学位論文　博士（理学）

海洋生物由来のマクロライド化合物 amphidinolide 類の合成研究

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目次

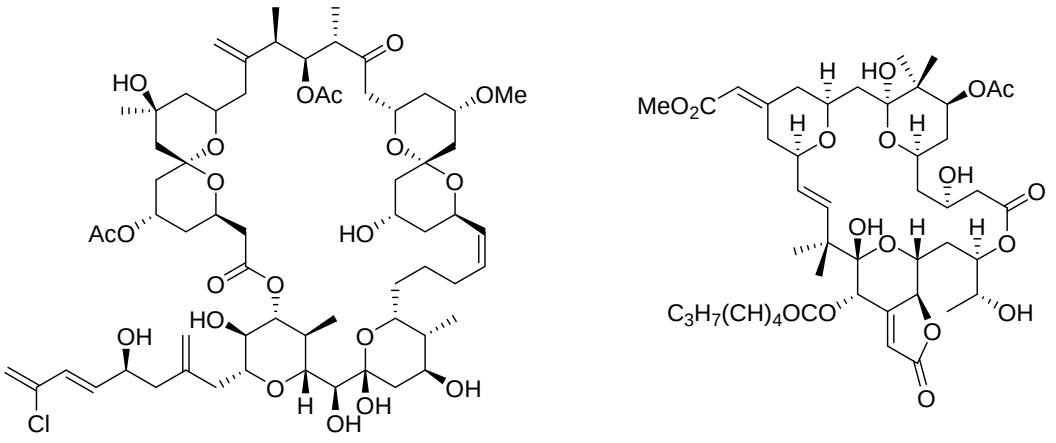
略号

Ac	acetyl
AD	asymmetric dihydroxylation
aq	aqueous
BAIB	bis(acetoxy)iodobenzene
Bu	butyl
CAN	ceric ammonium nitrate
CBS	Corey-Bakshi-Shibata
CSA	camphor-10-sulfonic acid
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DET	diethyl tartrate
DHQD	dihydroquinidine
DIBAL-H	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DIPT	diisopropyl tartrate
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
eq	equivalents
ESI	electrospray ionization
Et	ethyl
GPC	gel permeation chromatography
HPLC	high performance liquid chromatography
IBX	2-iodoxybenzoic acid
IR	infrared
KHMDS	potassium bis(trimethylsilyl)amide
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
Ms	methanesulfonyl
MS	mass spectroscopy

MP	*p*-methoxyphenyl
MS4A	molecular sieves 4A
MTPA	α-methoxy-α-trifluoromethylphenylacetic acid
NaHMDS	sodium bis(trimethylsilyl)amide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
Ph	phenyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
PYDZ	pyridazine
Pyr	pyridine
sat	saturated
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TPAP	tetra-*n*-propylammonium perruthenate
Ts	*p*-toluenesulfonyl
UV	ultraviolet

第 1 章　序論

海洋生物は陸上生物に比べるとその形態や生態が極めて多彩で、中には陸上生物に見られない特異的な代謝系を持つものもいる。それらが産生する代謝産物にはヒトをはじめ他の生物に対して生物活性を示す物質が見出されており、食品素材のみならず医薬品としての新規物質の発見が期待されている。このため、世界的な規模で海洋生物からの生物活性物質の探索が活発に行われ、魅力的な生物活性を有する化合物が次々と単離されてきた。例えば、1990 年初頭に海綿から単離された spongistatin 類 [1] は極めて強い抗腫瘍活性を有している。また、1960 年代にフサコケムシから単離された bryostatin 類 [2] は、種々の癌細胞に対して顕著な抗腫瘍活性を示すにも拘らず、臨床試験において骨髄抑制などの重篤な副作用を示さないことが報告されており、新規抗癌剤の候補として大きな期待が持たれている。(Figure 1)

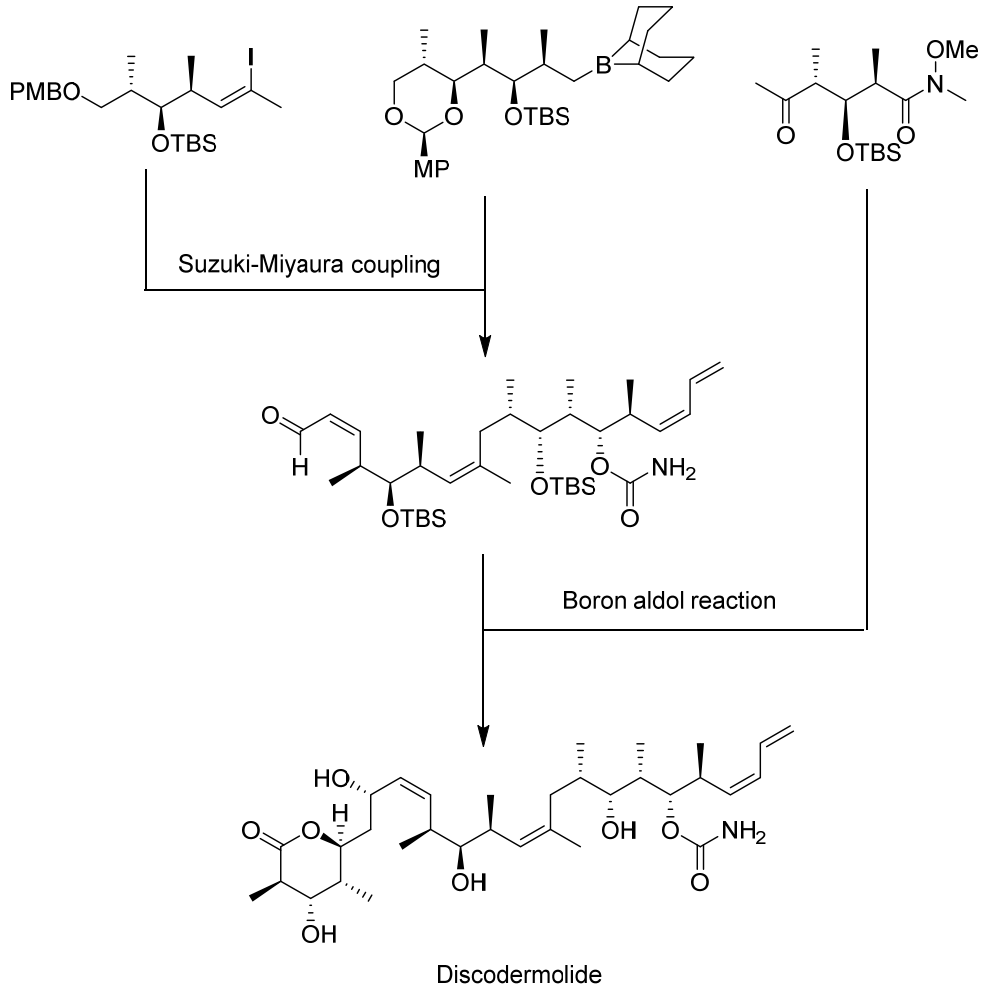


Spongistatin 1　　Bryostatin 3

Figure 1

しかし、医薬品として実用化が期待される海洋性天然有機化合物は、いずれも微量成分であるものが多く、生物から多量に抽出することは不可能に近いと考えられる。また、これらの化合物は陸上生物由来のものに比べて、数千から数十万倍も活性が強い反面、同時に毒性も強く、臨床応用への妨げとなっている。したがって、これらの化合物はそのまま薬剤として用いるよりも医薬品のリード化合物、あるいはドラッグデザインの分子プローブとして利用することが最も適していると考えられており、誘導体合成や構造活性相関研究を目的と

