Accepted Manuscript

Synthesis of the C18–C26 tetrahydrofuran-containing fragment of amphidinolide C congeners via tandem asymmetric dihydroxylation and S_N2 cyclization

Ye-Xiang Su, Wei-Min Dai

PII: S0040-4020(18)30146-7

DOI: 10.1016/j.tet.2018.02.021

Reference: TET 29292

To appear in: *Tetrahedron*

Received Date: 4 January 2018

Revised Date: 7 February 2018

Accepted Date: 8 February 2018

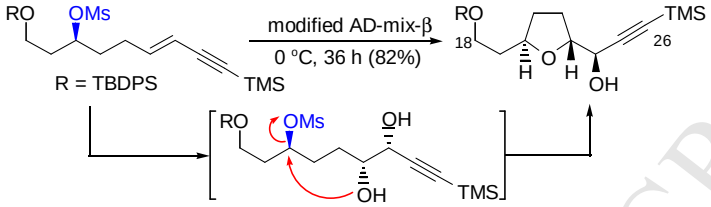
Please cite this article as: Su Y-X, Dai W-M, Synthesis of the C18–C26 tetrahydrofuran-containing fragment of amphidinolide C congeners via tandem asymmetric dihydroxylation and S_N2 cyclization, *Tetrahedron* (2018), doi: 10.1016/j.tet.2018.02.021.

Graphical Abstract

Synthesis of the C18–C26 tetrahydrofuran-containing fragment of amphidinolide C congeners via tandem asymmetric dihydroxylation and S_N2 cyclization

Ye-Xiang Su, Wei-Min Dai*

Leave this area blank for abstract info.



ELSEVIER

Tetrahedron
journal homepage: www.elsevier.com

Synthesis of the C18–C26 tetrahydrofuran-containing fragment of amphidinolide C congeners via tandem asymmetric dihydroxylation and S_N2 cyclization

Ye-Xiang Su, Wei-Min Dai*

Laboratory of Advanced Catalysis and Synthesis, Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

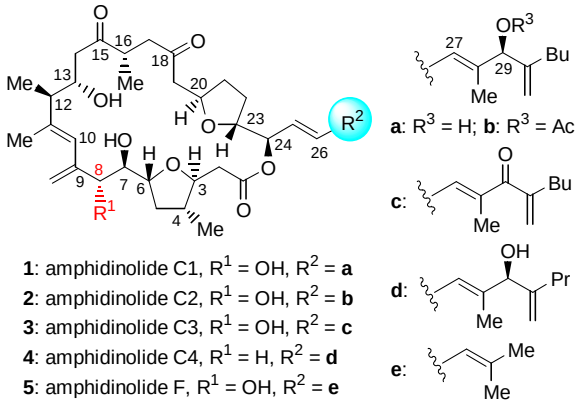
Keywords:
Amphidinolide C
Asymmetric dihydroxylation
Enyne
Intramolecular S_N2 reaction
Sonogashira cross-coupling
Tetrahydrofuran

ABSTRACT

The C18–C26 fragment of amphidinolide C congeners has been synthesized starting from methyl acetoacetate in 14 steps in >17.0% overall yield. The C20 stereogenic center was secured by asymmetric hydrogenation of a β-keto ester and the configuration at both C23 and C24 was introduced by asymmetric dihydroxylation (AD). The *trans*-2,5-disubstituted tetrahydrofuran ring was assembled via the tandem AD–S_N2 sequence. The latter protocol could be employed for accessing the corresponding *cis*-2,5-disubstituted tetrahydrofuran rings from the same alkene substrates simply by choosing a suitable AD ligand. Moreover, functional group compatibility was observed for the Ru(II)-catalyzed hydrogenation of β-keto esters and the Pd(0)–Cu(I)-catalyzed Sonogashira cross-coupling reaction. These findings should be valuable for general synthetic design and application.

1. Introduction

Amphidinolide C congeners have five known members, among which, amphidinolide C1–C3 (**1**–**3**)[1–3] and F (**5**)[4] were produced by symbiotic marine dinoflagellates *Amphidinum* spp. (Y-5, Y-26, Y-56, Y-59 and Y-71 strains) (Fig. 1). These macrolides consist of a common 25-membered macrolactone core featured with two 2,5-*trans*-substituted tetrahydrofuran subunits, and one each conjugated diene (at C9–C11), *anti*-vicinal diol (at C7–C8) and 1,4-diketone (at C15–C18) moieties. Their structures differ only from the alkenyl motif connected to C26 on the side chains which are remarkably important to their cytotoxicity against murine lymphoma L1210 and P388, and human epidermoid carcinoma KB cell lines (Fig. 1). Recently, amphidinolide C4 (**4**)[5] was isolated from the Brazilian octocoral *Stragulum bicolor* along with other amphidinolides.[6] It possesses essentially the same macrolactone core as the above-mentioned amphidinolide C congeners except for the depleted C8 hydroxy group in **4**. The preliminary cytotoxicity data given in Fig. 1 clearly indicate that both the C8 and C29 hydroxy groups are the structural requirements necessary for high cytotoxicity of this class of 25-membered macrolides.[7]



1: amphidinolide C1, R^1 = OH, R^2 = **a**
2: amphidinolide C2, R^1 = OH, R^2 = **b**
3: amphidinolide C3, R^1 = OH, R^2 = **c**
4: amphidinolide C4, R^1 = H, R^2 = **d**
5: amphidinolide F, R^1 = OH, R^2 = **e**

	1	**2**	**3**[b]	**4**	**5**
L1210[a]	0.0058	0.8	7.6	–[c]	1.5
KB[a]	0.0046	3.0	10.0	–[c]	3.2

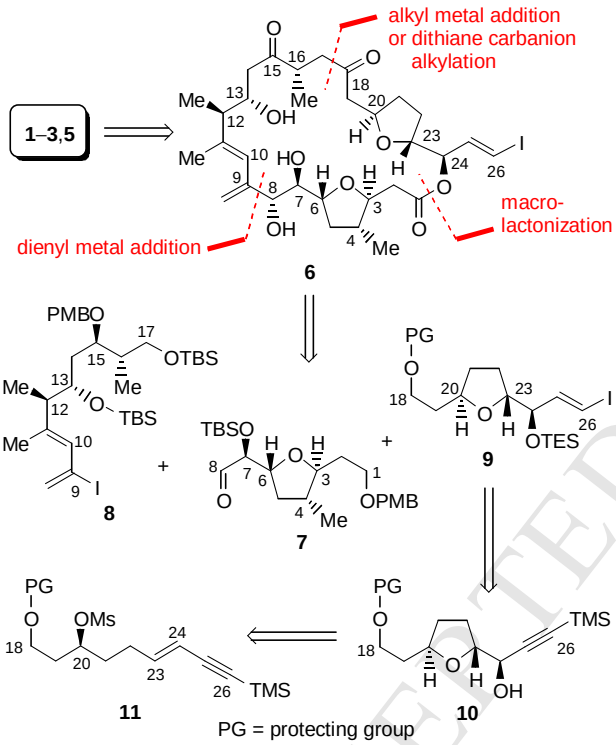
[a] IC_{50} in μg/mL. [b] 2.9 μg/mL for P388 cell line. [c] Inactive.

Fig. 1. The structures and cytotoxicity of ampidinolide C1–C4 and F.

The structural complexity and scarce availability of amphidinolide C1 and the congeners isolated from cell cultures render them suitable targets for chemical synthesis. Both Carter and Fürstner's groups have completed total synthesis of amphidinolide C1 and F via macrolactonization[8] and ring-closing

* Corresponding author. Tel.: +852 23587365; fax: +852 23581594; e-mail address: chdai@ust.hk.

