Natural Products

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Total Syntheses of Amphidinolides T1, T3, and T4**

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The amphidinolides are macrolides isolated from marine dinoflagellates of the genus *Amphidinium sp.*, which are symbionts found on acoel flatworms of the *Amphiscolops* species.[1] More than 30 amphidinolides have been isolated and most of them display cytotoxic activities.[1,2] Some of the amphidinolides possess other biological activities, but insufficient quantities of material are available to fully establish their therapeutic potential in most cases.

The amphidinolide T subgroup comprises five compounds (T1–T5), which exhibit cytotoxic activities against L1210 murine lymphoma cells and KB human epidermoid carcinoma cells.[1c] These compounds, first isolated and characterized by the Kobayashi group,[3] are 19-membered lactones possessing seven or eight stereogenic centers, an exocyclic alkene, an α-hydroxy ketone motif, and a trisubstituted tetrahydrofuran (Figure 1). Amphidinolides of the T series

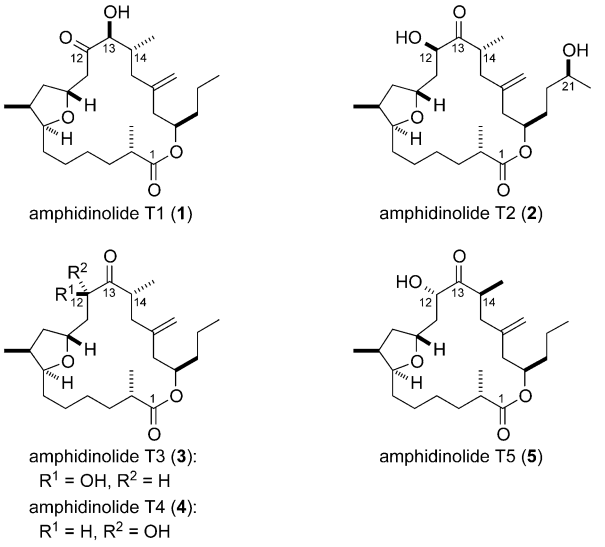


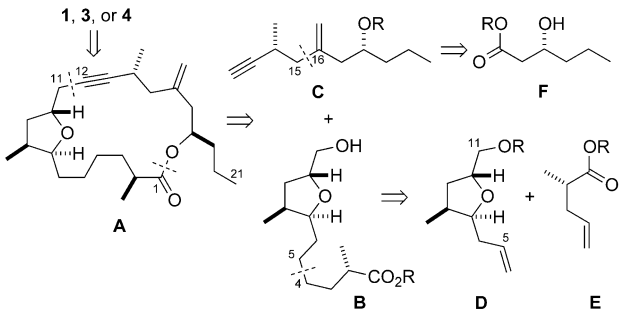
Figure 1. Amphidinolides T1–T5.

differ only in their oxygenation pattern and stereochemistry in the C12–C14 region with the exception of amphidinolide T2 (**2**), which possesses a longer, C21-hydroxylated side chain. Amphidinolide T1 (**1**) features a ketone at C12 flanked by a hydroxy group at C13. Amphidinolides T3–T5 are isomers of T1, displaying a reversal of the hydroxy ketone pattern and have diastereomeric relationships at C12 and C14.

The challenging structures and bioactivities of amphidinolides T1–T5 make them attractive synthetic targets.[2,4] Fürstner and co-workers completed the synthesis of amphidinolide T4 in 2002 and then used their elegant strategy to synthesize amphidinolides T1, T3, and T5.[5] The groups of Ghosh (T1),[6] Jamison (T1, T4),[7] Zhao (T3),[8] Yadav (T1),[9] and Dai (T1–T4)[10] have also completed syntheses of members of the family. In many of these syntheses, substituents and stereocenters in the C12–C14 region have been introduced before or during formation of the macrocycle, which has meant that the route to each member is differentiated at an early stage or that several steps are required to change oxidation states or invert stereocenters in order to access more than one natural product. The exception is the route of Dai and co-workers in which ring-closing metathesis (RCM) was used to close the macrocycle with C12–C13 bond formation and the resulting alkene was dihydroxylated.[10] In this case, however, the RCM and dihydroxylation reactions were not stereoselective and several steps were required to convert mixtures of isomeric products into each natural product.