した海洋性天然化合物の全合成研究は多くの研究グループで活発に行われている。例えば、製薬企業 Novartis 社の研究グループはパラジウムを用いたクロスカップリング反応を活用することで、微小管安定化作用を有する抗癌剤候補化合物 discodermolide の大量合成を達成した (Scheme 1)[3]。これほど複雑に官能基化された天然物を数十グラムのスケールで化学合成したという例は非常に少なく、天然物合成における金字塔的な成果であり、新規抗癌剤の臨床応用への道を切り開いた。



Scheme 1

また、海洋生物由来の有機化合物が新薬として承認されたことで注目を集めたのが、製薬企業エーザイが開発した局所再発性・転移性乳癌の治療薬ハラヴェン®である(Figure 2)。ハラヴェン®はクロイソカイメンから単離されたマクロライド化合物 halichondrin B[4] をリード化合物とした合成アナログ誘導体である。

エーザイ研究グループは、岸らによって開発された halichondrin B の合成経路[5]をもとに構造の最適化を行うことでハラヴェン®を創製することに成功し、さらに合成ルートを最適化することでハラヴェン®の安定供給という難題を成し遂げた[6]。天然物と比較し、構造的に約 3 分の 2 に簡略化されたとは言え、19 個の不斉炭素と高度に官能基化された環状骨格を有するハラヴェン®を工業スケールで合成した開発研究は、天然物化学と有機合成化学の融合がもたらした画期的成果であり、創薬における天然物合成の重要性を示す代表的な事例と言える。

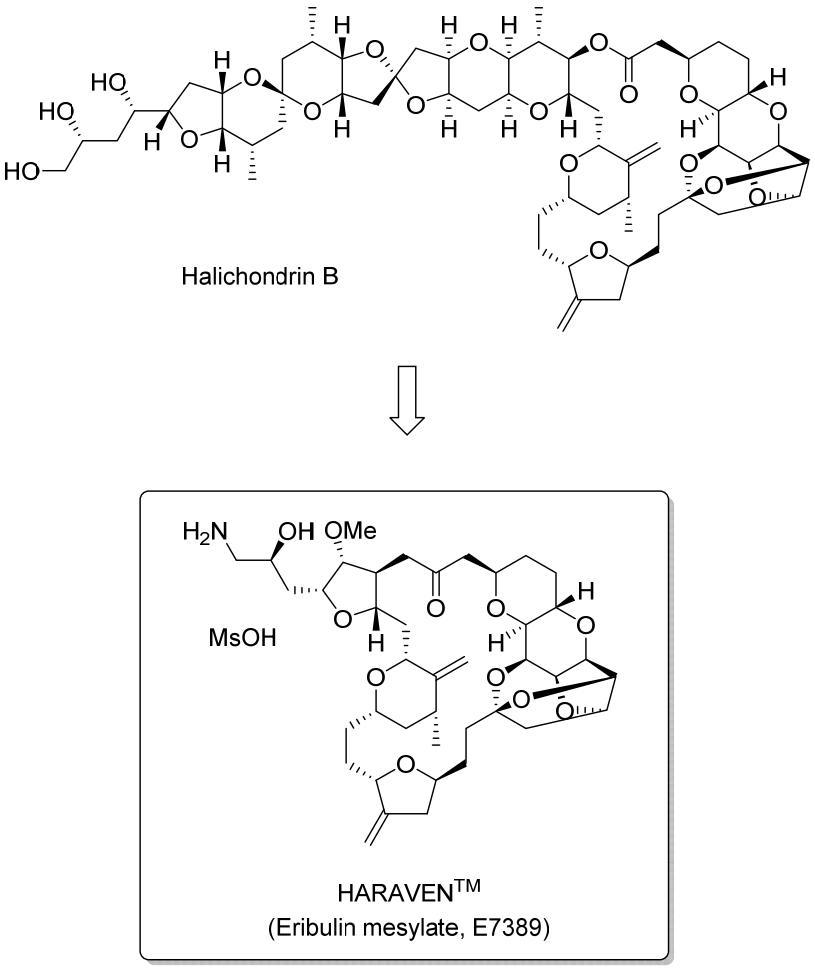


Figure 2

このような背景のもと、筆者は渦鞭毛藻から単離されたマクロライド化合物群 amphidinolide 類が有する特徴的な構造と強力な細胞毒性に注目した。沖縄産の扁形動物ヒラムシ類に属するアンフィスコロプス(*Amphiscolps* sp.)は、体長が 0.5-5.0 mm 程度で、その体内には特定の渦鞭毛藻が棲息している。1987 年に小林らは、このヒラムシの体内から分離した渦鞭毛藻アンフィジニウム (*Amphidinium* sp.)の粗抽出物が腫瘍細胞に対する顕著な細胞毒性を示すことを報告した。この知見に基づき、この渦鞭毛藻の活性成分の探索を行った結果、細胞毒性を示す一連のマクロライド化合物群 amphidinolide 類が単離された。現在までに、amphidinolide 類は amphidinolide A から Y までの 25 種類が報告されている (Figure 3)[7]。これらの化合物は単一種類の渦鞭毛藻から分離したにも拘らず、その基本骨格が各々異なっている点が特徴的である。