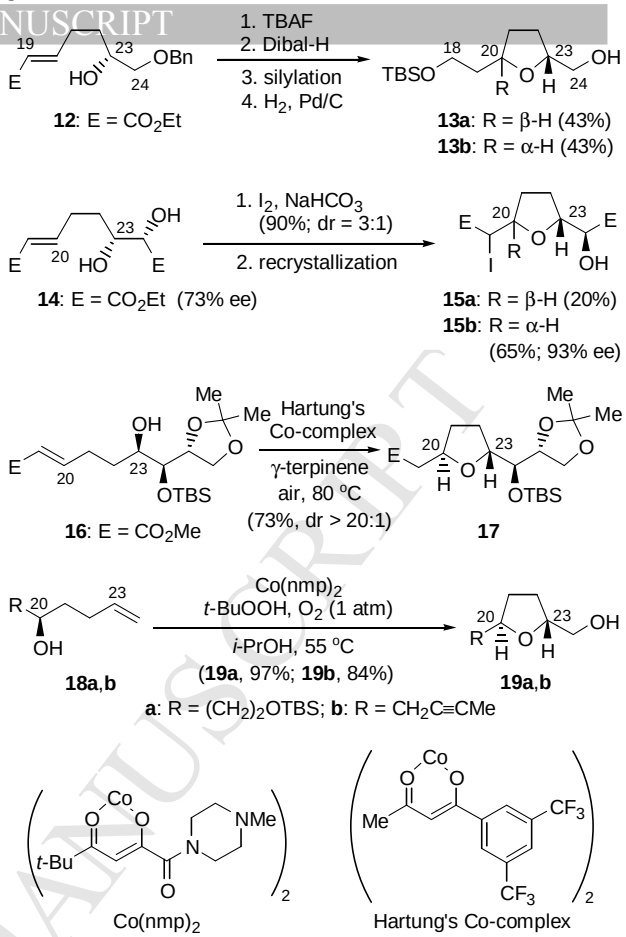
alkyne metathesis (RCAM)[9] as the key steps, respectively, for construction of the macrolactone core. In Carter's total synthesis,[8] amphidinolide C1 and F were disconnected into the C1–C8, C9–C14, and C15–C25 fragments; the side chains were coupled to the C25 aldehyde through Wittig olefination of the Tamura/Vedejs-type tributylphosphonium-derived allylic ylides[10] before macrolactonization. In our planned diverted total synthesis of amphidinolide C1–C3 and F, the macrolactone core **6** was envisioned as the common advanced intermediate which would be connected to different alkenyl motifs via Pd-catalyzed Suzuki–Miyaura or Stille cross-coupling reaction at C26 position.[11] Thus, the intermediate **6** would be assembled from the C1–C8, C9–C17, and C18–C26 fragments **7**–**9** by formation of the C8–C9 bond using a modified Carter's dienyllithium addition[8,12] and the C17–C18 bond through alkyl metal addition or dithiane carbanion alkylation.[11a,12] We report here on the synthesis of the C18–C26 alkenyl iodide fragment **9** from the propargylic alcohol **10** which could be obtained via tandem asymmetric dihydroxylation (AD) and S_N2 cyclization[13,14] from the enyne **11**.[15]



Scheme 1. Retrosynthetic bond disconnection of amphidinolide C congeners.

2. Results and discussion

The target C18–C26 fragment **9** contains a 2,5-*trans*-disubstituted tetrahydrofuran ring which has been accessed by different approaches as illustrated in Schemes 2 and 3. Cyclization of ε-hydroxy enoates seems a straightforward method to a THF ring system. The TBAF-mediated oxa-Michael addition within **12** was found non-stereoselective, after further transformations, to give both 2,5-*cis*-**13a** and 2,5-*trans*-**13b** in a 1:1 diastereomeric ratio (dr) (Scheme 2).[1d] Alternatively, an iodoetherification within **14** was performed to afford a 1:3 dr of 2,5-*cis*-**15a** and 2,5-*trans*-**15b**; after fractional recrystallization, the desired product **15b** was enriched to 93% ee.[16] Moreover, a much higher dr value of > 20:1 was reported for the product 2,5-*trans*-**17**[11b,17] formed from **16** via aerobic oxidative cyclization in the presence of Hartung's Co-complex.[18] In a similar manner, the terminal alkenols **18a**,**b** underwent the Mukaiyama-type aerobic oxidative cyclization using Pagenkopf's $Co(nmp)_2$ catalyst[19] to furnish the products 2,5-*trans*-**19a**,**b** in exellent yields.[9,20]

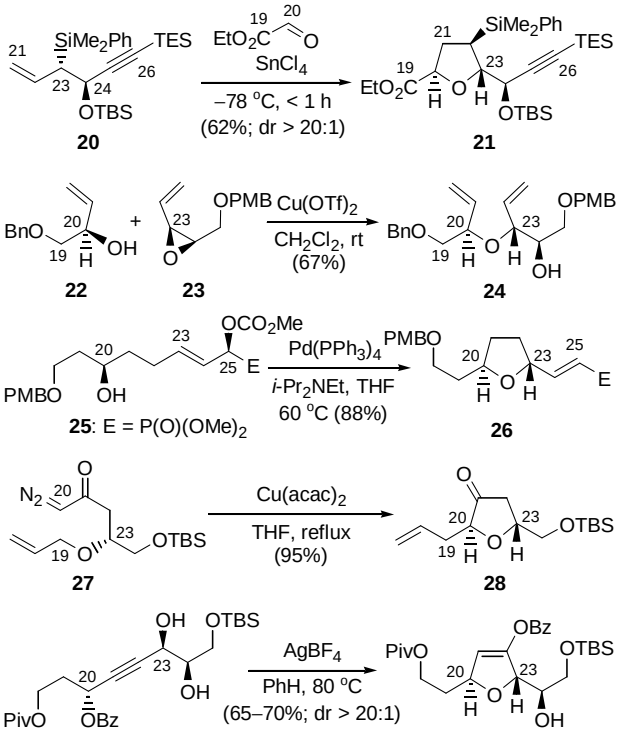


Scheme 2. The known synthesis of the C18–C25 fragment of amphidinolide C congeners via various alkenol cyclization processes.

Various metal-catalyzed processes have been used for the synthesis of the C18–C25 (or C26) fragment of amphidinolide C congeners (Scheme 3). The tetrahydrofuran compound **21** possessing an alkynyl group could be formed from **20** by the $SnCl_4$-mediated [3+2]-annulation in > 20:1 dr.[11a] A RCM–hydrogenation sequence was employed using the *seco* diene **24** as the substrate; the latter was obtained from the $Cu(OTf)_2$-catalyzed reaction of the chiral vinyl epoxide **23** with the chiral allylic alcohol **22**.[21] Cyclization within the allylic carbonate **25** (*E*:*Z* = ≥ 9:1) in the presence of $Pd(PPh_3)_4$ afforded the 2,5-*trans*-**26** in 88% yield along with 5–8% of the *cis* isomer.[22] Finally, two cyclization reactions were established for accessing the *trans*-2,5-disubstituted dihydrofuranone **28** and the dihydrofuran **30**, respectively, via the $Cu(acac)_2$-catalyzed cyclization of the diazo ketone **27**[23] and the Ag(I)-catalyzed cyclization of the propargylic benzoate **29**.[8] Both **28** and **30** were also transformed into the C1–C8 fragments of amphidinolide C congeners.[8,12]

Our work commenced with examination of the AD–S_N2 process using the substrate **35** (Schame 4). The chiral alcohol **31**[24] was oxidized to the corresponding aldehyde **32** which was then reacted with the stabilized phosphonium ylide, $Ph_3P{=}CHCO_2Me$, to give the methyl enoate **33**. Treatment of the acetal **33** with a catalytic amount of PPTS in MeOH formed the 1,3-diol **34**. The latter was then selectively converted into the primary TBDPS ether by reacting with TBDPSCl and imidazole in the presence of catalytic amounts of DMAP and *n*-Bu_4NI[25] in DMF at room temperature. *n*-Bu_4NI could shorten the reaction time from 10 h to 5 h. The resultant secondary alcohol was transformed into the mesylate **35** followed by the AD reaction using 1 mol% of Os and 10 mol% of $(DHQD)_2PHAL$ as the

catalyst. After 24 h at 0 ºC, the AD product was heated at 90 ºC in the presence of pyridine to furnish the tetrahydrofuran product **36** in 70% overall yield from the mesylate **35** (Scheme 4).

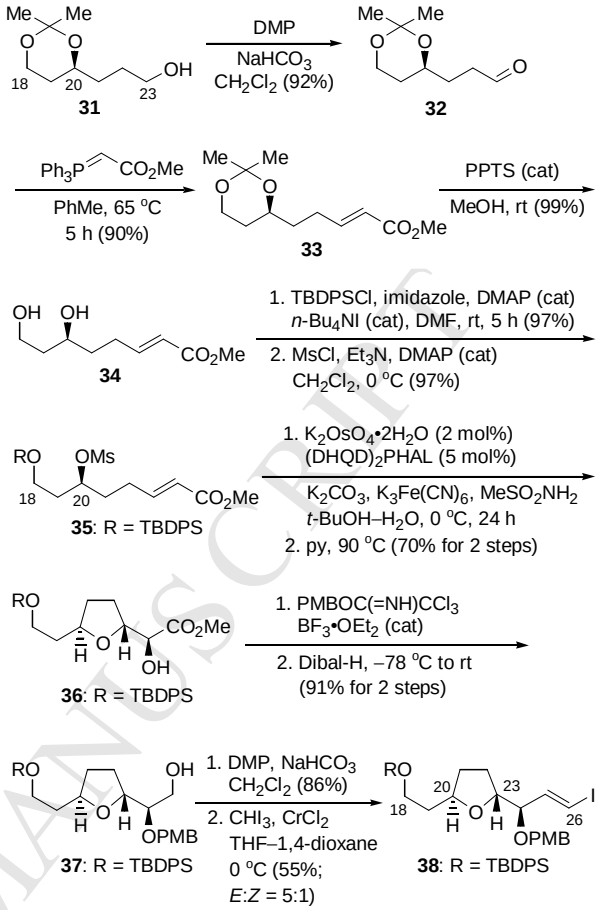


Scheme 3. The reported synthesis of the C18–C25 (or C26) fragment of amphidinolide C congeners via various processes.

