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Total Synthesis of Amphidinolide X

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Marine dinoflagellates of the genus *Amphidinium* sp. living in symbiosis with the Okinawan flatworm *Amphiscolops* spp. produce a host of secondary metabolites endowed with potent cytotoxicity against various cancer cell lines. Commonly called "amphidinolides",[1] these conspicuous marine natural products usually embed a "conserved" set of structural elements into highly diverse macrolactone backbones. Amphidinolide X (**1**), however, is a significant exception to this rule.[2] This compound has neither the characteristic *exo*-methylene group, nor a vicinal one-carbon branch, nor a 1,3-diene unit found in virtually all other members of this series. Moreover, **1** is the only naturally occurring macrodiolide known to date that consists of a diacid and a diol unit rather than of two hydroxyacid entities.[2]

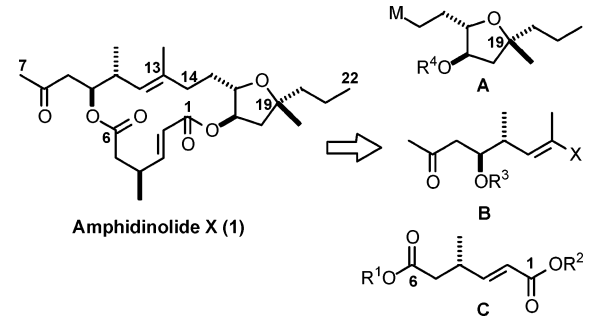
These rather unique structural features together with the promising cytotoxicity of **1** against murine lymphoma and human epidermoid carcinoma prompted us to pursue a total synthesis of this scarce compound.[3,4] While the ester linkages forming the macrodiolide ring constitute obvious sites of disconnection, it was envisaged to assemble the C7−C22 segment by metal-catalyzed cross coupling at the C13−C14 bond (Scheme 1). Not only does this strategy ensure high convergence and employs building blocks **A**−**C** of similar size, but also allows us to address the critical formation of the tetrasubstituted chiral center C19 residing at the ether bridge in an early stage of the synthesis campaign.

The chosen route to this key structural element hinges upon methodology recently developed in our laboratory (Scheme 2).[5] Specifically, it was planned to use a chiral allene as latent progenitor of the tetrahydrofuran ring, which can be formed stereoselectively by an iron-catalyzed reaction of a propargyl epoxide with a suitable Grignard reagent. This sequence should efficiently transfer the central chirality of a readily accessible epoxide to the tetrasubstituted chiral sp^3 center C19 via the axial chirality of an allene relay.

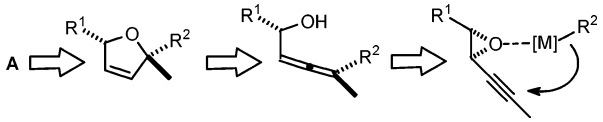
Toward this end, allylic alcohol **2**[6] was epoxidized by the Sharpless method to give product **3** in excellent yield and decent optical purity (ee = 83%) (Scheme 3).[7] Swern oxidation followed by treatment of the resulting aldehyde with the Ohira−Bestmann reagent[8] gave alkyne **4**, which was end-capped on treatment with LiHMDS and MeOTf. Gratifyingly, reaction of the resulting propargyl epoxide **5** with PrMgCl in the presence of cheap and benign $Fe(acac)_3$ as the precatalyst furnished, in less than 5 min, the desired allene **6** as a 8:1 mixture in favor of the required syn isomer. This pronounced selectivity likely results from a directed delivery of the nucleophile enforced by a precoordination of the oxophilic catalyst and/or reagent to the epoxide ring (Scheme 2) and nicely complements the anti selectivity of the standard copper-based methods for allenol formation.[5a]

