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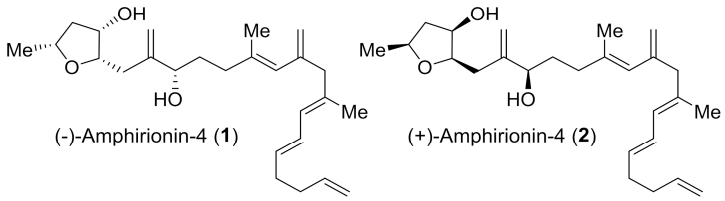

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Total syntheses of both enantiomers of amphirionin 4: A chemoenzymatic based strategy for functionalized tetrahydrofurans

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ABSTRACT

The total syntheses of (-)-amphirionin-4 and (+)-amphirionin-4 have been achieved in a convergent and enantioselective manner. The tetrahydrofuranol cores of amphirionin-4 were constructed in optically active form by enzymatic resolution of racemic *cis*-3-hydroxy-5-methyldihydrofuran-2(3*H*)-one. The polyene side chain was efficiently synthesized using Stille coupling. The remote C8-stereocenter was constructed using the Nozaki-Hiyama-Kishi coupling reaction. A detailed ^{1}H-NMR studies of Mosher esters of (-)-amphirionin-4 and (+)-amphirionin-4 were carried out to support the assignment of the absolute configurations of C-4 and C-8 asymmetric centers of amphirionin-4.

1. Introduction

The intriguing structural features and biological properties of natural products continue to fascinate chemists and biologists for decades.[1,2] Marine dinoflagellates of the genus *Amphidinium* have been producing bioactive polyketide-like metabolites containing polyene side chains.[3,4] These compounds have shown important biological properties with novel mechanisms of action. The majority of these natural products exhibit cytotoxic activities against tumor cells.[5-8] Recently, Tusda and co-workers isolated amphirionins-2, and -4 from a *Amphidinium* KCA09051 strain and amphirionin-5 from a KCA09053 strain in the sea sand collected off the Irimote Island.[9-11] Of these, amphirionin-4 exhibited an intensive proliferation-promoting activity (950%) in murine bone marrow stromal ST-2 cells at 0.1 ng/mL concentration.[10] Tusda and co-workers established the initial structure and stereochemical assignment of amphirionin-4 by NMR studies. The absolute configuration of the C-4 and C-8 hydroxy groups of amphirionin-4 were established using modified Mosher's method.[10,12]

The interesting structure and biological properties of amphirionin-4 attracted synthetic studies of amphirionin-4 for possible biological investigation. Britton and co-workers reported the first total synthesis of (-)-amphirionin-4, corrected the sign of the specific rotation of the published data, and provided support for the structural assignment.[13] Subsequently, Kuwahara and co-workers reported their total synthesis of (-)-amphirionin-4 featuring a Sharpless kinetic resolution and iodoetherification as the key steps.[14] Our interest in (-)-amphirionin-4 arose from its potent activity against ST-2 cells and its unique structural features. In this context, we sought to develop a concise and enantioselective synthesis of (-)-amphirionin-4. We recently reported an enantioselective synthesis of (+)-amphirionin-4.[15] We now report the full account of our work and provide details of our

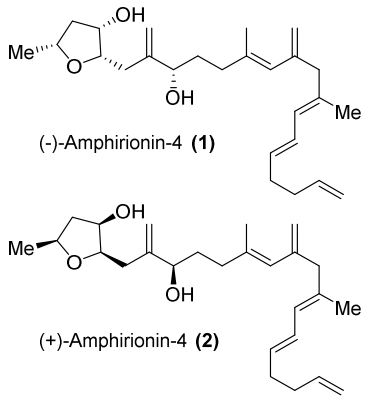


Figure 1: Structures of amphirionin-4 enantiomers.

convergent synthesis of (-)-amphirionin-4 (**1**) and (+)-amphirionin-4 (**2**). We have carried out Mosher's ester analysis[12] of both synthetic (-)-amphirionin-4 (**1**) and (+)-amphirionin-4 (**2**) to support the assignment of the absolute configuration at the C-4 and C-8 stereocenters.

2. Results and discussion

Our retrosynthetic analysis of (-)-amphirionin-4 is outlined in Figure 2. At the outset, we envisioned a Nozaki-Hiyama-Kishi (NHK)[16,17] reaction of optically active vinyl iodide **3** and aldehyde **4** to construct (-)-amphirionin-4 (**1**). A similar strategy was also utilized by Britton and co-workers.[13] We planned to synthesize the vinyl iodide **3** from the corresponding allyl derivative through a Lewis acid catalyzed allylation of an oxocarbenium ion generated from α–hydroxy lactone **5**. This optically active lactone **5** could be readily obtained by the ozonolysis and subsequent reduction of commercially available α-methylene-γ-valerolactone **6.** The racemic α–hydroxy lactone **5** can also be prepared from pyruvic acid as described previously.[15] We planned a Lipase (PS-30) catalyzed optical resolution of the racemic α–hydroxy lactone **5** to provide access to both enantiomers in optically active form. Aldehyde **4**, containing the polyene side chain, could be synthesized by Julia-Kocienski olefination[18] of an aldehyde derived from allylic alcohol **7**. The diene component of alcohol **7** could be constructed by iterative Stille cross-coupling of appropriate vinyl iodide and stannane derivatives.

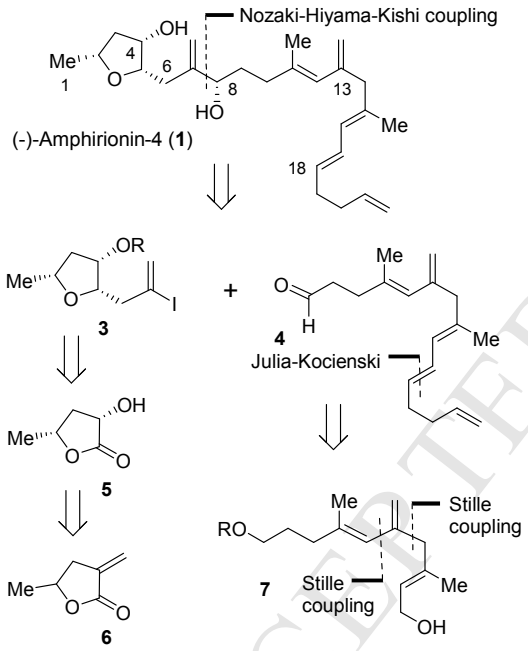
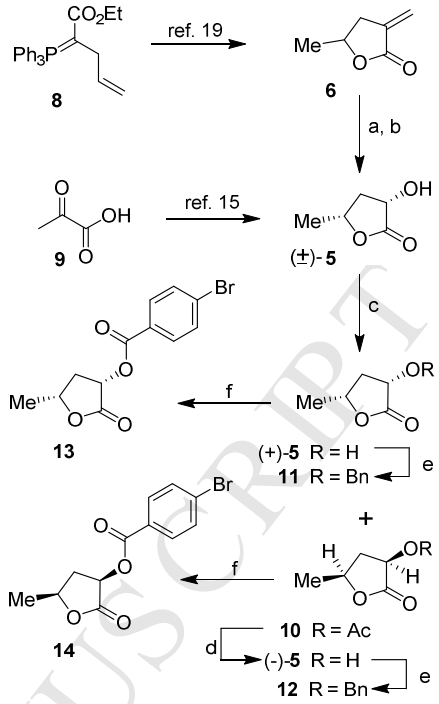


Figure 2: Retrosynthetic Analysis of (-)-amphirionin-4 (**1**).

The synthesis of racemic lactone **5** is shown in Scheme 1. Commercially available racemic α-methylene-γ-valerolactone **6** can be readily prepared from phosphorane **8** using the procedure reported by Amonkar and co-workers.[19] Oxidative cleavage of olefin **6** by ozonolysis at -78 °C in CH_2Cl_2 provided the corresponding ketolactone.[20] Catalytic hydrogenation of the resulting ketolactone in ethyl acetate in the presence of 10% Pd-C under a hydrogen-filled balloon afforded racemic *cis*-hydroxylactone **5** (*dr* = 97:3, determined by ^{1}H-NMR analysis) in 46% yield over two-steps. Racemic lactone **5** was also prepared by acid-catalyzed condensation of pyruvic acid **9** followed by hydrogenation of the resulting α-ketolactone as described previously.[15]



Scheme 1: Synthesis of α-hydroxy lactone (**5**). Reaction conditions: (a) O_3, Me_2S, CH_2Cl_2, -78 °C to 23 °C; (b) H_2 (1 atm), 10 % Pd/C, EtOAc, 24 h (*dr* = 97:3, 46% for 2-steps); (c) Lipase (PS-30), THF, vinyl acetate, 23 °C, 5 h; (d) aq NaOH, 23 °C, 82%; (e) benzyl bromide, Ag_2O, CH_2Cl_2, reflux, 24 h (f) 4-bromobenzoyl chloride, DMAP, pyridine, CH_2Cl_2, 4 h, 0 °C to 23 °C (98% for **13** and 90% for **14**).

Racemic lactone **5** was resolved by an enzyme-catalyzed process. As shown, racemic lactone was treated with lipase PS-30 in a mixture of THF and vinyl acetate at 23 °C for 5 h.[21,22] This resulted in optically active alcohol (+)-**5** in 47% yield and acetate derivative **10** in 50% yield. Saponification of acetate **10** with aqueous 10% NaOH in methanol at 23 °C for 12 h provided optically active alcohol (-)-**5** in 82% yield.[23] To determine enantiomeric purity, these alcohols were converted to the corresponding benzyl ethers by reaction with benzyl bromide in the presence of silver oxide in THF at 23 °C for 24 h to provide benzyl ethers **11** and **12**[15] in 90% and 96% yields respectively. HPLC analysis of these alcohols using a chiralpak IC-3 column showed optical purity of 99% *ee* for alcohol (+)-**5** and 92% *ee* for alcohol (-)-**5**.

We initially assigned the absolute configuration of alcohol (+)-**5** by comparing the sign magnitude of specific rotation with the literature reported.[24] However, due to small magnitude of the specific rotation, we decided to assign absolute stereochemistry using single crystal X-ray analysis. Alcohols (+)-**5** and (-)-**5** were converted to *p*-bromobenzoate derivatives by treatment with 4-bromobenzoyl chloride in CH_2Cl_2 in the presence of pyridine and DMAP at 0 °C to 23 °C for 4 h to provide **13**[15] and **14** in 98% and 90% yields, respectively. The single crystal X-ray analysis of benzoates **13** and **14** supported our assignment of the absolute configuration.[25,26] The ORTEP diagrams of these structures are shown in Figure 3.

