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1 Graphical Abstract

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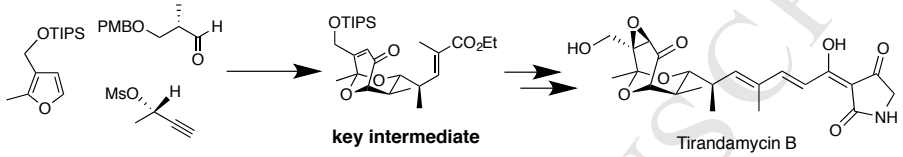

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ABSTRACT

A formal synthesis of tirandamycin B is described. The key intermediate is synthesised by Marshall allenyl zinc method, litiofuran coupling, and Achmatowicz reaction to construct the bicyclic core of tirandamycin B.

1. Introduction

In 2011, Shen et al. reported the isolation of tirandamycins from *Streptomyces* species,[1] among which tirandamycin B (**1**) was shown to exhibit potent inhibition activity toward the tRNA synthetase of the parasite *Brugia malayi*. This parasite causes lymphatic filariasis, a serious neglected tropical disease (NTD) affecting over 200 million people. Low concentrations of tirandamycin B efficiently kill the adult worm, and thus this natural product holds promise as a lead scaffold for drugs to combat lymphatic filariasis. The biological activities and its molecular architecture (involving a bicyclic core, triene, and tetramic acid) make **1** an attractive synthetic target. The first total synthesis of racemic **1** was reported by DeShong in 1990 [2a] followed by Miyashita's formal synthesis of the antipode of **1** in 1996.[2b] In 2016, Hatakeyama reported the enantioselective total synthesis of **1** in its natural form.[2c] In this paper, we report a formal synthesis of **1** based on the addition of a chiral allenyl zinc species to aldehyde **8**.

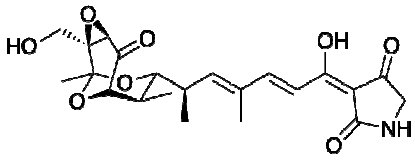

Figure 1. Tirandamycin B

2. Results and discussion

Our synthetic strategy is shown in Scheme 1. Tirandamycin B (**1**) can be synthesized by coupling **2** and **3**, developed previously.[2] Bicyclic compound **3** can be assembled by Achmatowicz reaction from furan derivative **4,** which is synthesized by cross-metathesis [3] between **5** and **6**. Intermediate **6**, possessing four stereocenters, can be synthesized from **7**, **8** and **9** using the Marshall method [4,5] and lithiofuran coupling. Marshall method is convenient for the construction of the two stereocenters at the same time.

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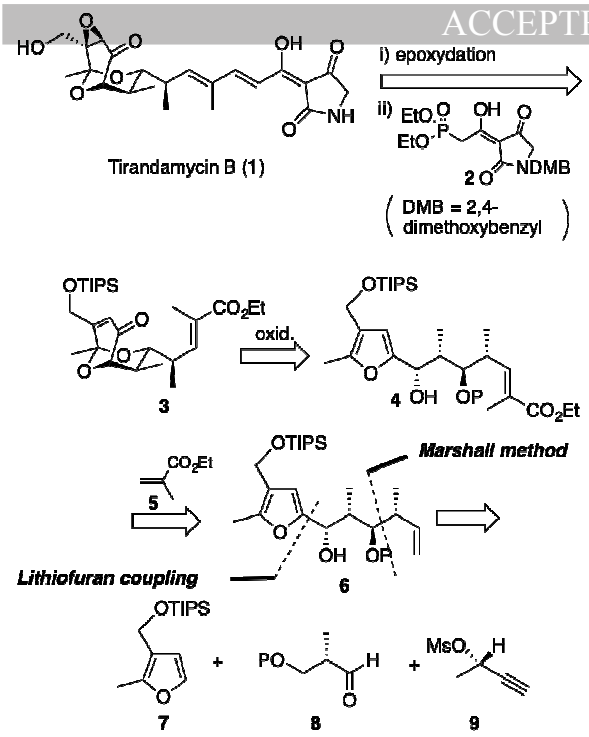
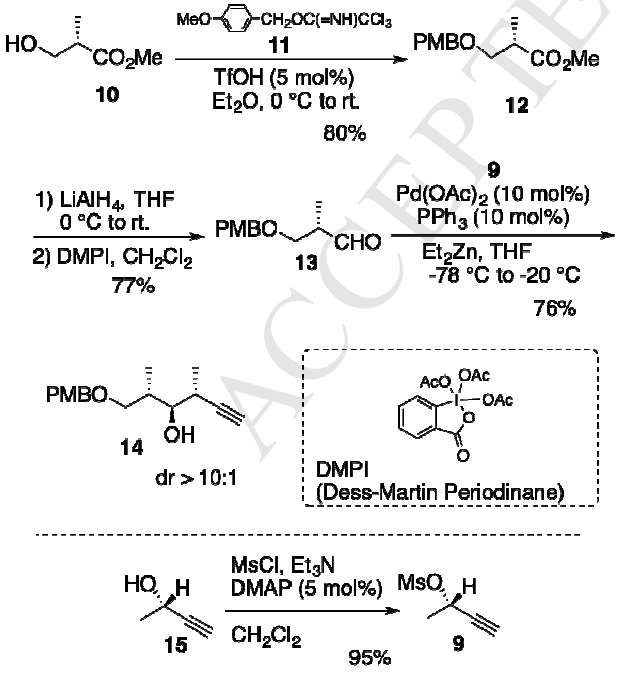


