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Towards the synthesis of amphidinolide B. An intramolecular Stille coupling approach

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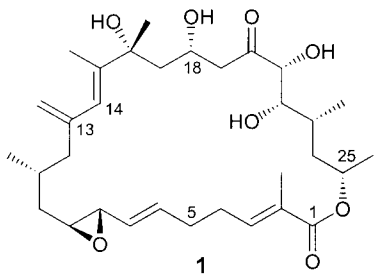
Abstract

A synthetic approach towards the cytotoxic polyene polyol macrolide amphidinolide B (**1**), based on elaboration of the C_1-C_{13} carboxylic acid **4** and the $C_{14}-C_{25}$ alcohol **3** units, their esterification to the iodostannyl ester **2**, and an intramolecular Stille sp^2–sp^2 coupling reaction, is described. In spite of adequate precedent and model experiments, circumstances conspired and the aforementioned coupling reaction was not realised in this case.

The amphidinolides are an ever-expanding family of novel polyene polyol-based macrolides produced by marine organisms. A majority of their number show pronounced toxicity against tumour cell lines and, as a consequence, are attracting considerable attention as potential anti-cancer drugs.[1] Amphidinolide B (**1**) has been isolated from dinoflagellates of the genus *Amphidinium* which enjoy a symbiotic relationship with marine flatworms *Amphiscolops* sp.[2] The compound features a 26-membered macrolide which accommodates nine chiral centres, an aldol unit, a 1,3-diene system, an allyl epoxide and a vicinal diol; the stereochemistry was established by X-ray analysis. Together with other biologically active amphidinolides, amphidinolide B has attracted significant attention from synthetic chemists.[3,4] In this Letter we describe our studies aimed at applying the intramolecular Stille sp^2–sp^2 coupling reaction[5,6] as a key strategy in the total synthesis of this polyene polyol macrolide.



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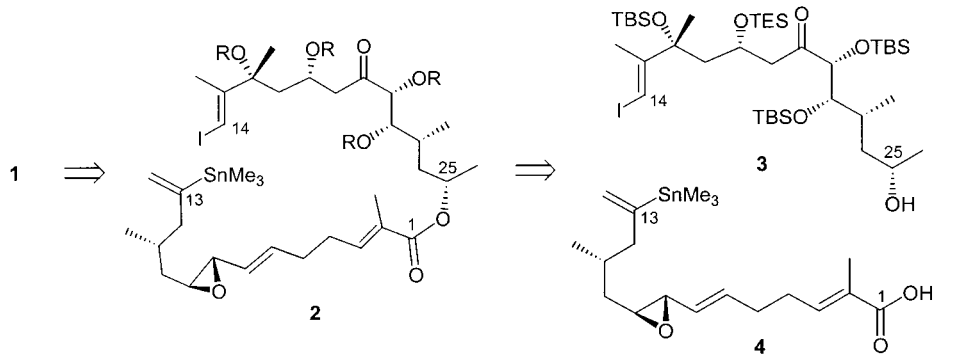
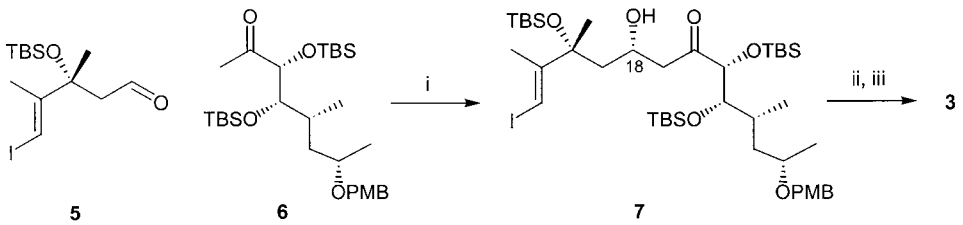
Thus, our overall strategy towards a synthesis of amphidinolide B was to elaborate the C_1-C_{13} and $C_{14}-C_{25}$ units, **4** and **3** respectively, then use these units to synthesise the iodostannyl ester **2**, and finally effect macrocyclisation of **2** under Pd(0)-catalytic conditions (Scheme 1). In earlier work, we had already developed a concise synthesis of the $C_{14}-C_{25}$ unit **7**, based on an aldol condensation strategy involving the ketone **6** and the aldehyde **5**.[7] This aldolisation produced both **7** and its C-18 epimer which could be easily separated by routine chromatography. As a prelude to connecting **3** to the C_1-C_{13} unit **4**, the C-18 hydroxyl group in **7** was next protected as its TES-ether, followed by deprotection of the C-25 *p*-methoxybenzyl ether group, leading to the secondary alcohol **3** (Scheme 2).[8]

