Synthetic Studies toward Potent Cytotoxic Agent Amphidinolide B: Synthesis of the C_8-C_{18} Fragment

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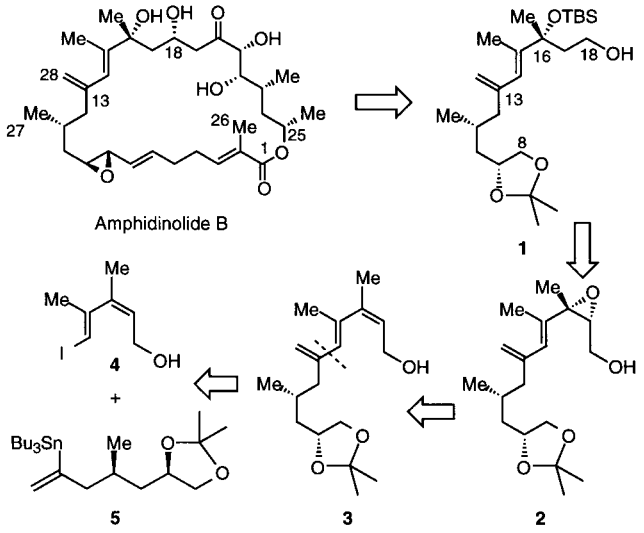
Abstract: A practical synthesis of the C_8-C_{18} fragment **1** of amphidinolide B is described in which the Stille coupling method was employed to construct the trisubstituted C_{28}=C_{13}–C_{14}=C_{15} "*s-cis*-1,3-diene" moiety from suitably functionalized vinyl iodide (**4**) and vinyl stannane (**5**) fragments, the former being prepared from an acetylene precursor using Negishi's carboalumination/iodination method.

Key words: Negishi reaction, Stille coupling, Amphidinolide B

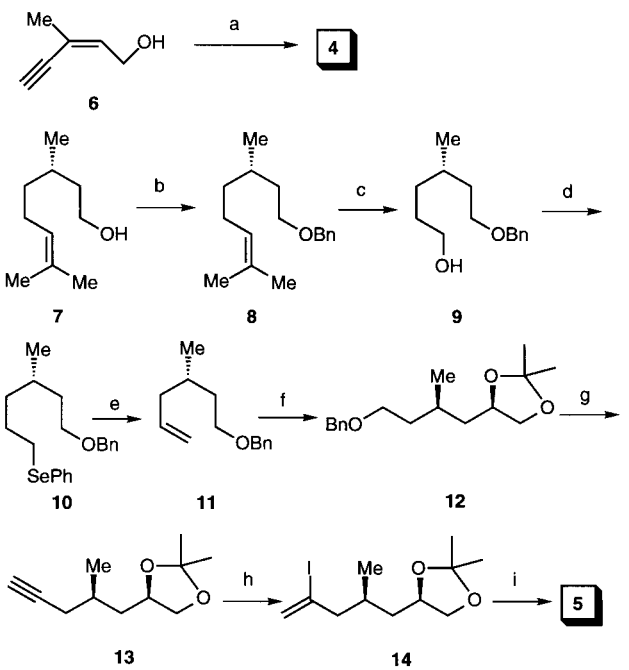
The potent cytotoxic activities and challenging structural features of amphidinolide molecules are attracting the attention of many synthetic organic chemists.[1] Though known for quite some time now, the total synthesis of none of these molecules has so far been achieved.[2] Recently Pattenden *et al.* have reported the synthesis of C_{14}-C_{26} fragment of amphidinolide B,[2c] where an initial attempt to apply Negishi's carboalumination/iodination method[3] to an α-alkoxy-substituted acetylene compound failed to provide an essential *E*-vinyl iodide intermediate, forcing them to devise an alternate lengthy route for its synthesis. This has prompted us to communicate our studies on the synthesis of the C_8-C_{18} fragment **1** of amphidinolide B where Negishi's method was successfully employed, albeit on a different substrate, to build the target *E*-vinyl iodide moiety required for the construction of the unique trisubstituted "*s-cis*-1,3-diene" moiety (C_{28}=C_{13}–C_{14}=C_{15}).



