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Stereoselective synthesis of the densely functionalized C1–C9 fragment of amphidinolides C and F

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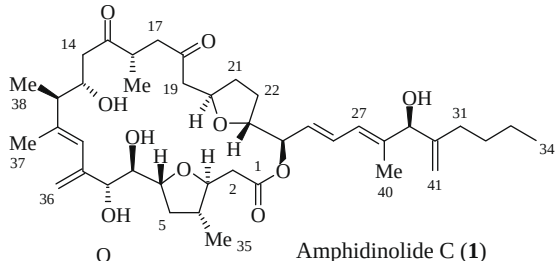
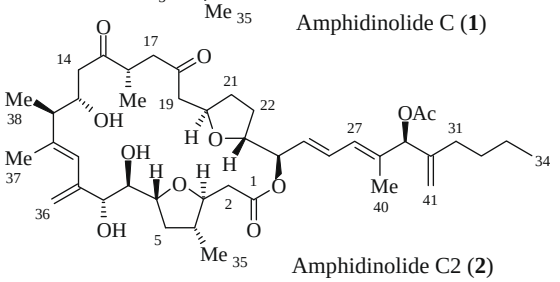
ABSTRACT

The synthesis of the C1–C9 subunit of amphidinolides C and F is described. Key steps include tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization reaction, Lewis acid-mediated epoxide opening, Wittig reaction, and Wacker oxidation.

Amphidinolides are a group of structurally unique macrolides isolated to date from laboratory-cultured dinoflagellates of the *Amphidinium* sp.[1] Many such amphidinolides exhibit potent antitumor activity against lymphoma L1210 and human carcinoma KB cells. Despite their common origin and uniformly high cytotoxicity against various cancer cell lines, the amphidinolides possess a high degree of structural diversity and incorporation of many interesting molecular scaffolds. Our target amphidinolide C (**1**), isolated from the marine dinoflagellates *Amphidinium* sp. (Y-5), is a 25-membered macrolide having two tetrahydrofuran rings decorated with vicinally juxtaposed one-carbon branches.[2] The gross structure of **1** was elucidated by 2D NMR data. Amphidinolide C (**1**) showed extremely potent in vitro cytotoxic activity against murine lymphoma L1210 and apidermoid carcinoma KB cells[3] (IC_{50} = 0.0058 and 0.0046 μg mL^{-1}); the structurally related C2 (**2**) and F (**3**) display significantly reduced activities against these cell lines, suggesting that the C25–C34 side chain plays a crucial role in the bioactivity of amphidinolides C, C2, and F. The structural complexity and scant availability from natural resources, has made amphidinolide C (**1**) an attractive target for us. Recently, we reported the synthesis of C19–C34 fragment of amphidinolide C;[4] we now report the synthesis of the C1–C9 fragment (**7**). During the course of our work, Roush and co-workers reported the first synthesis of C1–C9 fragment of amphidinolide C[5] (see Fig. 1).





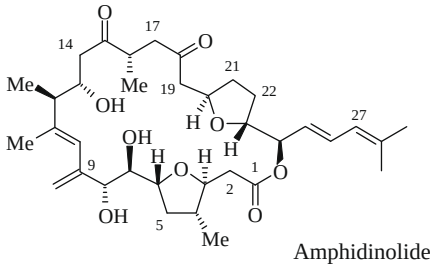


Figure 1. Structures of amphidinolide C, C2 and F.