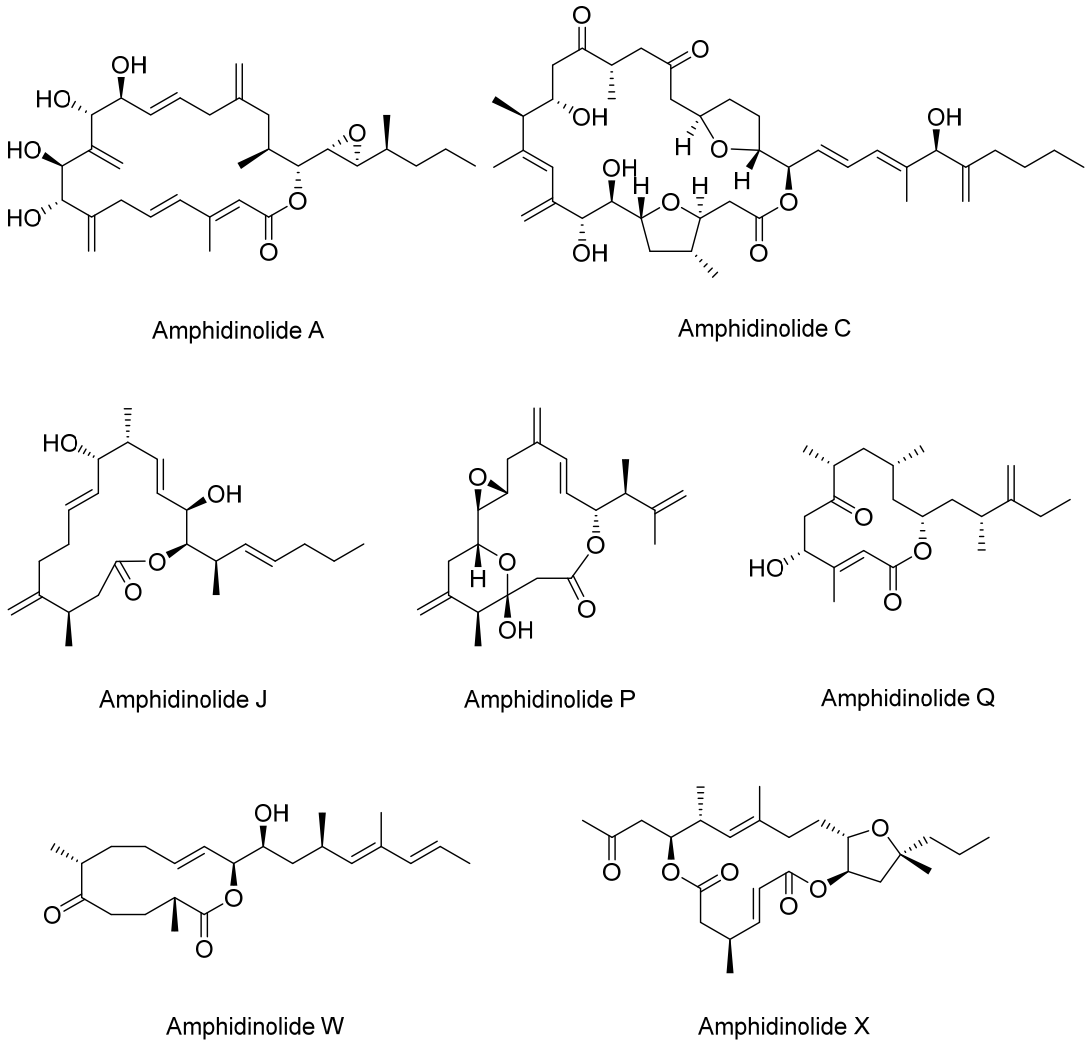
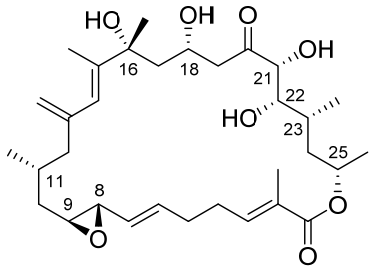


Figure 3

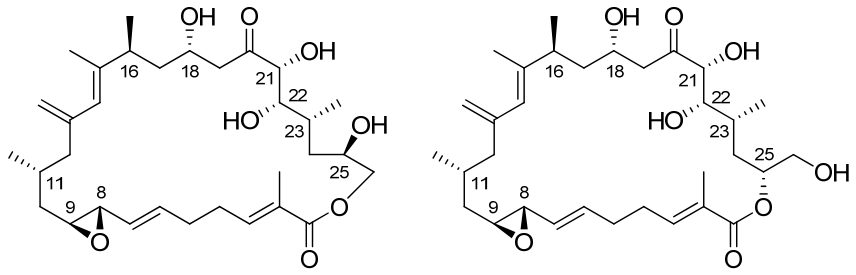
その中で、amphidinolide B (**1**)は 1987 年に単離され、マウス白血病細胞 L1210 及びヒト上皮癌細胞 KB に対して、数 ng/ml の低濃度で強力な細胞毒性を示すことが報告された[8]。また **1** は筋収縮系のカルシウムイオンの感受性を向上させることにより、ATPase 活性を上昇させて筋収縮力を増強させるという報告[9]もあり、新規抗癌剤のリード化合物として期待されている。その後、清水らは 1994 年に **1** の結晶化に成功し、単結晶 X 線構造解析により **1** の相対立体構造を決定した[10]。続いて小林らは相対立体配置の決定した **1** について、合成的手法を用いることで絶対立体配置を決定した[11]。すなわち C_{22}-C_{26} 位に相当するフラグメントの両鏡像異性体を合成し、天然物より得られたフラグメントと比較した。その結果、**1** の絶対立体構造は 8*S*、9*S*、11*R*、16*R*、18*S*、21*R*、22*S*、23*R* 及び 25*R* であることが明らかになり、Figure 4 に示した構造と決定された。



Amphidinolide B (**1**)
IC_{50} = 0.14 ng/mL (L1210)
4.2 ng/mL (KB)

Figure 4

一方で、amphidinolide G (**2**)及び H (**3**)は、1991 年に小林らにより単離され[12]、2000 年に **3** の X 線構造解析から、その相対立体配置が決定された[13]。続いて、相対立体配置の決定した **3** について、**1** の場合と同様に合成的手法を用いることで、その絶対立体配置を決定した[13]。すなわち、まず C_{22}-C_{26} 位に相当するフラグメントの両鏡像異性体を合成した後、これらの化合物と、天然物を分解反応に付すことにより得られたフラグメントとを比較した。その結果、**3** の絶対立体配置は、8*S*、9*S*、11*R*、16*S*、18*S*、21*R*、22*S*、23*R* 及び 25*R* であることが明らかになった(Figure 5)。また **2** 及び **3** に関しても生物活性試験が行われており、マウス白血病細胞 L1210 及びヒト上皮癌細胞 KB に対して顕著な細胞毒性を示すことが報告されている[12]。さらに、**3** は細胞骨格タンパク質アクチンと共有結合を形成し、その重合を促進・安定化する効果が報告されており[14]、アクチンを標的とした新規抗癌剤のリード化合物の候補としても注目を集めている。