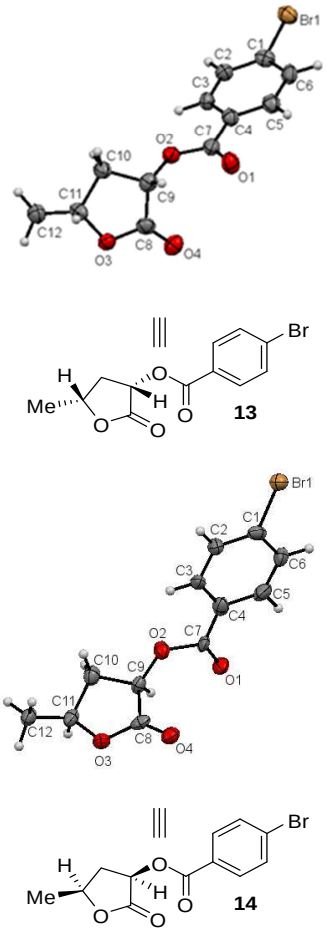
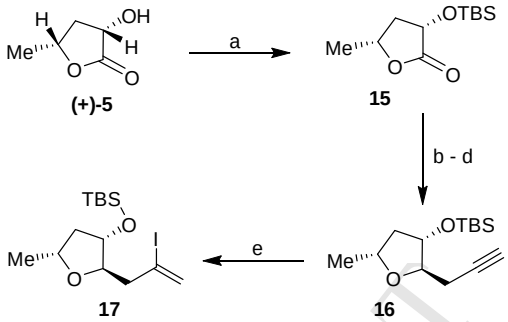


Figure 3: ORTEP drawing of bromo benzoates **13** and **14**. Grey = carbon, white = hydrogen, orange = bromine, red = oxygen.

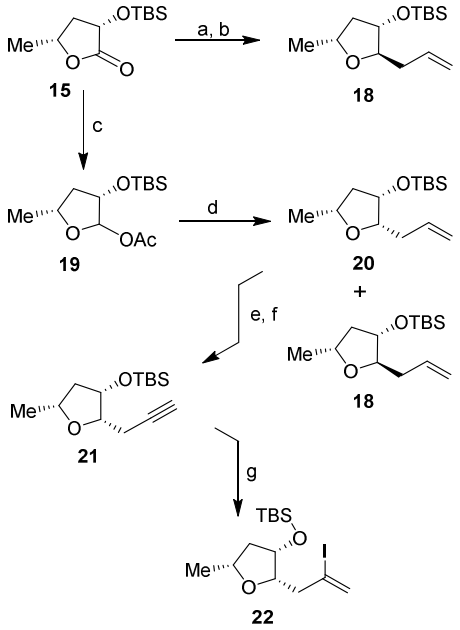
We utilized lactone (+)-**5** and converted to protected vinyl iodide **3**. As shown in Scheme 2, the C2-hydroxy group of (+)-**5** was protected as TBS-ether using TBSOTf and 2,6-lutidine in CH_2Cl_2 at 23 °C for 1 h to provide the TBS ether **15**. Treatment of **15** with 1-trimethylsilylpropynyllithium[27,28] in THF at -78 °C afforded C5-epimeric hemiketals as a mixture of isomers. Hydride reduction of hemiketals with Et_3SiH in the presence of $BF_3.OEt_2$ at -78 °C followed by deprotection of TMS group to afford **16** (*dr* = 94:6, determined by ^{1}H-NMR analysis) in 60 % yield over 3-steps. Initially, we assumed that exclusive deliver of hydride ion from the opposite direction of bulky silylether group of corresponding oxocarbenium ion would provide all *cis*-desired stereochemistry. However, our ^{1}H-NMR NOSEY studies revealed the formation of C-5 epimeric derivative **16**. The desired vinyl iodide **17** fragment was obtained by hydrosilylation of **16** with Et_3SiH in the presence of ruthenium complex $[Cp^*Ru(MeCN)_3]PF_6$ in CH_2Cl_2 at 0 °C to 23 °C for 2 h as developed by Trost and co-workers.[29] Treatment of the resulting silane derivative with *N*-iodosuccinimide and 2,6-lutidine in hexafluoroisopropanol (HFIP) at 0 °C for 15 min then afforded vinyl iodide **17** in 70% yield.[30]



Scheme 2: Synthesis of vinyl iodide **17**. Reaction conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to 23 °C (98 %); (b) 1-(Trimethylsilyl)propyne, n-BuLi, THF, -78 °C, 4 h (c) BF_3•OEt_2, Et_3SiH, CH_2Cl_2, -78 °C, 2 h; (d) K_2CO_3, MeOH, 0 °C to 23 °C, 3 h (*dr* = 94:6, 60 % for 3-steps); (e) cat. $[Cp^*Ru(MeCN)_3]PF_6$ (2 mol%), Et_3SiH, 0 °C to 23 °C, CH_2Cl_2, 2 h then NIS, 2,6-lutidine, HFIP, 0 °C, 15 min (70%).

We then converted TBS-ether **15** to desired C-5 derivative by alternative routes. As shown in Scheme 3, TBS protected lactone **15**, which was treated with allylmagnesium bromide in Et_2O at -78 °C. Reduction of the resulting hemiketals wtih Et_3SiH in the presence of $BF_3.OEt_2$ at -78 °C furnished **18** as a single isomer in 56 % yield over 2-steps. However, it turned out that allylation isomer **18** has the trans selectivity based on the 2D-NMR analysis. In an alternative approach using Woerpel protocols,[31] lactone **15** was reduced with DIBAL-H at -78 °C for 2 h. Acetylation of the resulting lactol with acetic anhydride and pyridine in the presence of DMAP at 0 °C afforded lactol acetate **19** in excellent yield. The ^{1}H-NMR analysis showed the diastereomeric ratio to be 10:1 and the mixture was used directly for the next reaction. The reaction of the acetate with allytrimethylsilane and $SnBr_4$ in CH_2Cl_2 at -78 °C to 23 °C for 2 h furnished allyl derivatives **20** and **18** in 78% combined yield.[31] The ^{1}H-NMR analysis of the mixture revealed a 10:1 diastereomeric ratio. The mixture was separated by silica gel chromatography and the relative stereochemistry of allyl derivative **20** was assigned based upon 2D-NOSEY spectra analysis.[32]

The desired allyl derivative **20** was then converted to its vinyl derivative as follows. Olefin **20** was exposed to oxidative cleavage using protocols developed by Nicolaou and co-workers.[33] Olefin was first treated with *N*-methylmorpholine-*N*-oxide (NMO) and a catalytic amount of osmium tetroxide in the presence of 2,6-lutidine in aqueous acetone at 23 °C for 2 h. Subsequent treatment of the reaction with $PhI(OAc)_2$ for 4 h at 23 °C provided the corresponding aldehyde.[33] Reaction of the resulting aldehyde with the Ohira-Bestman reagent[34,35] in a mixture of methanol and THF in the presence of MeONa at -40 °C for 1 h provided alkyne derivative **21** in 56 % yield over two-steps. Alkyne derivative **21** was converted to vinyl iodide **22** by hydrosilylation of **21** followed by desilylation to afford vinyl iodide **22** in 80% yield.[29,30]



Scheme 3: Synthesis of vinyl iodide **22.** Reaction conditions: (a) allylmagnesium bromide, Et_2O, -78 °C, 2 h; (b) BF_3. OEt_2, Et_3SiH, CH_2Cl_2, -78 °C, 2 h (56 % for 2-steps); (c) DIBAL-H, -78 °C, 2 h then Ac_2O, py, DMAP, 0 °C, CH_2Cl_2, 2 h, (90 %); (d) allylTMS, $SnBr_4$, CH_2Cl_2, -78 °C to 23 °C, 2 h (78%); (e) OsO_4 (2 mol%), NMO, 2,6-lutidine, aq acetone, 23 °C, 24 h, then $PhI(OAc)_2$, 4 h; (f) Ohira Bestmann reagent, MeONa, MeOH/THF, -40 °C, 1 h (56% for 2-steps); (g) cat. $[Cp^*Ru(MeCN)_3]PF_6$ (2 mol%), Et_3SiH, 0 °C to 23 °C, CH_2Cl_2, 2 h then NIS, 2,6-lutidine, HFIP, 0 °C, 15 min (80 %).

The stereochemical outcome of selective *cis*-allylation of acetate **19** can be explained using the stereochemical model shown in Figure 4. These models are similar to that proposed by Woerpel and co-workers for the related C2-benzyloxy substituted tetrahydrofuranyl derivatives.[31] The oxocarbenium ion intermediate **23** preferred over intermediate **24** due to pseudoequatorial orientation of both C-2-silyloxy and C4-methyl groups in **23** over the axial orientation in **24**. Furthermore, the $\sigma_{C\text{-}H}$ orbital at C2 in **23** presumably maximizes electron donation to the adjacent orbital of the oxocarbenium ion. This may explain overall high *cis*-selectivity for allyl derivative **20**.

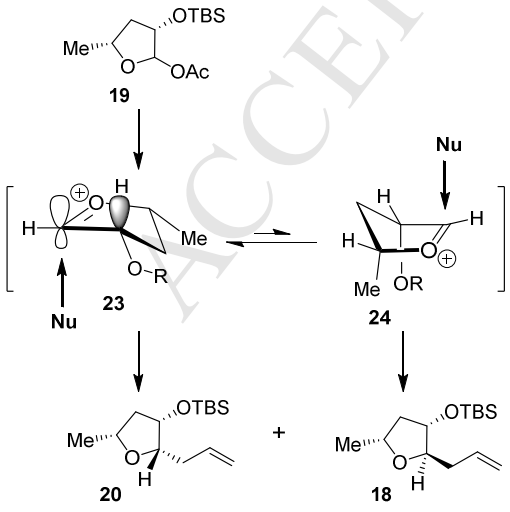
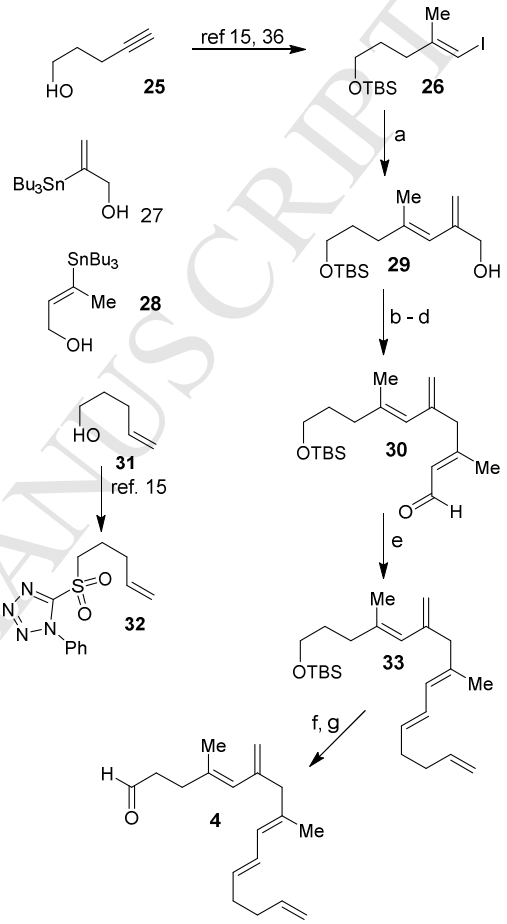


Figure 4: Stereochemical model for *cis*-allylation.