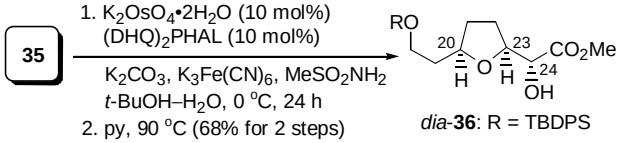
The mesylate **35** could be used for synthesis of the *cis*-2,5-disubstituted tetrahydrofuran via the similar AD–S_N2 protocol (Scheme 5). The AD reaction of **35** with $(DHQ)_2PHAL$ as the chiral ligand followed by heating the diol product in pyridine at 90 ºC gave the diastereomeric tetrahydrofuran product *dia*-**36** in 68% overall yield for the two steps.

With the compound **36** in hand, synthesis of the target C18–C26 alkenyl iodide **38** was carried out (Scheme 4). After the alcohol **36** was protected as the PMB ether, the ester group was reduced by Dibal-H to form the primary alcohol **37** in 91% overall yield. Oxidation of **37** with DMP gave an 86% yield of the corresponding aldehyde which was subjected to the Takai reaction (3 equiv of CHI_3, 10 equiv of $CrCl_2$, THF–1,4-dioxane = 1:6, 0 ºC) to furnish the alkenyl iodide **38** in 55% yield and in an *E*:*Z* ratio of 5:1.[26] Use of the mixed solvent system was expected to improve the *E*:*Z* ratio but no effect was observed for this substrate.[27] Due to large amount of the reagents were used, purification of the product **38** from the reaction mixture was difficult. In view of both the moderate yield and *E*:*Z* ratio of the Takai reaction, an alternative approach to the alkenyl iodide was required.

As depicted in Scheme 6, the enyne compound **40** was prepared from the aldehyde **32** and the phosphonate **39**[28] at –78 ºC in 80% yield and in an *E*:*Z* ratio of 4:1.[29] The HWE reaction at –90 ºC did not improve the *E*:*Z* ratio but gave a lower yield of 71%. The acetal **40** was converted into the 1,3-diol **41** (92%) which was selectively transformed into the mesylate **42** in excellent overall yield. Upon subjecting **42** to the AD conditions using $(DHQD)_2PHAL$ as the chiral ligand, the forming diol spontaneously cyclized to the tetrahydrofuran product **43** in 78% yield. These results were very encouraging and an improved synthetic sequence toward the geometrically pure enyne **42** was developed as described in Scheme 7.

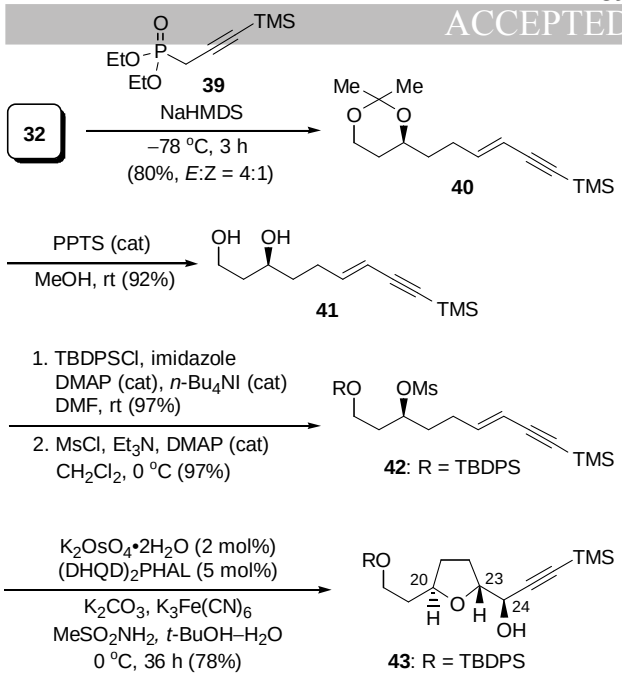


Scheme 4. Synthesis of the C18–C26 alkenyl iodide **38** via AD–S_N2.

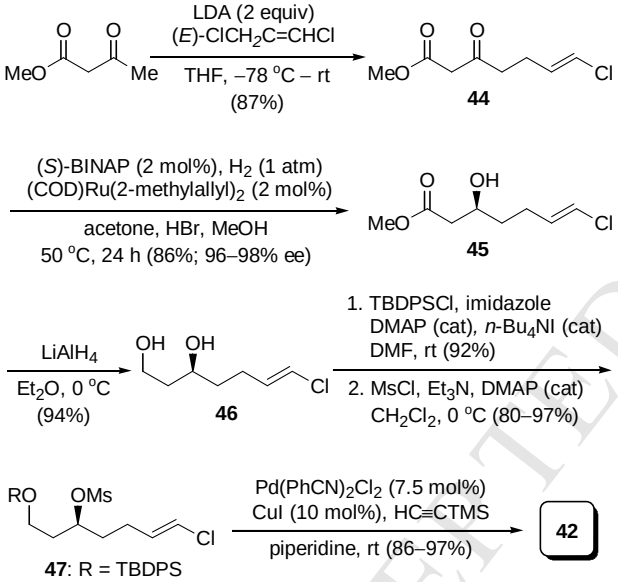


Scheme 5. Synthesis of the 2,5-*cis*-THF compound *dia*-**36** via AD–S_N2.

In order to obtain enyne compounds in pure *E* geometry, the Pd(0)–Cu(I)-catalyzed Sonogashira cross-coupling of the (*E*)-alkenyl chloride **44** was selected (Scheme 7). Starting from methyl acetoacetate, alkylation of the dianion of methyl acetoacetate with (*E*)-1,3-dichloropropene gave the (*E*)-alkenyl chloride **44** in 87% yield.[30] Initially, the Sonogashira cross-coupling reaction of **44** with ethynyltrimethylsilane was attempted and, after extensive screening on the reaction conditions, the enyne **48** was obtained in 60% yield with incomplete conversion of **44** (Table 1, entries 1–6). The sluggish cross-coupling reaction of **44** might be attributed to the complexation ability of the β-keto ester, resulting in catalyst poisoning. Unfortunately, catalyst deactivation was encountered again in the Noyori assymmetric hydrogenation of the β-keto ester **48** possessing the enyne moiety. Under the standard conditions using (*S*)-BINAP and Ru(II) as the catalyst,[31] the desired β-hydroxy ester **49** was obtained in only 7.8% yield after 48 h at 50 ºC (Scheme 8).

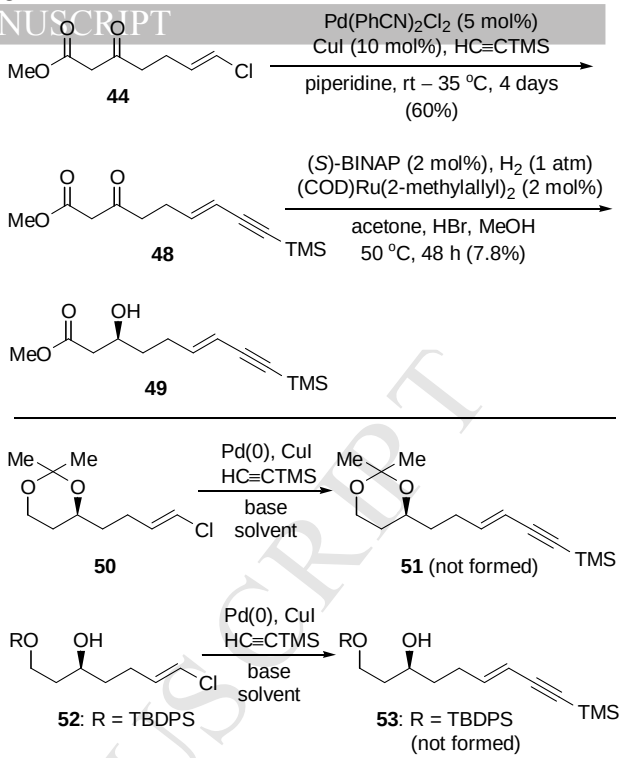


Scheme 6. Synthesis of the C18–C26 propargylic alcohol **43** via AD–S_N2.



Scheme 7. Improved synthesis of the enyne **42**.

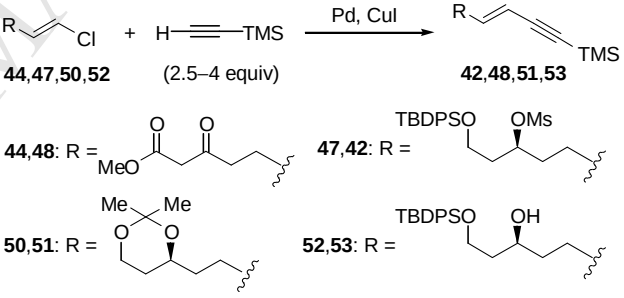
To circumvent the low reactivity of **48** toward Noyori asymmetric hydrogenation, the β-keto ester **44** was subjected to the same chiral catalyst in MeOH at 50 ºC for 24 h to afford the desired β-hydroxy ester **45** in 86% yield and in 96–98% ee (Scheme 7). Reduction of **45** using $LiAlH_4$ gave the 1,3-diol **46** in 94% yield. In order to facilitate the Sonogashira coupling, the diol **46** was treated with 2-methoxypropene in the presence of a catalytic amount of PPTS in acetone at room temperature to form the cyclic acetal **50** in 96% yield. However, the Pd(0)–Cu(I)-catalyzed cross-coupling of **50** with ethynyltrimethylsilane failed again (Scheme 8 and Table 1, entries 7 and 8). Alternatively, selective mono-silylation of the diol **46** was achieved to produce the alcohol **52** in 96% yield (Schemes 7 and 8). To our disappointment, the hydroxy alkenyl chloride **52** failed to form the enyne **53** under the similar conditions optimized for **44** (Scheme 8 and Table 1, entries 9 and 10). Finally, the diol **46** was converted into the mesylate **47** which furnished the enyne product **42** in excellent yields (Scheme 7 and Table 1, entry 11).