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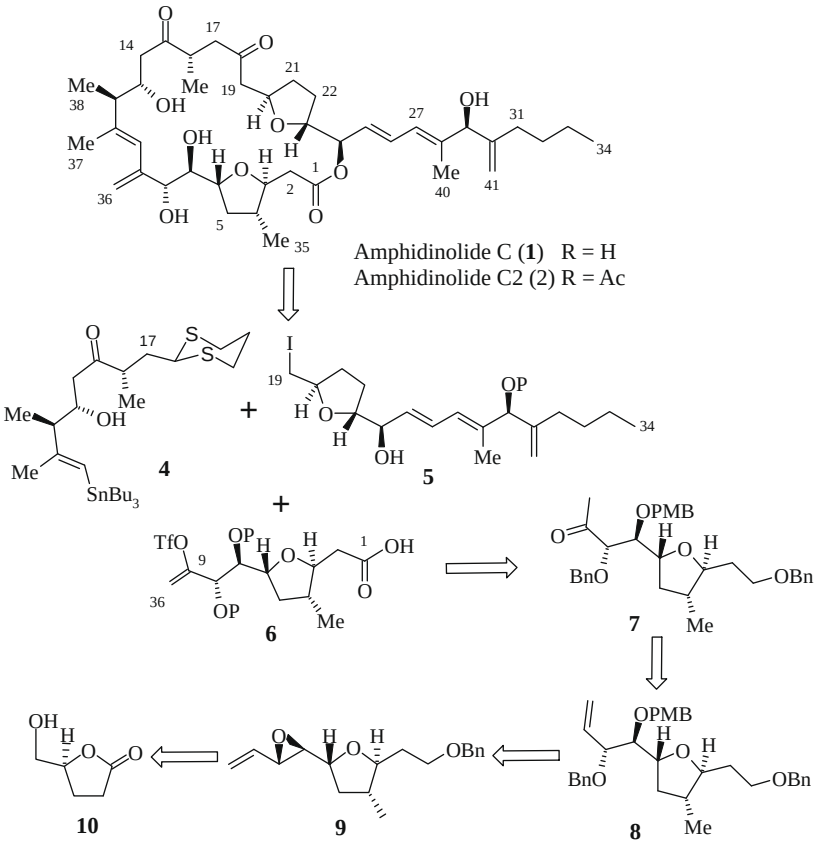
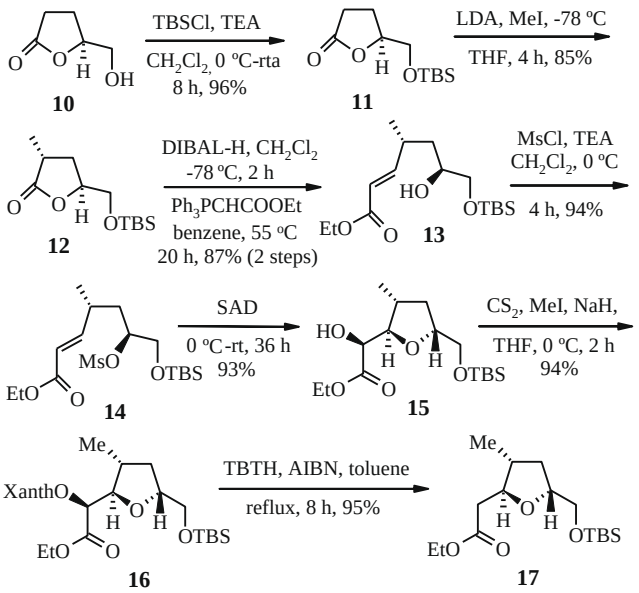


Scheme 1. Retrosynthetic analysis of amphidinolide C.

Our retro-synthetic analysis of **1** depicted in Scheme 1 suggested that the target could be assembled from fragments **4**, **5,** and **6** via a late-stage-cross esterification and coupling sequence. The keto functionality of **7** was envisaged to be generated from a vinyl group by the Wacker oxidation of **8**. The olefin intermediate **8** would be obtained by Lewis acid-mediated opening of vinyl epoxide **9** with benzyl alcohol. The vinyl epoxide **9**, in turn could be obtained from **10** via stereoselective alkylation, tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization on an α,β-unsaturated ester followed by Sharpless asymmetric epoxidation. The tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization to construct a tetrahydrofuran ring was particularly appealing to us, since an internal S_N2 displacement in a pre-organized substrate would be expected to be completely and predictably stereospecific and install correct stereochemistry at the ring junctions.