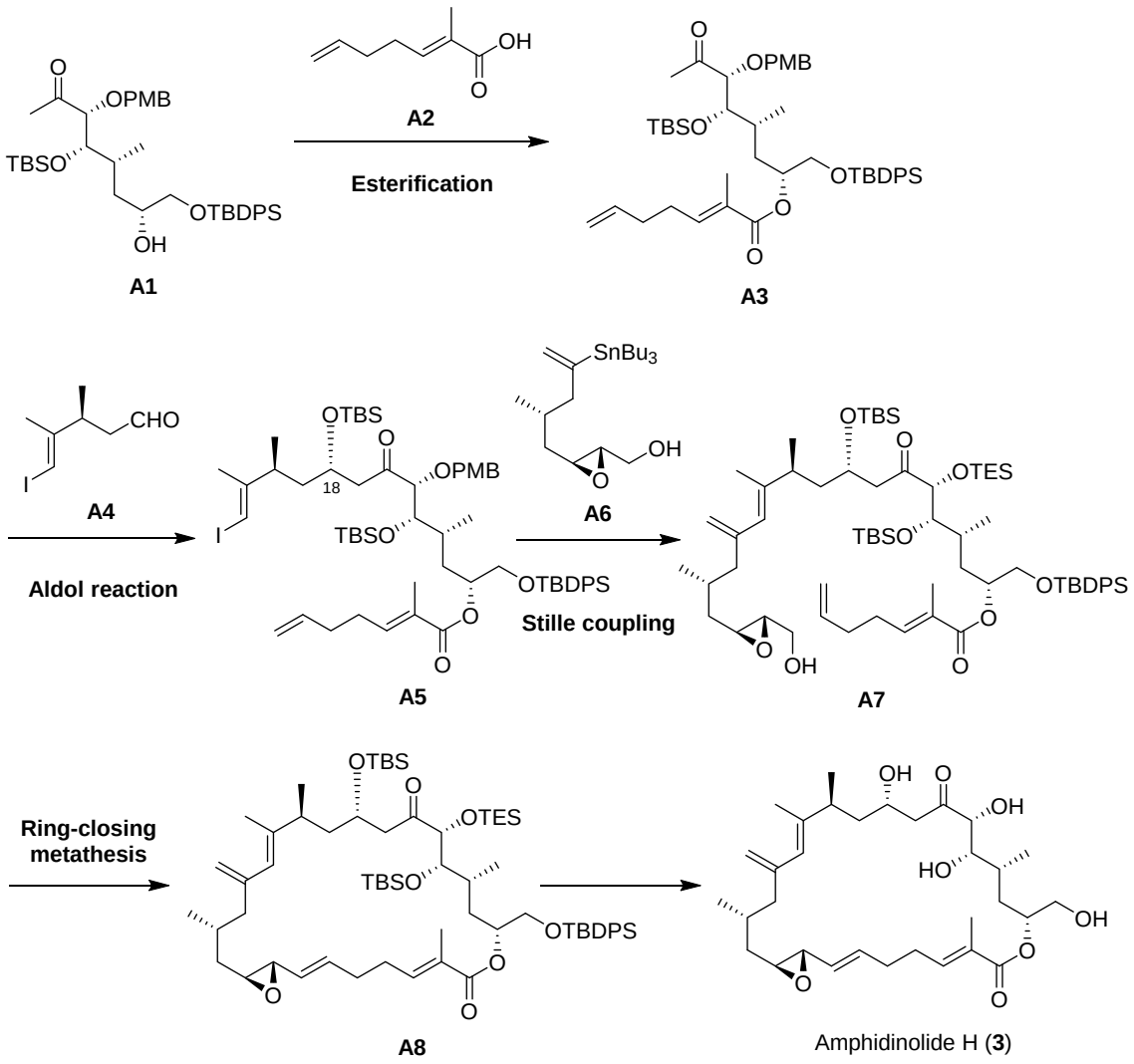
amphidinolide G (**2**)
IC_{50} = 5.4 ng/mL (L1210)
5.9 ng/mL (KB)

amphidinolide H (**3**)
IC_{50} = 0.48 ng/mL (L1210)
0.52 ng/mL (KB)

Figure 5

しかし、これらの化合物の渦鞭毛藻からの単離収率はいずれも低く、サンプル供給が難しいため、*in vivo* 試験を含む詳細な生物活性試験の評価は十分に行われていない。また **1-3** は C_6-C_9 位に位置する不安定なアリルエポキシド構造や C_{13}-C_{15} 位に位置するエキソオレフィンを含むジエン構造などの特徴的な構造を有しており、有機合成化学的な見地からも非常に興味深い。そのため、現在までに多くの研究グループによって合成が試みられており [15,16]、その全合成は Fürstner らによる **1-3** の全合成 [17,18] 及び Carter らによる **1** の全合成 [19] の 2 例が報告されている。以下では、Fürstner ら、Carter らのグループによって報告されている合成について、その概略を説明する。

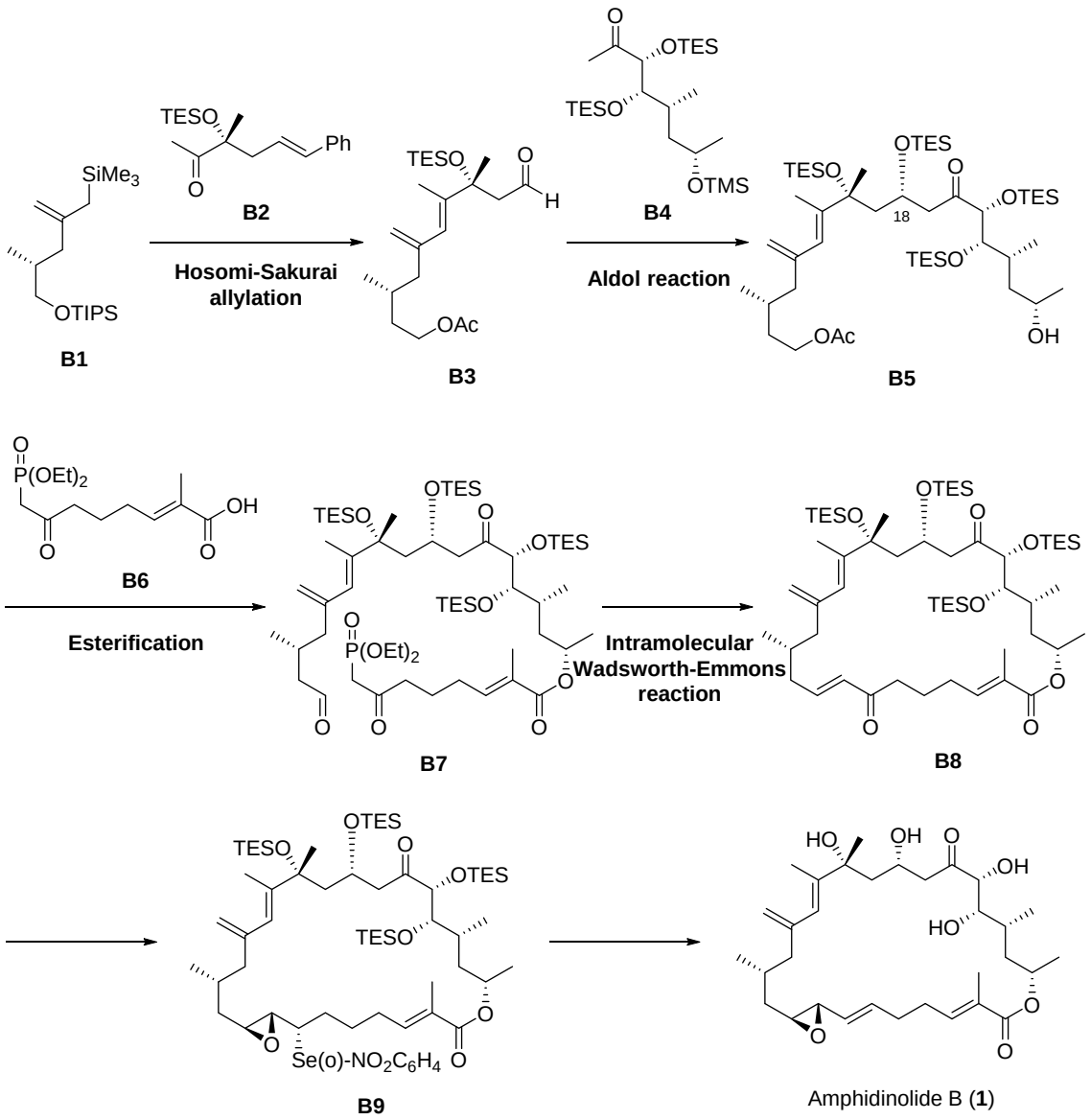
まず Fürstner らによって達成された amphidinolide H (**3**)の合成 [17] について説明する(Scheme 2)。Fürstner らは 2007 年にアルドール反応や閉環メタセシス反応などを鍵反応とした合成戦略により amphidinolide H (**3**)及び G (**2**)の全合成を達成した。アルコール **A1** とカルボン酸 **A2** とのエステル化によって得られた **A3** を、アルデヒド **A4** とのアルドール反応に付すことで **A5** を合成した。本反応では、ケトンα位の水酸基とアルデヒドの間に形成されるキレートを利用して、高い立体選択性(*S*:*R* = >10:1)で C_{18} 位の不斉点を構築することに成功している。続いて、ケトンα位の水酸基の保護基を PMB 基から TES 基に変換した後、**A6** との Stille カップリングによりジエン構造を構築することで **A7** へと誘導した。さらに、**A7** に対してアリルエポキシドを導入した後、閉環メタセシス反応によって 26 員環骨格を構築することで amphidinolide H (**3**)の初の全合成を達成した。また、Fürstner らは同様の合成戦略を用いることで 2009 年に amphidinolide B (**1**)の全合成 [18] も達成している。