Our synthesis of the polyene side chain of amphirionin-4 is shown in Scheme 4. Vinyl iodide **26**[36] was prepared from 4-pentyne-1-ol (**25**) by zirconium-catalyzed carboalumination followed by TBS protection of the alcohol as described previously.[15] Stille coupling of this vinyl iodide with the known tributylstannane derivative **27**[15,37] was carried out in the presence of CuCl and LiCl as described by Corey and co-workers[38] to give diene **29** in excellent yield. Diene **29** was transformed into aldehyde **30** in a three-step sequence involving: (1) protection of

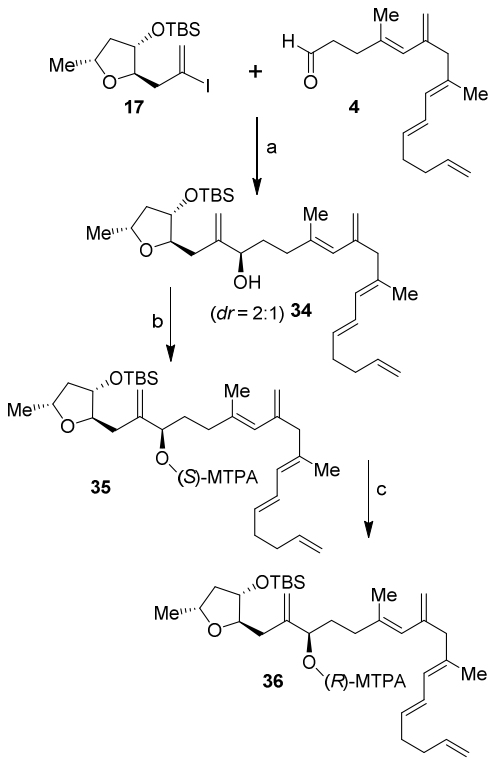


Scheme 4: Reaction conditions: (a) stannane **27**, $Pd(PPh_3)_4$, CuCl, LiCl, DMSO, 23 °C to 60 °C, 2 h (90 %); (b) Ac_2O, Et_3N, DMAP, CH_2Cl_2 , 0 °C to 23 °C, 1 h; (c) **28**, $Pd(dba)_2$, LiCl, DMF, 50 °C, 4 h; (d) MnO_2, Na_2CO_3, CH_2Cl_2, 23 °C, 12 h (73% for 3-steps); (e) **32**, KHMDS, THF, -78 °C, 1 h, then **30**, -78 °C to 23 °C, 4 h; (f) TBAF, THF, 0 °C to 23 °C, 3 h; (g) DMP, pyridine, CH_2Cl_2, 0 °C to 23 °C, 2 h (68% for 3-steps)

the alcohol as an acetate; (2) Stille coupling[39] of the allyl acetate with hydroxystannane **28**[40] in the presence of $Pd(dba)_2$ and LiCl in DMF at 50 °C for 4 h; and (3) MnO_2 oxidation of the resulting allyl alcohol in the presence of Na_2CO_3 in CH_2Cl_2 for 12 h to provide aldehyde **30** in 73% yield over three-steps. This aldehyde was then subjected to Julia-Kocienski olefination[18] with sulfone **32**. The requisite sulfone was readily prepared by reaction of 4-penten-1-ol (**31**) with 1-phenyl-1*H*-tetrazole-5-thiol in the presence of triphenylphosphine and diisopropylazodicarboxylate (DIAD) followed by oxidation of the resulting sulfide with a catalytic amount of ammonium molybdate and hydrogen peroxide as described previously.[15]

For Julia-Kocienski Olefination, sulfone **32** was deprotonated with KHMDS in THF at -78 °C. Aldehyde **30** was then added and the reaction was warmed to 23 °C for 4 h furnish *trans*-olefin

33 as a single isomer in 89% yield. Reaction of **33** with TBAF in THF at 0 °C to 23 °C provided an alcohol which was oxidized with DMP in the presence of pyridine to furnish aldehyde **4** in 78 % yield over two steps.



Scheme 5: Reaction conditions: (a) $CrCl_2$, $NiCl_2$, DMF, 0 °C to 23 °C, 24 h (63% dr = 2 : 1); (b) (*R*)-(-)-MTPACl, Et_3N, DMAP, CH_2Cl_2, 0 °C to 23 °C, 2 h (80%); (c) (*S*)-(+)- MTPACl, Et_3N, DMAP, CH_2Cl_2, 0 °C to 23 °C, 2 h (80%).

Having vinyl iodides **17** and **22** in hand, we then explore NHK coupling reaction as shown in Scheme 5. NHK coupling reaction between vinyl iodide **17** and aldehyde **4** in DMF at 0 °C to 23 °C for 24 h furnished **34** as a major diastereomer (2:1) in 63% yield. To establish the absolute configuration at C8 stereogenic center, we converted major diastereomer **34** to its corresponding (*S*)-and (*R*)-MTPA esters **35** and **36** respectively. By using modified Mosher ester analysis[12] we assigned the absolute configuration at C8 center of major diastereomer. The ^{1}H NMR data for (*S*)- and (*R*)-MTPA esters **35** and **36** respectively were assigned by the analysis of ^{1}H-^{1}H COSY spectra. The experimental difference data ($\Delta\delta_{SR}$) were obtained by the comparison of ^{1}H chemical shifts of esters **35** and **36** respectively. Negative $\Delta\delta_{SR}$ values were detected for protons H-4, H-5, H_2-6 and H_2-23, while H_2-9 displayed positive $\Delta\delta_{SR}$ values. The observed sign pattern of the protons around C8 center suggested *R* configuration as shown in Figure **5.**

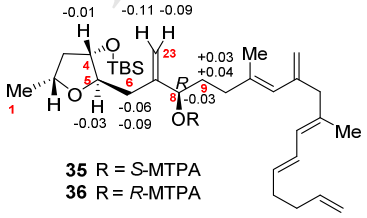
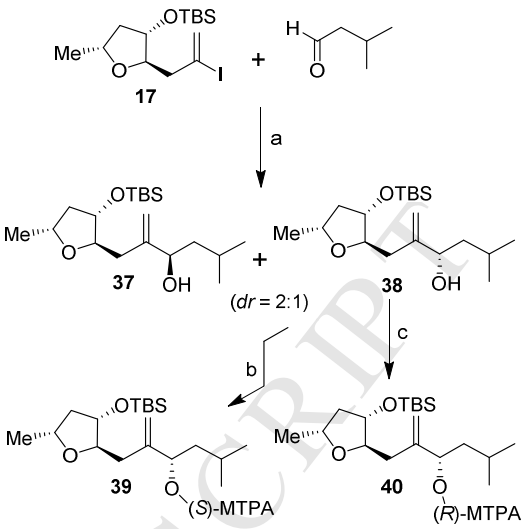


Figure 5: $\Delta\delta_{SR}$ values [$\Delta\delta_{SR}$ (in ppm) δ_s-δ_R] obtained for 8-(*S*) and (*R*)-MTPA esters **35** and **36** respectively



Scheme 6: Reaction conditions: (a) $CrCl_2$, $NiCl_2$, DMF, 0 °C, 24 h (94 % dr = 2 : 1); (b) (*R*)-(-)-MTPACl, Et_3N, DMAP, CH_2Cl_2, 0 °C to 23 °C, 4 h (80%); (c) (*S*)-(+)- MTPACl, Et_3N, DMAP, CH_2Cl_2, 0 °C to 23 °C, 4 h (80%).

As shown in Scheme 6, we have also carried out NHK coupling reaction between vinyl iodide **17** and isovaleraldehyde in DMF at 0 °C for 24 h. This has resulted alcohol **37** as a major diastereomer (2:1) in 94% combined yield. For assignment of stereochemistry of the alcohol, we converted minor diastereomer **38** to its corresponding (*S*)-and (*R*)-MTPA esters **39** and **40** respectively.[12] Applying the modified Mosher ester analysis as described for compounds **35** and **36**, we were also able to establish the absolute configuration at C8 stereogenic center as (*S*) (Figure 6).

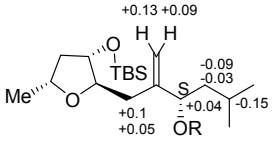
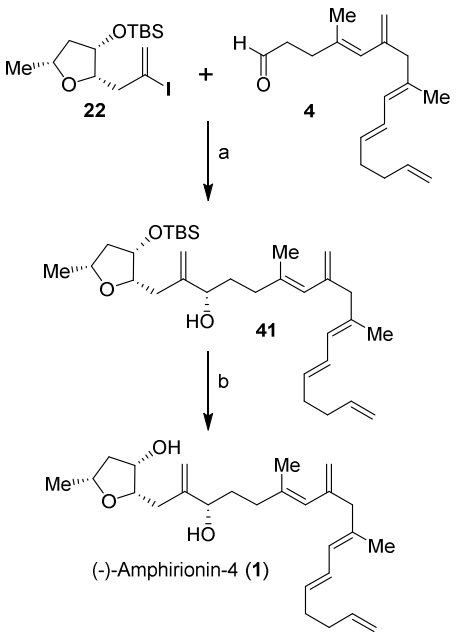


Figure 6: $\Delta\delta_{SR}$ values [$\Delta\delta_{SR}$ (in ppm) δ_s-δ_R] obtained for 8-(*S*) and (*R*)-MTPA esters **39** and **40** respectively

