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[17] The observed DSC melting endotherms, with a flat maximum at fairly high temperatures and a very long "tail" toward lower temperatures, are clearly indicative that L_{iso} is broadly distributed. This is consistent with the fact (already commented in the text) that the samples have a broad molecular mass distribution ($M_w/M_n \gg 2$) and can be solvent-separated in fractions widely differing in stereoregularity.

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Total Synthesis of the Presumed Amphidinolide A**

Hon Wai Lam and Gerald Pattenden*

The amphidinolides are a family of biologically active macrolides isolated from the marine dinoflagellate *Amphidinium sp.*, which lives in a symbiotic relationship with the Okinawan flatworm *Amphiscolops sp.*[1] Many of the amphidinolides show potent cytotoxic activity against murine lymphoma L1210 cells, human epidermoid carcinoma KB cells, and human colon tumor HCT 116 cells.[1] Amphidinolide A (**1**) was the first member of the family to be isolated and characterized.[2] Its structure incorporates a 20-membered macrolactone that contains six double bonds, three of which are exocyclic. The relative stereochemistry of the nine stereocenters in **1** was suggested by Kobayashi and co-workers on the basis of extensive NMR spectroscopy experiments.[3]

Studies towards the synthesis of amphidinolide A (**1**) have been described by O'Connor and Williard,[4] by Maleczka and co-workers,[5] and by ourselves. In an earlier communication, we described an approach to the macrolactone core of **1** in which a key step involved an intramolecular sp^2-sp^3 Stille reaction of a precursor that contains an alkenyl stannane and an allylic chloride.[6] In subsequent studies, we also described a concise synthesis of the C7–C13 fragment **2**, starting from commercially available methyl-α-D-glucopyranoside.[7] Herein we describe a total synthesis of **1**, the proposed structure of amphidinolide A, and also of the diastereomer **34**, which is epimeric to **1** at C20 and C21.

Our synthetic strategy to amphidinolide A (**1**) required the preparation of two major fragments **3** and **4**, which we planned to elaborate into **1** through the following sequence of operations: 1) an intermolecular sp^2-sp^2 Stille reaction[8] between the less sterically hindered C4 alkenyl stannane unit in **3** and the C3 alkenyl iodide of **4**; 2) deprotection of all the silyl ethers originally in **3**; and 3) an intramolecular sp^2-sp^3 Stille reaction[9] between the C14 alkenyl stannane and the C15 allylic acetate (Scheme 1). The intermolecular Stille reaction of **3** with **4** was deemed to be highly challenging, as it requires not only the discrimination between the two alkenyl stannane units in **3**, but also between the alkenyl iodide and the allylic acetate units in **4**, both of which are potentially reactive under palladium-catalyzed coupling conditions. However, the observation that sterically encumbered alkenyl stannanes are often poor substrates in the Stille reaction,[10] together with our expectation that an alkenyl iodide would be more reactive than an allylic acetate, led us to believe that the reaction could be selective. We planned to prepare the bis-alkenyl stannane **3** from the known aldehyde **5**,[7] and to prepare the iodide acetate **4** by using a modified Julia olefination reaction[11] between aldehyde **6** and benzothiazolyl sulfone **7** as a key step.

