Enantioselective Total Synthesis of (+)-Amphidinolide T1

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Amphidinolides are a series of unique cytotoxic macrolides isolated from the marine dinoflagellates *Amphidinium* sp., and they have shown significant antitumor properties against a variety of NCI tumor cell lines.[1] Amphidinolides are extremely scarce, and as a result, biological studies have been very limited. Amphidinolide T1 (**1**), a 19-membered macrolide, has shown potent activity against murine lymphoma L1210 as well as human epidermoid carcinoma KB cell lines.[2] The structure of **1** was initially established by NMR studies. Later, its absolute configuration was elucidated through X-ray analysis by Kobayashi and co-workers.[3] The significant clinical potential and unique structural features of the amphidinolide family of natural products have stimulated considerable interest in their syntheses and structure–function studies.[4] Herein, we report the first total synthesis of (+)-amphidinolide T1.

As outlined in Figure 1, our synthetic strategy for amphidinolide T1 is convergent and involves the assembly of C_1–C_{10} segment **2** and C_{11}–C_{21} segment **3** by an oxocarbenium ion-mediated alkylation and macrolactonization sequence. This alkylation is expected to proceed stereoselectively through a five-membered ring oxocarbenium ion intermediate derived from sulfone **2**. Our approach to the synthesis of fragment **2** involves an efficient cross metathesis and hydrogenation sequence between the terminal olefins of **5** and **6** to form the C_4–C_5-carbon–carbon bond. Enol ether **4** is designed to be the surrogate of fragment **3** where the sensitive C_{16}-*exo*-methylene and the C_{13}-hydroxyl group are being protected as a bromohydrin derivative during the Lewis acid-catalyzed alkylation and macrolactonization reactions. We planned to unravel this functionality at the final stage of the synthesis. Two of the three stereocenters in fragment **5** as well as the C_2 and C_3 stereocenters in fragment **4** are accessed by a highly diastereoselective ester-derived titanium enolate-mediated *syn*-aldol reaction.[5]

The synthesis of C_1–C_{10} segment **2** is outlined in Scheme 1. Aldol condensation of (1*R*,2*S*)-1-(*N*-tosylamino)-2-indanyl propionate (**7**) with benzyloxypropionaldehyde at −78 °C furnished aldol adduct **8** as a single diastereomer in 90% yield.[5] Reduction of **8** by lithium aluminum hydride in THF at 23 °C afforded diol **9**. This was transformed into γ-lactone **10** by selective sulfonylation of the primary alcohol, displacement of the resulting sulfonate with cyanide, followed by acid-promoted lactonization to afford **10** in 81% overall yield. DIBAL reduction of **10** at −78 °C in CH_2Cl_2 followed by reaction with trimethylsilylethanol and *p*-TsOH afforded acetal **11** and its isomer as a 3.5:1 mixture, which can be separated by column chromatography after removal of the benzyl group by hydrogenolysis. Swern oxidation of the resulting alcohol followed by Wittig olefination furnished alkene **5**, one of the substrates for cross metathesis.

Cross metathesis[6] of **5** with oxazolidinone derivative **6**[7] in the presence of 5 mol % second generation Grubbs's catalyst[9] afforded a 1:1 mixture (*E*:*Z*) of cross metathesis product **12** in 60% yield along with alkene dimers of **5** and **6** which can be separated by silica gel chromatography. Exposure of these alkene dimers to 5 mol % second generation Grubbs's catalyst further afforded cross
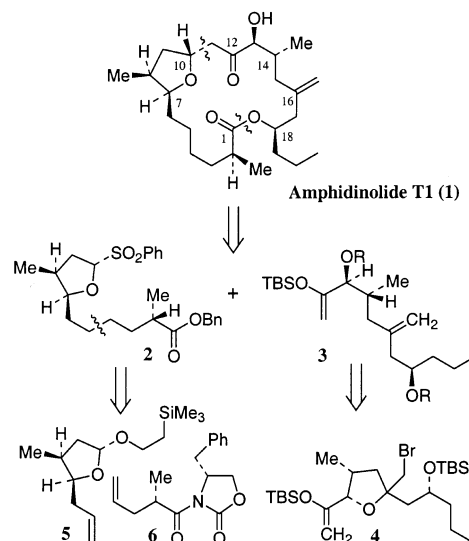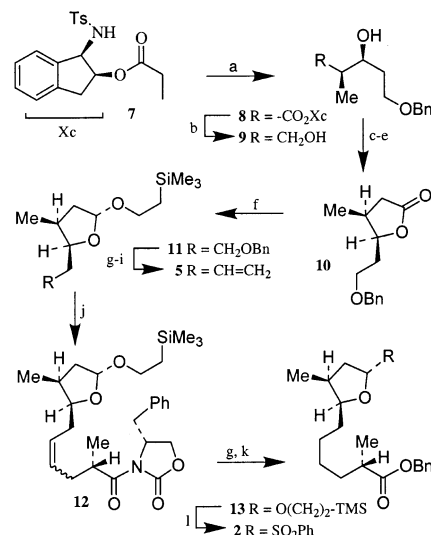