Scheme 8. Attempted synthesis of the enynes **49**, **51**, and **53**.

Table 1

Results of Sonogashira cross-coupling reactions of alkenyl chlorides



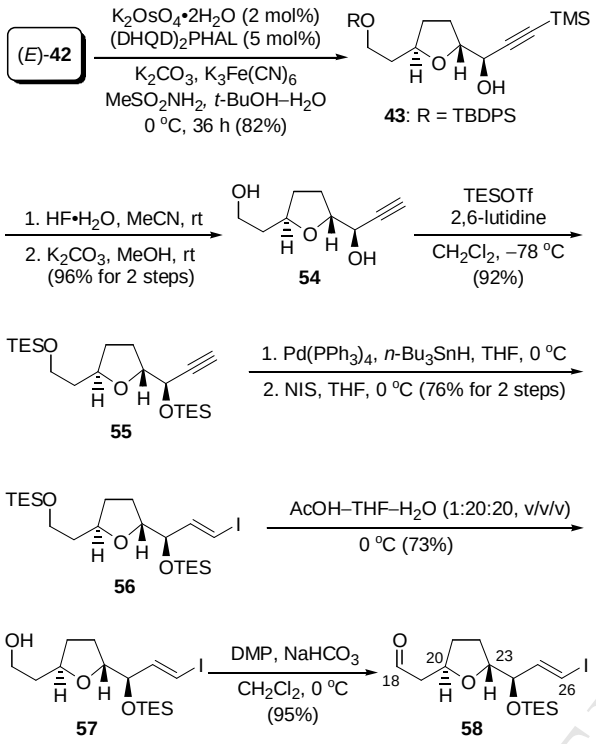
Entry	Sub.	Reaction Conditions[a]	Yield (%)[b]
1	**44**	**Cat A**, piperidine, THF, rt, 1 day	**48** (NR)
2	**44**	**Cat B**, piperidine, rt–35 ºC, 3 days	**48** (trace)
3	**44**	**Cat C**, piperidine, rt–35 ºC, 2 days	**48** (NR)
4	**44**	**Cat C**, *i*-PrNH$_2$, MeCN, rt–35 ºC, 3 days	**48** (trace)
5	**44**	**Cat D**, *i*-PrNH$_2$, dioxane, rt–35 ºC, 3 days	**48** (trace)
6	**44**	**Cat A**, piperidine, rt–35 ºC, 4 days	**48** (60)
7	**50**	**Cat A**, piperidine, rt–50 ºC, 1 day	**51** (NR)
8	**50**	**Cat D**, *i*-PrNH$_2$, rt–82 ºC, 1 day	**51** (NR)
9	**52**	**Cat A**, piperidine, rt–50 ºC, 2 days	**53** (NR)
10	**52**	**Cat D**, *i*-PrNH$_2$, dioxane, rt–82 ºC, 1 day	**53** (NR)
11	**47**	**Cat A**, piperidine, rt, 12–30 h	**42** (86–97)[c]

[a] **Cat A**: 5 mol% $Pd(PhCN)_2Cl_2$, 10 mol% CuI; **Cat B**: 5 mol% $Pd(MeCN)_2Cl_2$, 10 mol% CuI; **Cat C**: 5 mol% $Pd(PPh_3)_2Cl_2$, 10 mol% CuI; **Cat D**: 5 mol% $Pd(PhCN)_2Cl_2$, 10 mol% P(*t*-Bu)$_3$, 10 mol% CuI.

[b] Isolated yields. NR = no reaction

[c] 97% yield of **42** was obtained on 0.1 mmol scales and 86% of **42** was obtained on ca. 6 mmol scales. Addition of another portion of 2.5 mol% $Pd(PhCN)_2Cl_2$ and 2 equivalents of ethynyltrimethylsilane was necessary for completion of the cross-coupling reaction within 24 h.

From the geometrically pure enyne (*E*)-**42**, the tandem AD–S_N2 sequence was carried out to afford the tetrahydrofuran product **43** in a higher yield of 82% (Scheme 9). Removal of both TBDPS and TMS groups by treating with HF·H_2O in MeCN and K_2CO_3 in MeOH, respectively, gave the diol **54** in 96% overall yield for the 2 steps. Global silylation of **54** produced the bis-TES ether **55** (92%) which was transformed into the alkenyl iodide **56** by the Pd(0)-catalyzed hydrostannylation followed by iodination in 76% overall yield. Selective cleavage of the primary TES ether gave the alcohol **57** in 73% yield. Finally, Dess–Martin periodinane (DMP) oxidation of **57** furnished the aldehyde **58** in 95% yield.



Scheme 9. Synthesis of the C18–C26 aldehyde **58**.

3. Conclusion

In summary, we have established a synthesis of the C18–C26 fragment of amphidinolide C congeners starting from methyl acetoacetate in 14 steps in >17.0% overall yield. The C20 stereogenic center was secured by asymmetric hydrogenation of the β-keto ester and the configuration at both C23 and C24 was installed by asymmetric dihydroxylation (AD). The *trans*-2,5-disubstituted tetrahydrofuran ring was assembled via the tandem AD–S_N2 sequence. The latter protocol could be employed for accessing the corresponding *cis*-2,5-disubstituted tetrahydrofuran rings from the same alkene substrates simply by choosing a suitable AD ligand. By combination of both asymmetric hydrogenation of β-keto esters and asymmetric dihydroxylation, four diastereomers of *cis*- and *trans*-2,5-disubstituted tetrahydrofuran derivatives could be synthesized using the AD–S_N2 sequence. Moreover, the observed functional group compatibility for the Ru(II)-catalyzed hydrogenation of β-keto esters and the Pd(0)–Cu(I)-catalyzed Sonogashira cross-coupling reaction should be valuable for general synthetic application.

4. Experimental

4.1. General methods

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or acetone-d_6 (400 MHz for ^1H and 100 MHz for ^{13}C, respectively). Residual solvent peaks are used as the internal reference; the signals at 7.26 and 77.16 ppm are set for ^1H and ^{13}C NMR spectra, respectively, taken in $CDCl_3$ while the signals at 2.05 and 206.26 ppm are set for ^1H and ^{13}C NMR spectra, respectively, taken in acetone-d_6. IR spectra were taken on an FT-IR spectrophotometer. High resolution mass spectra (HRMS) were measured by TOF MS under the +CI or –CI conditions. Silica gel plates pre-coated on glass were used for thin-layer chromatography using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. Silica gel was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials. Reagents were obtained commercially and used as received unless otherwise mentioned. Dry THF, Et_2O and toluene were freshly distilled from sodium and benzophenone, and dry CH_2Cl_2 was freshly distilled over calcium hydride, respectively, under a N_2 atmosphere.

4.2. Methyl (*E*)-7-Chloro-3-oxohept-6-enoate (44)

To a solution of *i*-Pr_2NH (7.06 mL, 50.4 mmol, dried over CaH_2) in dry THF (50 mL) cooled at –78 °C under N_2 was added *n*-BuLi (24.6 mL, 49.2 mmol, 2.0 M) dropwise. The resultant solution was allowed to warm to 0 ºC followed by stirring for 1 h at the same temperature to form a yellow solution of lithium diisopropylamide (LDA).

To the above prepared LDA solution cooled at –78 °C, was added slowly methyl acetoacetate (2.59 mL, 24 mmol) followed by stirring at 0 °C for 1 h. To the resultant solution cooled at –78 ºC was added a solution of (*E*)-1,3-dichloropropene (1.85 mL, 20 mmol) in dry THF (10 mL) using a syringe followed by stirring for 10 min at the same temperature. The reaction was allowed to warm to 0 ºC; after stirring at 0 °C for 16 h and at room temperature for another 2 h, the reaction was quenched by addition of H_2O (50 mL). The reaction mixture was extracted with EtOAc (50 mL × 3). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (17% EtOAc in hexane) to afford the product **44** (3.31 g, 87%) as a colorless oil. IR (film): 2955, 2929, 1747, 1717, 1633, 1438, 1323, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.96 (d, *J*=13.2 Hz, 1H), 5.82 (dt, *J*=13.2, 7.2 Hz, 1H), 3.68 (s, 3H), 3.41 (s, 2H), 2.61 (t, *J*=7.2 Hz, 2H), 2.30 (dt, *J*=7.2, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 167.4, 131.7, 118.4, 52.5, 49.0, 41.8, 24.6; HRMS (+CI) calcd for $C_8H_{12}ClO_3$ 191.0475 ($M+H^+$), found 191.0470 and $C_8H_{12}{}^{37}ClO_3$ 193.0445 ($M+H^+$), found 193.0448.