Scheme 1. Retrosynthetic analysis

Retrosynthetic analysis (scheme 1) revealed that **1** could be obtained from chiral epoxide **2** by regioselective hydride opening of its epoxy ring. The triene **3**, precursor of epoxide **2**, was planned to be assembled, using Stille coupling method,[4] from smaller units, viz., the dienyl iodide **4** which was to be prepared by Negishi reaction and the vinyl stannane **5**.

Scheme 2[5] delineates the synthesis of the fragments **4** and **5**. The former was synthesized in a single step starting from *Z*-enynol **6**.[6] Treatment of **6** with Me_3Al and Cp_2ZrCl_2, followed by quenching the intermediate aluminate with I_2,[3] provided the desired iodide **4** in 65% yield.[7] The *E*-isomer of **6** happened to be the starting material for Pattenden *et al.* where Sharpless asymmetric epoxidation/hydride-reduction preceded the making of vinyl iodide moiety.[2c] It is noteworthy that by altering the sequence of reactions, i.e., subjecting **6** first to the Negishi reaction, we could successfully synthesize the desired *E*-vinyl iodide.



Scheme 2. Synthesis of 4 and 5. *Reagents and conditions* : (a) Me_3Al (4 eq., 2 M in toluene), Cp_2ZrCl_2 (1 eq.), 1,2-dichloroethane, 48 h, then I_2 in THF (4 eq.), -20 to 0 °C, 0.5 h, 65%; (b) NaH (1.1 eq.), BnBr (1.1 eq.), TBAI (cat.), THF, 0 to 25 °C, 95%; (c) (i) O_3, CH_2Cl_2, -78 °C, 0.5 h, then Me_2S, -78 to 25 °C, 1 h; (ii) $NaBH_4$ (1 eq.), MeOH, 0 °C, 15 min, 90% from 8; (d) (i) TsCl (1.2 eq.), Et_3N (1.5 eq.), DMAP

(0.1 eq.), CH_2Cl_2, 25 °C, 1 h; (ii) PhSeSePh (1 eq.), $NaBH_4$ (2 eq.), EtOH, 25 °C, 1 h, 85% from 9; (e) *m*CPBA (1.5 eq.), DIPA (2 eq.), CH_2Cl_2, 15 min, and then add to refluxing CCl_4, 5 min, 80%; (f) (i) AD-mix-β (1.4 g/mmol of 11), *t*BuOH-H_2O (1:1), 0 °C, 5 h; (ii) 2,2-dimethoxypropane, CSA (0.1 eq.), 0 °C, 0.5 h, 70% from 11; (g) (i) H_2, Pd-C, MeOH, 25 °C, 0.5 h; (ii) Ph_3P (4 eq.), CBr_4 (2 eq.), CH_2Cl_2, 25 °C, 15 min; (iii) EtMgBr (2 eq.), THF, 0 °C, 15 min, 75% from 12; (h) (i) NaI (4 eq.), TMSCl (4 eq.), H_2O (2 eq.), CH_3CN, 25 °C, 1 h; (ii) same as in f(ii), 74%; (i) *n*BuLi (1 eq.), *n*Bu_3SnCl (1 eq.), THF, -78 °C, 15 min, 72%.