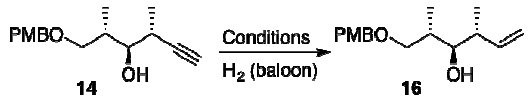
Scheme 1. Synthetic plan

The synthesis of **14** is depicted in Scheme 2. Methyl (*S*)-3-hydroxy-2-methylpropionate (**10**) was protected using **11** under acidic conditions to give PMB ether **12**. Intermediate **12** was subjected to LAH reduction followed by Dess-Martin oxidation to give aldehyde **13**. Significant racemization of aldehyde **13** was observed when prepared from **12** directly by using DIBALH. Following the procedure developed by Marshall et al.,[4,5] **13** was coupled with optically active mesylate **9** prepared from commercially available **15** to give **14** possessing three continuous stereocenters in satisfactory yield and with satisfactory stereoselectivity. [6]



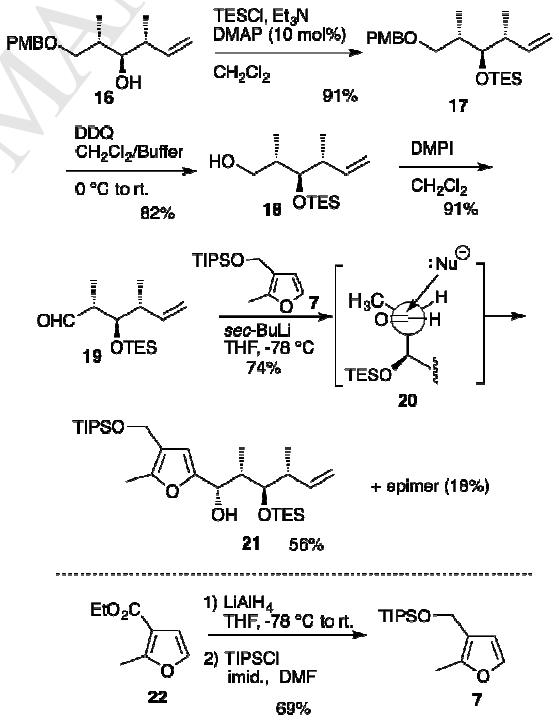
Scheme 2. Synthesis of **14**

Table 1. Hydrogenation of **14**



Entry	Conditions	Yield of **16**
1	Lidlar cat. 5 w%, AcOEt	63% (unreproducible)
2	5% Pd-PEI 10 w%, MeOH-Dioxane 1:4	no reaction
3	5% Pd-PEI 10 w%, MeOH	71%

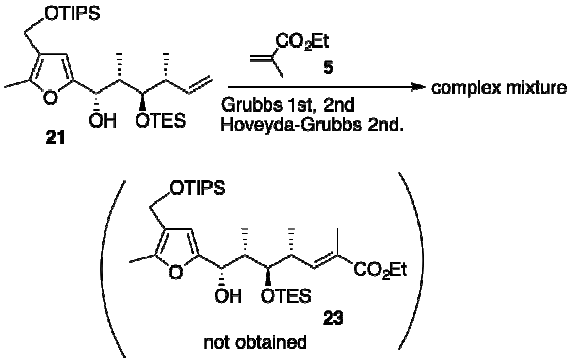
Partial hydrogenation of alkyne **14** was investigated as shown in Table 1. The initial attempt, using a typical poisoned catalyst gave **16** in moderate yield (entry 1) but the yield was not reproducible due to the reduction of alkene **16**. We next tried using the Pd-PEI (palladium-polyethyleneimine) catalyst developed by Sajiki et al. [7] Conditions using a 1:4 mixture of MeOH and dioxane as solvent did not give **16** (entry 2), whereas the reaction in MeOH proceeded efficiently to give **16** in satisfactory yield and with good reproducibility (entry3).