Scheme 2

次に、Carter らによって達成された amphidinolide B (**1**)の合成[19]について説明する (Scheme 3)。Carter らは 2008 年にアルドール反応や分子内 Horner-Wadsworth-Emmons 反応などを鍵反応とした合成戦略にて amphidinolide B (**1**)の全合成を達成した。アリルシラン **B1** とケトン **B2** を細見・櫻井アリル化反応によってカップリングした後、ジエン構造を導入することで**B3**を合成した。さらに、得られた **B3** とケトン **B4** をアルドール反応の条件に付すことで **B5** を合成した。本反応は高収率で進行したものの、ケトンα位の水酸基を保護する TES 基がキレート形成を阻害したため、その立体選択性はほとんど発現しなかった (*S*:*R* = 1.2:1)。続いて、**B6** とのエステル化により **B7** を合成した後、分子内 Horner-Wadsworth-Emmons 反応を用いることで 26 員環骨格を構築することに成功した。さらに、**B8** に対して CBS 還元、エポキシ化、光延反応によるセレニ

ド導入の 3 工程を経ることで **B9** へと誘導し、脱離反応を用いてアリルエポキシドを構築することで amphidinolide B (**1**)の初の全合成を達成した。



Scheme 3

このように、現在までに 2 つのグループによって amphidinolide 類(**1-3**)の全合成は達成されているものの、その詳細な生物活性試験の結果や構造活性相関に関する研究は未だ報告例がない。そこで、筆者は amphidinolide 類(**1-3**)のサンプル供給及びに構造活性相関の解明を目標として、その合成研究を開始した。

第 2 章　Amphidinolide B の合成研究

第 1 節　Amphidinolide B の合成戦略

筆者は amphidinolide B (**1**)を合成するにあたって収束的合成法を採用することとした。収束的合成法は、目的化合物を複数の部分構造に分割し、官能基や不斉中心を導入した後に結合させる方法論である。**1** は 9 つの不斉炭素に加えて、エキソオレフィンを含むジエン構造やアリルエポキシドなど不安定な官能基を数多く有している(Figure 6)ため、本化合物の合成においては収束的合成法が有効であると考えた。

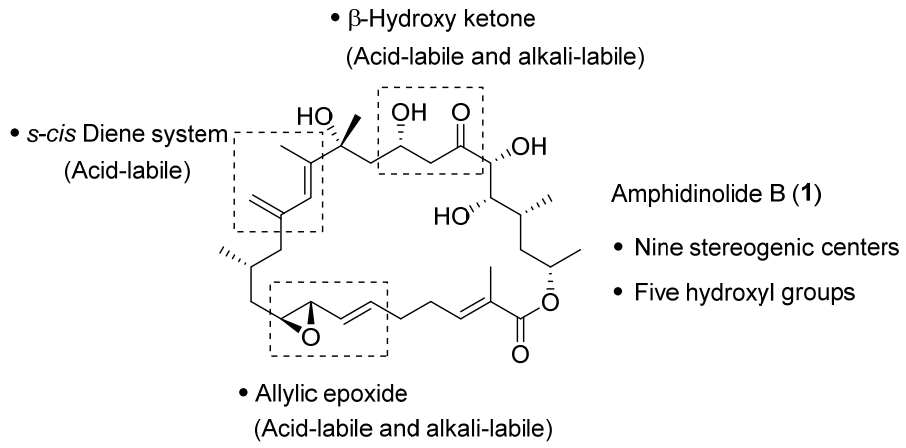
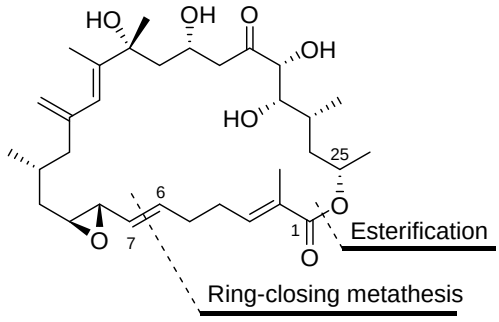


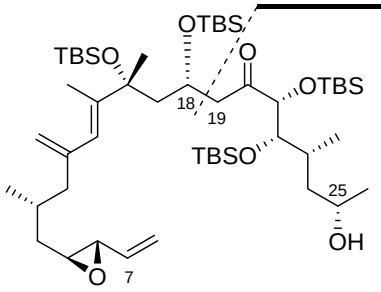
Figure 6

まず **1** は C_7-C_{26} 部分に相当する fragment ABC (**4**)と C_1-C_6 部分に相当する fragment D (**5**)からエステル化、閉環メタセシス反応を経て合成できると考えた。26 員環骨格の構築法に関しては、酸・塩基性条件に不安定なアリルエポキシドを合成の最終段階で導入できるという理由から、マクロラクトン化ではなく閉環メタセシス反応を選択した。さらに **4** はアルドール反応を用いることで C_7-C_{18} 部分に相当する fragment BC (**6**)と C_{19}-C_{26} 部分に相当する fragment A (**7**)から誘導することとし、**6** は大井・西山らによって開発されたジエン構築法 [15g] を利用することで不飽和ケトン **8** から得られると考えた。また、**8** は C_{14}-C_{18} 部分に相当する fragment B (**9**)と C_7-C_{13} 部分に相当する fragment C (**10**)からアセチリドカップリングを用いることで合成することとした(Scheme 4)。なお、水酸基の保護基に関しては、穏和な条件で脱保護が可能なシリル系保護基(TBS 基、TBDPS 基)及び PMB 基を用いることとした。

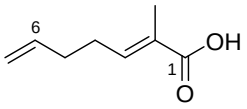


Amphidinolide B (**1**)

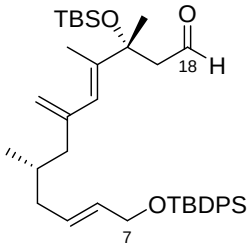
Aldol reaction



fragment ABC (**4**)



fragment D (**5**)



fragment BC (**6**)

