines.[1] Some of them also display activity toward rabbit skeletal muscle actomyosin ATPase. Many of these compounds are reported to be among the most potent of all substances tested to date in the NCI screen, and are attracting attention as potential cancer drugs. The cytotoxic activities of amphidinolide B (**1**)[2] and its related compounds amphidinolides D, G, H, and L[1] are extremely strong. The relative stereochemistry of amphidinolide B by a single crystal X-Ray[3] and its absolute stereochemistry on the basis of enantioselective synthesis of a degradation product[4] have been reported. This 26-membered polyene macrolide has nine chiral centres. These chiral centres coupled with the presence of four double bonds with their geometric constraints have made the total synthesis of this molecule a formidable task. Retrosynthetically, amphidinolide B can be divided into two halves, the top-half **2** and the bottom-half **3** which can be joined together by Stille coupling[5] followed by esterification or vice-versa. The top-half **2** can further be dissected into two smaller fragments, the C14-C18 unit **4** and the C19-C26 unit **5**. As part of our ongoing project on the syntheses of various amphidinolides, we report here the first syntheses of these two fragments **4** and **5**, and finally their coupling leading to the stereoselective construction of the entire C14-C26 segment of the top-half of the molecule.

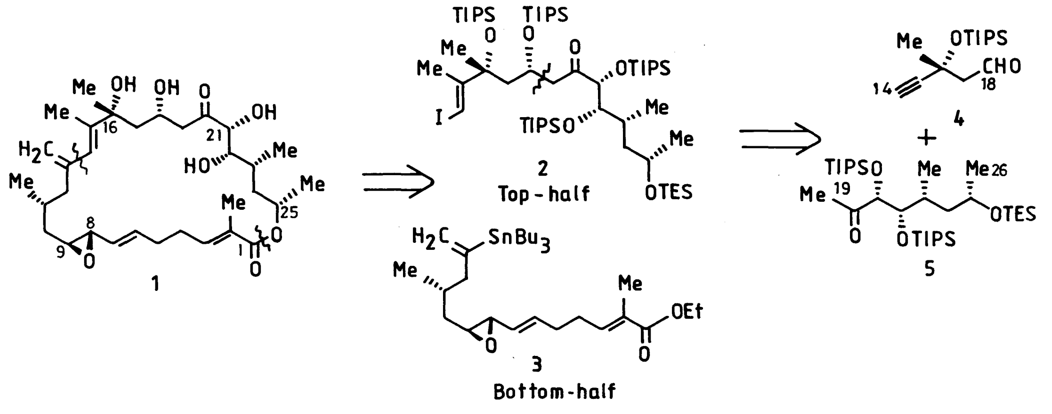
Our synthesis of **4** started with the α,β-unsaturated aldehyde **6** (Scheme 1) prepared by selenium dioxide oxidation of benzylether of 3-methyl-2-buten-1-ol.[6] Reduction of **6** was followed by Sharpless asymmetric epoxidation with natural tartrate. Regioselective opening of the resulting epoxide **7** gave the 1,2-diol **8**, exclusively. Routine functional group manipulations were carried out to furnish the alcohol **9** which was converted in two steps to **10**. The primary hydroxyl of **10** was then transformed into the acetylenic compond **11.** Swern oxidation of **11** finally led to the desired C14-C18 fragment **4**.

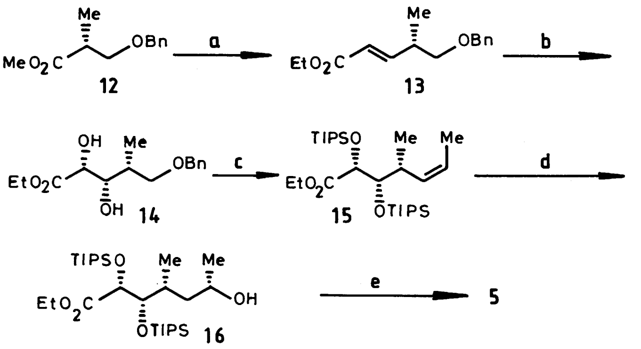
For the other fragment **5**, the starting material **12** (Scheme 2) was prepared by acid catalyzed benzylation[7] of commercially available methyl (*R*)-(-)-3-hydroxy-2-methylpropionate. Routine functional group manipulations gave α,β-unsaturated ester **13**. Treatment of **13** with AD-mix-α[8] (1.4 g per mmol of substrate) and methanesulfonamide (1 equiv.)



Reagents and Conditions: a) (i) DIBAL (1.2 eq.), hexane, - 78 °C, 15 min. (ii) Ti(*i*PrO)$_4$ (0.14 eq.), (+)-DET (0.14 eq.), TBHP (2.2 eq.), 4 A MS, CH_2Cl_2, - 20 °C, 5 h, 68% from **6**. b) DIBAL (5.0 eq.), toluene, - 15 °C, 15 min, 84%. c) (i) TBDMSCl (1.1 eq.), Et_3N (1.5 eq.), CH_2Cl_2, 0 °C to 25 °C, 12 h. (ii) TIPSOTf (1.5 eq.), 2,6-lutidine (2.0 eq.), CH_2Cl_2, 0 °C, 15 min. (iii) H_2, Pd/C, MeOH, 25 °C, 2.5 h, 80% from **8**. d) (i) Ac_2O (1.2 eq.), Et_3N (2.0 eq.), CH_2Cl_2, 25 °C, 15 min. (ii) HF / Py, THF, 25 °C, 12 h., 75% from **9**. e) (i) $(COCl)_2$ (1.2 eq.), DMSO (2.5 eq.), Et_3N (3.0 eq.), CH_2Cl_2, - 78 °C to 0 °C, 1.5 h. (ii) Ph_3P (4.0 eq.), CBr_4 (2.0 eq.), CH_2Cl_2, 25 °C, 15 min. (iii) EtMgBr (4.0 eq.), THF, 0 °C, 15 min, 85% from **10**. f) same as e(i), 90%.