Scheme 3. Coupling between **7** and **19**

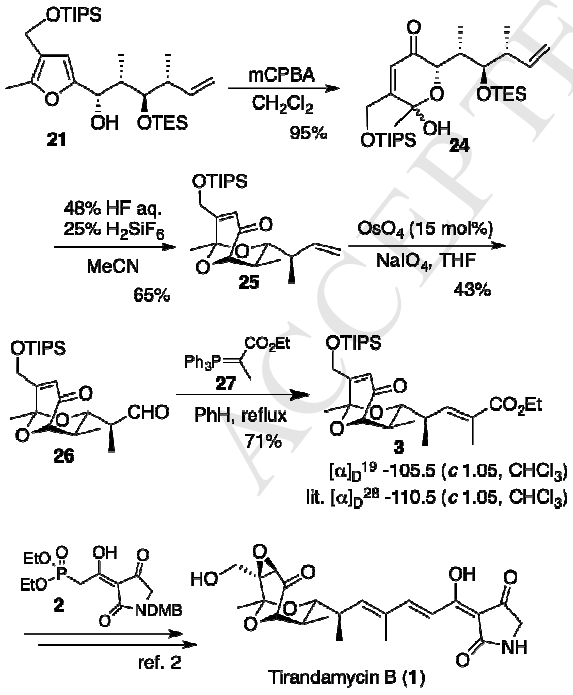
Aldehyde **19** was synthesized from **16** via a three-step sequence (Scheme 3); protection of the secondary alcohol **16**, followed by removal of the PMB group, afforded **18**, which was treated with Dess-Martin reagent to afforded aldehyde **19** in 68% yield. Furan derivative **7** was prepared from **22** in 2 steps. Lithiofuran generated from **7** was coupled with aldehyde **19** to give **21** as the

major product with 3:1 diastereoselectivity. The ratio of stereoisomers was determined from the ^{1}H NMR spectra of the crude product. This stereoselective outcome of the reaction can be explained by the Felkin-Anh model for **20**. At this point, the required four continuous stereocenters of **1** were fixed. Formation of MTPA ester [8] of **21** or conversion to the corresponding acetonide [9] from **21** were difficult due to the instability of the derivatives, configuration of the coupling product **21** and its epimer were estimated based on the coupling constants of the protons attached to the generated stereocenters.[10]



Scheme 4. Attempted Cross-metathesis

We attempted to synthesize known intermediate **23** [2] by cross-metathesis reaction[3] between obtained **21** and ethyl ester **5**. However, reactions employing Grubbs 1st, Grubbs 2nd, and Hoveyda-Grubbs 2nd catalysts did not give desired product **22** (Scheme 4). We attributed this disappointing result to the instability of the furan ring moiety in **21** and therefore decided to install the ethyl ester moiety after forming the bicyclic core of **1**.



Scheme 5. Formal Synthesis of Tirandamycin B

Based on a previously developed procedure,[2] **21** was subjected to Achmatowicz reaction using mCPBA to give **24** (Scheme 5). This result was gratifying because the terminal alkene of **21** was unaffected. Removal of the TES group from **24** using HF and H_2SiF_6 in acetonitrile promoted cyclization, forming the bicyclic core of **25**. Cross metathesis between **25** and **5** was unsuccessful, as with **21**, and thus we had to use an alternative method. Johnson-Lemieux oxidation [11] of **25** giving aldehyde **26**, and subsequent Wittig reaction using ylide **27**, furnished intermediate **3**. The synthetic route of **1** from **3** involving the coupling with **2** and epoxidation is reported in the literatures, [12,2] and thus we archived a formal synthesis of **1**. Proton and carbon NMR spectra, and optical rotation data of synthesized **3**, show good agreements with those reported in the literature.

3. Conclusions

We have developed a formal synthesis of tirandamycin B in 13 steps starting from methyl (*S*)-3-hydroxy-2-methylpropionate (**10**). This synthetic route involves the Marshall's method, Sajiki hydrogenation of terminal alkyne, lithiofuran coupling, and construction of the bicyclic core based on the Achmatowicz reaction.

4. Experimental

4.1 General

Where appropriate, reactions were performed in flame-dried glassware under argon atmosphere under room temperature. All extracts were dried over $MgSO_4$ and concentrated by rotary evaporation below 30 °C at 25 Torr unless otherwise noted. Commercial reagents and solvents were used as supplied. Column chromatography was performed using silica gel (particle size 100-210 μm (regular), 40-50 μm (flush)). Optical rotations were recorded on a digital polarimeter at ambient temperature. Infrared spectra were measured on a Fourier transform infrared spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured using $CDCl_3$ as solvent, and chemical shifts are reported as δ values in ppm based on internal $(CH_3)_4Si$ (0.00 ppm, ^{1}H) or solvent peak. HRMS spectra were taken in EI (dual focusing sector field) or FAB (dual focusing sector field) mode.