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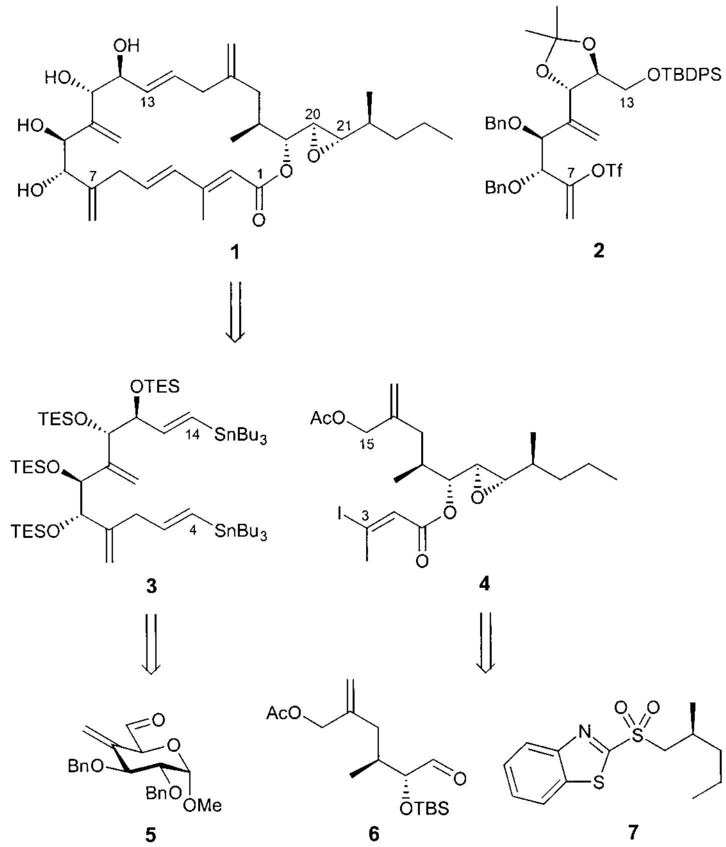
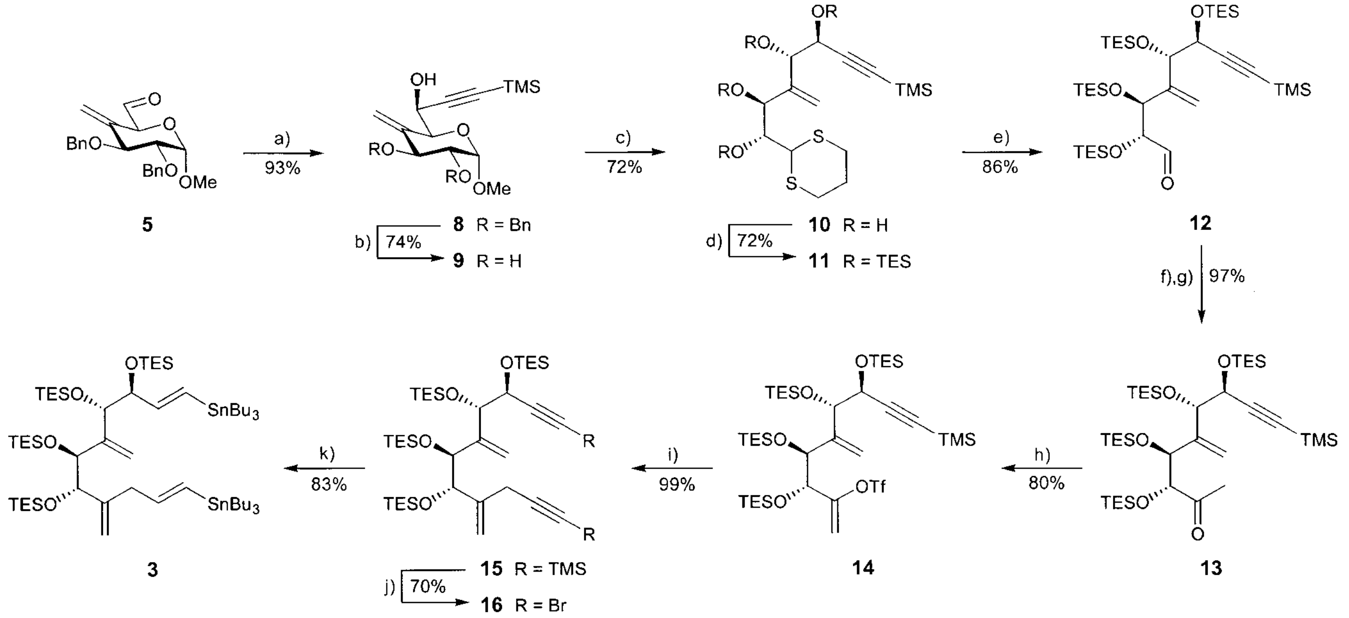