Because the allene isomers were not readily separable, the mixture was treated with $AgNO_3/CaCO_3$ in aqueous acetone to afford the corresponding dihydrofuran **7** with strict chirality transfer.[9] While we had originally envisaged to install the missing −OH group at C17 via hydroboration/oxidation, this sequence turned out to be low yielding. A satisfactory alternative was found

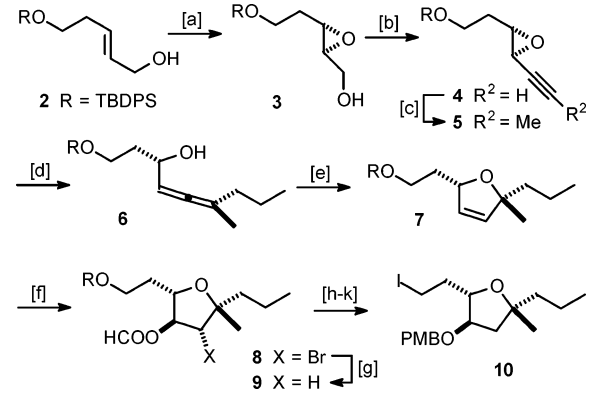
Scheme 1



Scheme 2



Scheme 3 [a]



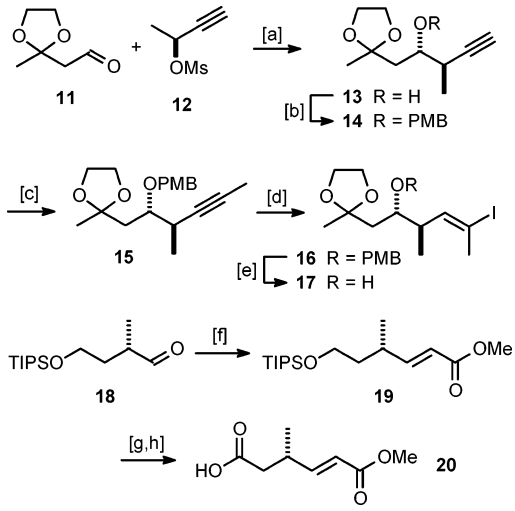
[a] Conditions: [a] $Ti(OiPr)_4$ cat., L-(+)-DET, tBuOOH, MS 4 Å, CH_2Cl_2, 97% (ee = 83%); [b] (i) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2; (ii) $(MeO)_2P(O)C(N_2)COMe$, K_2CO_3, MeOH, 67%; [c] LiHMDS, MeOTf, THF, 95%; [d] PrMgCl, $Fe(acac)_3$ cat., toluene, 62% (syn:anti = 8:1); [e] $AgNO_3$, $CaCO_3$, aqueous acetone, 90%; [f] NBS, DMF/H_2O (15/1), 65%; [g] AIBN, $(TMS)_3SiH$, toluene; [h] $NaHCO_3$, MeOH, 90% (over both steps); [i] PMBOC(=NH)CCl_3, PPTS, CH_2Cl_2/C_6H_{12}, 76%; [j] TBAF, THF, 97%; [k] I_2, PPh_3, imidazole, MeCN/Et_2O, 92%.

in the bromo-esterification of **7** with NBS in aqueous DMF.[10] From a practical perspective, this detour was even rewarding as the C19 isomers could be separated at that stage by flash chromatography. Removal of the bromide in **8** using $(Me_3Si)_3SiH$ and AIBN[11] followed by standard protecting group manipulations furnished product **10** as adequate surrogate of synthon **A**.