4.2 Experimental procedures

*4.2.1.Methyl(S)-3-((4-methoxybenzyl)oxy)-2-methylpropanoate (**12**).*

To a stirred solution of **11** (3.4 g, 12.1 mmol) in Et_2O (51 mL) at 0 °C, were added **10** (1.0 g, 8.47 mmol) and TfOH (34 μL, 0.33 mmol). After being stirred under room temperature for 16 h, saturated $NaHCO_3$ was added. The mixture was extracted with Et_2O, washed with brine, dried, concentrated and chromatographed (SiO_2 50 g, hexane: AcOEt = 10:1) to give **12** (1.61 g, 6.8 mmol, 80%) as a colorless oil. $[\alpha]_D^{17}$+9.34 (*c* 1.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.45 (s, 2H), 3.79 (s, 3H), 3.68 (s, 3H), 3.62 (dd, *J* = 7.2, 8.8 Hz, 1H), 3.45 (dd, *J* = 6.0, 8.8 Hz, 1H), 2.81-2.72 (m, 1H), 1.16, (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 159.2, 130.1, 129.1, 113.6, 72.6, 71.5, 55.1,

51.6, 40.1, 13.9; FT-IR (KBr) 2950, 2862, 1738, 1613, 1514, 1248, 1091 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{18}O_4$ (M^+), 238.1205, found 238.1205.

*4.2.2. (S)-3-((4-Methoxybenzyl)oxy)-2-methylpropanal (**13**).*

To a suspension of $LiAlH_4$ (1.6 g, 42 mmol) in THF (160 mL) was added **12** (20 mL THF solution, 6.7 g, 28 mmol) dropwisely over 30 min at -78 °C. The mixture was gradually warmed up to room temperature, stirred for 13 h and then cooled to 0 °C. Water (1.5 mL), 15% NaOH (1.5 mL) and additional water (4.6 mL) were added to the mixture. The mixture was filtered through Celite, concentrated and chromatographed (SiO_2 200 g, hexane: AcOEt = 2:1) to give the corresponding alcohol (4.8 g, 23 mmol, 82%) as a colorless oil. $[\alpha]_D^{23}$+18.1 (*c* 1.00, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.44 (s, 2H), 3.79 (s, 3H), 3.61-3.56 (m, 2H), 3.51 (ddd, *J* = 0.8, 4.8, 9.2 Hz, 1H), 3.39 (dd, *J* = 8.0, 9.2 Hz, 1H), 2.72 (s, 1H), 2.10-1.99 (m, 1H), 0.87 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 159.2, 130.0, 129.2, 113.7, 75.0, 72.5, 67.7, 55.2, 35.5, 13.4.; FT-IR (KBr) 3434, 2955, 2867, 1514, 1249, 1176, 1035 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{18}O_3$ (M^+), 210.1256, found 210.1256. To a stirred solution of the alcohol above obtained (449 mg, 2.13 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added DMPI (1.27 g, 3.00 mmol). After being stirred under the room temperature for 1 h, saturated $Na_2S_2O_3$ (20 mL) was added to the mixture at 0 °C. The mixture was extracted with Et_2O, washed with saturated $NaHCO_3$ and brine, dried, concentrated and chromatographed (SiO_2 10 g, hexane:AcOEt = 4:1) to give **13** (418 mg, 2.01 mmol, 94%) as a colorless oil. $[\alpha]_D^{21}$+30.5 (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 1.6 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.67-3.58 (m, 2H), 2.68-2.60 (m, 1H), 1.11, (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 203.9, 159.2, 129.9, 129.2, 113.7, 72.9, 69.7, 55.2, 46.7, 10.6; FT-IR (KBr) 2936, 2861, 1724, 1514, 1248, 1094, 1034 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{16}O_3$(M^+) 208.1099, found 208.1100.

*4.2.3. (S)-But-3-yn-2-yl methanesulfonate (**9**).*

To a stirred solution of **15** (2.0 g, 28.5 mmol) in CH_2Cl_2 (50 mL) were added Et_3N (6.0 mL, 42. 8 mmol), MsCl (2.6 mL, 34. 2 mmol) and DMAP (206 mg, 1.43 mmol) under the room temperature. After being stirred for 3 h, water (50 mL) was added at 0 °C. The mixture was extracted with Et_2O, washed with saturated $NaHCO_3$ and brine, dried, concentrated and chromatographed (SiO_2 58 g, hexane: Et_2O = 3:2) to give **9** (4.0 g, 27.2 mmol, 95%) as a colorless oil. $[\alpha]_D^{17}$-119.7 (*c* 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (ddd, *J* = 2.0, 6.8, 13.2 Hz, 1H), 3.13 (s, 3H), 2.72 (d, *J* = 2.0 Hz, 1H), 1.66 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 80.1, 76.3, 67.4, 39.1, 22.4; FT-IR (KBr) 3283, 3029, 2998, 2942, 2125, 1358, 1177, 1123, 1090, 1017 cm^{-1}; HRMS (EI) calcd for $C_5H_7O_3S$ [(M-H)$^+$] 147.0116, found 147.0116.