Figure 1. Retrosynthetic analysis.

Scheme 1 [a]

[a] Reaction conditions: (a) $TiCl_4$, *i*-Pr_2NEt; $BnO(CH_2)_2CHO$ (90%); (b) LAH, THF, 23 °C (91%); (c) PhLi, TrisCl, THF, −78 to 23 °C (86%); (d) NaCN, DMSO, 80 °C (95%); (e) aq. HCl, MeOH, 23 °C (98%); (f) Dibal-H, −78 °C, then $TMS(CH_2)_2OH$, *p*-TsOH, $MgSO_4$, 23 °C (91%); (g) H_2, Pd/C, EtOAc (98%); (h) Swern Ox; (i) $Ph_3P=CH_2$, THF (84%): (j) **6**, CH_2Cl_2, 40 °C $Cl_2(PCy_3)(IMes)Ru=CHPh$ (96%); (k) BnOH, BuLi, THF, 0 °C (85%); (l) HSO_2Ph, $CaCl_2$, CH_2Cl_2, 23 °C (95%).

metathesis product **12** in 36% yield (1:1 mixture of *E*:*Z* olefins). Thus, the overall yield of cross metathesis product **12** was 96% after two cycles. Catalytic hydrogenation of the alkene mixture followed by treatment of the saturated derivative with lithium phenylmethoxide furnished benzyl ester **13** in 85% yield. Exposure of **13** to phenylsulfinic acid and $CaCl_2$ afforded sulfone derivative **2** and its isomer as a 7:1 mixture in 95% yield.[8]

Scheme 2 [a]
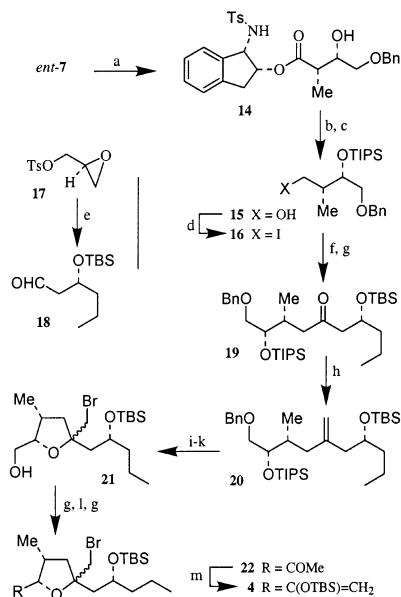
[a] Reaction conditions: (a) TiCl$_4$, i-Pr$_2$NEt; BnOCH$_2$CHO (93%); (b) TIPSOTf, i-Pr$_2$NEt, 0 °C (95%); (c) Dibal-H, −40 °C (91%); (d) I$_2$, PPh$_3$, Imidazole, 23 °C (95%); (e) i. BuLi, 1,3-dithiane; ii. EtMgBr, CuI (64%, two steps); iii. TBSOTf, i-Pr$_2$NEt; iv. MeI, CaCO$_3$, aq. MeCN (73%, two steps); (f) t-BuLi, Et$_2$O, −78 to 23 °C, then 18 (80%); (g) TPAP, NMO, 23 °C; (h) Cp$_2$TiMe$_2$, THF, 80 °C (84%); (i) Li/NH$_3$, −33 °C, THF; (j) LAH, THF, 23 °C (90%); (k) NBS, 0 to 23 °C (91%); (l) MeMgBr, −78 to 23 °C; (m) LiHMDS, TBSCl, HMPA, −78 to 23 °C (95%).