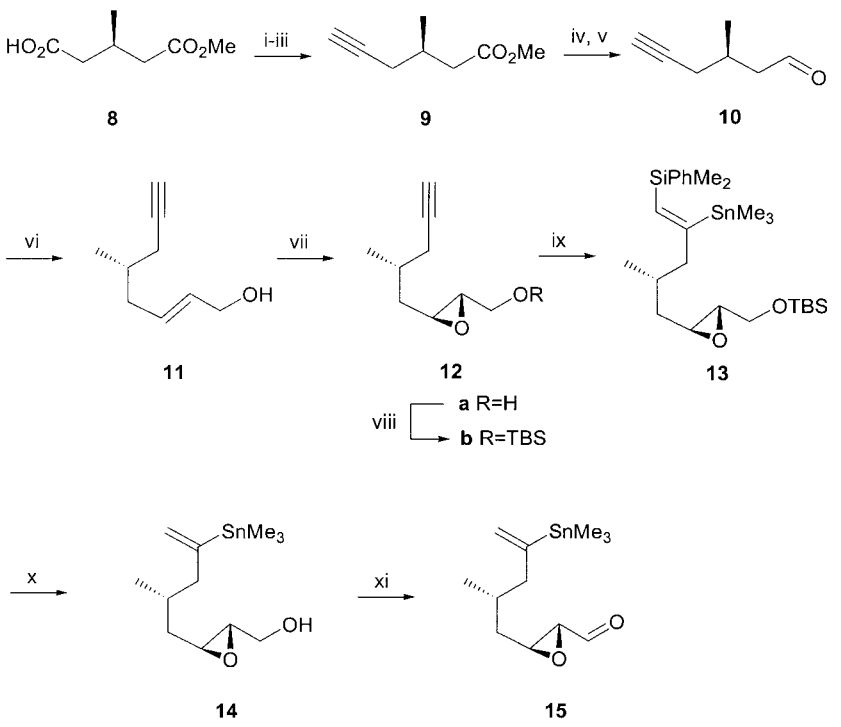


Scheme 1.

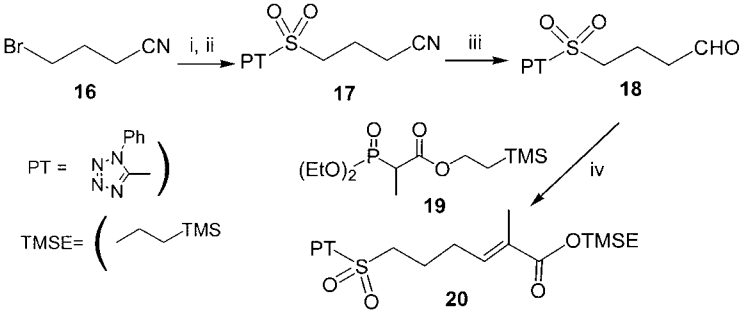


Scheme 2. **Reagents and conditions:** (i) LiHMDS, THF, –78°C; (ii) 6 equiv. Et_3N, 0.5 equiv. DMAP, 4 equiv. TESCl, CH_2Cl_2, 0°C, 12 h, 80%; (iii) 1.16 equiv. DDQ, wet CH_2Cl_2, rt, 1 h, 98%