As part of our programme concerning the synthesis of marine natural products, we became interested in synthesizing amphidinolides T1 and T3–T5 from a single macrocycle. Because of the similarities between targets **1** and **3**–**5**, we proposed that they could be accessed from the common intermediate **A**. The desired α-hydroxy ketone motif could be installed thereafter by sequential hydrosilylation of the alkyne, epoxidation of the resulting vinyl silane, and Fleming–Tamao oxidation[11] (Scheme 1).

Disconnection of the intermediate **A** through the lactone C–O bond and the C11–C12 bond gave the western and eastern fragments **B** and **C**, respectively (Scheme 1). Fragment **B** could be prepared from the alkene **E**[5] and the *trans*



Scheme 1. Retrosynthetic analysis of amphidinolides T1, T3, and T4.

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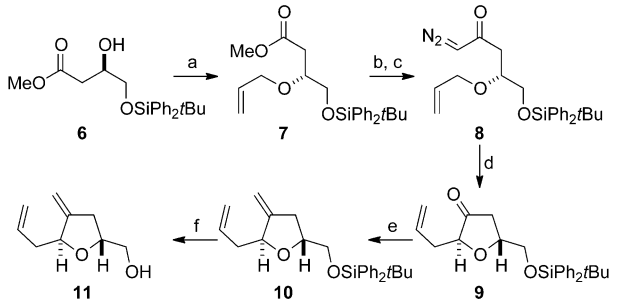
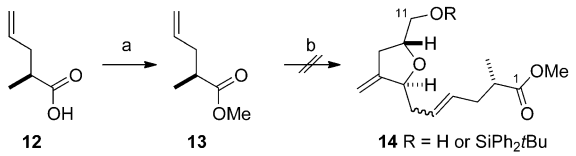
2,5-disubstituted dihydrofuranone **D**, which should be readily accessible by rearrangement of an oxonium ylide or a metal-bound ylide equivalent generated from a metal carbenoid.[12] Fragment **C** could be synthesized from protected β-hydroxy ester **F** (Scheme 1).

The tetrahydrofuran-containing fragment **11** was prepared from the commercially available alcohol **6**, which can be obtained from dimethyl D-malate in two steps (Scheme 2).[13] The alcohol **6** was converted into the corresponding allyl ether **7** under acidic conditions. Sequential ester saponification, activation of the acid as a mixed anhydride, and treatment with diazomethane afforded the α-diazo ketone **8**. Treatment of **8** with $[Cu(acac)_2]$ in THF at reflux delivered the required trans dihydrofuranone **9** in 91% yield with excellent diastereocontrol (d.r. ≥ 98:2).[12d,f,i–k] Ketone methylenation gave the diene **10** and subsequent cleavage of the silyl ether provided the alcohol **11**.



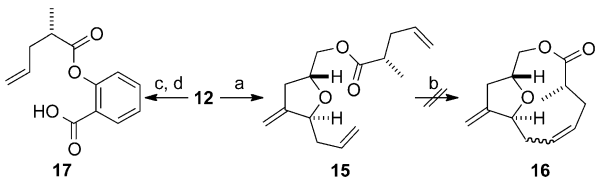
Scheme 2. a) $CH_2CHCH_2OC(NH)CCl_3$, CF_3SO_3H, petroleum ether, RT, 87%; b) KOH, MeOH, RT, 83%; c) $iBuO_2CCl$, Et_3N, Et_2O, RT, then CH_2N_2, 88%; d) $[Cu(acac)_2]$ (10 mol%), THF, reflux, 91%; e) $[Ph_3PCH_3]^+Br^-$, tBuOK, THF, RT; f) nBu$_4$NF, THF, RT, 99% over two steps. acac = acetylacetonate.