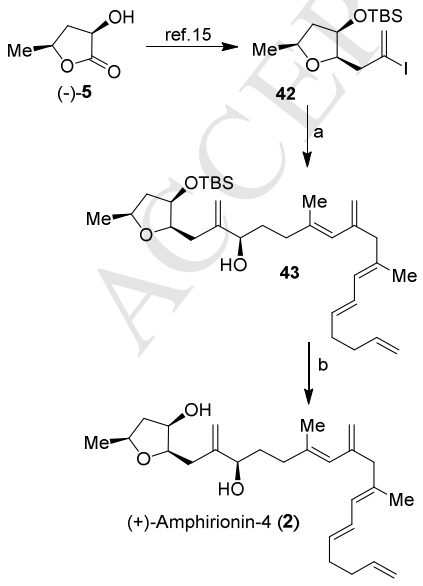
We performed NHK coupling reaction to synthesize (-)-amphirionin-4 (**1**) as outlined in Scheme 7. NHK coupling[16,17] between aldehyde **4** and vinyl iodide **22** in DMF at 0 °C to 23 °C for 24 h provided TBS protected amphirionin-4 as a major diastereomer in 60 % yield. The diastereoselectivity of this reaction was increased to (4:1)[13] in favor of the desired isomer **41** through strong 1,4-stereoinduction. Deprotection of the TBS-group with 70% HF, 30% pyridine in the presence of excess pyridine furnished (-)-amphirionin-4 (**1**) in excellent yield. The ^{1}H and ^{13}C NMR spectra of our synthetic (-)-amphirionin-4 (**1**) were in complete agreement with the natural amphirionin-4.[10] However, the specific rotation {$[\alpha]_D^{23}$ = -6 (*c* 0.1, $CHCl_3$)} was

opposite in sign to that reported for natural amphirionin-4.[10] This is consistent with the report of Britton and co-workers.[13]



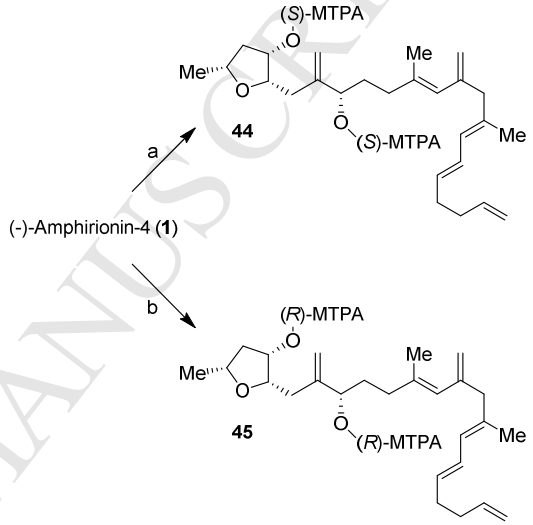
Scheme 7: Reaction conditions: (a) $CrCl_2$, $NiCl_2$, DMF, 0 °C to 23 °C, 24 h (60% dr = 4 : 1); (b) HF•py, THF, pyridine, 0 °C to 23 °C, 9 h (90%).

Our synthesis of (+)-amphirionin-4 is shown in Scheme 8. Optically active alcohol (-)-**5** was converted to vinyl iodide **42** as described previously.[15] Coupling of this vinyl iodide **42** with aldehyde **4** afforded TBS-protected derivative **43** in 65% yield as a mixture (4:1) of diasteromers. Removal of the TBS group by exposure to 70 % HF, 30% pyridine in the presence of the pyridine afforded (+)-amphirionin-4 (**2**). The ^1H and ^{13}C NMR spectra of synthetic (+)-amphirionin-4 (**2**) {$[\alpha]_D^{23}$ = + 6.4 (*c* 0.08, $CHCl_3$)} were in agreement with spectra reported for the natural amphirionin-4 structure.

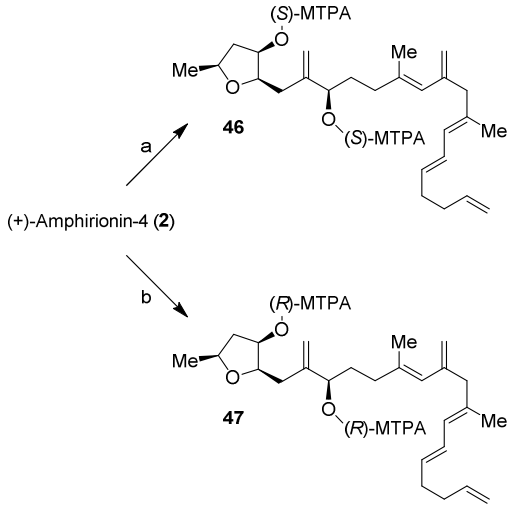


Scheme 8: Reaction conditions: (a) **42**, $CrCl_2$, $NiCl_2$, DMF, 0 °C to 23 °C, 24 h (65% dr = 4 : 1); (b) HF•py, THF, pyridine, 0 °C to 23 °C, 9 h (98%).

As mentioned earlier, natural amphirionin-4 showed a rather small specific rotation. Therefore, we planned further synthesis of the corresponding Mosher esters to elucidate the absolute stereochemistry of (-)-amphirionin-4 (**1**) and corroborate structure reported by Tusda and co-workers.[10] As shown in Schemes 9 and 10, we converted our synthetic (-)-amphirionin-4 (**1**) and (+)-amphirionin-4 (**2**) to their 4,8-*bis*-(*S*) and *bis*-(*R*)-MTPA esters.[41] The ^1H-NMR data recorded for 4,8-*bis*-(*S*) and *bis*-(*R*)-MTPA esters of (-)-amphirionin-4 (1) were identical to those reported by Tusda and co-workers,[10] thus supporting the absolute configuration of our synthetic (-)-amphirionin-4 (**1**).



Scheme 9 : Reaction conditions: (a) (*R*)-(-)-MTPACl, Et_3N, DMAP, CH_2Cl_2, 0 °C to 23 °C, 3 h (80%); (b) (*S*)-(+)- MTPACl, Et_3N, DMAP, CH_2Cl_2, 0 °C to 23 °C, 3 h (76%).



Scheme 10: Reaction conditions: (a) (*R*)-(-)- MTPACl, Et_3N, DMAP, CH_2Cl_2, 0 °C to 23 °C, 3 h (75%); (b) (*S*)-(+)- MTPACl, Et_3N, DMAP, CH_2Cl_2, 0 °C to 23 °C, 3 h (80%).

3. Conclusion

In summary, we have accomplished enantioselective syntheses of both enantiomers of amphirionin-4 in a convergent manner. The absolute configuration of (-)-amphirionin-4 and (+)-amphirionin-4 were established by formation of the respective Mosher ester and NMR studies. It turned out that the natural isomer is (-)-amphirionin-4. During isolation, amphirionin-4, was reported as (+)-amphirionin-4. The synthesis highlights enzyme-catalyzed optical resolution of *cis*-α-hydroxy-γ-butyrolactone with high enantiomeric purity. An oxocarbenium ion mediated alkylation provided a *cis*-allyl derivative with high diastereoselectivity. The synthesis also features the use of Stille coupling reactions to efficiently construct the polyene side chain and Nozaki-Hiyama-Kishi coupling to install the C8 allylic alcohol through 1,4-stereoinduction. The synthesis has been accomplished in a linear nine step sequence utilizing readily available racemic butyrolactone. The current synthesis will provide access to structural variants of amphirionin-4 for structure-activity relationship studies. Further work and investigation of biological studies are in progress.

4. Experimental section

All chemicals and reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. The following reaction solvents were distilled prior to use: Dichloromethane from calcium hydride, diethyl ether and tetrahydrofuran from Na/Benzophenone, methanol and ethanol from activated magnesium under argon. All reactions were carried out under an argon atmosphere in either flame or oven-dried (120 ^{o}C) glassware. TLC analysis was conducted using glass-backed Thin-Layer Silica Gel Chromatography Plates (60 Å, 250 µm thickness, F-254 indicator). Column chromatography was performed using 230-400 mesh, 60 Å pore diameter silica gel. ^{1}H, ^{13}C NMR, COSY and NOESY spectra were recorded at room temperature on a Bruker DRX-500. Chemical shifts (δ values) are reported in parts per million, and are referenced to the deuterated residual solvent peak. NMR data is reported as: δ value (chemical shift, J-value (Hz), integration, where s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet). Optical rotations were recorded on a Perkin Elmer 341 polarimeter. IR spectra were recorded on a Varian 2000 Infrared spectrophotometer and are reported as cm^{-1}. HRMS spectra were recorded at the Purdue University Department of Chemistry Mass Spectrometry Center.

3-Hydroxy-5-methyldihydrofuran-2(3*H*)-one (5): To a stirred solution of α-methylene-γ-valerolactone **6** (0.52 g, 4.64 mmol) in CH_2Cl_2 (5 mL) at -78 ^{o}C was bubbled a stream of ozone until a blue color persisted. The ozone stream was stopped and a stream of oxygen was bubbled through the reaction mixture to remove the excess ozone. After adding dimethyl sulfide (1.02 mL, 13.92 mmol), the reaction mixture was warmed to 23 ^{o}C and stirred for 4h. The reaction mixture was concentrated under reduced pressure and the crude product was purified by flash column chromatography (40% EtOAc in hexane) to give lactone.

To a stirred solution of above lactone in EtOAc (5 mL) was added 10% Pd/C (30 mg). The resulting solution was stirred at 23 ^{o}C under 1 atm H_2 gas over 24 h. Upon completion, the mixture was filtered through a plug of Celite and solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (50% EtOAc in hexane) to afford **5** (0.25 g, 46% over two steps). ^{1}H-NMR analysis of product showed a pair of diastereomers in 97:3 ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.57 (dd, *J* = 11.3, 8.4 Hz, 1H), 4.54 – 4.45 (m, 1H), 4.03 (brs, 1H), 2.70 (ddd, *J* = 12.6, 8.4, 5.1 Hz, 1H), 1.90 – 1.80 (m, 1H), 1.43 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 73.9, 69.1, 38.8, 20.9; IR: 3418, 2985, 2359, 1790, 1770, 1760, 1748, 1732, 1462, 1455, 1392, 1335, 1206, 1134, 1048, 1001, 946, 802, 711 cm^{-1}.

(3*S*,5*R*)-3-Hydroxy-5-methyldihydrofuran-2(3*H*)-one (+5) and (3*R*,5*S*)-5-methyl-2-oxotetrahydro furan-3-yl acetate (10): To a solution of alcohol **5** (1.58 g, 13.6 mmol) in THF (25 mL) were added vinyl acetate (22 mL, 239.4 mmol) and Lipase PS-30 (1.5 g) at 23 ^{o}C under argon atmosphere. The reaction mixture was stirred for 5 h (50:50 by ^{1}H-NMR). After this period, the reaction mixture was filtered through a plug of Celite and solvents were removed under reduced pressure. The crude product was purified via silica gel column chromatography (30% to 50% EtOAc in hexane) to yield alcohol (+)-**5** (740 mg, 47%). $[\alpha]_D^{20}$ +2.8 (*c* 1.35, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.58 (dd, *J* = 11.2, 8.4 Hz, 1H), 4.52 – 4.44 (m, 1H), 4.18 (brs, 1H), 2.69 (ddd, *J* = 12.9, 8.3, 5.1 Hz, 1H), 1.89 – 1.79 (m, 1H), 1.42 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 73.9, 69.0, 38.8, 20.9; IR: 3398, 2983, 2937, 2360, 1778, 1458, 1390, 1330, 1204, 1132, 1048, 1000, 946, 878, 801, 711, 623 cm^{-1}; LRMS-ESI (*m/z*): 139.2 $[M+Na]^+$.