*4.2.4. (2S,3R,4R)-1-((4-Methoxybenzyl)oxy)-2,4-dimethylhex-5-yn-3-ol (**14**).*

$Pd(OAc)_2$ (163 mg, 0.73 mmol) and PPh_3 (204 mg, 0.78 mmol) were dissolved in THF (25 mL) and cooled to -78 °C. **13** (1.45 g, 7.0 mmol) and **9** (2.0 g, 14.0 mmol) were added via cannula. After 10 minutes, Et_2Zn (1 M in THF, 14 mL, 14 mmol) was added at the same temperature. The resulting mixture was stirred for 15 h at -20 °C . 1 N HCl was added to the mixture. The mixture was extracted with Et_2O, washed with $NaHCO_3$, and brine, dried, concentrated and chromatographed (SiO_2 100 g, hexane:AcOEt = 10:1) to give **14** (1.39 g, 5.3 mmol, 76%) as a colorless oil. $[\alpha]_D^{16}$+9.8 (*c* 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.60-3.48 (m, 3H), 3.36-3.32 (m, 1H), 2.71-2.64 (m, 1H), 2.17-2.06 (m, 1H), 2.09 (d, *J* = 2.4 Hz, 1H), 1.29 (d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 129.8, 129.3, 113.7, 85.0, 78.2, 74.7, 73.0, 70.2, 55.2, 37.2, 30.1, 17.8, 13.8; FT-IR (KBr) 3464, 3292, 2967, 2934, 2872, 1513, 1247, 1080 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{22}O_3$ (M^+) 262.1569, found 262.1569.

*4.2.5. (2S,3R,4R)-1-((4-Methoxybenzyl)oxy)-2,4-dimethylhex-5-en-3-ol (**16**).*

Under argon atmosphere, 5% Pd-PEI (13 mg) was added to a solution of **15** (131 mg, 0.50 mmol) in MeOH (2 mL) and then a hydrogen gas balloon was attached. The mixture was stirred for 7 h, diluted with Et_2O, washed with water, brine, dried, concentrated, and chromatographed (SiO_2 8 g, hexane:AcOEt = 25:1) to give **16** (94 mg, 0.36 mmol, 71%) as a colorless oil. $[\alpha]_D^{17}$ +11.2 (*c* 1.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.94-5.85 (m, 1H), 5.07 (d, *J* = 0.7 Hz, 1H), 5.04-5.02 (m, 1H), 4.44 (s, 2H), 3.79 (s, 3H), 3.55 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.49-3.45 (m, 2H), 3.37-3.33 (m, 1H), 2.38-2.30 (m, 1H), 1.96-1.86 (m, 1H), 1.09, (d, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 159.2, 139.7, 129.8, 129.3,115.1, 113.4, 79.2, 75.1, 73.1, 55.2, 41.0, 36.1, 17.7, 13.9; FT-IR (KBr) 3493, 2963, 2932, 1248, 1084, 1036, cm^{-1}; HRMS (EI) calcd for $C_{16}H_{24}O_3$ (M^+) 264.1725, found 264.1726.

*4.2.6. Triethyl(((2S,3R,4R)-1-((4-methoxybenzyl)oxy)-2,4-dimethylhex-5-en-3-yl)oxy)silane (**17**).*

To a solution of **16** (1.21 g, 4.59 mmol) in CH_2Cl_2 (36 mL), were added Et_3N (1.28 mL, 9.19 mmol), TESCl (1.15 mL, 6.89 mmol) and DMAP (55 mg, 0.45 mmol) at 0 °C. After being stirred for 19 h under room temperature, The mixture was diluted with AcOEt, washed with 1 M HCl, saturated $NaHCO_3$ and brine, dried, concentrated and chromatographed (SiO_2 89 g, hexane:AcOEt = 50:1) to give **17** (1.58 g, 4.2 mmol, 91%) as a colorless oil. $[\alpha]_D^{17}$-14.9 (*c* 0.82, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.86 (ddd, *J* = 8.0, 10.6, 18.8 Hz, 1H), 5.00-4.97 (m, 1H), 4.95 (d, *J* = 0.7, 1H), 4.44 (d, *J* = 11.7 Hz, 1H), 4.38 (d, *J* = 11.7 Hz, 1H), 3.80 (s, 3H), 3.53-3.48 (m, 2H), 3.30 (dd, *J* = 7.3, 8.9 Hz, 1H), 2.39-2.31 (m, 1H), 1.94-1.84 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.96-0.94 (m, 12H), 0.59 (q, *J* = 8.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 141.1, 131.0, 129.1, 114.1, 113.6, 78.4, 72.7, 72.5, 55.2, 41.7, 37.9, 18.1, 14.9, 7.1, 5.4; FT-IR (KBr) 2957, 2877, 1513, 1246, 1090, 1041 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{38}O_3Si$ (M^+) 378.2590, found 378.2590.