Scheme 1. Retrosynthetic analysis of **1**, the proposed structure of amphidinolide A

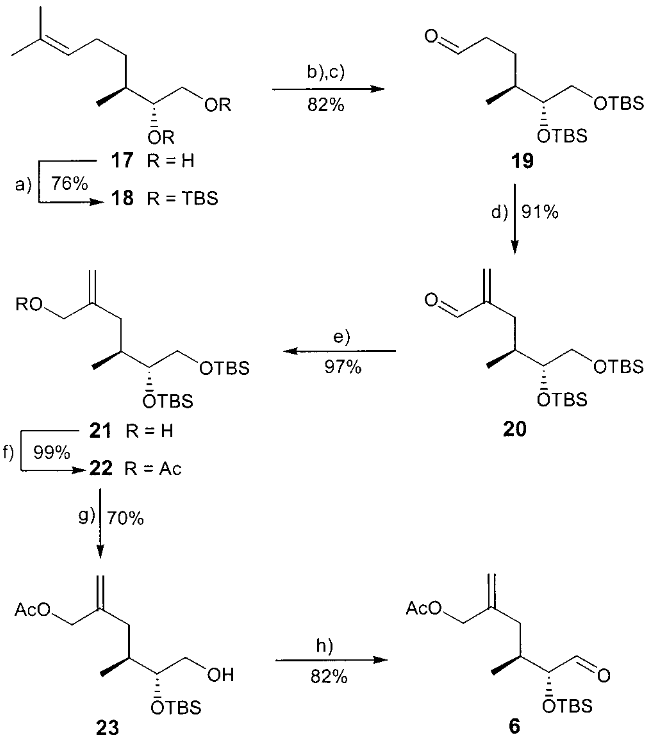
Thus, the chelation-controlled addition of trimethylsilylethynylmagnesium bromide to aldehyde **5** first gave alcohol **8**, which was isolated as a single diastereomer in 93% yield (Scheme 2).[12, 13] Debenzylation of **8** by using DDQ,[14] followed by a thioacetalization/ring-opening reaction of the resulting cyclic acetal **9** with propane-1,3-dithiol next led to the acyclic tetraol **10**. After silylation of the hydroxy groups in **10**, the thioacetal group in the product **11** was removed by using NBS in aqueous acetone[15] to reveal aldehyde **12**. A straightforward homologation of **12** to the corresponding methyl ketone **13** was followed by the formation of alkenyl triflate **14**, which upon reaction with the Gilman reagent derived from (3-trimethylsilylprop-2-ynyl)lithium and copper(I) iodide, gave the bis-TMS-alkyne **15** in excellent yield. After exchanging the alkyne TMS protecting groups in **15** for bromides by the action of NBS and $\mathrm{AgNO_3}$,[16] palladium-catalyzed hydrostannylation[17] of the resulting bis-bromoalkyne **16** finally gave (*E*,*E*)-bis-alkenyl stannane **3** in 83% yield.

Aldehyde **6**, which is required for elaboration into **4**, was synthesized as shown in Scheme 3 starting from the previously described diol **17**.[18] Thus, protection of **17** as its bis-TBS ether **18**, followed by oxidative cleavage of the alkene gave aldehyde **19**. Reaction of **19** with Eschenmoser's salt[19] next gave α,β-unsaturated aldehyde **20**, which upon reduction under Luche conditions followed by acetylation of the resulting allylic alcohol **21** gave **22**. The primary TBS ether group in **22** was removed selectively by using CSA, thus leading to alcohol **23**, along with 12% of recovered **22**, which could be recycled. Finally, oxidation of **23** with TPAP/NMO,[20] gave aldehyde **6**.