Acetate **10** (1.07 g, 50 %). $[\alpha]_D^{20}$ -18.45 (*c* 0.92, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (dd, *J* = 10.9, 8.6 Hz, 1H), 4.59 – 4.47 (m, 1H), 2.76 (ddd, *J* = 12.7, 8.5, 5.3 Hz, 1H), 2.10 (s, 3H), 1.83 (dt, *J* = 12.5, 10.6 Hz, 1H), 1.43 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 169.8, 73.6, 69.0, 36.7, 21.0, 20.6; IR: 2984, 2939, 2878, 1789, 1747, 1451, 1377, 1233, 1199, 1126, 1103, 1054, 1021, 954, 939, 905, 815, 703 cm^{-1}; LRMS-ESI (*m/z*): 181.2 $[M+Na]^+$.

(3*R*,5*S*)-3-Hydroxy-5-methyldihydrofuran-2(3*H*)-one (-5): To a stirred solution of acetate **10** (1 g, 6.32 mmol) in MeOH (15 mL) was added aqueous NaOH (10 % solution, 15 mL) and the mixture was stirred at 23 ^{o}C for 12 h. After this period, the reaction mixture was acidified with 1N HCl solution and solvents were removed under reduced pressure. The aqueous layer was extracted with EtOAc (4×), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified via silica gel column chromatography (60% EtOAc in hexane) to afford alcohol (-)-**5** (600 mg, 82%) as a colorless oil. $[\alpha]_D^{20}$ -2.3 (*c* 1.0, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.56 (dd, *J* = 11.2, 8.4 Hz, 1H), 4.44 (tt, *J* = 11.4, 6.0 Hz, 2H), 2.65 (ddd, *J* = 13.0, 8.3, 5.1 Hz, 1H), 1.84 – 1.70 (m, 1H), 1.37 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 73.7, 68.9, 38.7, 20.8; IR: 3398, 2983, 2937, 2360, 1778, 1458, 1390, 1330, 1204, 1132, 1048, 1000, 946, 878, 801, 711, 623 cm^{-1}; LRMS-ESI (*m/z*): 139.2 $[M+Na]^+$.

(3*S*,5*R*)-3-(Benzyloxy)-5-methyldihydrofuran-2(3*H*)-one (11): To a stirred solution of Lactone (+)- **5** (270 mg, 2.33 mmol) in CH_2Cl_2 (6 mL) were added benzyl bromide (0.33 mL, 2.8 mmol) and silver oxide (0.8 g, 3.5 mmol) at 23 ^{o}C under argon atmosphere. The reaction mixture was stirred at reflux for 24 h. Upon completion, the reaction mixture was filtered through a plug of Celite and solvents were removed under reduced pressure. The crude product was purified by silica gel column chromatography (10% EtOAc in hexane) to give **11** (430 mg, 90%) as a colorless oil. $[\alpha]_D^{20}$ -63 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.29 (m, 5H), 4.98 (d, *J* = 11.8 Hz, 1H), 4.75 (d, *J* = 11.8 Hz, 1H), 4.49 – 4.41 (m, 1H), 4.26 (dd, *J* = 10.0, 8.2 Hz, 1H), 2.59 (ddd, *J* = 13.4, 8.2, 5.5 Hz, 1H), 1.88 (dt, *J* = 12.6, 9.8 Hz, 1H), 1.44 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 137.2, 128.7, 128.2, 74.1, 73.5, 72.4, 37.5, 21.3; IR: 2980, 2933, 1779, 1454, 1389, 1333, 1199, 1129, 1053, 947,

740, 698 cm^{-1}; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{14}O_3Na$, 229.0841; found 229.0837.

(3*R*,5*S*)-5-Methyl-2-oxotetrahydrofuran-3-yl 4-bromobenzoate (14): To a stirred solution of **(-)-5** (13 mg, 0.11 mmol) in dichloromethane (2 mL) were added DMAP (1.4 mg, 0.011 mmol), pyridine (0.036 mL, 0.44 mmol) and 4-bromobenzoyl Chloride (49 mg, 0.22 mmol) at 0 ^oC under argon atmosphere. The reaction mixture was warmed to 23 ^oC and stirred for 4 h. After this period, the reaction mixture was quenched by the addition of water and extracted with dichloromethane. The extracts were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (25% EtOAc in hexane) to afford **14** (30 mg, 90%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.89 (m, 2H), 7.62 – 7.56 (m, 2H), 5.71 (dd, *J* = 10.9, 8.6 Hz, 1H), 4.68 – 4.59 (m, 1H), 2.92 (ddd, *J* = 12.6, 8.5, 5.3 Hz, 1H), 2.00 (ddd, *J* = 12.6, 10.8, 10.1 Hz, 1H), 1.51 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 164.8, 132.0, 131.6, 129.1, 127.7, 73.7, 69.8, 36.9, 21.2; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{11}BrO_4Na$, 320.9739; found 320.9734.

(3S,5R)-3-((Tert-butyldimethylsilyl)oxy)-5-methyldihydrofuran-2(3H)-one (15): To a stirred solution of **(+)-5** (244 mg, 2.1 mmol) in dichloromethane (5 mL) were added 2,6-lutidine (0.74 mL, 6.3 mmol) and TBSOTf (0.73 mL, 3.15 mmol) at 0 ^oC under argon atmosphere. The reaction mixture was warmed to 23 ^oC and stirred for 1 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10 % EtOAc in hexane) to afford TBS protected lactone **15** (475 mg, 98%) as a white solid. $[\alpha]_D^{20}$ -16.4 (*c* 0.96, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.46 – 4.35 (m, 2H), 2.56 (ddd, *J* = 13.0, 8.1, 5.3 Hz, 1H), 1.77 (dt, *J* = 12.3, 10.3 Hz, 1H), 1.36 (d, *J* = 6.4 Hz, 3H), 0.89 – 0.82 (m, 9H), 0.09 (d, *J* = 17.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 72.7, 69.8, 40.0, 25.7, 21.1, 18.2, -4.7, -5.3; IR: 2929, 2858, 2770, 1462, 1394, 1254, 1210, 1155, 11229, 1050, 1011, 951, 937, 899, 842, 779, 696 cm^{-1}; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{11}H_{22}O_3SiNa$, 253.1236; found 253.1233.

Tert-butyldimethyl(((2R,3S,5R)-5-methyl-2-(prop-2-yn-1-yl)tetrahydrofuran-3-yl)oxy)silane (16): To a stirred solution of 1- (trimethylsilyl)propyne (0.3 mL, 2 mmol) in THF (3 mL) at -78 ^oC was added *n*-BuLi (1.6 M in Hexane, 1.28 mL, 2 mmol) under argon atmosphere. After 1h, to the above reaction mixture was added **15** (235 mg, 1 mmol) in THF (3 mL). The reaction mixture was stirred at -78 ^oC for 3 h. After this period, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc. The extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4) and concentrated under reduced pressure.

To the above crude in dichloromethane (4 mL) was added BF_3OEt_2 (0.19 mL, 1.5 mmol) at -78 ^oC under argon atmosphere followed by Et_3SiH (0.24 mL, 1.5 mmol). The reaction mixture was stirred at -78 ^oC for 2 h. After this period, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (5 % EtOAc in hexane) to afford TMS protected alkyne as a single isomer (232 mg, 70% over two steps).

To the above alkyne (174 mg, 0.53 mmol) in MeOH (4 mL) was added K_2CO_3 (110 mg, 0.8 mmol) at 0 ^oC under argon atmosphere. The reaction mixture was warmed to 23 ^oC and stirred for 3 h. After this period, solvent was removed under reduced pressure and extracted with dichloromethane. The extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (5 % EtOAc in hexane) to afford **16** (114 mg, 85 % yield). ^1H-NMR analysis of product showed a pair of diastereomers in 94:6 ratio. ^1H NMR (500 MHz, $CDCl_3$) δ 4.25 – 4.19 (m, 2H), 3.87 (q, *J* = 5.2 Hz, 1H), 2.37 (qdd, *J* = 16.9, 5.5, 2.7 Hz, 2H), 2.25 (dt, *J* = 12.8, 6.6 Hz, 1H), 1.96 (t, *J* = 2.6 Hz, 1H), 1.60 – 1.52 (m, 1H), 1.27 (d, *J* = 6.3 Hz, 3H), 0.86 (s, 9H), 0.05 (d, *J* = 3.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.6, 80.9, 75.8, 74.6, 70.0, 42.4, 25.8, 22.9, 22.2, 18.0, -4.6, -4.7; LRMS-ESI *(m/z)*: 277.5 $[M+Na]^+$.

Tert-butyl(((2R,3S,5R)-2-(2-iodoallyl)-5-methyltetrahydrofuran-3-yl)oxy)dimethylsilane (17): To a solution of alkyne **16** (10 mg, 0.04 mmol) in CH_2Cl_2 (1 mL) was added Et_3SiH (7.5 µL, 0.05 mmol) at 23 ^oC under argon atmosphere. After addition of $[Cp^*Ru(MeCN)_3]PF_6$ (1 mg) at 0 ^oC, the reaction mixture was warmed to 23 ^oC and stirred for 2 h. Upon completion, solvents were removed under reduced pressure and the crude product was passed through a plug of silica gel. To the crude product in HFIP (0.5 mL) was added 2,6-lutidine (6.4 µL, 0.06 mmol) at 23 ^oC under argon atmosphere. After addition of NIS (13 mg, 0.06 mmol) at 0 ^oC, the reaction mixture was stirred for 15 min. The reaction mixture was quenched by the addition of water (0.3 mL) and extracted with CH_2Cl_2. The extracts were washed with saturated aqueous $Na_2S_2O_3$, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (3% EtOAc in hexane) to afford vinyl iodide **17** (10.5 mg, 70 %); ^1H NMR (500 MHz, $CDCl_3$) δ 6.16 – 6.14 (m, 1H), 5.80 (s, 1H), 4.17 (q, *J* = 6.6 Hz, 1H), 4.04 (tt, *J* = 8.4, 4.7 Hz, 2H), 2.58 (dd, *J* = 14.8, 3.5 Hz, 1H), 2.51 (dd, *J* = 14.9, 7.0 Hz, 1H), 2.25 (dt, *J* = 12.6, 6.5 Hz, 1H), 1.62 – 1.56 (m, 1H), 1.30 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.07 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.6, 107.0, 83.2, 76.5, 74.1, 49.2, 42.5, 25.9, 22.3, 18.1, -4.4, -4.6; LRMS-ESI *(m/z)*: 383.3 $[M+H]^+$.