Assembly of the C1–C11 fragment by cross-metathesis (CM) of the dienes **10** or **11** with the alkene **13** was attempted (Scheme 3). The carboxylic acid **12**, which can be accessed by using Evans' methodology[14,15] and has been prepared by us and others,[5,12i] was methylated to give ester **13**. Unfortunately, it was not possible to effect cross-metathesis of dienes **10** or **11** with the alkene **13** to give **14**, a finding that contrasts with the outcome of the cross-metathesis reaction of closely related substrates.[6]



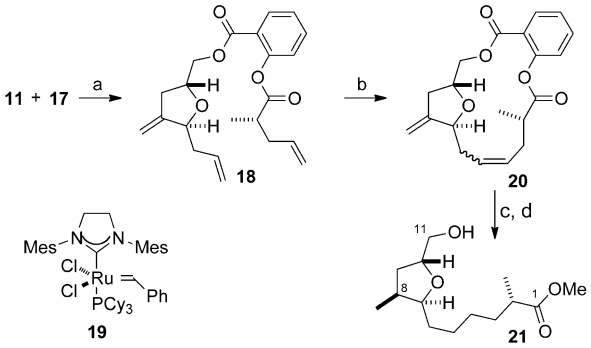
Scheme 3. a) Me_3SiCHN_2, Et_2O, MeOH, 0°C, 61%; b) CM with **10** or **11**.

To avoid using cross-metathesis, we decided to couple the acid **12** to the alcohol **11** to give the ester **15** and then perform RCM (Scheme 4). However, attempted formation of the 11-membered lactone **16** by RCM of the diene **15** failed.[16] In order to circumvent this problem, the use of a salicylate spacer group to facilitate RCM was explored.



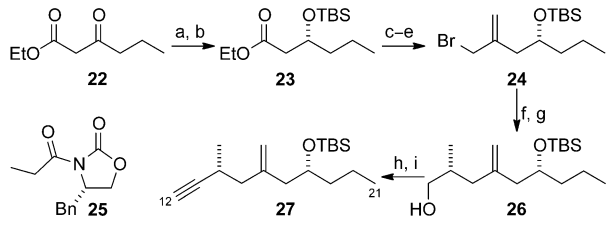
Scheme 4. a) **11**, EDC, DMAP, CH_2Cl_2, RT, 85%; b) RCM; c) EDC, DMAP, salicylaldehyde, CH_2Cl_2, RT; d) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, 2-methyl-2-butene, tBuOH/H_2O, RT, 76% over two steps. EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride.

Esterification of carboxylic acid **12** with salicylaldehyde and subsequent oxidation of the aldehyde gave carboxylic acid **17** (Scheme 4). Coupling of the alcohol **11** to acid **17** proceeded under Mitsunobu conditions[17] and delivered triene **18** (Scheme 5). The RCM reaction of **18**, promoted by catalyst **19**, afforded an inconsequential isomeric mixture (E/Z = 1.2:1) of the lactone **20**.[18] Base-mediated excision of the spacer group and directed hydrogenation of the resulting diene provided the complete western (C1–C11) fragment **21** as a single diastereomer with the required configuration at C8.[19]



Scheme 5. a) Ph_3P, DIAD, THF, 0°C→RT, 99%; b) **19** (12 mol%), CH_2Cl_2, reflux, 96% (E/Z = 1.2:1); c) KOH, MeOH, RT; d) [Ir(cod)-(PCy_3)(py)]PF_6, H_2, CH_2Cl_2, RT, 85% over two steps. DIAD = diisopropyl azodicarboxylate.

Synthesis of the eastern fragment commenced with asymmetric reduction[20] of ethyl 3-oxohexanoate (**22**) and protection of the resulting alcohol to give **23** (Scheme 6). Treatment of the ester **23** with an excess of the organocerium reagent prepared from trimethylsilylmethylmagnesium chloride resulted in double Grignard addition.[21,22] Base-mediated Peterson elimination of the intermediate tertiary alcohol delivered an allylic silane, which was then converted into the bromide **24** by treatment with pyrrolidone hydrotribromide (PHT).[23] Deprotonation of *N*-propionyloxazolidinone (**25**) with NaHMDS and enolate alkylation with bromide **24** followed by reductive cleavage of the oxazolidinone auxiliary provided alcohol **26**.[24] Oxidation of the alcohol **26** and conversion of the resulting aldehyde into the corresponding