The C_1-C_{13} fragment **4** in amphidinolide B features an unusual *E*-allyl epoxide unit, which is also present in amphidinolides D, G and L.[1c] Our approach to **4** was based on a Julia olefination reaction[9] between the chiral epoxyaldehyde **15** and the arylsulphone **20**, which, in turn, were synthesized from methyl hydrogen (*R*)-3-methylglutarate **8** and 4-bromobutyronitrile **16**, respectively, as shown in Schemes 3 and 4. Thus, elaboration of **8** to the terminal acetylene **9**, followed by conversion into the aldehyde **10** and a Wittig olefination-reduction sequence first led to the *E*-allylic alcohol **11**. Sharpless epoxidation[10] of **11** followed by protection of the epoxy alcohol **12a** as its TBS ether **12b**, silylstannylation[11] and subsequent cleavage of the silicon groups in the product **13** next led to the vinylstannane alcohol **14**. A straightforward oxidation of the alcohol **14**, using TPAP, then produced the epoxyaldehyde **15** in readiness for coupling to the



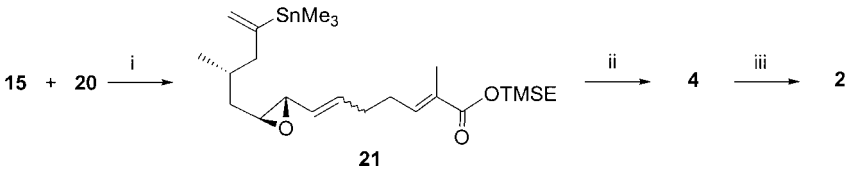
Scheme 3. **Reagents and conditions:** (i) 1.3 equiv. BH_3-SMe_2, –20°C to rt, 18 h, 95%; (ii) 0.01 equiv. TPAP, 1.5 equiv. NMO, 4 Å MS, rt, 3 h, 70%; (iii) $CH_3COC(N_2)P(O)(OMe)_2$, MeOH, K_2CO_3, rt, 6 h, 71%; (iv) DIBAL-H, CH_2Cl_2, –78°C, 6 h, 75%; (v) $(COCl)_2$, DMSO, CH_2Cl_2, –60°C, then Et_3N to 0°C, 1.5 h; (vi) $Ph_3P{=}CHCO_2Me$, rt, 18 h, 90%, then DIBAL-H, CH_2Cl_2, –78°C, 5 h, 80%; (vii) 0.18 equiv. (+)-DET, 0.15 equiv. $Ti(O^iPr)_4$, 2 equiv. ^{t}BuOOH, 4 Å MS, –20°C, 18 h, 62%; (viii) TBSOTf, Et_3N, CH_2Cl_2, –78°C, 1.5 h, 86%; (ix) 1 equiv. $PhMe_2Si{-}SnMe_3$, DME, 4% $Pd(OAc)_2$, 18% PPh_3, 30°C, 2 days, 83%; (x) 6 equiv. TBAF, DMSO, 80°C, 0.5 h to rt over 0.5 h, 35–70%; (xi) 0.05 equiv. TPAP, 1.5 equiv. NMO, 4 Å MS, rt, 4 h, 80%



Scheme 4. **Reagents and conditions:** (i) K_2CO_3, ArSH, dioxane, reflux, 18 h; (ii) MCPBA, rt, 3 h, 60%; (iii) DIBAL-H, toluene, –78°C to –20°C, 6 h, then MeOH, then H_2O/silica/EtOAc to rt, 1 h, 50%; (iv) LiCl, EtN^iPr_2, CH_3CN, rt, 24 h, 26%

sulphone **20**. The phenyltetrazole sulphone **20** was synthesised from **16** in four straightforward steps, (i) alkylation of 1-phenyl-1*H*-tetrazole with **16** in the presence of K_2CO_3; (ii) oxidation of the resulting sulphide to the sulphone **17**; (iii) reduction of **17** to the aldehyde **18**; and (iv) a

Wadsworth–Emmons olefination between **18** and the phosphonate **19**[12] which, under the Masamune–Roush conditions[13] led exclusively to the *E*-alkene **20**. A one-pot Julia olefination reaction[9e] between the sulphone **20** and the aldehyde **15** then gave the allyl epoxide **21**, as a 3:1 mixture of geometrical isomers[14] about the newly introduced double bond, which on hydrolysis with TBAF produced the carboxylic acid **4** (Scheme 5).[8] Esterification of **4** with the secondary alcohol **3** under Yamaguchi conditions finally produced the key ester intermediate **2**.