(((2R,3S,5R)-2-allyl-5-methyltetrahydrofuran-3-yl)oxy)(tert-butyl)dimethylsilane (18): To a stirred solution of **15** (75 mg, 0.33 mmol) in Et_2O (4 mL) at -78 ^oC was added allylmegnesium bromide (1.0 M in Et_2O, 0.4 mL, 0.39 mmol) under argon atmosphere. The reaction mixture was stirred at -78 ^oC for 2 h. After this period, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc. The extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was passed through a flash column to afford the mixture of isomers (66 mg, 75 %)

To the above mixture (66 mg, 0.24 mmol) in dichloromethane (2 mL) was added Et_3SiH (0.23 mL, 1.5 mmol) at -78 ^oC under argon atmosphere followed by BF_3OEt_2 (90 µL, 0.73 mmol). The reaction mixture was stirred at -78 ^oC for 2 h. After this period, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (7 % EtOAc in hexane) to afford **18** as a single isomer (47 mg, 75%). ^1H NMR (500 MHz, $CDCl_3$ δ 5.84 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.13 – 5.03 (m, 2H), 4.16 (h, *J* = 6.3 Hz, 1H), 4.04 – 3.98 (m, 1H), 3.85 – 3.79 (m, 1H), 2.34 – 2.27 (m, 1H), 2.27-2.17 (m, 2H), 1.57 – 1.50 (m, 1H), 1.28 (d, *J* = 6.2 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.0, 117.1, 83.8,

76.4, 73.8, 42.7, 37.9, 25.9, 22.29, 18.1, -4.4, -4.6. LRMS-ESI *(m/z)*: 279.5 $[M+Na]^+$.

(((2*S*,3*S*,5*R*)-2-Allyl-5-methyltetrahydrofuran-3-yl)oxy)(tert-butyl)dimethylsilane (20): To a stirred solution of the TBS protected lactone **15** (1 g, 4.34 mmol) in dichloromethane (10 mL) at -78 ^oC was added DIBAL-H (5.2 mL, 5.2 mmol) under argon atmosphere and stirred at the same temperature for 2 h. After this period, the reaction mixture was quenched by the addition of MeOH (3 mL) and warm to 23 ^oC. Then, Saturated aqueous solution of sodium potassium tartarate was added and stirred vigorously at 23 ^oC for 2 h until it forms white suspension. The suspension was filtered through a plug of Celite and solvents were removed under reduced pressure.

To a crude lactol were added DMAP (53 mg, 0.43 mmol), Et_3N (1.2 mL, 8.68 mmol) and Ac_2O (0.62 mL, 6.51 mmol) at 0 ^oC under argon atmosphere and the mixture was stirred for 2 h. Upon, completion, solvents were removed under reduced pressure and crude product was purified by silica gel column chromatography (15% EtOAc in hexane) to give acetate **19** (1.07 g, 10:1 diastereomeric ratio, 90 %) as a light yellow oil.

To a solution of acetate **19** (540 mg, 1.97 mmol) in dichloromethane (20 mL, 0.1 M) was added allyltrimethylsilane (1.25 mL, 7.88 mmol) at 23 ^oC under argon atmosphere and then cooled to -78 ^oC. After addition of $SnBr_4$ (1.04 g, 2.36 mmol), the reaction mixture was warmed to 23 ^oC over 2 h. After this period, the reaction mixture was quenched by the addition of saturated aqueous Na_2HPO_4, and extracted with dichloromethane. The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. NMR analysis of the unpurified curde product showed a pair of diastereomers **20** and **18** in an 10:1 ratio of 1,2-*cis:trans* diastereomers. The crude product was purified by silica gel column chromatography (70% CH_2Cl_2 in hexane) to give major diastereomer **20** (360 mg, 71%) as a colorless oil. $[\alpha]_D^{20}$ +17 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.11 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.07 – 4.99 (m, 1H), 4.22 (dq, *J* = 6.6, 3.9, 3.5 Hz, 1H), 3.97-3.91 (m, 1H), 3.63 (ddd, *J* = 7.3, 5.9, 4.2 Hz, 1H), 2.43-2.33 (m, 2H), 2.28 (ddd, *J* = 13.6, 7.5, 6.3 Hz, 1H), 1.48 (ddd, *J* = 13.1, 6.6, 2.9 Hz, 1H), 1.30 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.05 (d, *J* = 4.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 116.5, 83.2, 73.7, 73.4, 43.5, 34.4, 25.9, 22.3, 18.2, -4.3, -4.9; IR: 3077, 2957, 2931, 2897, 2858, 1642, 1472, 1463, 1438, 1368, 1255, 1091, 956, 912, 836,774 cm^{-1}; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{14}H_{28}O_2SiNa$, 279.1756; found 279.1752.

***tert*-Butyldimethyl(((2*S*,3*S*,5*R*)-5-methyl-2-(prop-2-yn-1-yl)tetrahydrofuran-3-yl)oxy)silane (21):** To a stirred solution of **20** (500 mg, 1.95 mmol) in acetone:water (10:1, 16.5 mL) were added 2,6-lutidine (0.45 mL, 3.9 mmol), NMO (340 mg, 2.93 mmol) and OsO_4 (0.05 mL, 0.039 mmol) at 23 ^oC. The reaction mixture was stirred for 24 h as monitor by TLC and then $PhI(OAc)_2$ (940 mg, 2.93 mmol) was added. After stirring for 4h, the reaction mixture was quenched by the addition of Saturated aqueous $Na_2S_2O_3$ and extracted with EtOAc. The extracts were washed with saturated aqueous $CuSO_4$, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10% EtOAc in hexane) to afford the aldehyde (402 mg, 80%) as a colorless oil. $[\alpha]_D^{20}$ +30.6 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.82 (t, *J* = 1.6 Hz, 1H), 4.36 (dt, *J* = 6.4, 4.2 Hz, 1H), 4.16 – 4.10 (m, 1H), 3.98-3.92 (m, 1H), 2.77 – 2.67 (m, 2H), 2.32 (dt, *J* = 13.3, 6.8 Hz, 1H), 1.48 (ddd, *J* = 13.0, 7.3, 3.6 Hz, 1H), 1.29 (d, *J* = 6.2 Hz, 3H), 0.86 (s, 9H), 0.02 (d, *J* = 18.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4, 78.2, 74.1, 73.5, 44.4, 43.5, 25.9, 21.9, 18.1, -4.5, -5.0; IR: 3431, 2956, 2931, 2858, 1726, 1372, 1256, 1089, 837, 776 cm^{-1}; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{26}O_3SiNa$, 281.1549; found 281.1545.

To a solution of dimethyl(1-diazo-2-oxopropyl)phosphonate (0.11 mL, 0.72 mmol) in THF (2 mL) at -78 ^oC was added MeONa (3.0 M in MeOH, 0.24 mL, 0.72 mmol) under argon atmosphere and stirred for 20 min. To the resulting yellow solution above aldehyde (47 mg, 0.18 mmol) in THF (2 mL) was added and the reaction mixture was stirred for 1h at -40 ^oC. After this period the reaction mixture was warmed to 23 ^oC and quenched by the addition of saturated aqueous NH_4Cl (2 mL). At this temperature the reaction mixture was vigorously stirred for 10 min and the layers were seperated. The aqueous layer was extrated with EtOAc, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (5% EtOAc in hexane) to give alkyne **21** (33 mg, 70%) as a colorless oil. $[\alpha]_D^{20}$ +29.8 (*c* 0.55, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.30 (dt, *J* = 6.3, 3.8 Hz, 1H), 4.07 – 3.99 (m, 1H), 3.83 (td, *J* = 6.8, 4.1 Hz, 1H), 2.57 – 2.47 (m, 2H), 2.29 (ddd, *J* = 13.5, 7.6, 6.1 Hz, 1H), 1.96 (t, *J* = 2.7 Hz, 1H), 1.53 (ddd, *J* = 13.1, 6.1, 2.7 Hz, 1H), 1.31 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.08 (d, *J* = 5.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 82.1, 81.9, 74.3, 72.9, 69.3, 43.0, 25.9, 22.4, 19.9, 18.2, -4.4, -5.0; IR: 3314, 2929, 2856, 2358, 1472, 1253, 1083, 978, 837, 776 cm^{-1}; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{14}H_{26}O_2SiNa$, 277.1600; found 277.1594.

tert-Butyl(((2*S*,3*S*,5*R*)-2-(2-iodoallyl)-5-methyl tetrahydrofuran-3-yl)oxy)dimethylsilane (22): The vinyl iodide (**22**) was obtained by following the procedure outlined for compound **17** (36 mg, 80 % yield). $[\alpha]_D^{20}$ +0.48 (*c* 0.42, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.20 – 6.14 (m, 1H), 5.79 (s, 1H), 4.28 (dt, *J* = 6.2, 4.1 Hz, 1H), 3.99 (dq, *J* = 12.9, 6.3 Hz, 1H), 3.91 (dt, *J* = 7.6, 4.5 Hz, 1H), 2.72-2.63 (m, 2H), 2.35 – 2.28 (m, 1H), 1.50 (dq, *J* = 10.0, 3.4 Hz, 1H), 1.30 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.06 (d, *J* = 5.2 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 127.4, 108.7, 81.4, 73.9, 73.5, 46.1, 43.4, 26.0, 22.4, 18.2, -4.3, -4.8; IR: 2950, 2929, 2840, 2360, 2342, 1654, 1560, 1458, 1110, 668 cm^{-1}; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{14}H_{27}IO_2SiNa$, 405.0723; found 405.0718.

(*R*,6*E*,10*E*,12*E*)-2-(((2*R*,3*S*,5*R*)-3-((Tert-butyldimethylsilyl)oxy)-5-methyltetrahydrofuran-2-yl)methyl)-6,10-dimethyl-8-methyleneheptadeca-1,6,10,12,16-pentaen-3-ol (34): To a degassed (for 15 min with an argon purge) solution of vinyl iodide **17** (18 mg, 0.047 mmol) and aldehyde **4**[15] (13.4 mg, 0.052 mmol) in DMF (1.0 mL) were added $NiCl_2$ (0.6 mg, 0.0047 mmol) and $CrCl_2$ (29 mg, 0.24 mmol) at 0 ^oC. The reaction mixture was warmed to 23 ^oC and stirred for 24 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc. The extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give the curde product in 2:1 mixture of diastereomers. The major diastereomer was purified by silica gel column chromatography (10% EtOAc in hexane) to give **34** (10 mg, 42 %) as a colorless oil. $[\alpha]_D^{20}$ +42 (*c* 0.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.25 (dd, *J* = 15.1, 10.8 Hz, 1H), 5.87 – 5.78 (m, 2H), 5.62 – 5.54 (m, 2H), 5.06 – 4.92 (m, 5H), 4.86 (s, 1H), 4.24 – 4.17 (m, 1H), 4.04 (t, *J* = 6.6 Hz, 1H), 3.97 (q, *J* = 6.9 Hz, 1H), 3.81 (ddd, *J* = 9.4, 6.0, 3.3 Hz, 2H), 2.77 (s, 2H), 2.33 – 2.25 (m, 2H), 2.21 – 2.14 (m, 4H), 2.09 (td, *J* = 9.9, 9.4, 5.0 Hz, 1H), 2.00 (ddd, *J* = 14.4, 9.9, 5.8 Hz, 1H), 1.79 – 1.77 (m, 3H), 1.68 (s, 3H), 1.59 – 1.55 (m, 3H), 1.54 (d, *J* = 7.6 Hz, 1H), 1.27 (d, *J* = 6.3 Hz, 3H), 0.90 (s, 9H), 0.07 (d, *J* = 3.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 143.9, 138.5, 138.3, 134.6, 132.0, 127.2, 126.5, 125.8, 114.8, 114.6, 114.5, 84.9, 75.2, 73.7, 48.4, 42.5, 36.8, 35.4, 34.5, 33.9, 29.9, 25.9, 22.2, 18.2, 18.1, 16.4, -4.3, -4.6. LRMS-ESI *(m/z)*: 537.6 $[M+Na]^+$.