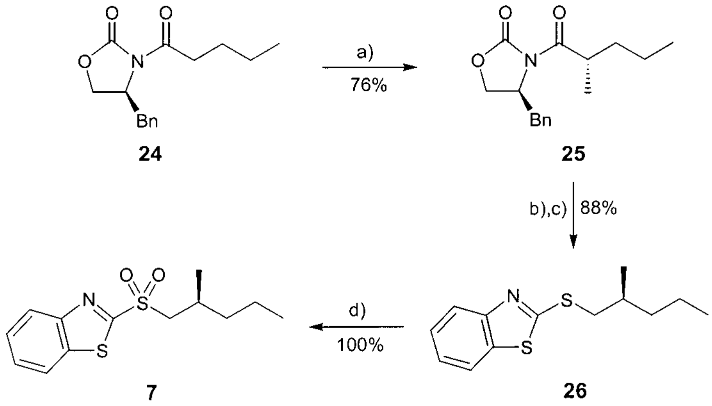
The chiral benzothiazolyl sulfone **7**, which is required for coupling to aldehyde **6**, was prepared from the known acylated oxazolidinone **24**[21] (Scheme 4). Methylation of the sodium enolate derived from **24** proceeded with 91:9 diastereoselectivity and gave, after purification, the diastereomerically pure alkylated product **25** in 76% yield.[22] Reductive



Scheme 2. Reagents and conditions: a) (trimethylsilyl)acetylene, *n*BuLi, $\mathrm{Et_2O}$, 0 °C→RT, 15 min, then $\mathrm{MgBr_2}$, RT, 15 min, then **5**, $\mathrm{MgBr_2}$, −30 °C→RT, 1 h; b) DDQ, $\mathrm{CH_2Cl_2/H_2O}$ (19:1), Δ, 24 h; c) propane-1,3-dithiol, $\mathrm{BF_3\cdot OEt_2}$, $\mathrm{CH_2Cl_2}$, 0 °C, 4 h; d) TESOTf, 2,6-lutidine, $\mathrm{CH_2Cl_2}$, 0 °C, 5 h; e) NBS, 2,6-lutidine, acetone/$\mathrm{H_2O}$ (9:1), RT, 40 min; f) MeMgBr, $\mathrm{CH_2Cl_2}$, −78 °C, 15 min; g) Dess–Martin periodinane, $\mathrm{NaHCO_3}$, $\mathrm{CH_2Cl_2}$, RT, 35 min; h) KHMDS, $\mathrm{PhNTf_2}$, THF, −78→0 °C, 3 h; i) $\mathrm{LiCu(CH_2C{\equiv}CTMS)_2}$, THF, −20 °C→RT, 12 h; j) NBS, $\mathrm{AgNO_3}$, acetone, RT, 10 h; k) $\mathrm{Bu_3SnH}$, $\mathrm{Pd(PPh_3)_4}$, THF, RT, 4 h. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TESOTf = triethylsilyl trifluoromethanesulfonate, NBS = *N*-bromosuccinimide, HMDS = bis(trimethylsilyl)amide.