4.3. General procedure for Sonogashira cross-coupling

To a suspension of $PdCl_2(PhCN)_2$ (124.1 mg, 3.23×10^{-1} mmol, 5 mol%), alkenyl chloride **47** (3.11 g, 6.46 mmol), and CuI (123.2 mg, 6.46 mmol × 10^{-1}, 10 mol%) in piperidine (32 mL) under a N_2 atmosphere was added ethynyltrimethylsilane (2.29 mL, 16.15 mmol, 2.5 equiv) via a syringe. The resultant mixture was stirred at room temperature for 30 h. The reaction was treated with saturated aqueous solution of NH_4Cl (15 mL). The aqueous layer was extracted with Et_2O (150 mL × 3). The combined organic layer was washed sequentially with aqueous HCl (0.2 M, 100 mL), aqueous $NaHCO_3$ (100 mL) and H_2O (200 mL × 2). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (14% EtOAc in hexane) to afford the enyne **42** (3.02 g, 86%).

*4.3.1. (4E,1S)-1-[2'-((tert-Butyldiphenylsilyl)-oxy)ethyl]-7-trimethylsilylhept-4-en-6-ynyl Methanesulfonate (**42**)*

Prepared from **47** at room temperature for 30 h, (if adding another 2.5 mol% $Pd(PhCN)_2Cl_2$ and 2.0 equiv of ethynyltrimethylsilane, the reaction was completed at room temperature for 24 h), in 82–97% yields as a colorless oil. $[\alpha]_D^{25}$ +32.8 (*c* 1.0, $CHCl_3$); IR (film): 2958, 2932, 2858, 2137, 1356, 1175, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.60 (m, 4H), 7.45–7.38 (m, 6H), 6.16 (dt, *J*=16.0, 6.8 Hz, 1H), 5.55 (d, *J*=16.0 Hz, 1H), 4.99–4.89 (m, 1H), 3.81–3.68 (m, 2H), 2.94 (s, 3H), 2.21 (td, *J*=7.6, 6.8 Hz, 2H), 1.97–1.75 (m, 4H), 1.07 (s, 9H), 0.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 135.7 (×4), 133.5, 133.4, 130.0, 130.0, 127.9 (×4), 111.1, 103.7, 93.6, 80.2, 59.6, 38.5, 37.2, 33.9, 28.5, 27.0 (×3), 19.3, 0.1 (×3); HRMS (+CI) calcd for $C_{29}H_{43}O_4SSi_2$ 543.2421 ($M+H^+$), found 543.2415.

*4.3.2. Methyl (E)-3-oxo-9-trimethylsilylnon-6-en-8-ynoate (**48**)*

Prepared from **44** at room temperature to 35 ºC for 4 days in 60% yield as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.14 (dt, *J*=16.0, 7.2 Hz, 1H), 5.51 (d, *J*=15.6 Hz, 1H), 3.71 (s, 3H), 3.42 (s, 2H), 2.62 (t, *J*=7.2 Hz, 2H), 2.37 (dt, *J*=7.2, 7.2 Hz, 2H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 167.5, 143.3, 111.2, 103.5, 93.7, 52.5, 49.1, 41.7, 26.7, 0.0 (×3).

4.4. General procedure for asymmetric hydrogenation of β-keto esters

A flame dried two-necked flask was charged with (*S*)-BINAP (280.2 mg, 0.45 mmol) and $(COD)Ru(2\text{-methylallyl})_2$ (143.8 mg, 0.45 mmol). The load flask was evacuated and backfilled with N_2 for three times. Degassed dry acetone (25 mL) and a solution of HBr in dry MeOH (3.88 mL, 1.13 mmol, 0.29 M solution prepared from diluting 48% aqueous HBr in MeOH) were added via a syringe. After the resultant dark red mixture was stirred at room temperature for 30 min, the solvent was removed under reduced pressure to give a reddish brown solid, which was used as the hydrogenation catalyst.

The flask with the chiral Ru(II) catalyst was evacuated and backfilled with H_2 for 3 times and degassed dry MeOH (30 mL) was added to dissolve the catalyst. The β-ketone ester **44** (2.99 g, 15.73 mmol) was added and the resultant mixture was stirred at 50 °C for 24 h. The reaction mixture was allowed to cool to room temperature and the volatile components were removed under reduced pressure. The residue was purified by flash column chromatography over silica gel (14% EtOAc in hexane) to afford the product **45** (2.60 g, 86%).

*4.4.1. Methyl (6E,3S)-7-Chloro-3-hydroxyhept-6-enoate (**45**)*

Prepared from β-keto ester **44** at 50 ºC for 24 h in 86% yield as a colorless oil. $[\alpha]_D^{25}$ +8.7 (*c* 1.0, $CHCl_3$); IR (film): 3425 (br), 2954, 2923, 1732, 1440, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.97 (d, *J*=13.2 Hz, 1H), 5.88 (dt, *J*=13.2, 6.8 Hz, 1H), 4.05–3.93 (m, 1H), 3.69 (s, 3H), 3.10–2.85 (br s, 1H, O*H*), 2.48 (ABqd, *J*=16.4, 2.8 Hz, 1H), 2.41 (ABqd, *J*=16.4, 8.4 Hz, 1H), 2.29–2.10 (m, 2H), 1.66–1.55 (m, 1H), 1.55–1.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 133.1, 117.7, 67.0, 51.9, 41.2, 35.6, 27.0; HRMS (+CI) calcd for $C_8H_{14}ClO_3$ 193.0631 ($M+H^+$), found 193.0633 and $C_8H_{14}{}^{37}ClO_3$ 195.0601 ($M+2+H^+$), found 195.0616.

*4.4.2. Methyl (6E,3S)-3-Hydroxy-9-trimethylsilyl-non-6-en-8-ynoate (**49**)*

Prepared from the β-keto ester **48** at 50 ºC for 48 h in 7.8% yield as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.20 (dt, *J*=15.6, 6.8 Hz, 1H), 5.54 (d, *J*=15.6 Hz, 1H), 4.05–3.96 (m, 1H), 3.71 (s, 3H), 2.97 (br s, 1H, O*H*), 2.49 (ABqd, *J*=16.4, 3.2 Hz, 1H), 2.41 (ABqd, *J*=16.4, 8.8 Hz, 1H), 2.36–2.14 (m, 2H), 1.67–1.56 (m, 1H), 1.56–1.44 (m, 1H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 145.1, 110.6, 104.0, 93.2, 67.2, 52.0, 41.2, 35.3, 29.2, 0.1 (×3).

4.5. (6*E*,3*S*)-7-Chlorohept-6-ene-1,3-diol (46)

To the stirred solution of the ester **45** (4.44 g, 23.04 mmol) in dry Et_2O (115 mL) cooled at 0 ºC was added $LiAlH_4$ (2.62 g, 69.14 mmol) in portions. The resultant mixture was stirred for 1 h at the same temperature. The reaction was quenched at 0 ºC by sequentially adding EtOAc and saturated aqueous sodium potassium tartrate (100 mL), and the solution was stirred for overnight. The reaction mixture was extracted with EtOAc (50 mL × 3) and the combined organic layer was washed with brine (00 mL), dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (50% EtOAc in hexane) to afford the 1,3-diol **46** (3.45 g, 91%) as a colorless oil. $[\alpha]_D^{25}$ –4.0 (*c* 1.0, $CHCl_3$); IR (film): 3380 (br), 2955, 2920, 1726, 1446, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.97 (d, *J*=13.6 Hz, 1H), 5.89 (dt, *J*=13.6, 6.4 Hz, 1H), 3.98–3.72 (m, 3H), 3.15 (s, 2H, O*H* ×2), 2.30–2.06 (m, 2H), 1.75–1.47 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.4, 117.5, 71.0, 61.5, 38.4, 36.7, 27.1; HRMS (+CI) calcd for $C_7H_{14}ClO_2$ 165.0682 ($M+H^+$), found 165.0685.

4.6. (6*E*,3*S*)-1-[(*tert*-Butyldiphenylsilyl)oxy]-7-chlorohept-6-en-3-ol (52)

To a stirred solution of the 1,3-diol **46** (3.45 g, 20.96 mmol), DMAP (256.5 mg, 2.1 mmol), imidazole (2.85 mg, 41.96 mmol) and *n*-Bu_4NI (775.7 mg, 2.1 mmol) in dry DMF (35 mL) was added TBDPSCl (5.99 mL, 23.05 mmol) at room temperature under N_2. The resultant mixture was stirred for 5 h at room temperature and was then quenched by saturated aqueous $NaHCO_3$ (50 mL). The reaction mixture was extracted with EtOAc (50 mL × 3), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (6% EtOAc in hexane) to afford the alcohol **52** (7.77 g, 92%) as a colorless oil. $[\alpha]_D^{25}$ –13.8 (*c* 1.0, $CHCl_3$); IR (film): 3447 (br), 2932, 2858, 1637, 1428, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J*=6.9 Hz, 4H), 7.50–7.38 (m, 6H), 6.00 (d, *J*=13.6 Hz, 1H), 5.93 (dt, *J*=13.6, 6.8 Hz, 1H), 3.96–3.84 (m, 3H), 3.36 (br s, 1H, O*H*), 2.33–2.11 (m, 2H), 1.81–1.68 (m, 1H), 1.68–1.57 (m, 2H), 1.57–1.47 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (×2), 135.7 (×2), 133.7, 133.0, 132.9, 130.0, 130.0, 128.0 (×4), 117.3, 71.0, 63.6, 38.4, 36.6, 27.1, 26.9 (×3), 19.1; HRMS (+CI) calcd for $C_{23}H_{32}ClO_2Si$ 403.1860 ($M+H^+$), found 403.1866 and $C_{23}H_{32}{}^{37}ClO_2Si$ 405.1833 ($M+H^+$), found 405.1819.