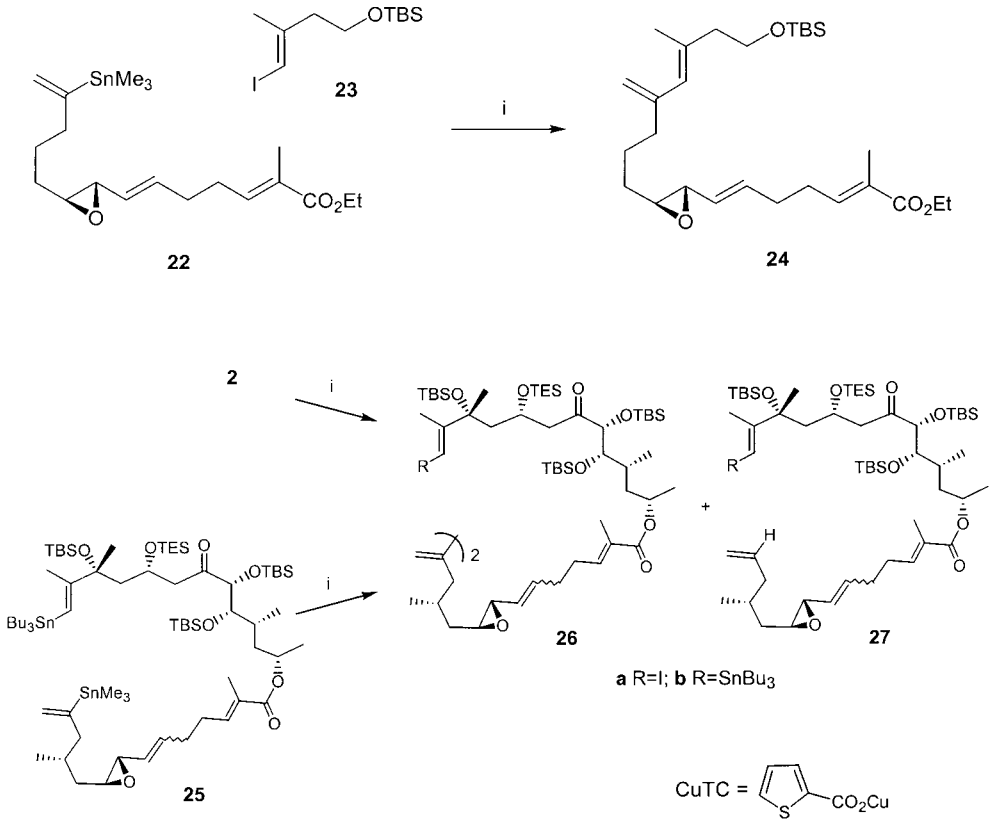


Scheme 5. **Reagents and conditions:** (i) KHMDS, DME, –78°C, 65%; (ii) TBAF, THF, 95%; (iii) **4**, $C_6H_2Cl_3COCl$, Et_3N, then **3**, DMAP, 40°C, 20 h, 70%

The palladium(0) catalysed Stille reaction is one of the most revered methods for the coupling of olefinic sp^2 centres, and a number of spectacular illustrations of its use in the synthesis of polyene macrocyclic structures have been published.[5b] Its main benefits lie in the fact that the reaction can be carried out under relatively mild conditions and a range of sensitive functionality can be accommodated. The recent introduction of copper(I)-coupling reagents[6] has added even more scope for the reaction in synthesis. Situations where the Stille reaction has not been fully tested include: (i) when the alkene bonds are sterically compromised, as with the iodide residue in **3**;[6d] and (ii) where the reaction is carried out in the presence of an allyl epoxide unit when competitive metal-mediated reactions might be expected. In model work we addressed the latter issue when we showed that the vinyl stannane allyl epoxide model **22** underwent smooth intermolecular coupling with the iodide **23** in the presence of copper(I) thiophene-2-carboxylate (CuTC), leading to the polyene **24** in an acceptable 60% yield.[15] It was to our immense frustration, then, to find that when the iodostannane **2** was treated with CuTC under similar conditions, the major product we isolated was the dimer **26a** resulting from vinylstannane–vinylstannane coupling, together with smaller amounts of the product **27a** from straightforward destannylation of **2** (Scheme 6).