The starting material for the synthesis of **5** was (*S*)-(-)-β-citronellol (**7**, scheme 2) which was benzylated to get the Bn-ether **8** in 95% yield. Ozonolysis of the double bond of **8** was followed by the borohydride reduction of the resulting aldehyde to get alcohol **9** in 90% yield in two steps. Next, a three-step protocol[8] was employed to convert **9** to the terminal double bond containing intermediate **11**. Tosylation of the primary hydroxyl of **9** was followed by nucleophilic substitution of the tosylate group by $PhSe^-$, generated *in-situ* by sodium borohydride reduction of diphenyl diselenide, giving the phenylselenide intermediate **10**, in 85% overall yield, which was then subjected to an oxidation-elimination process. Oxidation of selenide **10** using *m*CPBA and subsequent β-elimination of the resulting selenoxide generated the terminal olefin **11** in 80% yield. Sharpless asymmetric dihydroxylation of **11** with AD-mix-β[9] in *t*BuOH-H_2O (1:1) at 0 °C gave the *syn*-product as the major isomer (3:1 ratio). The minor isomer could be separated chromatographically. The diol moiety of the major isomer was protected as acetonide to get **12** in 70% yield from **11**. Debenzylation of **12** gave the free alcohol which was converted to the terminal acetylene **13** by a standard two-step procedure (75% from **12**). Treatment of **13** with trimethylsilyl iodide (TMSI), generated *in situ* from NaI and TMSCl, in the presence of requisite amount of water led to the formation of HI-adduct with internal iodide as the only product.[10] During the reaction, the acetonide also got deprotected which was restored to furnish **14** in 74% yield. The Li-anion generated from vinyl iodide **14** was reacted with tri-*n*-butyltin chloride to get the vinylstannane **5**[11] in 72% yield.

Scheme 3 Synthesis of 1. *Reagents and conditions* : (a) $Pd(CH_3CN)_2Cl_2$ (10 mol %), DIPEA (3 eq.), DMF, 25 °C, 12 h, 60%; (b) Ti(*i*PrO)$_4$ (0.2 eq.), (-)-DIPT (0.22 eq.), TBHP (2 eq.), CH_2Cl_2, -10 °C, 12 h, 85%; (c) (i) Red-Al (1.2 eq.), THF, 0 °C, 1 h; (ii) TBSOTf (2.2 eq.), 2,6-lutidine (3 eq.), CH_2Cl_2, 0 °C, 0.5 h; (iii) HF-Py, THF, 25 °C, 1 h, 65% from 2.

The stage was now set to try the Stille coupling reaction between **4** and **5**. Treatment of a mixture of equimolar amounts of **4** and **5** in DMF with $Pd(CH_3CN)_2Cl_2$ in presence of *N*,*N*-diisopropylethylamine gave the desired coupled product **3**[12] in 60% yield (scheme 3[5]). Sharpless asymmetric epoxidation[13] of **3** with unnatural (-)-diisopropyl-D-tartrate gave the expected epoxy alcohol **2** in 85% yield. Regioselective opening of the epoxy ring using Red-Al in THF at 0 °C gave the 1,3-diol intermediate which was converted to the target C_8-C_{18} fragment **1**,[14] following standard protection-deprotection protocol, in 65% yield from **2**.

In conclusion, a concise synthesis of C_8-C_{18} segment **1** of amphidinolide B is described here which contains the crucial trisubstituted C_{28}=C_{13}–C_{14}=C_{15} "*s-cis*-1,3-diene" moiety. The intermediate **1** also carries suitable functional groups at both ends which are amenable to further extrapolation, work on which is currently under progress.

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References and Notes

(1) (a) Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543-572. (b) Kobayashi, J.; Ishibashi, M. *Chem. Rev*. **1993**, *93*, 1753-1789.