4.7. (4*E*,1*S*)-1-[2′-((*tert*-Butyldiphenylsilyl)oxy)ethyl]-5-chloropent-4-enyl Methanesulfonate (47)

To a solution of the alcohol **52** (5.65 g, 14.01 mmol) in dry CH_2Cl_2 (60 mL) cooled at 0 °C was added DMAP (256.6 mg, 2.1 mmol), Et_3N (19.55 mL, 140.1 mmol), and MsCl (2.71 mL, 35.04 mmol) followed by stirring at room temperature for 1 h. The reaction was quenched by addition of H_2O (40 mL) and the reaction mixture was extracted with CH_2Cl_2 (50 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue

was purified by flash column chromatography over silica gel (9% EtOAc in hexane) to afford the mesylate **47** (6.25 g, 93%) as a colorless oil. $[\alpha]_D^{25}$ +11.3 (*c* 1.0, $CHCl_3$); IR (film): 2931, 2857, 1353, 1173, 1108, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.60 (m, 4H), 7.44–7.35 (m, 6H), 6.00 (d, *J*=13.2 Hz, 1H), 5.86 (dt, *J*=13.2, 7.2 Hz, 1H), 4.94 (quintet, *J*=6.0 Hz, 1H), 2.93 (s, 3H), 2.17 (dt, *J*=7.2, 7.2 Hz, 2H), 1.96–1.87 (m, 1H), 1.87–1.75 (m, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (×4), 133.4, 132.3 (×2), 130.0 (×2), 130.0, 128.0 (×4), 118.4, 80.1, 59.6, 38.5, 37.2, 34.2, 27.0 (×3), 26.5, 19.3; HRMS (+CI) calcd for $C_{24}H_{34}ClO_4SSi$ 481.1636 ($M+H^+$), found 481.1631 and $C_{24}H_{34}{}^{37}ClO_4SSi$ 483.1606 ($M+H^+$), found 483.1611.

4.8. (1*R*,2′*R*,5′*R*)-1-{5′-[2"-((*tert*-Butyldiphenylsilyl)oxy)-ethyl]tetrahydrofuran-2′-yl}-3-trimethylsilylprop-2-yn-1-ol (43)

A mixture of $(DHQD)_2PHAL$ (474.2 mg, 6.08×10^{-1} mmol, 5 mol%), $K_3Fe(CN)_6$ (12.02 g, 36.51 mmol), K_2CO_3 (5.05 g, 36.51 mmol), $MeSO_2NH_2$ (2.32 g, 24.34 mmol) in a mixed *t*-BuOH and H_2O (1:1 v/v, 50 mL) was stirred at 0 °C for 1 h. Then, $K_2OsO_4 \cdot 2H_2O$ (89.7 mg, 2.43×10^{-1} mmol, 2 mol%) was added. After stirring for 30 min, the enyne **42** (6.61 g, 12.17 mmol) was added followed by stiring at 0 ºC for 36 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$. After stirring for 1.5 h at room temperature, the organic layer was extracted with EtOAc (50 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (12.5% EtOAc in hexane) to afford the product **43** (4.79 g, 82%) as a colorless oil. $[\alpha]_D^{25}$ +2.73 (*c* 1.0, $CHCl_3$); IR (film): 3416, 2958, 2859, 2174, 1251, 1109, 1084 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–7.69 (m, 4H), 7.48–7.36 (m, 6H), 4.18 (d, *J*=7.2 Hz, 1H), 4.20–4.10 (m, 1H), 3.99 (dt, *J*=6.8, 6.8, 6.0 Hz, 1H), 3.86–3.73 (m, 2H), 2.68 (br s, 1H, O*H*), 2.08–1.96 (m, 2H), 1.94–1.83 (m, 2H), 1.83–1.71 (m, 1H), 1.64–1.52 (m, 1H), 1.08 (s, 9H), 0.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (×4), 133.9, 133.8, 129.7 (×2), 127.7 (×4), 103.9, 90.3, 81.7, 78.1, 66.4, 61.4, 39.0, 31.4, 27.9, 27.0 (×3), 19.3, –0.1 (×3); HRMS (–CI) calcd for $C_{28}H_{40}O_3Si_2$ 480.2516 (M^-), found 480.2517.

4.9. (1*R*,2′*R*,5′*R*)-1-[5′-(2"-Hydroxyethyl)tetrahydrofuran-2′-yl]propynol (54)

To the stirred solution of the silyl ether **43** (3.81 g, 7.92 mmol) in MeCN (16 mL) was added aqueous HF (5.74 mL, 48%, 158.5 mmol) at room temperature followed by stirring for 4 h at the same temperature. The reaction was quenched by adding solid $NaHCO_3$, and the reaction mixture was filtered through a pad of $NaHCO_3$. The filtrate was concentrated under reduced pressure and the residue was used for the next step. An analytic sample was used for collecting the characterization data. $[\alpha]_D^{25}$ –1.1 (*c* 1.0, $CHCl_3$); IR (film): 3428 (br), 2958, 2892, 2173, 1251, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (dd, *J*=6.8, 4.4 Hz, 1H), 4.16–4.10 (m, 1H), 4.06 (dt, *J*=6.8, 6.8 Hz, 1H), 3.80–3.67 (m, 2H), 3.40 (d, *J*=4.4 Hz, 1H, O*H*), 3.11 (br s, 1H, O*H*), 2.11–2.00 (m, 2H), 1.87–1.70 (m, 3H), 1.63–1.50 (m, 1H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.9, 90.4, 82.1, 79.0, 65.6, 60.9, 37.5, 32.2, 28.0, –0.1 (×3).

A suspension of the above crude product and solid K_2CO_3 (832.0 mg, 6.02 mmol) in wet MeOH (40 mL) was stirred at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (66% EtOAc in hexane) to afford the terminal alkyne **54** (3.03 g, 96% for the 2 steps) as a colorless oil. $[\alpha]_D^{25}$ –12.8 (*c* 1.0, $CHCl_3$); IR (film): 3391 (br), 3289, 2939, 2885, 1640, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.23–4.08 (m, 3H), 3.83–3.70 (m, 2H), 3.29 (br s, 1H, O*H*), 2.90 (br s, 1H, O*H*), 2.43 (dd, *J*=5.8, 2.2 Hz, 1H), 2.16–1.97 (m, 2H), 1.90–1.58 (m, 3H), 1.67–1.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.3, 81.9, 79.3, 73.8, 65.0, 61.1, 37.5, 32.3, 27.9; HRMS (–CI) calcd for $C_9H_{14}O_3$ 170.0943 (M^-), found 170.0949.

4.10. (2*R*,5*R*,1"*R*)-2-[(2′-Triethylsilyloxy)ethyl]-5-[(1"-triethylsilyloxy)prop-2"-ynyl]tetrahydrofuran (55)

To a solution of the diol **54** (1.13 g, 6.63 mmol) and 2,6-lutidine (3.48 mL, 29.88 mmol) in dry CH_2Cl_2 (60 mL) cooled at –78 °C was added TESOTf (4.80 mL, 26.55 mmol) under N_2. The resultant mixture was stirred at the same temperature for 3 h and the reaction was quenched by saturated aqueous $NaHCO_3$ (20 mL). The reaction mixture was extracted with CH_2Cl_2 (50 mL × 3) and the combined organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (2% Et_2O in hexane) to afford the bis-TES ether **55** (2.43 g, 92%) as a colorless oil. $[\alpha]_D^{25}$ –17.6 (*c* 1.0, $CHCl_3$); IR (film): 2955, 2924, 2877, 1461, 1087, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.38 (dd, *J*=6.0, 2.0 Hz, 1H), 4.16–4.06 (m, 1H), 4.03 (td, *J*=6.8, 6.0 Hz, 1H), 3.76–3.62 (m, 2H), 2.34 (d, *J*=2.0 Hz, 1H), 2.13–2.01 (m, 2H), 2.01–1.87 (m, 1H), 1.88–1.76 (m, 1H), 1.75–1.61 (m, 1H), 1.58–1.45 (m, 1H), 1.04–0.89 (m, 18H), 0.71–0.53 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.1, 83.5, 81.4, 73.1, 66.0, 60.4, 39.0, 32.3, 27.9, 6.9 (×3), 6.8 (×3), 4.8 (×3), 4.5 (×3); HRMS (+CI) calcd for $C_{21}H_{43}O_3Si_2$ 399.2751 ($M+H^+$), found 399.2752.