The preparation of (*S*)-5-hydroxyl methyl butyrolactone **10** was achieved in 60% overall yield from commercially available L-glutamic acid by a published procedure.[6] The hydroxyl group of **10** was protected as its TBS-ether **11**; stereoselective methylation[6] of the lactone **11** with LDA and MeI in THF at −78 °C afforded **12** in 85% yield. The trans relationship between the two substituents on the five-membered ring was confirmed by NOESY experiment at a later stage of the synthesis. Lactone **12** was reduced by DIBAL-H at −78 °C; the corresponding hemiacetal was quickly exposed to ethoxycarbonylmethylene-triphenylphosphorane[6] in



Scheme 2. Synthesis of **17**.

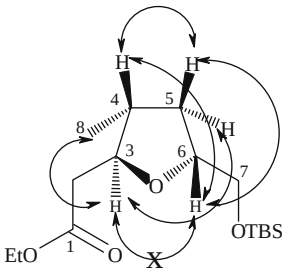


Figure 2. Selected NOE correlations of **17**.

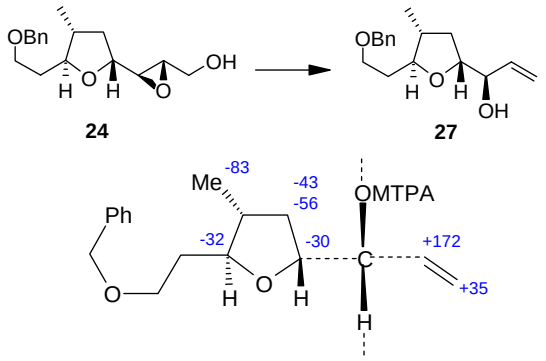
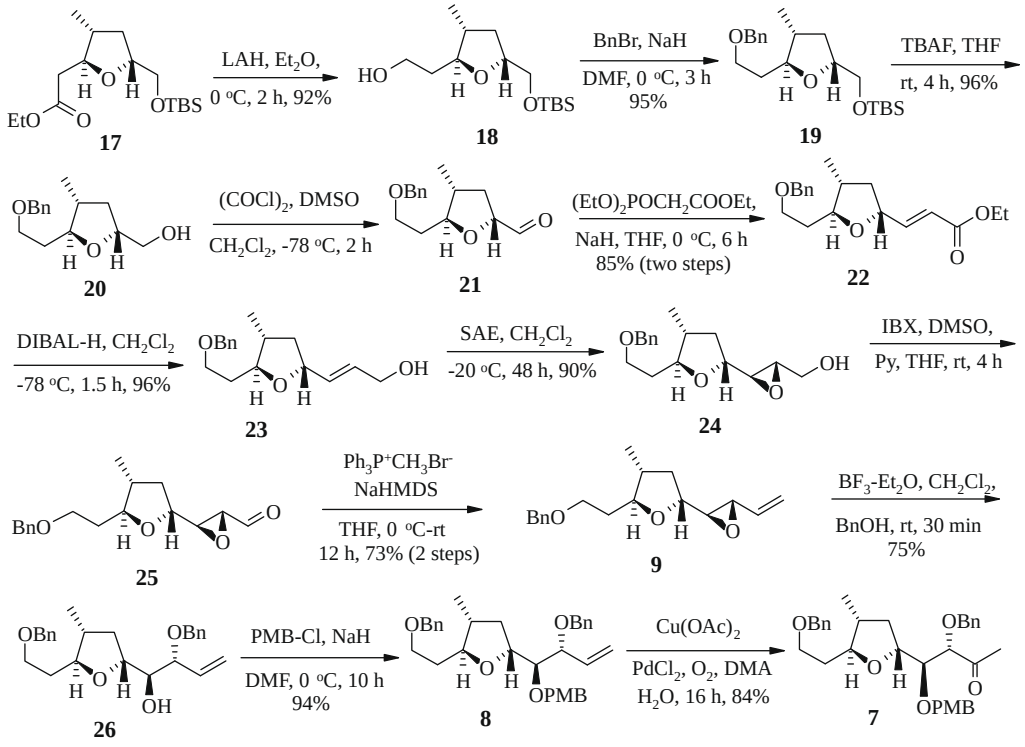


Figure 3. $\Delta\delta = (\delta_S - \delta_R) \times 10^3$ for (*R*)-and (*S*)-MTPA esters of compound **27**.