*4.2.7. (2S,3R,4R)-2,4-Dimethyl-3-((triethylsilyl)oxy)hex-5-en-1-ol (**18**).*

To a solution of **17** (1.48 g, 3.9 mmol) in CH_2Cl_2 (64 mL) were added phosphate buffer (pH 7, 0.4 M, 16 mL) and DDQ (2.5 g, 11.0 mmol) at 0 °C. After being stirred for 15 minutes under room temperature, the mixture was diluted with Et_2O, washed with 2 M NaOH and brine, dried, concentrated and chromatographed (SiO_2 55 g, hexane: AcOEt = 15:1) to give **18** (825 mg, 3.2 mmol, 82%) as a colorless oil. $[\alpha]_D^{20}$-8.36 (*c* 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 7.7, 10.4, 17.2 Hz, 1H), 5.06 (t, *J* = 1.4 Hz, 1H), 5.03-5.00 (m, 1H), 3.68-3.61 (m, 1H), 3.61-3.57 (m, 2H), 2.69 (t, *J* = 5.8 Hz, 1H), 2.43-2.41 (m, 1H), 1.87-1.78 (m, 1H), 1.04, (d, *J* = 6.4 Hz, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.96 (d, *J* = 6.4 Hz, 3H), 0.65, (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 115.3, 82.1, 66.7, 43.7, 38.1, 16.9, 16.4, 7.6, 5.9; FT-IR (KBr) 3396, 2958, 2878, 1459, 1239, 1037, 1007 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{25}O_2$ Si [(M-Et)$^+$] 229.1624, found 229.1624.

*4.2.8. (2R,3R,4R)-2,4-Dimethyl-3-((triethylsilyl)oxy)hex-5-enal (**19**).*

To a stirred solution of **18** (387 mg, 1.50 mmol) in CH_2Cl_2 (6 mL), was added DMPI (1.0 g, 2.4 mmol) at 0 °C. After being stirred for 2 h under room temperature, saturated $Na_2S_2O_3$ was added at 0 °C and stirred for 30 minutes. The mixture was extracted with Et_2O, washed with $NaHCO_3$ and brine, dried, concentrated and chromatographed (SiO_2 35 g, hexane:AcOEt = 50:1) to give **19** (348 mg, 1.36 mmol, 91%) as a colorless oil. $[\alpha]_D^{20}$-53.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (d, *J* = 2.4 Hz, 1H), 5.88-5.79 (m, 1H), 5.08-5.07 (m, 1H), 5.05-5.03 (m, 1H), 3.82 (dd, *J* = 4.0, 5.2 Hz, 1H), 2.57-2.50 (m, 1H), 2.44-2.38 (m, 1H), 1.06, (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.62, (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100MHz, $CDCl_3$) δ 205.3, 139.9, 115.4, 78.1, 50.0, 42.9, 16.3, 11.9, 6.9, 5.2; FT-IR (KBr) 2959, 2879, 1726, 1460, 1240, 1120, 1075 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{23}O_2$ Si [(M-Et)$^+$] 227.1467, found 227.1467.

*4.2.9 Triisopropyl((2-methylfuran-3-yl)methoxy)silane (**7**).*

To a suspension of $LiAlH_4$ (2.4 g, 64 mmol) in THF (140 mL) was added **22** (10 mL THF solution, 5.0 g, 32 mmol) dropwisely over 30 min at -78 °C. The mixture was gradually warmed up to room temperature, stirred for 2.5 h and then cooled to 0 °C. Water (2.0 mL), 15% NaOH (2.5 mL) and additional water (6.5 mL) were added to the mixture. The mixture was filtered through Celite and concentrated. The resulting crude alcohol was dissolved in CH_2Cl_2 (37 mL). Imidazole (3.6 g, 32 mmol) and TIPSCl (10. 1 mL, 48 mmol) were added. The mixture was stirred under room temperature for 15 h, diluted with Et_2O, washed with 1 M HCl, saturated $NaHCO_3$ and brine, dried, concentrated and chromatographed (SiO_2 160 g, hexane: AcOEt = 80:1) to give **7** (5.8 g, 22 mmol, 69%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 1.8 Hz, 1H), 6.35 (d, *J* = 1.6 Hz, 1H), 4.58 (s, 2H), 2.26 (s, 3H), 1.18-1.05 (m, 21H); ^{13}C NMR (100MHz, $CDCl_3$) δ 147.7, 140.0, 119.3, 110.9, 57.5, 18.0, 12.0, 11.8; FT-IR (KBr) 2943, 2867, 1465, 1085, 1066 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{28}O_2Si$ (M)$^+$ 268.1859, found 268.1857.

*4.2.10. (1S,2S,3R,4R)-2,4-Dimethyl-1-(5-methyl-4-(((triisopropylsilyl)oxy)methyl)furan-2-yl)-3-((triethylsilyl)oxy)hex-5-en-1-ol (**21**).*