4.11. (2*R*,5*R*,1"*R*)-2-[(3"-Iodo-1"-triethylsilyloxy)allyl]-5-[(2′-triethylsilyloxy)ethyl]tetrahydrofuran (56)

To a solution of the terminal alkyne **55** (2.10 g, 5.626 mmol) and $Pd(PPh_3)_4$ (303.9 mg, 2.63×10^{-1} mmol) in degassed THF (25 mL) cooled at 0 °C was added *n*-Bu_3SnH (1.74 mL, 6.31 mmol) followed by stirring at the same temperature for 20 min. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (2% Et_2O in hexane) to afford the alkenyl tin as a colorless oil which was used directly in the next step.

To a solution of the above alkenyl tin in dry THF (40 mL) cooled at 0 ºC was added a solution of NIS (1.42 g, 6.31 mmol, dissolved in 12 mL of THF). The reaction was stirred at 0 ºC for 30 min, and was quenched with saturated aqueous Na_2SO_3 (30 mL) and KF (30 mL, 1 M). The reaction mixture was extracted with Et_2O (50 mL × 3) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (2% Et_2O in hexane) to afford the alkenyl iodide **56** (2.10 g, 76%) as a colorless oil. $[\alpha]_D^{25}$ –12.7 (*c* 1.0, $CHCl_3$); IR (film) 2955, 2877, 1461, 1088, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.58 (dd, *J*=14.4, 5.2 Hz, 1H), 6.31 (dd, *J*=14.4, 1.2 Hz, 1H), 4.14 (ddd, *J*=5.2, 5.2, 1.2 Hz, 1H), 4.03–3.95 (m, 1H), 3.93 (td, *J*=7.2, 5.2 Hz, 1H), 3.75–3.62 (m, 2H), 2.03–1.84 (m, 2H), 1.82–1.62 (m, 3H), 1.55–1.42 (m, 1H), 0.96 (t, *J*=8.0 Hz, 9H), 0.94 (t, *J*=8.0 Hz, 9H), 0.60 (q, *J*=8.0 Hz, 6H), 0.59 (q, *J*=8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 81.1, 77.5 (overlapped with a solvent residual peak), 77.1, 77.1, 60.4, 39.1, 32.3, 27.1, 6.9 (×3), 6.9 (×3), 5.0 (×3), 4.6 (×3); ^{13}C NMR (100 MHz, acetone-d_6) δ 147.3, 82.2, 78.7, 78.3, 77.5, 61.1, 40.2, 33.2, 28.4, 7.4 (×6), 5.7 (×3), 5.3 (×3); HRMS (+CI) calcd for $C_{21}H_{44}IO_3Si_2$ 527.1874 ($M+H^+$), found 527.1863.

4.12. (2*R*,5′*R*,1"*R*)-2-{5′-[(3"-Iodo-1"-triethylsilyloxy)allyl]-tetrahydrofuran-2′-yl}ethanol (57)

To a solution of the bis-TES ether **56** (104.0 mg, 1.97×10^{-1} mmol) in THF (11.1 mL) and H_2O (11.1 mL) cooled at 0 °C was added AcOH (0.55 mL) followed by stirring at the same temperature for 1 h. The reaction was quenched by saturated aqueous $NaHCO_3$ (15 mL) and the reaction mixture was extracted with CH_2Cl_2 (15 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (17% EtOAc in hexane) to afford the alcohol **57** (59.0 mg, 73%) as a colorless oil. $[\alpha]_D^{25}$ –4.43 (*c* 1.0, $CHCl_3$); IR (film): 3421 (br), 2955, 2878, 1063, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.56 (dd, *J*=14.4, 5.6 Hz, 1H), 6.33 (dd, *J*=14.4, 1.2 Hz, 1H), 4.16–4.06 (m, 2H), 4.01–3.93 (m, 1H), 3.84–3.72 (m, 2H), 2.75 (br s, 1H, O*H*), 2.05–1.86 (m, 2H), 1.73–1.65 (m, 3H), 1.60–1.50 (m, 1H), 0.94 (t, *J*=8.0 Hz, 9H), 0.59 (q, *J*=8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 81.5, 80.2, 77.9, 77.0, 61.9, 37.4, 32.4, 26.9, 6.9 (×3), 4.9 (×3); HRMS (+CI) calcd for $C_{15}H_{30}IO_3Si$ 413.1009 ($M+H^+$), found 413.0995.

4.13. (2*R*,5′*R*,1"R)-{5′-[(3"-Iodo-1"-triethylsilyloxy)allyl]-tetrahydrofuran-2′-yl}acetaldehyde (58)

To a suspension of the alcohol **57** (60.7 mg, 1.47×10^{-1} mmol) and solid $NaHCO_3$ (123.5 mg, 1.47 mmol) in dry CH_2Cl_2 (1 mL) cooled at 0 ºC was added DMP (187.3 mg, 0.44 mmol, dissolved in 6 mL CH_2Cl_2) followed by stirring at the same temperature for 10 min and at room temperature for another 1.5 h. The reaction was quenched at 0 °C by saturated aqueous $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (5 mL) and the reaction mixture was extracted with CH_2Cl_2 (5 mL × 3). The combined organic layer was washed with brine (5 mL) and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography over silica gel (6% Et_2O in hexane) to afford the aldehyde **58** (57.3 mg, 95%) as a colorless oil. $[\alpha]_D^{25}$ –11.1 (*c* 1.0, $CHCl_3$); IR (film): 2955, 2877, 1725, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (dd, *J*=2.4, 1.6 Hz, 1H), 6.57 (dd, *J*=14.4, 5.6 Hz, 1H), 6.34 (dd, *J*=14.4, 1.2 Hz, 1H), 4.42–4.30 (m, 1H), 4.13 (ddd, *J*=5.6, 5.6, 1.2 Hz, 1H), 4.00–3.95 (m, 1H), 2.65 (ABqdd, *J*=16.4, 7.2, 2.4 Hz, 1H), 2.54 (ABqdd, *J*=16.0, 5.2, 1.8 Hz, 1H), 2.15–2.07 (m, 1H), 2.00–1.88 (m, 1H), 1.81–1.70 (m, 1H), 1.60–1.50 (m, 1H), 0.97–0.90 (m, 9H), 0.63–0.53 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 145.4, 81.6, 77.9, 76.9, 74.7, 49.6, 32.2, 27.0, 6.9 (×3), 4.9 (×3); HRMS (+CI) calcd for $C_{15}H_{28}IO_3Si$ 411.0852 ($M+H^+$), found 411.0856.

Acknowledgements

This work is supported in part by a General Research Fund grant (600913) from the Research Grant Council, The Hong Kong Special Administrative Region, P. R. China and the Department of Chemistry, HKUST.

Supplementary data

Synthetic procedures for compounds **31**–**43** of Schemes 4–6 and copies of ^1H and ^{13}C NMR spectra for the compounds **31**–**49**, **52**, **54**–**58**, and the related compounds are available. Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2018.00.000.