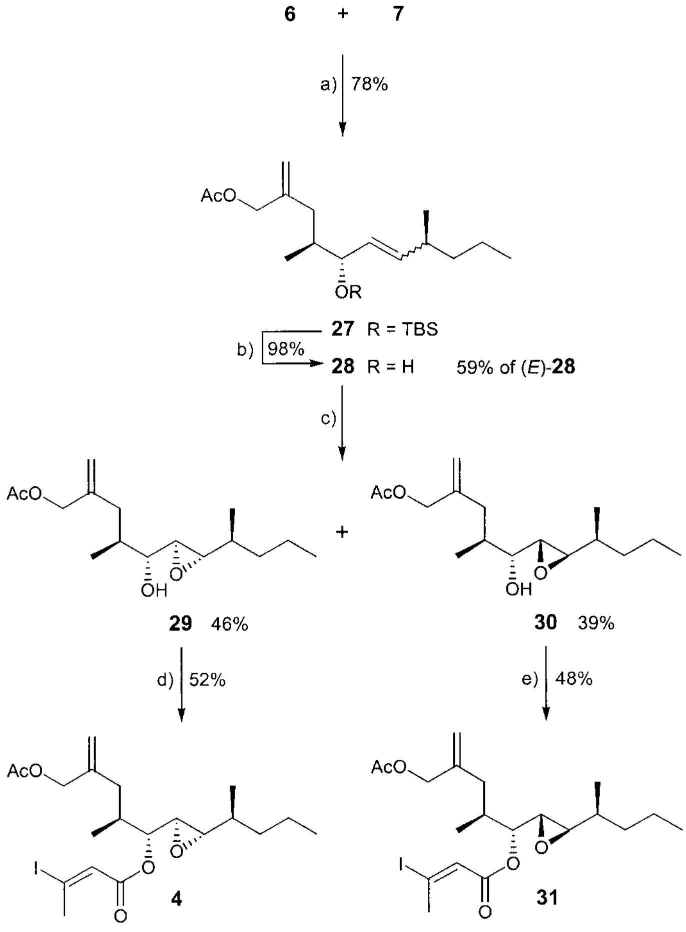
Scheme 3. Reagents and conditions: a) TBSOTf, Et_3N, CH_2Cl_2, RT, 12 h; b) OsO_4, NMO, acetone/H_2O (10:1), RT, 3d; c) $NaIO_4/SiO_2$, CH_2Cl_2, RT, 3 h; d) $CH_2{=}NMe_2{}^+I^-$, Et_3N, CH_2Cl_2, RT, 12 h; e) $NaBH_4$, $CeCl_3\cdot 7H_2O$, MeOH, 0 °C, 30 min; f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, RT, 3 h; g) CSA, MeOH, 0 °C, 3.5 h; h) TPAP, NMO, 4-Å molecular sieves, CH_2Cl_2, RT, 1 h. TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate, NMO = 4-methylmorpholine-*N*-oxide, DMAP = 4-dimethylaminopyridine, CSA = camphorsulfonic acid, TPAP = tetrapropylammonium perruthenate.



Scheme 4. Reagents and conditions: a) NaHMDS, MeI, THF, −78 °C→RT, 5 h; b) $LiBH_4$, MeOH, Et_2O, 0 °C, 3 h; c) 2-mercaptobenzothiazole, DEAD, PPh_3, THF, RT, 12 h; d) *m*CPBA, CH_2Cl_2, RT, 4 h. DEAD = diethyl azodicarboxylate, *m*CPBA = 3-chloroperbenzoic acid.

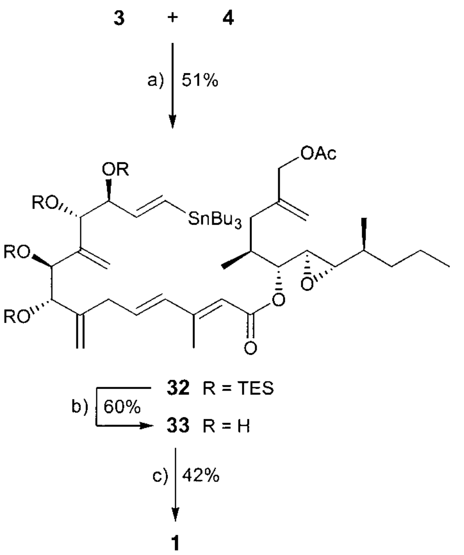
removal of the chiral auxiliary in **25**, followed by a Mitsunobu reaction of the resulting crude alcohol with 2-mercaptobenzothiazole gave sulfide **26** in 88 % yield over two steps. Oxidation of **26** with *m*CPBA finally gave the sulfone **7** in virtually quantitative yield.

A one-pot Julia reaction[11] between **6** and **7**, using KHMDS in THF, led to alkene **27** as an inseparable mixture of *E* and *Z* isomers (4:1; Scheme 5). Removal of the TBS ether group in **27** with HF·pyridine allowed the isolation of pure allylic alcohol (*E*)-**28**, which was epoxidized by using *t*BuOOH and $Ti(OiPr)_4$ to give the diastereomeric epoxides **29** and **30**. Epoxy alcohol **29**, which is required for the synthesis of **1** was used to esterify (*E*)-iodobut-2-enoic acid,[23] leading to **4**. Similarly, diastereomer **30** was converted into **31**.