To circumvent this problem, which could have its origin in steric congestion associated with the bulky TBS protected *t*-alcohol adjacent to the vinyl iodide residue in **2**, we thought we would capitalise on the known propensity for vinyl stannanes to undergo tin–tin coupling.[5,16] Accordingly, we prepared the vinyl stannane corresponding to **3**, by iodine–tin exchange, and coupled it to the acid **4** leading to the bis vinyl stannane **25**. Alas, this di-stannane was also reluctant to engage in intramolecular sp^2–sp^2 (tin–tin) coupling. Instead only the dimer **26b** and the mono-destannylated product **27b** were obtained from these reactions.

We are now examining in more detail the effects of steric encumbrance at centres participating in the Stille reaction. In addition we are re-evaluating our strategy and tuning the substrates and reacting partners in the aforementioned intramolecular coupling strategy, in order to reach a successful conclusion to our synthetic investigations towards amphidinolide B. These studies will be reported in due course.



Scheme 6. **Reagent**: (i) CuTC, NMP, rt

Acknowledgements

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8. Selected ^{1}H NMR data (amphidinolide numbering). Alcohol **3** ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 6.28$ (bs, 1H, C_{14}−H); 4.18 (m, 2H, C_{18}−H, C_{21}−H); 3.78–3.70 (m, 1H, C_{25}−H); 3.58 (dd, J = 5.8, 4.3, 1H, C_{22}−H); 2.80 (dd, J = 18, 4.4, 1H, C_{19}−H); 2.69 (dd, J = 18, 7.6, 1H, C_{19}−H); 2.00–1.73 (m, 4H, C_{17}−H_2, C_{24}−H and C_{23}−H); 1.89 (s, 3H, CH_3); 1.46 (s, 3H, CH_3); 1.17 (d, J = 6.2, 3H, CH_3); 1.13 (m, 1H, C_{24}−H); 0.96 (s, 9H, $3CH_3$); 0.94 (t, J = 7.8, 9H, $3CH_3$); 0.92 (s, 9H, $3CH_3$); 0.88 (s, 9H, $3CH_3$); 0.85 (d, J = 6.6, 3H, CH_3); 0.58 (q, J = 7.8, 6H, $3CH_2$); 0.16 (s, 3H, CH_3); 0.12 (s, 3H, CH_3); 0.10 (s, 3H, CH_3); 0.06 (s, 3H, CH_3); 0.04 (s, 3H, CH_3) and 0.02 (s, 3H, CH_3). Carboxylic acid **4** ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 6.88$ (bt, J = 6.6, 1H, C_3−H); 5.90 (dt, J = 15.4, 6.1, 1H, C_6−H); 5.63 (bs, $J_{Sn-H} = 152$, 1H, C_{28}−H); 5.25 (dd, J = 15.4, 8, 1H, C_7−H); 5.20 (bs, $J_{Sn-H} = 72$, 1H, C_{28}−H); 3.04 (dd, J = 8, 1.9, 1H, C_8−H); 2.84 (td, J = 5.9, 1.9, 1H, C_9−H); 2.40–2.14 (m, 6H, C_4H_2, C_5H_2, $C_{12}H_2$); 1.85 (bs, 3H, $C_{26}H_3$); 1.80–1.70 (m, 1H, C_{11}−H); 1.65 (dt, J = 13.8, 5.9 Hz, 1H, C_{10}−H); 1.27 (ddd, J = 13.8, 8.4 and 5.9, 1H, C_{10}−H); 0.93 (d, J = 6.6, 3H, C_{27}−H_3); 0.15 (s, J_{Sn-H}, 54 and 52, 9H, $3CH_3$).
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12. The phosphonate **19** was obtained by esterification of trimethylsilylethanol with 2-(diethoxyphosphoryl)propionic acid which, in turn, was obtained by hydrolysis of 2-(diethoxyphosphonyl)propionic acid ethyl ester as described by Roush, W. R.; Sciotli, R. J. *J. Am. Chem. Soc*. **1998**, *120*, 7411.
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14. When benzothiazole was used as the heterocycle instead of phenyltetrazole, a lower selectivity ($E/Z = 2{:}1$) was observed.
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