benzene at 55 °C to provide the corresponding α,β-unsaturated ester as a mixture of geometrical isomers (9.5:0.5 by ^{1}H NMR). The minor (*Z*)-isomer was separated from the major (*E*)-isomer **13** by silica gel column chromatography. The ^{1}H NMR spectrum of (*E*)-isomer **13** revealed a characteristic coupling constant (J = 15.6 Hz) for the olefinic protons. The hydroxyl group of **13** was converted into its mesylate[7] ester **14** with $MeSO_2Cl$, Et_3N and DMAP (catalytic) in CH_2Cl_2. The mesyl ester was to play a dual role as a protecting group and a leaving group at a later stage. The mesylate derivative **14** was subjected to the Sharpless asymmetric dihydroxylation[8] (Scheme 2) with ligand $(DHQD)_2$ PHAL, $K_3Fe(CN)_6$, K_2CO_3, $MeSONH_2$, and OsO_4 in *t*-BuOH/H_2O (1:1) for 36 h to afford the *trans,syn*-tetrahydrofuran 15[9] in 93% yield (no traces of the other isomer was detectable by NMR and HPLC) (Scheme 2). Our next objective was to deoxygenate the hydroxyl group at C2 using Barton's radical deoxygenation protocol.[10] The hydroxyl group of **15** was converted to its corresponding xanthate derivative **16** with NaH/CS_2/MeI in THF at 0 °C. Compound **16** when treated with TBTH in presence of AIBN in refluxing toluene for 8 h furnished the 2-deoxy derivative **17**.[11] The NOE correlations for compound **17** observed for H3/H8, H3/H5, H6/H4, and H6/H5, indicated the relative stereochemistries between H3 and H6 and between H3 and H4, respectively, to be trans-oriented (Fig. 2).

Compound **17** was then treated with $LiAlH_4$ in anhydrous diethyl ether at 0 °C to afford the alcohol **18** in 92% yield. The primary hydroxyl moiety of **18** was protected as its benzyl ether to provide **19** in 95% yield. The TBS ether of **19** was cleaved by treatment with 1 M solution of $Bu_4N^+F^-$ in THF to afford the alcohol **20**. The Swern oxidation[12] of **20** followed by the Wittig-Horner reaction on the crude aldehyde with triethylphosphonoacetate and NaH at 0 °C afforded the desired *E*-isomer **22** as the only product. Reduction of ester **22** using DIBAL-H in dichloromethane at −78 °C furnished the allylic alcohol derivative **23**. The Sharpless asymmetric epoxidation of the *E*-allylic alcohol **23** with L(+)-DET, Ti(*i*PrO)$_4$, and TBHP in CH_2Cl_2 at −20 °C provided the corresponding epoxy alcohol **24**[13] with excellent diastereoselectivity (95% ee confirmed by spectroscopic analysis).[14] To assign the absolute stereochemistry of the epoxide, compound **24** was converted to its benzoate derivatives to obtain single crystal that was not successful. We then transformed compound **24** to **27** following a standard protocol of iodination, followed by a reductive opening of the iodoepoxide with Zn/NaI in refluxing methanol.[15] Following modified Mosher's method,[16] the newly created stereogenic center of compound **27** bearing the hydroxyl group was assigned and found to be an *R*-configuration (Fig. 3), which established the absolute stereochemistry of the epoxide of **24**. The alcohol derivative **24** was efficiently oxidized with IBX in DMSO/THF at ambient temperature to provide the aldehyde **25**; exposure to methylene- triphenylphosphorane (generated in situ from $CH_3P^+Ph_3Br^-$ and NaHMDS) in THF gave Wittig methylenation to the requisite vinyl-substituted epoxide intermediate **9**[17] (Scheme 3).