Scheme 1.



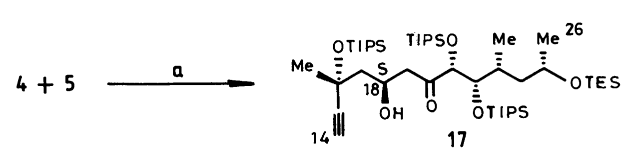


Reagents and Conditions: a) (i) LAH (1.0 eq.), Et_2O, 1 h. (ii) $(COCl)_2$ (1.5 eq.), DMSO (3.2 eq.), Et_3N (5 eq.), CH_2Cl_2, - 78 °C to 0 °C, 1.5 h. (iii) Ph_3P=$CHCO_2Et$ (1.2 eq.), CH_2Cl_2, 25 °C, 3 h, 81% from **12**. b) AD-mix-α, *t*BuOH: H_2O (1:1), 0 °C, 8 h, 85% (*syn*: *anti* = 6:1). c) (i) TIPSOTf (1.1 eq.), 2,6-lutidine (2.0 eq.), CH_2Cl_2, 0 °C to 25 °C, 12 h. ii) H_2, Pd/C, MeOH, 25 °C, 1 h. iii) same as a(ii). (iv) $Ph_3P^+EtBr^-$ (1.2 eq.), $NaNH_2$ (2.5 eq.), Et_2O, 0 °C, 15 min., 78% from **14**. d) (i) 9-BBN (2.0 eq.), THF, 25 °C, 16 h, then, MeOH (4.0 eq.), 3N aq. NaOH (2.2 eq.) and 30% H_2O_2 (6.0 eq.), 0 °C to 60 °C, 2 h. (ii) PDC, 4 A MS, CH_2Cl_2, 25 °C, 3 h. (iii) 9-BBN (2.0 eq.), THF, 0 °C to 25 °C, 1 h, 90% (*syn*: *anti* = 9:1) from **15**. e) (i) TESOTf (1.1 eq.), 2,6-lutidine (2.0 eq.), CH_2Cl_2, 0 °C, 15 min. (ii) DIBAL (2.2 eq.), CH_2Cl_2, - 78 °C, 15 min. (iii) same as a(ii). (iv) MeMgI (1.2 eq.), Et_2O, - 78 °C, 15 min. (v) same as a(ii), 75% from **16**.

Scheme 2.

in *t*BuOH-H_2O (1:1) at 0 °C gave the all *syn*-product **14**. The minor isomer was easily separated by silica gel column chromatography after the TIPS-protection step. Debenzylation, Swern oxidation of the resulting alcohol and finally Wittig olefination gave the *Z*-olefin **15**. There was no trace of any *E*-isomer. Regioselective hydroboration of the Z-olefin **15** with 9-BBN gave C25-hydroxy compound in excellent yield as a mixture of two diastereomers (*syn*: *anti* = 27:73). Oxidation of the mixture of alcohols was followed by diastereoselective reduction of the resulting β-methyl methylketone intermediate. 9-BBN gave slightly better selectivity (~9:1) compared to lithium trisiamylborohydride (~4:1), the major product being the required *syn*-isomer **16**. The minor isomer was separated easily after the TES protection step. The stereochemistry of C25 was confirmed by converting **16** to *syn*-2,4-dimethyl-γ-butyrolactone following a three-step procedure : desilylation followed by the cleavage of resulting diol with sodium periodate and finally PDC oxidation of the lactol to lactone. The lactone was identical (NMR, optical rotation) with an authentic sample prepared by reported method.[9] Protection of the C25-hydroxy of **16** was followed by transformation of the terminal ester group into the desired methylketone unit leading to the targetted C19-C26 fragment **5**.

Finally, the sodium enolate of **5** was added to the aldehyde **4** to get the coupled product **17**[10] (Scheme 3), the entire C14-C26 segment of amphidinolide B. The major isomer (ratio 3:2) was assigned with 18*S* stereochemistry on the basis of our earlier work on a similar system.[11] Further work is under progress.



Reagents and conditions: a) **5**, NaHMDS (1.1 eq., 1.0 M in THF), THF, - 78 °C, 30 min, then **4**, - 78 °C, 30 min.

Scheme 3.

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10 ^1H NMR ($CDCl_3$, 400 MHz) : δ 4.42 (d, J = 4.3 Hz, 1H, C21-*H*), 3.92 (dd, J = 4.3, 3.9 Hz, 1H, C22-*H*), 3.78 (m, 1H, C25-*H*), 3.56 (m,1H, C18-*H*), 2.77 (m, 2H, C19-H_2), 2.52 (s, 1H, acetylenic *H*), 2.0, 1.7, and 1.1 (m, 5H, CH_2 and *CH*), 1,6 (s, 3H, C16-CH_3), 1.14 - 1.0 (singlets, 66H, TIPS and C25-CH_3), 0.94 (t, J = 7.9 Hz, 9H, $SiCH_2CH_3$), 0.77 (d, J = 6.8 Hz, 3H, C23-CH_3), 0.58 (q, J = 7.9 Hz, 6H, $SiCH_2CH_3$).

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