8-(*S*)-MTPA ester of 34 (35): To a stirred solution of **34** (3 mg) in CH_2Cl_2 (1.0 mL) were added DMAP (0.07 mg), triethylamine (10 µL) and (*R*)-(-)-MTPACl (2.2 mg) at 0 ^oC under argon

atmosphere. The reaction mixture was warmed to 23 °C and stirred for 2h. Upon completion, the reaction mixture was purified by silica gel column chromatography (5% EtOAc in hexane) to give **35** (3.4 mg, 80%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.50 (m, 2H), 7.38 (dd, *J* = 5.2, 1.8 Hz, 3H), 6.29 – 6.21 (m, 1H), 5.84 (dq, *J* = 9.7, 3.0 Hz, 1H), 5.80 (dd, *J* = 10.7, 4.3 Hz, 1H), 5.62 – 5.55 (m, 1H), 5.51 (s, 1H), 5.40 (dd, *J* = 7.3, 5.0 Hz, 1H), 5.04 (s, 2H), 5.00 (d, *J* = 4.5 Hz, 2H), 4.98 – 4.94 (m, 1H), 4.86 (s, 1H), 4.19 – 4.14 (m, 1H), 3.95 (q, *J* = 6.6 Hz, 1H), 3.88 (ddd, *J* = 8.1, 5.4, 3.9 Hz, 1H), 3.56 (s, 3H), 2.75 (s, 2H), 2.29 – 2.26 (m, 1H), 2.25 (d, *J* = 4.8 Hz, 1H), 2.22 (d, *J* = 6.7 Hz, 1H), 2.20 – 2.15 (m, 3H), 2.10 (d, *J* = 8.0 Hz, 1H), 2.09 – 2.06 (m, 1H), 2.03 (dd, *J* = 11.1, 4.7 Hz, 1H), 1.88-1.8 (m, 2H), 1.75 (d, *J* = 1.0 Hz, 3H), 1.68 (s, 3H), 1.53-1.48 (m, 1H), 1.27-1.25 (m, 3H), 0.87 (s, 9H), 0.04 (d, *J* = 6.4 Hz, 6H). LRMS-ESI *(m/z)*: 753.7 $[M+Na]^+$.

8-(*R*)-MTPA ester of 34 (36): 34 (3 mg) was treated with (*S*)-(+)-MTPACl (2.2 mg) by following the above esterification procedure to afford **36** (3.3 mg, 80%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.51 (m, 2H), 7.38 (dd, *J* = 5.3, 1.9 Hz, 3H), 6.29 – 6.22 (m, 1H), 5.87 – 5.82 (m, 1H), 5.80 (dd, *J* = 11.1, 5.1 Hz, 1H), 5.63 – 5.55 (m, 1H), 5.45 (s, 1H), 5.44 – 5.42 (m, 1H), 5.15 (s, 1H), 5.14 – 5.11 (m, 1H), 5.05 – 5.00 (m, 1H), 4.99 – 4.98 (m, 1H), 4.98 – 4.95 (m, 1H), 4.84 (s, 1H), 4.19 – 4.14 (m, 1H), 3.96 (q, *J* = 6.6 Hz, 1H), 3.91 (ddd, *J* = 9.2, 5.5, 3.9 Hz, 1H), 3.54 (s, 3H), 2.75 (s, 2H), 2.31 (dd, *J* = 15.6, 3.6 Hz, 1H), 2.28 – 2.22 (m, 1H), 2.21 – 2.13 (m, 5H), 1.91 (dt, *J* = 8.9, 5.9 Hz, 2H), 1.83 – 1.75 (m, 2H), 1.71 (d, *J* = 1.1 Hz, 3H), 1.68 (s, 3H), 1.55 – 1.49 (m, 1H), 1.27-1.26 (m, 3H), 0.88 (s, 9H), 0.04 (d, *J* = 6.1 Hz, 6H); LRMS-ESI *(m/z)*: 753.7 $[M+Na]^+$.

(*R*)-2-(((2*R*,3*S*,5*R*)-3-((Tert-butyldimethylsilyl)oxy)-5-methyltetrahydrofuran-2-yl)methyl)-5-methylhex-1-en-3-ol (37): To a degassed (for 15 min with an argon purge) solution of vinyl iodide **17** (20 mg, 0.05 mmol) and isovaleraldehyde (11 µL, 0.1 mmol) in DMF (1.0 mL) were added $NiCl_2$ (0.7 mg, 0.005 mmol) and $CrCl_2$ (32 mg, 0.26 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 24 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc. The extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give the curde product in 2:1 mixture of diastereomers. The major diastereomer was purified by silica gel column chromatography (10% EtOAc in pentane) to give **37** (12 mg, 67 %)as a light yellow oil. $[\alpha]_D^{20}$ +50.7 (*c* 0.38, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.93 (s, 1H), 4.21 (dt, *J* = 7.9, 6.3 Hz, 1H), 4.18 – 4.13 (m, 1H), 3.97 (q, *J* = 7.0 Hz, 1H), 3.81 (ddd, *J* = 9.5, 6.0, 3.3 Hz, 1H), 3.70 (s, 1H), 2.33 – 2.18 (m, 3H), 1.68 (dp, *J* = 13.3, 6.7 Hz, 1H), 1.58 – 1.47 (m, 2H), 1.32 – 1.28 (m, 1H), 1.27 (d, *J* = 6.2 Hz, 3H), 0.93 – 0.90 (m, 6H), 0.89 (s, 9H), 0.07 (d, *J* = 4.1 Hz, 6H): ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 114.0, 84.9, 73.7, 45.5, 42.6, 35.3, 25.9, 24.7, 23.1, 22.6, 22.2, 18.1, -4.3, -4.6. LRMS-ESI *(m/z)*: 365.3 $[M+Na]^+$.

8-(*S*)-MTPA ester of 38 (39): To a stirred solution of **38** (2 mg) in CH_2Cl_2 (1.0 mL) were added DMAP (0.07 mg), triethylamine (10 µL) and (*R*)-(-)-MTPACl (2.2 mg) at 0 °C under argon atmosphere. The reaction mixture was warmed to 23 °C and stirred for 4h. Upon completion, the reaction mixture was purified by silica gel column chromatography (5% EtOAc in hexane) to give **39** (2.6 mg, 80%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.49 (m, 2H), 7.40 – 7.36 (m, 3H), 5.56 (dd, *J* = 8.7, 4.7 Hz, 1H), 5.22 (s, 1H), 5.19 – 5.17 (m, 1H), 4.16 (h, *J* = 6.3 Hz, 1H), 3.94 (pd, *J* = 5.2, 1.5 Hz, 2H), 3.54 – 3.52 (m, 3H), 2.37 – 2.28 (m, 1H), 2.28 – 2.21 (m, 1H), 2.17 – 2.09 (m, 1H), 1.66 – 1.62 (m, 1H), 1.55 – 1.50 (m, 1H), 1.47 – 1.42 (m, 2H), 1.27 (d, *J* = 6.2 Hz, 3H), 0.90 – 0.87 (m, 6H), 0.87 (s, 9H), 0.03 (d, *J* = 9.0 Hz, 6H). LRMS-ESI *(m/z)*: 581.6 $[M+Na]^+$.

8-(*R*)-MTPA ester of 38 (40): 38 (2 mg) was treated with (*S*)-(+)-MTPACl (2.2 mg) by following the above esterification procedure to afford **40** (2.6 mg, 80%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 2H), 7.4 – 7.36 (m, 3H), 5.52 (dd, *J* = 8.4, 5.3 Hz, 1H), 5.11 – 5.08 (m, 2H), 4.12 (p, *J* = 6.5 Hz, 1H), 3.94 – 3.88 (m, 2H), 3.55 – 3.51 (m, 3H), 2.27 – 2.17 (m, 2H), 2.12 – 2.04 (m, 1H), 1.7 – 1.66 (m, 1H), 1.63 – 1.57 (m, 1H), 1.55 – 1.52 (m, 1H), 1.51 – 1.48 (m, 1H), 1.27 – 1.25 (m, 3H), 0.92 (t, *J* = 6.4 Hz, 6H), 0.88 (s, 9H), 0.04 (d, *J* = 5.1 Hz, 6H). LRMS-ESI *(m/z)*: 581.5 $[M+Na]^+$.