The epoxide **9** was treated with BnOH in the presence of $BF_3{\cdot}Et_2O$[18] in anhydrous dichloromethane to furnish β-hydroxy allyl ether **26**.[19] The secondary hydroxyl group of **26** was converted



Scheme 3. Synthesis of the C1–C9 fragment **7**.

to its PMB-ether using PMBCl and NaH in DMF to provide **8** (Scheme 3). Finally, compound **8** was subjected to a modified Wacker oxidation protocol[20] with $Cu(OAc)_2{\cdot}H_2O$ (0.2 equiv) and 10 mol % of $PdCl_2$ in a mixture of DMA:H_2O (7:1) under oxygen atmosphere at ambient temperature for 16 h to afford **7**[21] in 84% yield.

We have thus achieved a stereoselective linear synthesis of the C1–C9 segment of amphidinolides C (**1**) and F (**3**). The construction of *trans*-2,5-disubstituted tetrahydrofuran ring was accomplished by a tandem dihydroxylation-S_N2 cyclization sequence. Synthesis of other fragments required for the total synthesis of amphidinolide C is in progress in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.001.

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13. *Analytical and spectral data of* **24**: $[\alpha]_D^{25}$ −21.82 (*c* 1.1, $CHCl_3$); IR (neat): 3430, 3063, 2957, 2929, 2871 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.97 (d, *J* = 6.6 Hz, 3H), 1.32–1.42 (m,1H), 1.58–1.68 (m, 1H), 1.80–1.88 (m, 2H), 2.09–2.17 (m, 1H), 2.95–2.99 (m, 2H), 3.43–3.59 (m, 4H), 3.83–3.90 (m, 2H), 4.44 (s, 2H), 7.19–7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.1, 34.0, 37.3, 39.6, 56.5, 57.1, 61.3, 67.5, 72.9, 76.4, 82.9, 127.4, 127.6, 128.2, 138.4; Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.71; H, 8.17.
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17. *Analytical and spectral data of* **9**: $[\alpha]_D^{25}$ −26.1 (*c* 1.15, $CHCl_3$); IR (neat): 2960, 2928, 2871 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.97 (d, *J* = 6.6 Hz, 3H), 1.31–1.41 (m, 1H), 1.59–1.67 (m, 1H), 1.79–1.88 (m, 2H), 2.08–2.17 (m, 1H), 2.84 (dd, *J* = 2.1, 4.5 Hz, 1H), 3.13 (dd, *J* = 2.1, 7.5 Hz, 1H), 3.45–3.59 (m, 3H), 3.86 (ddd, *J* = 4.6, 6.6, 9.0 Hz, 1H), 4.44 (s, 2H), 5.20 (dd. *J* = 1.4, 10.3 Hz, 1H), 5.39 (dd, *J* = 1.4, 17.2 Hz, 1H), 5.48–5.57 (m, 1H), 7.17–7.26 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.2, 34.1, 37.3, 39.8, 56.7, 61.7, 67.7, 73.0, 76.7, 82.9, 119.4, 127.5, 127.6, 128.3, 135.1, 138.5; Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.88; H, 8.28.
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21. *Analytical and spectral data of* **7**: $[\alpha]_D^{25}$ +9.52 (*c* 1.05, $CHCl_3$); IR (neat): 3370, 2927, 1719 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.86 (d, *J* = 6.6 Hz, 3H), 1.22–1.36 (m, 2H), 1.50–1.65 (m, 1H), 1.70–1.87 (m, 2H), 2.07 (s, 3H), 3.23 (dt, *J* = 2.8, 9.0 Hz, 1H), 3.34–3.54 (m, 2H), 3.67–3.73 (m, 1H), 3.73 (s, 3H), 3.88 (d, *J* = 3.2 Hz, 1H), 4.15 (q, *J* = 7.6 Hz, 1H), 4.34–4.49 (m, 4H), 4.50–4.63 (m, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 7.17–7.25 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.2, 27.4, 34.0, 38.0, 40.2, 55.2, 67.9, 72.5, 73.0, 73.2, 76.2, (77.2), 82.1, 83.4, 83.6, 113.8, 127.5, 127.7, 127.9, 128.0, 128.3, 128.4, 129.8, 130.0, 131.9, 133.2, 137.6, 138.5, 141.9, 159.3, 209.6; Anal. Calcd for $C_{33}H_{40}O_6$: C, 74.41; H, 7.57. Found: C, 74.31; H, 7.48.