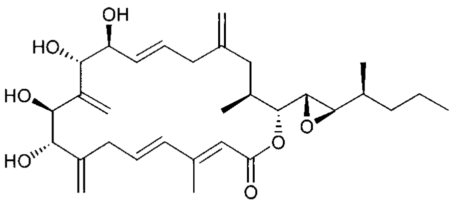
Scheme 5. Reagents and conditions: a) **7**, KHMDS, THF, −78 °C, 30 min, then **6**, −78 °C→RT, 3 h 45 min; b) HF·pyridine, 2,6-lutidine, THF, RT, 15 h; c) *t*BuOOH, $Ti(OiPr)_4$, CH_2Cl_2, −20 °C, 6 h; d) (*E*)-3-Iodobut-2-enoic acid, DIC, DMAP, CH_2Cl_2, −20 °C, 6 h; e) (*E*)-3-Iodobut-2-enoic acid, EDC, DMAP, CH_2Cl_2, −20 °C, 12 h. DIC = 1,3-diisopropylcarbodiimide, EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride.

With both key fragments **3** and **4** in hand, a novel selective intermolecular sp^2-sp^2 Stille reaction that entails the use of Farina's catalyst combination[24] in refluxing THF gave diene (*E*,*E*)-**32**, which was isolated in 51 % yield (Scheme 6). The alkenyl stannane unit in **32** was rendered more reactive to the final sp^2-sp^3 Stille macrocyclization by deprotection of its TES ethers with PPTS, to give tetraol **33**. Finally, an sp^2-sp^3 Stille macrocylization of **33** by using Farina's catalyst in the presence of lithium chloride in cyclohexane gave the polyene polyol macrolide **1** in an unoptimized 42 % yield. To the best of our knowledge, this macrocyclization represents the first example of an intramolecular sp^2-sp^3 Stille reaction between an alkenyl stannane and an allylic acetate.[25]



Scheme 6. Reagents and conditions: a) Pd$_2$(dba)$_3$, Ph$_3$As, THF, 60 °C, 4 h; b) PPTS, MeOH, CH$_2$Cl$_2$, RT, 6 h; c) Pd$_2$(dba)$_3$, Ph$_3$As, LiCl, cyclohexane, Δ, 3 h. dba = dibenzylideneacetone, PPTS = pyridinium *p*-toluenesulfonate.

Comparison of the ^{1}H and ^{13}C NMR spectroscopic data of **1** with those reported for amphidinolide A[3] revealed that they were not identical, and showed that we had, in fact, prepared a diastereomer of the natural product. The NMR spectroscopic data of synthetic **1** are fully consistent with the structure proposed for amphidinolide A,[2] and assignments for **1** were made on the basis of a combination of chemical shift and coupling constant data, along with HMQC and HMBC spectral data. However, there are significant discrepancies in the chemical shift values compared to those reported for the natural product. Kobayashi and co-workers proposed the relative stereochemistry of amphidinolide A purely on the basis of NOESY data.[3] Since the interpretation of the relative configuration of stereogenic centers in macrocyclic compounds by spectral means is not trivial, their assignment was only tentative, and it seems likely that the actual structure of amphidinolide A is epimeric to the proposed structure **1** at one or more stereocenters. It would appear therefore, that a revision of the stereochemistry of the natural product is required. Similarly, **31** was subjected to the identical sequence of reactions depicted in Scheme 6 to give **34**, the C20, C21 bis-epimer of **1**, which was also shown to be a diastereomer of the natural product.



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In conclusion, we have synthesized **1**, which has the proposed structure of amphidinolide A, along with a diastereomer **34**. The synthesis proceeded in 21 steps for the longest linear sequence, starting from methyl-α-D-glucopyranoside, and relied heavily on the judicious use of both inter- and intramolecular Stille reactions for key bond constructions.

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