To a stirred solution of **7** (318 mg, 1.17 mmol) in THF (1 mL) was added *sec*-BuLi (0.7 M in hexane, 1.1 mL, 0.77 mmol) at -78 °C. After being stirred for 40 minutes, **19** (150 mg, 0.59 mmol) was added and stirred for 1 h under the same temperature. The reaction was quenched with water, and the mixture was extracted with Et_2O. The organic phase was washed with brine, dried concentrated and chromatographed (SiO_2 14 g, hexane:AcOEt = 50:1) to give **21** (173 mg, 0.33 mmol, 56%) and its epimer (56 mg, 0.11 mmol, 18%) as a colorless oil. Data for 21; $[\alpha]_D^{14}$-6.6 (*c* 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (s, 1H), 5.90 (ddd, *J* = 7.2, 10.4, 17.2 Hz, 1H), 5.11-4.99 (m, 3H), 4.54 (s, 2H), 3.65 (t, *J* = 4.6 Hz, 1H), 3.14 (d, *J* = 2.8 Hz, 1H), 2.52-2.47 (m, 1H), 2.23 (s, 3H), 2.07-2.04 (m, 1H), 1.16-0.95 (m, 27H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.67 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 146.5, 141.2, 119.7, 114.9, 107.0, 80.8, 68.4, 57.6, 42.5, 39.3, 18.0, 17.1, 12.7, 11.9, 11.8, 7.07, 5.4; FT-IR (neat) 3493, 2954, 2870, 1462, 1132, 1060, 1004 cm^{-1}; HRMS (EI) calcd for $C_{29}H_{56}O_4Si_2$ (M$^+$) 524.3717, found 524.3717. *Data for the epimer of **21**;* $[\alpha]_D^{15}$+10.5 (*c* 0.89, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (s, 1H), 5.87 (ddd, *J* = 7.2, 10.0, 17.6 Hz, 1H), 5.06-5.00 (m, 2H), 4.54 (s, 2H), 4.52 (dd, *J* = 2.4, 8.8 Hz, 1H), 3.70 (dd, *J* = 4.0, 6.0 Hz, 1H), 3.66 (d, *J* = 2.4 Hz, 1H), 2.52-2.44 (m, 1H), 2.24 (s, 3H), 2.23-2.18 (m, 1H), 1.15-0.98 (m, 33H), 0.73-0.61 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 147.0, 140.8, 119.7, 114.5, 108.6, 81.0, 71.3, 57.5, 43.2, 40.9, 18.0, 16.1, 15.4, 12.0, 11.9, 6.9, 5.2; FT-IR (KBr) 3451, 2955, 2870, 1462, 1240, 1063, 1008 cm^{-1}; HRMS (EI) calcd for $C_{29}H_{56}O_4Si_2$ (M$^+$) 524.3717, found 524.3719.

*4.2.11. (2S)-6-Hydroxy-6-methyl-2-((2S,3R,4R)-4-methyl-3-((triethylsilyl)oxy)hex-5-en-2-yl)-5-(((triisopropylsilyl)oxy)methyl)-2H-pyran-3(6H)-one (**24**).*

To a stirred solution of **21** (104 mg, 0.20 mmol) in CH_2Cl_2 was added *m*CPBA (48 mg, 0.28 mmol) at 0 °C. After being stirred for 4 h at the same temperature, the mixture was diluted with AcOEt, washed with saturated $Na_2S_2O_3$, saturated $NaHCO_3$, and brine, dried, concentrated and chromatographed (SiO_2 8 g, hexane:AcOEt = 50:1) to give **24** (100 mg, 0.19 mmol, 95%) as a colorless solid. $[\alpha]_D^{15}$-10.7 (*c* 0.98, $CHCl_3$); mp 73-76 °C ;^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (t, *J* = 1.6 Hz, 1H), 5.97-5.88 (m, 1H), 5.02 (d, *J* = 2.4 Hz, 1H), 5.00 (s, 1H), 4.70 (d, *J* = 2.0 Hz, 1H), 4.49 (t, *J* = 2.0 Hz, 2H),3.69 (dd, *J* = 2.0, 10.4 Hz, 1H), 2.84 (s, 1H), 2.46-2.40 (m, 1H), 2.34 (s, 1H), 1.56 (s, 3H), 1.20-0.96 (m, 33H), 0.75-0.60 (m, 9H); ^{13}C NMR (100MHz, $CDCl_3$) δ 198.3, 160.8, 140.0, 121.5, 114.4, 93.4, 76.5, 75.1, 61.5, 41.2, 38.7, 26.5, 17.9, 17.7, 11.8, 7.1, 5.5; FT-IR (KBr) 3410, 2948, 2871, 1669, 1463, 1118, 1054, 1011 cm^{-1}; HRMS (FAB) calcd for $C_{29}H_{56}O_5Si_2Na$ [(M+Na)$^+$] 563.3564, found 563.3563.