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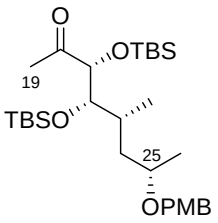
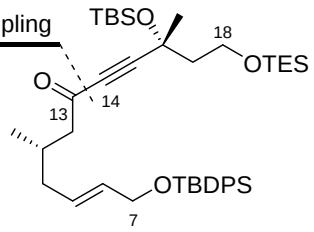


fragment A (**7**)

Diene system construction

Acetylide coupling



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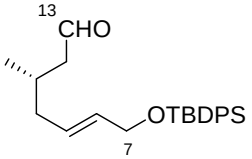
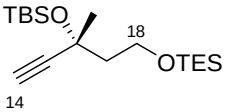


fragment C (**10**)

+



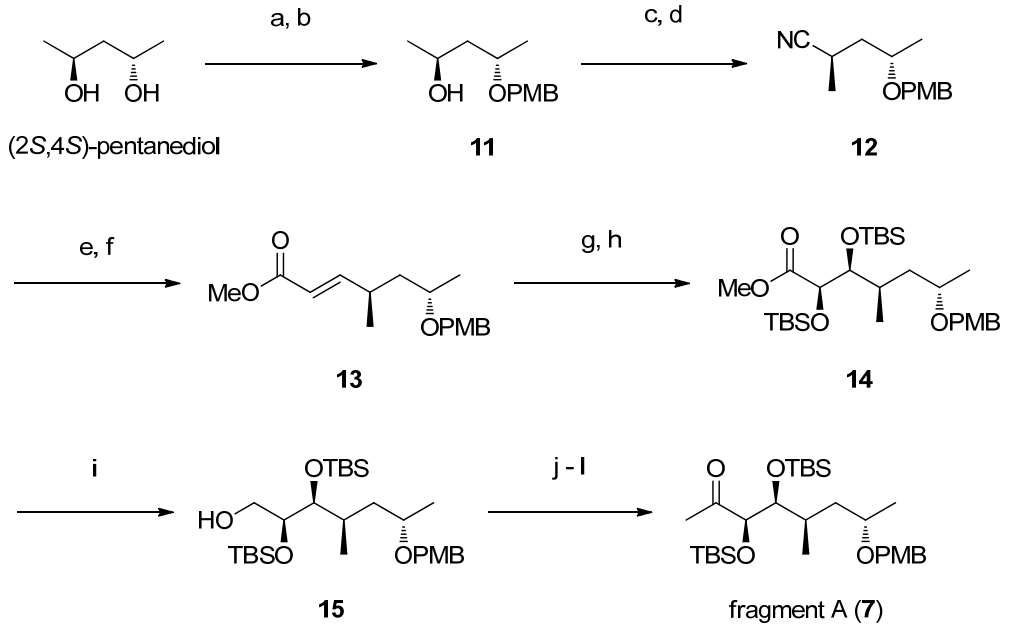
fragment B (**9**)

Scheme 4

第 2 節　Fragment A-D の合成

第 1 項　Fragment A の合成

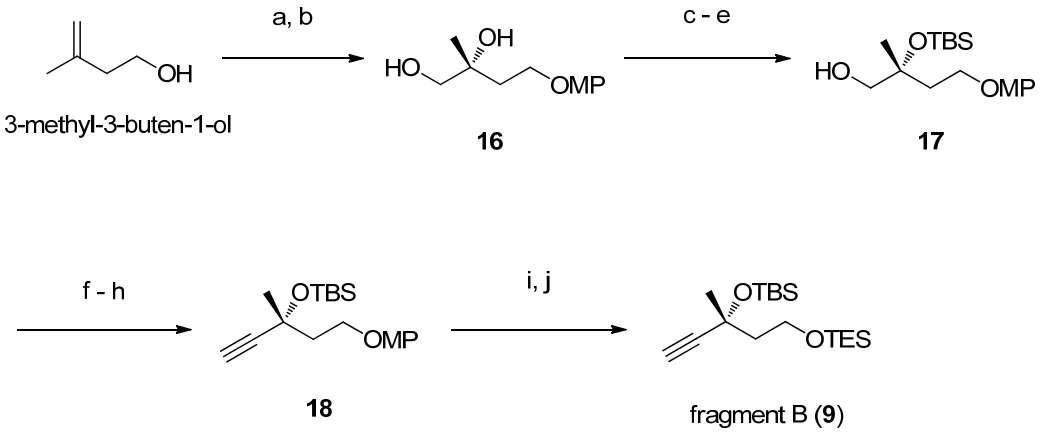
出発原料である(2*S*,4*S*)-pentanediol の一方の水酸基を PMB 基で保護することでアルコール **11** を合成した後、もう一方の水酸基をトシル化、ニトリル化によって一炭素増炭することで、既知化合物であるニトリル体 **12**[15f] を合成した。続いて DIBAL を用いてアルデヒドへとし還元し、Wittig 反応によって α,β-不飽和エステル **13** を合成した。**13** に対して Sharpless の不斉ジヒドロキシル化 [20] を行って単一でジオールを合成した後、水酸基を TBS 基で保護することでエステル **14** へと誘導した。LAH を用いてエステル **14** を還元したところ TBS 基が脱保護されたため、DIBAL による還元を行うことでアルコール **15** を得た。最後に、**15** の一級水酸基を SO_3・pyr.、DMSO[21] によってアルデヒドへと酸化した後、MeLi を用いて増炭、生じた二級水酸基を再び SO_3・pyr.、DMSO によって酸化することで fragment A (**7**)を 8 工程、総収率 36%で合成した(Scheme 5)。



Scheme 5. Synthesis of fragment A (**7**). Reagents and conditions: (a) *p*-anisaldehyde dimethyl acetal, CSA, DMF, rt, 86%; (b) DIBAL, CH_2Cl_2, -78 °C, 78% ; (c) TsCl, Et_3N, DMAP, rt; (d) NaCN, DMSO, rt, 64% (2 steps); (e) DIBAL, CH_2Cl_2, -78 °C; (f) Ph_3PCHCO_2Me, CH_2Cl_2, rt, 76% (2 steps); (g) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C, 78%; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 88%; (i) DIBAL, CH_2Cl_2, -78 °C, 91%; (j) SO_3･pyr., DIPEA, DMSO, CH_2Cl_2, rt; (k) MeLi, Et_2O, -78°C; (l) SO_3･pyr., DIPEA, DMSO, CH_2Cl_2, rt, 75% (3 steps).