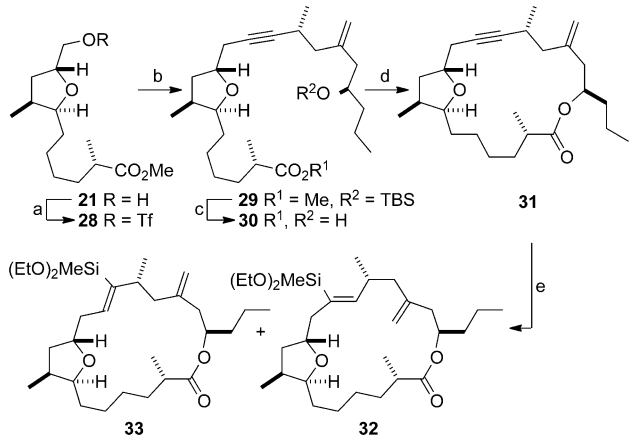


Scheme 6. a) [{(*R*)-Tol-BINAP}$RuCl_2$], H_2 (5 bar), EtOH, 95 °C, 97% (98% *ee*); b) TBSCl, imidazole, DMF, 0 °C → RT, 98%; c) $CeCl_3$, Me_3SiCH_2MgCl, THF, −78 °C → RT; d) NaHMDS, THF, 0 °C, 93% over two steps; e) PHT, pyridine, THF, −10 °C → RT, 96%; f) **25**, NaHMDS, −78 °C, THF, then **24**, nBu_4NI, −30 °C, 60% (76% brsm), d.r. = 15:1; g) $LiBH_4$, H_2O, Et_2O, 0 °C, 99%; h) DMP, CH_2Cl_2, RT; i) dimethyl 1-diazo-2-oxopropylphosphonate, K_2CO_3, THF/MeOH, 0 °C → RT, 82% over two steps. TBS = *tert*-butyldimethylsilyl; NaHMDS = sodium hexamethyldisilazide; PHT = pyrrolidone hydrotribromide; DMP = Dess–Martin periodinane.

alkyne using the Ohira–Bestmann reagent[25] afforded the eastern (C12–C21) fragment **27**.

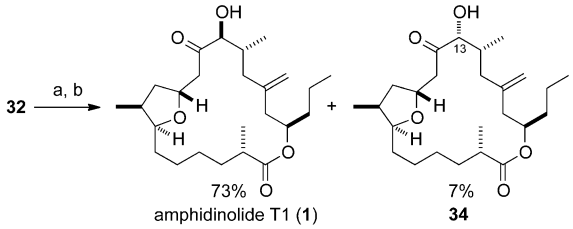
Coupling of the eastern and western fragments was accomplished by conversion of the alcohol **21** into the triflate **28** and subsequent displacement of triflate by the alkynyl lithium species generated by deprotonation of fragment **27** (Scheme 7). The coupled product **29** was obtained in 68% yield and competitive addition of the alkynyl lithium intermediate to the ester was not observed. The seco acid **30**, which was required for lactonization, was produced in a one-pot fashion by ester cleavage using potassium trimethylsilanolate[26] and quenching the reaction with concentrated HCl. Macrolactonization of **30** under Yamaguchi conditions[27] gave the common late-stage intermediate **31**, corresponding to **A** in our retrosynthetic analysis (Scheme 1).

Following the preparation of lactone **31**, installation of the various oxygenation patterns found in amphidinolides T1, T3, and T4 was explored. Catalytic hydrosilylation of the alkyne



Scheme 7. a) Tf_2O, 2,6-lutidine, CH_2Cl_2, −78 °C; b) **27**, *n*BuLi, HMPA, Et_2O, −78 °C, 68% over two steps; c) Me_3SiOK, THF, RT, then conc. HCl, 86%; d) 2,4,6-$Cl_3PhCOCl$, *i*Pr_2NEt, toluene, RT, then DMAP, 45 °C, 80%; e) [Cp*$Ru(MeCN)_3$]PF_6, $(EtO)_2MeSiH$, CH_2Cl_2, 0 °C → RT, 44% of **32** and 45% of **33**. Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl; Tf = SO_2CF_3. HMPA = hexamethylphosphoramide.

using [Cp*$Ru(CH_3CN)_3$]PF_6 delivered a separable mixture (1:1) of the isomeric *Z*-vinylsilanes **32** and **33** in a combined yield of 89% (Scheme 7).[28,29] Pleasingly, treatment of **32** with *m*-CPBA resulted in selective epoxidation of the vinylic silane, rather than the exocyclic alkene (Scheme 8). Fleming–Tamao oxidation[11] of the resulting silyl-substituted epoxide