*4.2.12. (1S,3R,4R,5S)-3-((R)-But-3-en-2-yl)-1,4-dimethyl-8-(((triisopropylsilyl)oxy)methyl)-2,9-dioxabicyclo[3.3.1]non-7-en-6-one (**25**).*

To a stirred solution of **24** (141 mg, 0.26 mmol) in MeCN (40 mL) were added 48% HF (13 μL) and 25% H_2SiF_6 (14 μL) under room temperature. After being stirred for 2 minutes, saturated $NaHCO_3$ was added. The mixture was diluted with Et_2O, washed with water and brine, dried, concentrated and chromatographed (SiO_2 15 g, hexane : AcOEt = 40:1) to give **25** (68 mg, 0.17 mmol, 65%) as a colorless solid. $[\alpha]_D^{19}$-163.9 (*c* 1.28, $CHCl_3$); mp 54-56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (t, *J* = 2.0 Hz, 1H), 5.86 (ddd, *J* = 9.2, 10.4, 19.4 Hz, 1H), 5.08-5.05 (m, 1H), 5.05-5.00 (m, 1H), 4.50 (dd, *J* = 2.4, 17.6 Hz, 1H), 4.22 (dd, *J* = 2.4, 18.0 Hz, 1H), 4.05 (d, *J* = 6.0 Hz, 1H), 3.40 (dd, *J* = 2.4, 11.2 Hz, 1H), 2.43-2.35 (m, 1H), 2.20-2.10 (m, 1H), 1.45 (s, 3H), 1.18-1.06 (m, 21H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.73 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 195.7, 158.2, 138.7, 123.2, 115.7, 94.6, 79.1, 60.8, 39.3, 33.0, 24.1, 18.0, 18.0, 17.5, 11.9, 11.3; FT-IR (KBr) 2954, 2867, 1679, 1460, 1141, 1061 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{41}O_4Si$ [(M+H)$^+$] 409.2274, found 409.2275.

*4.2.13. (S)-2-((1S,3S,4R,5S)-1,4-dimethyl-6-oxo-8-(((triisopropylsilyl)oxy)methyl)-2,9-dioxabicyclo[3.3.1]non-7-en-3-yl)propanal (**26**).*

To a stirred solution of **25** (32.7 mg, 0.08 mmol) in THF (0.4 mL) were added OsO_4 (0.1M in H_2O, 100 μL, 0.01 mmol) and $NaIO_4$ (42 mg, 0,20 mmol) at room temperature. After being stirred for 2 h, saturated $Na_2S_2O_3$ was added. The mixture was extracted with AcOEt, washed with brine, dried, concentrated and chromatographed (SiO_2 4 g, hexane : AcOEt = 15:1) to give **26** (14 mg, 0.034 mmol, 43%) as a colorless oil. $[\alpha]_D^{17}$-142.1 (*c* 0.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (d, *J* = 2.4 Hz, 1H), 6.56 (dd, *J* = 1.6. 2.0 Hz, 1H), 4.51 (dd, *J* = 2.4, 18.4 Hz, 1H), 4.23 (dd, *J* = 2.0, 18.4 Hz, 1H), 4.11 (d, *J* = 5.6 Hz, 1H), 3.73 (dd, *J* = 2.0, 11.6 Hz, 1H), 2.58-2.51 (m, 1H), 2.41-2.31 (m, 1H), 1.46 (s, 3H), 1.25-1.06 (m, 24H), 0.82 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 203.4, 194.7, 157.6, 123.7, 94.9,

78.8, 76.2, 60.8, 47.0, 33.3, 24.0, 17.99, 17.96, 11.9, 11.7, 11.2; FT-IR (KBr) 2943, 2874, 1727, 1687, 1466, 1376, 1225, 1139, 1058 cm^{-1}. HRMS (FAB) calcd for $C_{22}H_{39}O_5Si$ $[(M+H)^+]$ 411.2567, found 411.2560.

*4.2.14. Intermediate **3**.*

To a stirred solution of **26** (14 mg, 0.034 mmol) in benzene (0.5 mL) was added ylide **27** (24 mg, 0.066 mmol). The mixture was refluxed for 6 h, evaporated, chromatographed (SiO_2 4 g, hexane : AcOEt = 20:1) to give **3** (12 mg, 0.024 mmol, 71%) as a colorless oil. $[\alpha]_D^{19}$-105.5 (*c* 1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (dd, *J* = 1.2, 10.0 Hz, 1H), 6.51 (t, *J* = 1.6 Hz, 1H), 4.45 (dd, *J* = 2.4, 17.2 Hz, 1H), 4.23-4.17 (m, 3H), 4.03 (d, *J* = 6.0 Hz, 1H), 3.46 (dd, *J* = 2.0, 11.2 Hz, 1H), 2.81-2.73 (m, 1H), 2.04-1.94 (m, 1H), 1.83 (d, *J* = 1.6 Hz, 3H), 1.47 (s, 3H), 1.30 (t, *J* = 6.8 Hz, 3H), 1.19-1.05 (m, 21H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 195.4, 168.0, 158.2, 141.3, 128.4, 123.3, 94.7, 78.9, 60.8, 60.6, 34.0, 33.5, 24.1, 18.01, 17.97, 16.4, 14.3, 12.5, 11.9, 11.7; FT-IR (KBr) 2941, 2867, 1709, 1459, 1383, 1298, 1250, 1132 cm^{-1}. HRMS (FAB) calcd for $C_{27}H_{47}O_6Si$ $[(M+H)^+]$ 495.3142, found 495.3099.

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References and notes

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Supplementary Material

^1H and ^{13}C NMR spectra of synthesized compounds.