Synthesis of the C$_{11}$–C$_{22}$ fragment is outlined in Scheme 2. Aldol reaction of *ent*-**7** with benzyloxyacetaldehyde afforded a single *syn*-diastereomer (**14**) in 95% yield.[5] Protection of the resulting alcohol as a TIPS ether followed by Dibal-H reduction furnished alcohol **15** which was readily converted into the corresponding iodide (**16**). Reaction of glycidyl tosylate **17** with lithium 1,3-dithiane followed by ethyl cuprate provided the corresponding secondary alcohol which, after protection as a TBS ether and removal of dithiane, afforded aldehyde **18**.[9] Treatment of iodide **16** with *t*-BuLi generated the corresponding alkanyllithium, which was reacted with aldehyde **18** to afford a 1:1 diastereomeric mixture of alcohols which, upon TPAP oxidation, provided ketone **19**.[10] Olefination of **19** utilizing Petasis conditions[11] furnished alkene **20**. Reductive removal of the benzyl and TIPS ethers[12] followed by reaction of the resulting diol with NBS afforded bromotetrahydrofuran **21** as a 3:1 diastereomeric mixture. Our motive for forming this bromolactone is to protect the C$_{13}$-alcohol as well as to protect the sensitive *exo*-methylene group during the oxocarbenium ion-mediated alkylation process.[13] The hydroxymethyl group of **21** was then converted to methyl ketone **22** in 60% overall yield. Treatment of **22** with LiHMDS followed by reaction of the resulting enolate with TBSCl furnished the vinyl ether segment (**4**).

Our subsequent synthetic strategy calls for the assembly of fragments **2** and **4** by an oxocarbenium ion-mediated alkylation reaction; however, this proved to be a formidable task. Our successful path using modified Ley's protocol[14] is presented here.[15] Treatment of **2** and **4** in the presence of 2 equiv of AlCl$_3$ at −35 °C resulted in only very low yield (10%) of desired product **23**. Under optimized conditions in the presence of excess AlCl$_3$ (6 equiv) and DTBMP (1.2 equiv) coupling product **23** was obtained in 73% yield as a single isomer (by ^{1}H- and ^{13}C NMR analysis).[16] The depicted *trans*-stereochemistry is assigned on the basis of analysis of NOESY data. The C$_{18}$-silyl ether was then removed by exposure to HF·Py, and subsequent hydrogenolysis removed the benzylester. Macrolactonization of the resulting hydroxy acid under

Scheme 3 [a]
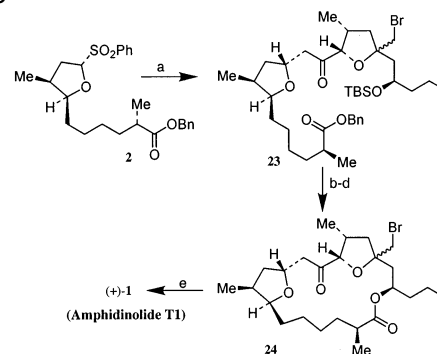
[a] Reaction conditions: (a) **4**, DTBMP, AlCl$_3$, −35 °C (73%); (b) HF·Py, Py (87%); (c) H$_2$, 10% Pd−C; (d) 2,4,6-(Cl$_3$)PhCOCl, i-Pr$_2$NEt, then DMAP, toluene (71%); (e) Zn, NH$_4$Cl, EtOH, 80 °C (61%).

Yamaguchi conditions[17] afforded macrolactone **24** in 71% yield (Scheme 3). Reductive unmasking of the bromoether with Zn and NH$_4$Cl in ethanol provided synthetic amphidinolide T1 (**1**). Spectral data (^{1}H and ^{13}C NMR) of synthetic **1** ([α]$^{23}_D$ +16, c 0.1, CHCl$_3$) is in agreement to that of natural amphidinolide T1 (lit.[3] [α]$_D^{23}$ +18, c 0.3, CHCl$_3$).

Thus, a stereocontrolled and convergent synthesis of (+)-amphidinolide T1 has been achieved. The functional group tolerabilty of the oxocarbenium ion-mediated alkylation reaction along with efficient cross methathesis, diastereoselective aldol reactions, and use of a cyclic bromoether as a novel protection of the *exo*-methylene group are noteworthy features.

Supporting Information Available: Experimental procedures and spectral data for compounds and ^{13}C NMR for compounds **2**, **4**−**24** and **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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