(2) (a) The total synthesis of amphidinolide J has just appeared: Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc*. **1998**, *120*, 11198-11199. For previous synthetic studies toward various amphidinolides see: (b) Chakraborty, T. K.; Suresh, V. R. *Tetrahedron Lett*. **1998**, *39*, 7775-7778. (c) Cid, M. B.; Pattenden, G. *Synlett* **1998**, 540-542. (d) Hollingworth, G. J.; Pattenden, G. *Tetrahedron Lett*. **1998**, *39*, 703-706. (e) Kobayashi, J.; Hatakeyama, A.; Tsuda, M. *Tetrahedron* **1998**, *54*, 697-704. (f) Tsuda, M.; Hatakeyama, A.; Kobayashi, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 149-155. (g) Lee, D. -H.; Lee, S. -W. *Tetrahedron Lett*. **1997**, *38*, 7909-7910. (h) Chakraborty, T. K.; Suresh, V. R. *Chemistry Lett*. **1997**, 565- 566. (i) Chakraborty, T. K.; Thippeswamy, D.; Suresh, V. R.; Jayaprakash, S. *Chemistry Lett*. **1997**, 563-564. (j) Eng, H. M.; Myles, D. C. Abstracts of the papers of the American Chemical Society **1995**, *209*, No. Pt 2, 405 ORGN1. (k) Ishibashi, M.; Ishiyama, H.; Kobayashi, J. *Tetrahedron Lett*. **1994**, *35*, 8241- 8242. (l) Tsuda, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem*. **1994**, *59*, 3734-3737. (m) Boden, C.; Pattenden, G. *Synlett* **1994**, 181-182. (n) O'Connor, S. J.; Williard, P. G. *Tetrahedon Lett*. **1989**, *30*, 4637-4640.

(3) (a) Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc*. **1985**, *107*, 6639-6647. (b) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem*. **1981**, *46*, 4093-4096.

(4) (a) Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc*. **1987**, *109*, 813-817. (b) For a review see: Mitchell, T. N. *Synthesis* **1992**, 803-815.

(5) All compounds were characterized by NMR, IR and mass spectral analysis. Yields refer to chromatographically and spectroscopically homogeneous materials.

(6) Compound **6** can be purchased from Aldrich. We prepared it from but-2-yn-1-ol in 3 steps: (i) treatment with Red-Al in ether at 0 °C followed by quenching with I_2 in THF at -78 °C to get (*Z*)-3-iodo-2-buten-1-ol; (ii) Pd-catalyzed coupling of this vinyl iodide with TMS-acetylene to get (*Z*)-5-trimethylsilyl-3-methyl-2-penten-4-yn-1-ol; and finally, (iii) deprotection of silyl group using anhydrous K_2CO_3 in MeOH to get **6**.

(7) Synthesis of vinyl iodide **4**: A suspension of Cp_2ZrCl_2 (0.584 g, 2 mmol) in dry 1,2-dichloroethane (10 mL) was treated with Me_3Al (4 mL, 2 M solution in toluene, 8 mmol) at room temperature (r.t.), followed by the addition of a solution of **6** (0.192 g, 2 mmol) in the same solvent (2 mL). The reaction mixture was stirred at r.t. for 48 h. It was then cooled to -20 °C and I_2 (1.016 g, 8 mmol) in THF (3 mL) was slowly added. The mixture was stirred for 30 min., during which time it was allowed to warm up to 0 °C. It was then quenched by slow addition of H_2O (5 mL), extracted with EtOAc (2x10 mL), washed with brine (5 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification by column chromatography (SiO_2, 5-10% EtOAc in petroleum ether eluant) gave the iodide **4** (0.309 g, 65%) as a syrupy liquid. R_f = 0.3 (silica gel, 25% EtOAc in petroleum ether). ^{1}H NMR ($CDCl_3$, 200 MHz, amphidinolide B numbering): δ 6.0 (s, 1 H, C_{14}-*H*), 5.4 (t, J = 7 Hz, 1 H, C_{17}-*H*), 4.1 (d, *J* = 7 Hz, 2 H, C_{18}-H_2), 1.95 (s, 3 H, CH_3), 1.85 (s, 3 H, CH_3). EIMS: *m/z* 111 (M^+-I).

(8) (a) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem*. **1978**, *43*, 1697-1705. (b) Clark, R. D.; Heathcock, C. H. *J. Org. Chem*. **1976**, *41*, 1396-1403.