References and notes

1. For isolation and structure of amphidinolide C1, see: (a) Kobayashi, J.; Ishibashi, M.; Wälchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Ohizumi, Y. *J. Am. Chem. Soc*. **1988**, *110*, 490−494. (b) Kubota, T.; Tsuda, M.; Kobayashi, J. *Org. Lett.* **2001**, *3*, 1363−1366. (c) Kubota, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron* **2001**, *57*, 5975−5977. (d) Kubota, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 1613−1625.
2. For isolation and structure of amphidinolide C2, see: Kubota, T.; Sakuma, Y.; Tsuda, M.; Kobayashi, J. *Mar. Drugs* **2004**, *2*, 83–87.
3. For isolation and structure of amphidinolide C3, see: Kubota, T.; Suzuki, A.; Yamada, M.; Baba, S.; Kobayashi, J. *Heterocycles* **2010**, *82*, 333–338.
4. For isolation and structure of amphidinolide F, see: Kobayashi, J.; Tsuda, M.; Ishibashi, M.; Shigemori, H.; Yamasu, T.; Hirota, H.; Sasaki, T. *J. Antibiot.* **1991**, *44*, 1259–1261.
5. For isolation and structure of amphidinolide C4, see: Nuzzo, G.; Gomes, B. A.; Luongo, E.; Torres, M. C. M.; Santos, E. A.; Cutignano, A.; Pessoa, O. D. L.; Costa-Lotufo, L. V.; Fontana, A. *J. Nat. Prod*. **2016**, *79*, 1881–1885.
6. For reviews on amphidinolides, see: (a) Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543−572. (b) Chakraborty, T. K.; Das, S. *Curr. Med. Chem. Anti-cancer Agents* **2001**, *1*, 131−49. (c) Kobayashi, J.; Shimbo, K.; Kubota, T.; Tsuda, M. *Pur. App. Chem.* **2003**, *75*, 337−342. (d) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77−93. (e) Colby, E. A.; Jamison, T. F. *Org. Biomol. Chem.* **2005**, *3*, 2675−2684. (f) Jia, R.; Huang, X.-C.; Guo, Y.-W. *Chin. J. Nat. Med*. **2006**, *4*, 15–24. (g) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451−460. (h) Kobayashi, J. *J. Antibiot.* **2008**, *61*, 271−284. (i) Fürstner, A. *Israel J. Chem*. **2011**, *51*, 329−345. (j) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Álvarez, M. *Chem. Rev*. **2013**, *113*, 4567−4610.
7. Amphidinolide U, a 20-membered macrolide possessing the same side chain as amphidinolide C1, exhibiting significantly reduced cytotoxicity against murine lymphoma L1210 and human epidermoid carcinoma KB cell lines (IC_{50}: 12 and 20 μg/mL), see: Tsuda, M.; Endo, T.; Kobayashi, J. *Tetrahedron* **1999**, *55*, 14565–14570.
8. For Carter's total synthesis of amphidinolide C1 and F, see: (a) Mahapatra, S. Carter, R. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 7948–7951. (b) Mahapatra, S.; Carter, R. G. *J. Am. Chem. Soc.* **2013**, *135*, 10792–10803.
9. For Fürstner's total synthesis of amphidinolide C1 and F, see: (a) Valot, G.; Regents, C. S.; O'Malley, D. P.; Godineau, E.; Takikawa, H.; Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 9534–9538. (b) Valot, G.; Malihol, D.; Regents, C. S.; O'Malley, D. P.; Godineau, E.; Takikawa, H.; Philipps, P.; Fürstner, A.. *Chem. Eur. J.* **2015**, *21*, 2398–2408.
10. (a) Tamura, R.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1988**, *53*, 2723–2728. (b) Vedejs, E.; Marth, C. F.; Ruggeri, R. *J. Am. Chem. Soc.* **1988**, *110*, 3940–3948. (c) Wang, Y,; Panagabko, C.; Atkinson, J. *Bioorg. Med. Chem.* **2010**, *18*, 777–786.
11. For proposed Stille cross-coupling approaches, see: (a) Shotwell, J. B.; Roush, W. R. *Org. Lett.* **2004**, *6*, 3865–3868. (b) Akwaboah, D. C.; Wu, D.; Forsyth, C. J. *Org. Lett.* **2017**, *19*, 1180–1183.
12. For a proposed dithiane carbanion alkylation approach, see: Clark, J. S.; Yang, G.; Osnowski, A. P. *Org. Lett.* **2013**, *15*, 1460–1463.
13. For seleted examples of formation THF rings via S_N2 cyclization, see: (a) Kalantar, T. H.; Sharpless, K. B. *Acta Chem. Scand*. **1993**, *47*, 307–313. (b) Beauchamp, T. J.; Powers, J. P.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **1995**, *117*, 12873–12874. (c) Avedissian, H.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **2000,** *65*, 6035–6051. (d) Kojima, N.; Maezaki, N.; Tominaga, H.; Yanai, M.; Urabe, D.; Tanaka, T. *Chem. Eur. J*. **2004**, *10*, 672–680. (e) Adamo, M. F. A.; Pergoli, R. *Org. Lett.* **2007**, *9*, 4443–4446. (f) Rothman J. H. *J. Org. Chem.* **2009**, *74*, 925–928. (g) Zou, Y.; Wu, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 4968–4971. (h) Kölmel, D. K.; Barandun, L. J.; Kool, E. T. *Org. Biomol. Chem.* **2016**, *14*, 6406–6412. For a review, see: (i) Wu, Y. *Snylett* **2013**, *24*, 1623–1636.
14. For selected examples of formation THF rings via AD–S_N2 cyclization sequence, see: (a) Das, S.; Li, L.-S.; Abraham, S.; Chen, Z.; Sinha, S. C. *J. Org. Chem*. **2005,** *70*, 5922–5931. (b) Marshall, J. A.; Sabatini, J. J. *Org. Lett.* **2006**, *8*, 3557–3560. (c) Mohapatra, D. K.; Dasari, P.; Rahaman, H.; Pal, R. *Tetrahedron Lett.* **2009**, *50*, 6276–6279. (d) Kanto, M.; Sasaki, M. *Org. Lett.* **2016**, *18*, 112–115.
15. For our previous studies on total synthesis of amphidinolide T1–T4, X, and Y, see: (a) Chen, Y.; Jin, J.; Wu, J.; Dai, W.-M. *Synlett* **2006**, 1177–1180. (b) Jin, J.; Chen, Y.; Li, Y.; Wu, J.; Dai, W.-M. *Org. Lett.* **2007**, *9*, 2585–2588. (c) Dai, W.-M.; Chen, Y.; Jin, J.; Wu, J.; Lou, J.; He, Q. *Synlett* **2008**, 1737–1741. (d) Luo, J.; Li, H.; Wu, J.; Xing, X.; Dai, W.-M. *Tetrahedron* **2009**, *65*, 6828–6833. (e) Li, H.; Wu, J.; Luo, J.; Dai, W.-M. *Chem. Eur. J.* **2010**, *16*, 11530–11534. (f) Wu, D.; Li, H.; Jin, J.; Wu, J.; Dai, W.-M.

Synlett **2011**, 895–898. (g) Sun, L.; Wu, D.; Wu, J.; Dai, W.-M. *Synlett* **2011**, 3036–3040.
16. Armstrong, A.; Pyrkotis, C. *Tetrahedron Lett.* **2009**, *50*, 3325–3328.
17. Wu, D.; Forsyth, C. J. *Org. Lett.* **2013**, *15*, 1178–1181.
18. (a) Pérez, B. M.; Schuch, D.; Hartung, J. *Org. Biomol. Chem.* **2008**, *6*, 3532–3541. (b) Schuch, D.; Fries, P.; Dönges, M.; Pérez, B. M.; Hartung, J. *J. Am. Chem. Soc.* **2009**, *131*, 12918–12920.
19. (a) Palmer, C.; Morra, N. A.; Stevens, A. C.; Bajtos, B.; Machin, B. P.; Pagenkopf, B. L. *Org. Lett.* **2009**, *11*, 5614–5617. (b) Wang, J.; Morra, N. A.; Zhao, H.; Gorman, J. S. T.; Lynch, V.; McDonald, R.; Reichwein, J. F.; Pagenkopf, B. L. *Can. J. Chem.* **2009**, *87*, 328–334.
20. (a) Morra, N. A.; Pagenkopf, B. L. *Org. Lett.* **2011**, *13*, 572–575. Also see: (b) Morra, N. A.; Pagenkopf, B. L. *Eur. J. Org. Chem.* **2013**, 756–760. (c) Roushanbakhti, A.; Liu, Y.; Winship, P. C. M.; Tucker, M. J.; Akhtar, W. M.; Walter, D. S.; Wrigley, G.; Donohoe, T. J. *Angew. Chem. Int. Ed.* **2017**, *56*, 14883–14887.
21. (a) Mohapatra, D. K.; Rahaman, H.; Chorghade, M. S.; Gurjar, M. K. *Synlett* **2007**, 567–570. (b) Prestat, G.; Baylon, C.; Heck, M.-P.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 3829–3831.
22. Roy, S.; Spilling, C. D. *Org. Lett.* **2010**, *12*, 5326–5329.
23. (a) Clark, J. S.; Yang, G.; Osnowski, A. P. *Org. Lett.* **2013**, *15*, 1464–1467.
24. Su, Y.-X. PhD Thesis, The Hong Kong University of Science and Technology, P. R. China, **2017**.
25. For similar silylation conditions, see: (a)Manthey, M. K.; González-Bello, C.; Abell, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 625–628. (b) Lehr, K.; Mariz, R.; Leseurre, L.; Gabor, B.; Fürstner, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 11373–11377.
26. For Takai reaction of α-PMBO-substituted aldehydes, see: (a) Barloy-Da Silva, C.; Pale, P. *Tetrahedron: Asymmetry* **1998**, *9*, 3951–3954. (b) Liu, Z.; Byun, H.-S.; Bittman, R. *Org. Lett.* **2010**, *12*, 2974–2977.
27. For Evans' modification, see: Evans, D. A.; Ng, H. P. *Tetrahedron Lett.* **1993**, *34*, 2229–2232.
28. (a) Gibson, A. W.; Humphrey, G. R.; Kennedy, D. J.; Wright, S. H. B. *Synthesis* **1991**, 414–416. (b) Brummond, K. M.; Lu, J.; Petersen, J. *J. Am. Chem. Soc.* **2000**, *122*, 4915–4920. (c) Yao, G.; Steliou, K. *Org. Lett.* **2002**, *4*, 485–488.
29. Low *E*:*Z* ratios were reported for enynes using Wittig olefination, see: (a) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958–5966. (b) Hartung, I. V.; Niess, B.; Haustedt, L. O.; Hoffmann, H. M. R. *Org. Lett.* **2002**, *4*, 3229–3242.
30. For similar alkylation using 1,3-dihalopropenes, see: (a) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143–147. (b) Buchanan, G. S.; Cole, K. P.; Li, G.; Tang, Y.; You, L.-F.; Hsung, R. P. *Tetrahedron* **2011**, *67*, 10105–10118.
31. Genêt, J. P.; Ratovelomanana-Vidal, V.; Caňo de Andrade, M. C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y.; *Tetrahedron Lett.* **1995**, *36*, 4801–4804.