第 2 項　Fragment B の合成

3-Methyl-3-buten-1-ol を既知の方法[15m]に従い、光延反応によって 1 級水酸基をメトキシフェニル基で保護した後、bis(dihydroquinidine)-pyridazine を配位子として用いた不斉ジヒドロキシル化に付すことで高エナンチオ選択的(94%ee)にジオール **16** を合成した。さらに、再結晶を行うことで **16** の光学純度を 99%ee 以上にまで高めることに成功した。続いて、**16** の一級水酸基を Piv 基、三級水酸基を TBS 基で保護した後、Piv 基を DIBAL 還元に付し脱保護することで、三級水酸基のみを TBS 基で保護したアルコール **17** を合成した。**17** の一級水酸基を SO_3-pyr.、DMSO によってアルデヒドへと酸化した後、四臭化炭素、トリフェニルホスフィンによってジブロモオレフィンへ誘導した。さらに、Corey-Fuchs 法[22]の変法として、塩基に EtMgBr を用いることでアルキン **18** を合成した。最後にメトキシフェニル基を CAN によって脱保護し、TES 基で再保護することで fragment B (**9**)を 8 工程、総収率 61%で合成した（Scheme 6）。

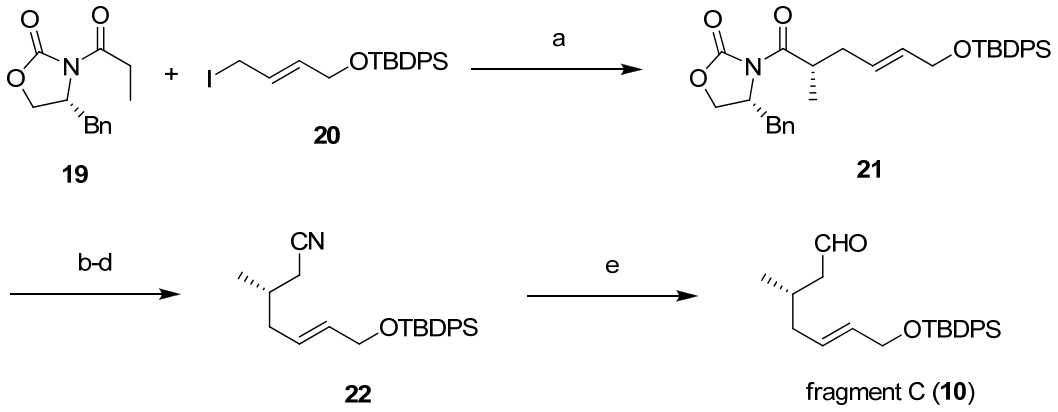


Scheme 6. Synthesis of fragment B (**9**). Reagents and conditions: (a) *p*-methoxyphenol, Ph_3P, DEAD, THF, 80 °C, 91%; (b) K_2CO_3, $K_3Fe(CN)_6$, K_2OsO_4･$2H_2O$, $(DHQD)_2PYDZ$, *t*-BuOH/H_2O, 0 °C, 99%, 94%ee; (c) PivCl, pyr., rt, 95%; (d) TBSOTf, 2,6-lutidine, rt, 82%; (e) DIBAL, CH_2Cl_2, -78 °C, 95%; (f) SO_3-pyr, DIPEA, DMSO,CH_2Cl_2, rt, 98%; (g) CBr_4, PPh_3, Et_3N, tol., rt, 98%; (h) EtMgBr, THF, 0 °C, 96%; (i) CAN, MeCN/H_2O, rt, 94%; (j) TESCl, imid., CH_2Cl_2, rt, 95%.

第 3 項　Fragment C の合成

既知のオキサゾリジノン **19**[23]と、*cis*-1,4-butenediol から 5 工程で得られるヨウ化アリル化合物 **20**[24]を出発原料として、fragment C (**10**)の合成を行った。まず、**19** 及び **20** を Evans の不斉アルキル化[25]の条件に付すことで、C_{11} 位の不斉点を構築し、**21** を単一で合成することに成功した。さらに、LAH を用いて不斉補助基を除去し、トシル化、ニトリル化を行うことでニトリル体 **22** へと誘導した。

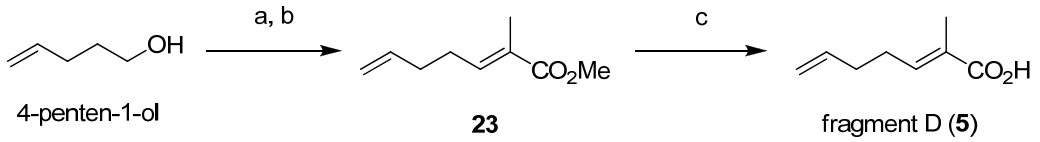
最後に、DIBAL を用いてニトリルをアルデヒドへと還元することで、5 工程、総収率 59%で fragment C (**10**)の合成を達成した(Scheme 7)。



Scheme 7. Synthesis of fragment C (**10**). Reagents and conditions: (a) LHMDS, **20**, THF, -40→-20 °C, 81%; (b) LAH, THF, 0 °C, 81%; (c) TsCl, pyr., rt, quant.; (d) NaCN, DMSO, 40 °C, 91%; (e) DIBAL, CH_2Cl_2, -78 °C, 98%.

第 4 項　Fragment D の合成

4-Penten-1-ol を出発原料として、fragment D (**5**)の合成を行った。まず、一級水酸基を PCC[26] によってアルデヒドへと酸化し、Wittig 反応によって増炭することで不飽和エステル **23** へと誘導した。最後に、塩基性条件下でエステルを加水分解することで、3 工程、総収率 32%で fragment D (**5**)の合成を達成した(Scheme 8)。

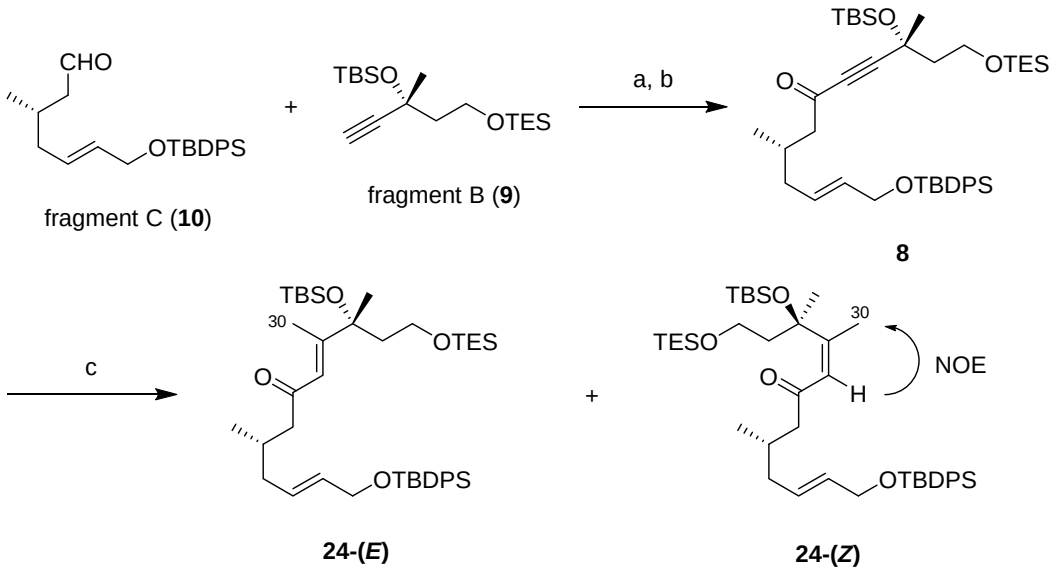


Scheme 8. Synthesis of fragment D (**5**). Reagents and conditions: (a) PCC, CH_2Cl_2, rt; (b) $Ph_3PC(CH_3)CO_2Me$, benzene, rt, 34% (2 steps); (c) NaOH, THF/H_2O, 80 °C, 93%.