The second building block was accessed by the palladium-catalyzed, Et_2Zn-mediated addition of the enantiopure propargyl mesylate **12** to aldehyde **11** (Scheme 4).[12] The major anti isomer **13** (ee = 93%) was protected as a PMB-ether prior to C-methylation. Hydrozirconation/iodination[13] of the alkyne group in **15** afforded vinyl iodide **16** in good overall yield. Cleavage of the

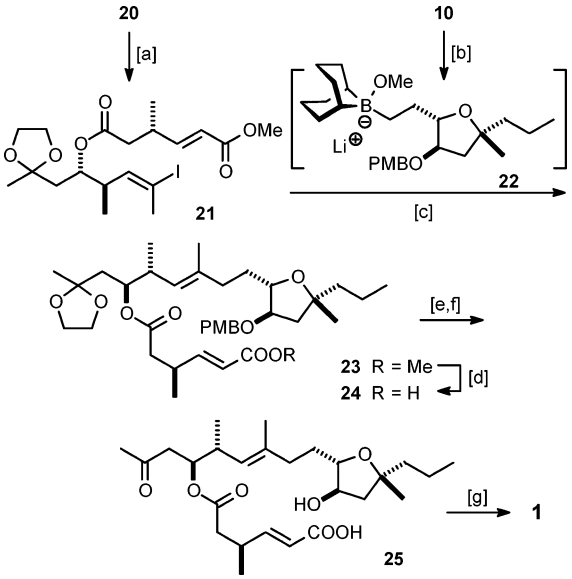
10.1021/ja044130+ CCC: $27.50

Scheme 4 [a]



[a] Conditions: [a] Et_2Zn, $Pd(OAc)_2$ cat., PPh_3 cat., THF, 65% (anti:syn = 4.5:1); [b] PMBCl, NaH, TBAI, DMF, 94%; [c] LiHMDS, MeI, THF, 95%; [d] (i) Cp_2ZrHCl, C_6H_6; (ii) I_2, CH_2Cl_2, 61%; [e] DDQ, CH_2Cl_2, pH 7 buffer, 89%; [f] $(EtO)_2P(O)CH_2COOMe$, LiCl, DBU, MeCN, 94%; [g] HF·pyridine, MeCN, quant.; [h] (i) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2; (ii) $NaClO_2$, NaH_2PO_4, $(CH_3)_2C{=}CHCH_3$, tBuOH, 92%.

Scheme 5 [a]



[a] Conditions: [a] 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene; then **17**, DMAP, 96%; [b] tBuLi, Et_2O/THF; then 9-MeO-9-BBN; [c] $(dppf)PdCl_2$, Ph_3As, K_3PO_4, aqueous DMF, 74%; [d] LiI, pyridine, 125 °C; [e] aqueous HOAc, 53% (over both steps); [f] DDQ, CH_2Cl_2, pH 7 buffer, 84%; [g] 2,4,6-trichlorobenzoyl chloride, Et_3N, THF; then DMAP, toluene, 62%.

O-PMB group with DDQ preceded a Yamaguchi esterification of alcohol **17** with acid **20**, which was derived from the known aldehyde **18** (ee = 95%)[14] as shown in Scheme 4.

With the required building blocks in hand, the stage was set for the crucial segment couplings (Scheme 5). Previous work from this laboratory had shown that Suzuki reactions can be conveniently performed with borate complexes derived from 9-MeO-9-BBN and a suitable organolithium reagent;[15] the latter can also be formed in situ.[16] Application of this method to the present case resulted in efficient alkyl-alkenyl cross coupling[17] of segments **21** and **10**. Specifically, alkyl iodide **10** was treated with *t*-BuLi at −78 °C followed by addition of excess 9-MeO-9-BBN to give the corresponding borate **22**, which transfers its functionalized alkyl group to the organopalladium species derived from alkenyl iodide **21** and $(dppf)PdCl_2/AsPh_3$, thus delivering product **23** in 74% isolated yield. Selective cleavage of the methyl ester in diester **23** with LiI in pyridine[18] followed by successive removal of the remaining acetal moiety and the PMB ether gave *seco*-acid **25**. The final macrocyclization of this compound proceeded smoothly under Yamaguchi conditions,[19,20] affording amphidinolide X **1** in 62% yield, thereby completing the first total synthesis of this bioactive marine natural product. Its analytical data are in excellent agreement with those reported in the literature.[2]

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Supporting Information Available: Experimental details and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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