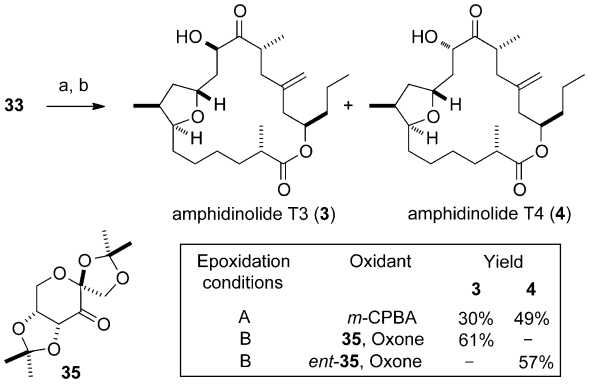


Scheme 8. a) *m*-CPBA, CH_2Cl_2, 0 °C; b) KHF_2, $KHCO_3$, 30% H_2O_2, THF, MeOH, RT. *m*-CPBA = 3-$ClC_6H_4CO_3H$.

afforded amphidinolide T1 in 73% yield over two steps, along with a minor product, the data for which are consistent with 13-*epi*-amphidinolide T1 (**34**). Spectroscopic and other data for synthetic **1** are identical to those reported for amphidinolide T1.[3a]

Treatment of **33** under the same conditions as **32** delivered amphidinolides T4 (**4**) and T3 (**3**) as a separable mixture (d.r. = 1.6:1) of diastereomers in 79% yield (Scheme 9). Spectroscopic and other data for synthetic **3** and **4** are identical to those reported in the literature.[3b,5]

The efficiency of the route to **3** and **4** could be improved by increasing the diastereoselectivity of the epoxidation reaction. Epoxidation of the vinylic silane **33** under Shi conditions,[30,31] employing the D-fructose-derived ketone **35**, followed by Fleming–Tamao oxidation afforded amphidinolide T3 in 61% yield over two steps (Scheme 9). Furthermore, when the vinylic silane **33** was subjected to the same conditions, but using the L-fructose-derived ketone *ent*-**35** to perform epoxidation, amphidinolide T4 was formed in 57% yield over two steps. In each case, a high degree of reagent control was observed and the other diastereomer was not obtained. Amphidinolide T4 can be epimerized at C14 to give



Epoxidation conditions	Oxidant	Yield 3	Yield 4
A	*m*-CPBA	30%	49%
B	**35**, Oxone	61%	–
B	*ent*-**35**, Oxone	–	57%

Scheme 9. a) Epoxidation conditions A: oxidant, CH_2Cl_2, 0 °C; conditions B: oxidant, $Na_2B_4O_7{\cdot}10H_2O$, nBu_4NHSO_4, $KHCO_3$, Na_2EDTA, H_2O, MeCN, DMM, 0 °C; b) KHF_2, $KHCO_3$, 30% H_2O_2, THF, MeOH, RT.

amphidinolide T5,[3c] so a formal synthesis of this natural product has also been achieved.

In conclusion, efficient and high-yielding synthetic routes to members of the amphidinolide T family of natural products via a single late-stage intermediate (**31**) have been established. The syntheses of amphidinolides T1, T3, and T4 were completed in 17 steps from the alcohol **6**. The macrolactone **31** was prepared from **6** in 14 steps and 21.6% yield; the overall yields of amphidinolides T1, T3, and T4 were 6.9%, 5.9%, and 5.5%, respectively. The key tetrahydrofuran unit was assembled by rearrangement of an oxonium ylide, or its metal-bound equivalent, generated from a copper carbenoid, further demonstrating the utility of this methodology for the synthesis of complex natural products.[12f,i–k,32]

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[31] For examples of Shi epoxidation of vinylic silanes, see: a) J. D. Warren, Y. Shi, *J. Org. Chem.* **1999**, *64*, 7675 – 7677; b) T. P. Heffron, T. F. Jamison, *Org. Lett.* **2003**, *5*, 2339 – 2442; c) G. L. Simpson, T. P. Heffron, E. Merino, T. F. Jamison, *J. Am. Chem. Soc.* **2006**, *128*, 1056 – 1057.

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