(*S*,6*E*,10*E*,12*E*)-2-(((2*S*,3*S*,5*R*)-3-((Tert-butyldimethylsilyl)oxy)-5-methyltetrahydrofuran-2-yl) methyl)-6,10-dimethyl-8-methyleneheptadeca-1,6,10,12,16-pentaen-3-ol (41): To a degassed (for 15 min with an argon purge) solution of vinyl iodide **22** (4 mg, 0.01 mmol) and aldehyde **4**[15] (3 mg, 0.01 mmol) in DMF (0.5 mL) were added $NiCl_2$ (0.14 mg, 0.001 mmol) and $CrCl_2$ (6 mg, 0.05 mmol) at 0 °C. The reaction mixture was warmed to 23 °C and stirred for 24 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl and extracted with EtOAc. The extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give the curde product in 4:1 mixture of diastereomers. The major diastereomer was purified by silica gel column chromatography (10% EtOAc in Pentane) to give **41** (3 mg) as a colorless oil. $[\alpha]_D^{20}$ -8.7 (*c* 0.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25 (dd, *J* = 15.1, 10.8 Hz, 1H), 5.87-5.79 (m, 2H), 5.62 – 5.52 (m, 2H), 5.13 – 4.91 (m, 5H), 4.87 (brs, 1H), 4.29 – 4.25 (m, 1H), 4.00 (ddt, *J* = 23.4, 12.7, 6.8 Hz, 3H), 3.74 (ddd, *J* = 10.2, 4.4, 2.8 Hz, 1H), 2.77 (brs, 2H), 2.51 (dd, *J* = 14.5, 10.3 Hz, 1H), 2.32-2.26 (m, 1H), 2.25-2.11 (m, 5H), 2.1-2.06 (m, 1H), 2.03-1.97 (m, 1H), 1.83-1.75(m, 3H), 1.74 – 1.70 (m, 1H), 1.69 (brs, 3H), 1.62 – 1.58 (m, 1H), 1.55 (dt, *J* = 6.5, 3.3 Hz, 1H), 1.35 – 1.29 (d, *J* = 6.2 Hz, 3H), 0.91 (s, 9H), 0.07 (d, *J* = 2.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 143.9, 138.5, 138.4, 134.6, 132.0, 127.2, 126.5, 125.8, 114.8, 114.5, 114.2, 84.4, 75.5, 74.3, 73.9, 48.4, 43.2, 36.9, 34.7, 33.9, 32.5, 32.0, 25.9, 22.2, 18.3, 18.1, 16.4, -4.4, -4.9; IR: 3400, 2930, 2857, 2360, 2343, 1256, 1067, 836, 775, 668 cm^{-1}; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{32}H_{54}O_3SiNa$, 537.3740; found 537.3734.

(-)-Amphirionin-4 (1): To a solution of **41** (3 mg, 0.006 mmol) in THF/pyridine (0.4 mL/0.6 mL) in a plastic vessel was added HF•py complex (0.3 mL) at 0 °C under argon atmosphere. The reaction mixture was warmed to 23 °C and stirred for 9 h. Upon completion, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ at 0 °C and stirred for 15 min at 23 °C. The mixture was extracted with EtOAc (×3) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (40% EtOAc in Hexane) to give (-)-amphirionin-4 (**1**) (2.1 mg, 90%) as a colorless oil. $[\alpha]_D^{20}$ -6 (*c* 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 6.34 (dd, *J* = 15.0, 10.8 Hz, 1H), 5.98 (brd, *J* = 10.8 Hz, 1H), 5.81 (brs, 1H), 5.76 (ddd, *J* = 17.0, 6.4, 3.8 Hz, 1H), 5.58 (brdt, *J* = 14.4, 6.7 Hz, 1H), 5.12 – 5.08 (m, 1H), 5.06 (brs, 1H), 5.05 – 5.01 (m, 1H), 5.01 – 5.00 (m, 1H), 4.99 – 4.96 (m, 1H), 4.92 (brs, 1H), 4.15 – 4.10 (m, 1H), 3.77 (dt, *J* = 6.2, 3.5 Hz, 1H), 3.61 – 3.56 (m, 1H), 3.48 (dt, *J* = 8.6, 4.4 Hz, 1H), 2.83 (brs, 2H), 2.63 (dd, *J* = 14.5, 8.8 Hz, 1H), 2.29 – 2.24 (m, 1H), 2.22 (dd, *J* = 8.6, 5.6 Hz, 1H), 2.20 – 2.13 (m, 1H), 2.13 – 2.09 (m, 2H), 2.09 – 2.03 (m, 2H), 1.90 – 1.87 (m, 1H), 1.85 (dd, *J* = 6.0, 3.3 Hz, 1H), 1.84 – 1.79 (m, 3H), 1.77 – 1.72 (m, 1H), 1.72 – 1.67 (m, 3H), 1.19 (ddd, *J* = 13.5, 6.7, 2.4 Hz, 1H), 1.14 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 150.1, 144.3, 138.7, 138.5, 134.2, 132.1, 127.5, 127.4, 126.3, 114.9, 114.8, 112.8, 84.2, 75.2, 73.9, 73.4, 48.8, 43.2, 37.2, 35.0, 34.2, 32.8, 31.6, 22.0, 18.2, 16.4; IR: 3394, 2925,

2853, 2359, 2340, 1560, 1458, 1377, 1076, 908, 800 cm^{-1}; HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{26}H_{40}O_3Na$, 423.2875; found 423.2867.

4,8-Bis-(*S*)-MTPA ester of (-)-amphirionin-4 (1) (44): To a stirred solution of (-)-amphirionin-4 (**1**) (1 mg) in CH_2Cl_2 (0.3 mL) were added DMAP (0.03 mg), triethylamine (10 µL) and (*R*)-(-)-MTPACl (2 mg) at 0 ^oC under argon atmosphere. The reaction mixture was warmed to 23 ^oC and stirred for 3h. Upon completion, the reaction mixture was purified by silica gel column chromatography (7% EtOAc in hexane) to give **44** (1.6 mg, 80%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.49 (m, 4H), 7.39 – 7.36 (m, 6H), 6.26 (dd, *J* = 15.1, 10.8 Hz, 1H), 5.86 – 5.77 (m, 2H), 5.59 (dt, *J* = 14.1, 6.5 Hz, 1H), 5.44 (brs, 1H), 5.36 – 5.33 (m, 1H), 5.32 (dd, *J* = 5.1, 2.7 Hz, 1H), 5.17 (s, 1H), 5.04 (s, 1H), 5.01 (d, *J* = 5.5 Hz, 1H), 5.00 (s, 1H), 4.98 – 4.94 (m, 1H), 4.85 (s, 1H), 3.96 – 3.91 (m, 1H), 3.91 – 3.87 (m, 1H), 3.51 (s, 3H), 3.49 (s, 3H), 2.75 (s, 2H), 2.51 (ddd, *J* = 14.5, 7.9, 6.6 Hz, 1H), 2.40 – 2.33 (m, 1H), 2.27 (dt, *J* = 16.0, 6.5 Hz, 2H), 2.23 – 2.10 (m, 5H), 1.87-1.85 (m, 1H), 1.74-1.70 (m, 1H), 1.69 (d, *J* = 1.1 Hz, 3H), 1.68 (brs, 3H), 1.49 – 1.44 (m, 1H), 1.10 (d, *J* = 6.2 Hz, 3H); HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{46}H_{54}F_6O_7Na$, 855.3672; found 855.3679.

4,8-Bis-(*R*)-MTPA ester of (-)-amphirionin-4 (1) (45): (-)-amphirionin-4 (**1**) (0.8 mg) was treated with (*S*)-(+)-MTPACl (2 mg) by following the above esterification procedure to afford **45** (1.3 mg, 76%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 4H), 7.40-7.37 (m, 6H), 6.26 (dd, *J* = 15.1, 10.8 Hz, 1H), 5.87-5.75 (m, 2H), 5.64 – 5.54 (m, 1H), 5.49 (s, 1H), 5.26-5.22 (m, 1H), 5.22 – 5.20 (m, 1H), 5.04 – 5.02 (m, 1H), 5.02 – 5.00 (m, 1H), 4.98 – 4.95 (m, 1H), 4.95 (s, 1H), 4.87 (s, 1H), 3.94-3.89 (m, 1H), 3.83 – 3.78 (m, 1H), 3.54 (s, 3H), 3.53 (s, 3H), 2.76 (s, 2H), 2.51 (dt, *J* = 14.5, 7.2 Hz, 1H), 2.28 – 2.11 (m, 8H), 1.97 – 1.94 (m, 1H), 1.80-1.76 (m, 1H), 1.75 – 1.73 (m, 3H), 1.68 (s, 3H), 1.50 (dd, *J* = 6.7, 1.8 Hz, 1H), 1.21 (d, *J* = 6.1 Hz, 3H); HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{46}H_{54}F_6O_7Na$, 855.3672; found 855.3664.

4,8-Bis-(*S*)-MTPA ester of (+)-amphirionin-4 (2) (46): (+)-amphirionin-4 (**2**) (1 mg) was treated with (*R*)-(-)-MTPACl (2 mg) by following the above esterification procedure to afford **46** (1.5 mg, 75%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 4H), 7.40-7.37 (m, 6H), 6.26 (dd, *J* = 15.1, 10.8 Hz, 1H), 5.86-5.77(m, 2H), 5.59 (dt, *J* = 15.0, 6.7 Hz, 1H), 5.49 (s, 1H), 5.25-5.22 (m, 1H), 5.22 – 5.19 (m, 1H), 5.05 – 5.03 (m, 1H), 5.02 – 5.00 (m, 1H), 4.98 – 4.96 (m, 1H), 4.95 (s, 1H), 4.87 (s, 1H), 3.94 – 3.89 (m, 1H), 3.83 – 3.78 (m, 1H), 3.54 (s, 3H), 3.53 (s, 3H), 2.76 (s, 2H), 2.51 (dt, *J* = 14.4, 7.2 Hz, 1H), 2.32 – 2.10 (m, 8H), 1.98 – 1.93 (m, 1H), 1.81 – 1.75 (m, 1H), 1.75 – 1.73 (m, 3H), 1.68 (s, 3H), 1.50 (dd, *J* = 6.8, 1.8 Hz, 1H), 1.22 (s, 3H); HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{46}H_{54}F_6O_7Na$, 855.3672; found 855.3666.

4,8-Bis-(*R*)-MTPA ester of (+)-amphirionin-4 (2) (47): (+)-Amphirionin-4 (**2**) (1.2 mg) was treated with (*S*)-(+)-MTPACl (3 mg) by following the above esterification procedure to afford **47** (2 mg, 80%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.49 (m, 4H), 7.40 – 7.37 (m, 6H), 6.26 (dd, *J* = 15.1, 10.9 Hz, 1H), 5.87 – 5.78 (m, 2H), 5.59 (dt, *J* = 14.4, 6.5 Hz, 1H), 5.44 (s, 1H), 5.36 – 5.33 (m, 1H), 5.33 – 5.31 (m, 1H), 5.17 (s, 1H), 5.05-4.99 (m, 3H), 4.98 – 4.94 (m, 1H), 4.85 (s, 1H), 3.95 – 3.91 (m, 1H), 3.90-3.87 (m, 1H), 3.51 (s, 3H), 3.49 (s, 3H), 2.75 (s, 2H), 2.54 – 2.47 (m, 1H), 2.40 – 2.33 (m, 1H), 2.28 (d, *J* = 4.7 Hz, 1H), 2.26 – 2.05 (m, 6H), 1.89-1.85 (m, 1H), 1.77-1.72 (m, 1H), 1.70 – 1.69 (m, 3H), 1.68 (s, 3H), 1.49 – 1.44 (m, 1H), 1.10 (d, *J* = 6.2 Hz, 3H). HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_{46}H_{54}F_6O_7Na$, 855.3672; found 855.3663.

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Supplementary Material

Supporting Information available: Crystallographic data Collection, Refinement Statistics and NMR spectra of all new compounds are available.

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