(9) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Grispino, G. A.; Hartung, J.; Jeong, K. -S.; Kwong, H. -L.; Morikawa, K.; Wang, Z. -M.; Xu, D.; Zhang, X. -L. *J. Org. Chem*. **1992**, *57*, 2768-2771.

(10) Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675-676.

(11) Vinyl stannane **5**: ^{1}H NMR ($CDCl_3$, 200 MHz, amphidinolide B numbering): δ 5.6 (s, 1 H, olefin H), 5.12 (s, 1 H, olefin H), 4.1 (dq, *J* = 8 Hz, 1 H, C_9-*H*), 3.96 (t, *J* = 8 Hz, 1 H, C_8-*H*), 3.38 (t, *J* = 8 Hz, 1 H, C_8-*H*'), 2.32 (dd, *J* = 5 and 14 Hz, 1 H, C_{12}-*H*), 1.96 (dd, *J* = 8 and 14 Hz, 1 H, C_{12}-*H*'), 1.6-1.2 (m, 15 H, CH_2 and C*H*), 1.36 and 1.3 (two s, 6 H, acetonide CH_3), 1.05-0.65 (m, 15 H, CH_2 and CH_3).

(12) Synthesis of triene **3**: A solution of **4** (0.15 g, 0.63 mmol) and **5** (0.298 g, 0.63 mmol) in dry DMF (3 mL) was degassed by bubbling argon through it for 15 min. Then a solution of diisopropylethylamine (0.33 mL, 1.89 mmol) in degassed THF (1 mL) and $Pd(CH_3CN)_2Cl_2$ (0.016 g, 0.063 mmol) in degassed DMF (1 mL) were added, successively. The reaction mixture was stirred in the dark at r.t. for 12 h, diluted with water (10 mL), and extracted with EtOAc (3x10 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 5-10% EtOAc in petroleum ether eluant) to afford the triene **3** (0.111g, 60%) as a syrupy liquid. R_f = 0.3 (silica gel, 25% EtOAc in petroleum ether). ^{1}H NMR ($CDCl_3$, 200 MHz, amphidinolide B numbering): δ 5.55 (s, 1 H, C_{14}-*H*), 5.05 (s, 1 H, C_{28}-*H*), 4.9 (s, 1 H, C_{28}-*H*'), 4.2-4.05 (m, 3 H, C_9-*H*, C_{18}-H_2), 4.0 (dd, *J* = 5.6 and 8 Hz, 1 H, C_8-*H*), 3.43 (t, *J* = 8 Hz, 1 H, C_8-*H*'), 2.35-1.95 (m, 2 H, C_{12}-H_2), 1.88 (s, 3 H, C_{15}-CH_3), 1.85 (s, 3 H, C_{16}-CH_3), 1.9-1.5 (m, 3 H, CH_2, C*H*), 1.4 and 1.35 (two s, 6 H, acetonide CH_3), 0.95 (d, *J* = 7 Hz, C_{11}-CH_3). EIMS: *m/z* 279 (M^+-CH_3).

(13) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc*. **1987**, *109*, 5765-5780.

(14) Diene **1**: ^{1}H NMR ($CDCl_3$, 400 MHz, amphidinolide B numbering): δ 6.0 (s, 1 H, C_{14}-*H*), 5.0 (s, 1 H, C_{28}-*H*), 4.8 (s, 1 H, C_{28}-*H*'), 4.1, 4.0, 3.65 and 3.4 (m, 5 H, CH_2-O and C*H*-O), 2.2-1.8 (m, 3 H, CH_2, C*H*), 1.8 (s, 3 H, C_{15}-CH_3), 1.45 (s, 3 H, C_{16}-CH_3), 1.37 and 1.32 (two s, 6 H, acetonide CH_3), 0.92 (d, *J* = 7 Hz, 3 H, C_{11}-CH_3), 0.9 (s, 9 H, Si-*t*-butyl), 0.05 and 0.07 (s, 6 H, $SiMe_2$).