第 3 節　Fragment BC の合成

第 1 項　アセチリドカップリング

前節で amphidinolide B (**1**)を構成する全てのフラグメントの合成を達成したので、合成した fragment B (**9**)及び C (**10**)を用いてカップリングを行い、アルドール反応前駆体である fragment BC (**6**)の合成を行った。まず、**9** から *n*-BuLi を用いてアセチリドを調製し、そのアセチリドを **10** のアルデヒドに求核付加させることで両フラグメントを結合した。そして得られたアルコールに対して TPAP 酸化 [27] を行うことでケトン **8** を合成した後、CuI 及び MeLi から調製した Gilman 試薬を用いて 1,4-付加反応を行った。その結果、目的とする **24-(*E*)**を高い位置選択性(*E*:*Z* = 9:1)で得ることに成功した。*E* 体及び *Z* 体の構造決定に関しては、両異性体をシリカゲルカラムクロマトグラフィーで分割した後、^{13}C-NMR における C_{30} 位の化学シフト値を比較することで決定した。すなわち *E* 体の C_{30} 位のシグナル(16.2 ppm)は、立体障害のために Z 体のシグナル(26.0 ppm)に比べて高磁場にシフトしていることが観測された。また **24-(*Z*)**に関しては、Scheme 9 に示すような NOE 相関が観察されたことからも、その立体化学について決定することができた。



Scheme 9. Synthesis of compound **24-(*E*)**. Reagents and conditions: (a) *n*-BuLi, THF, -78→0 ^{o}C, then **10** in THF, rt, 96%; (b) TPAP, NMO, MS4A, CH_2Cl_2, rt, 84%; (c) MeLi, CuI, Et_2O, -78 →-30 ^{o}C, 90% (*E*:*Z* = 9:1)

次に Gilman 試薬を用いた 1,4-付加反応の幾何選択性について考察する。Et_2O 溶媒中における Gilman 試薬を用いた 1,4-付加反応では、-78 °C のような低温下

においても Figure 7 に示す様な平衡が成立することが Corey らによって報告されている[28]。

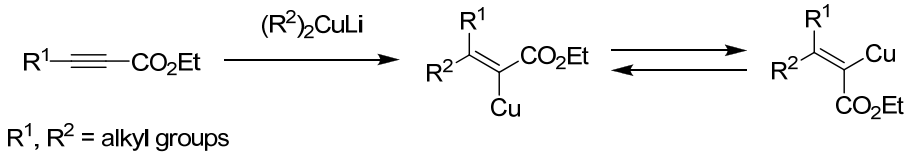


Figure 7

この報告をもとに反応機構について考察を行うと、本反応では **A** と **B** の二つの中間体の間に平衡関係が成立することが予測できる(Figure 8)。続いて、立体効果の観点から二つの中間体を比較すると、**A** は立体障害の大きな二つのアルキル基が *trans* の関係にあるのに対して、**B** は *cis* の関係にあることが分かる。このためエネルギー的に有利である **A** の方向に平衡が偏り、最終的に **A** からの生成物である **24-(*E*)**が優先して得られたと考えられる。

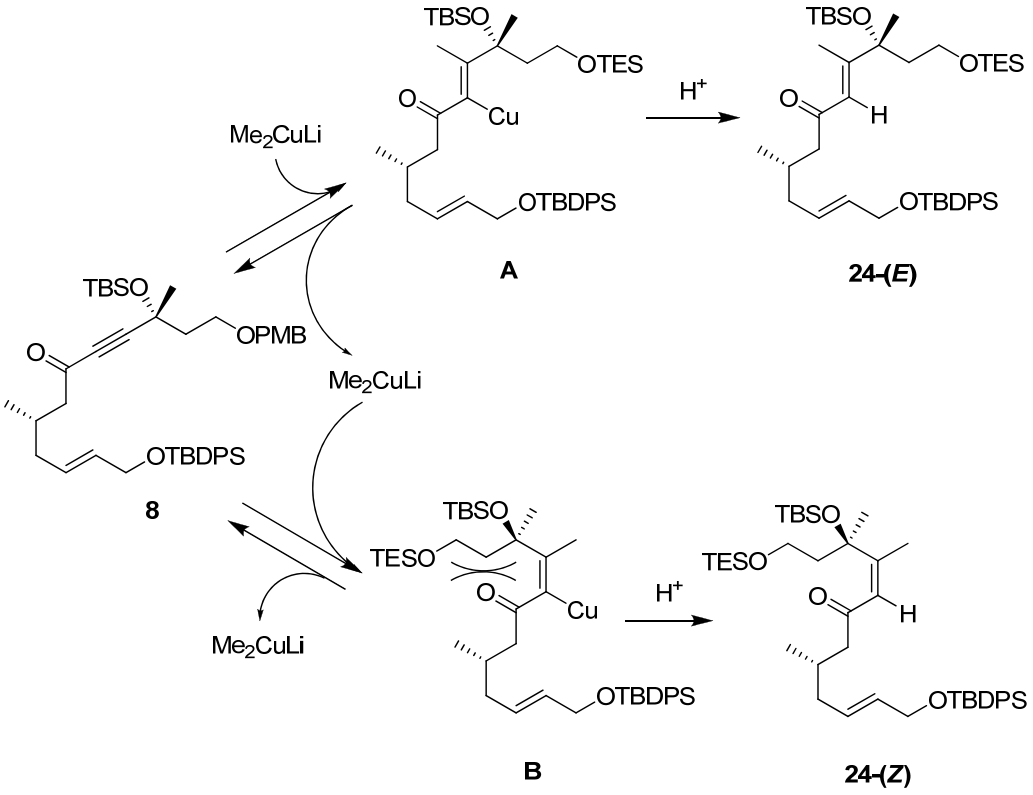
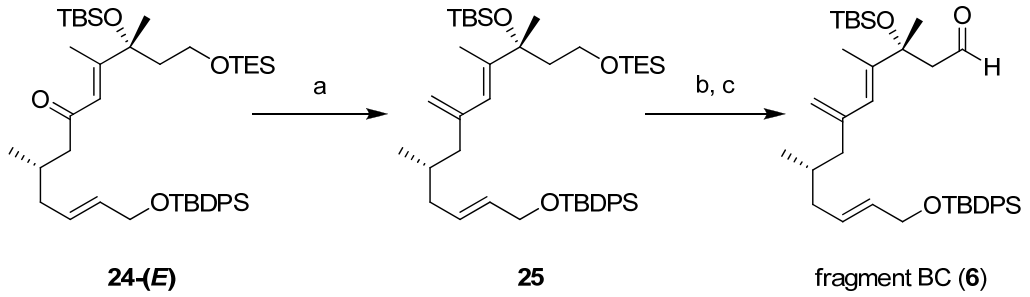


Figure 8

第 2 項　ジエン構造の構築

続いて、大井・西山らの方法に従って **24-(*E*)**に対して Wittig 反応を行うことで特徴的なジエン構造を有する **25** を合成した。最後に、PPTS を用いて TES 基を除去した後、一級水酸基を Dess-Martin 試薬 [29] によってアルデヒドへと酸化することで、アルドール前駆体である fragment BC (**6**)の合成を達成した(Scheme 10)。



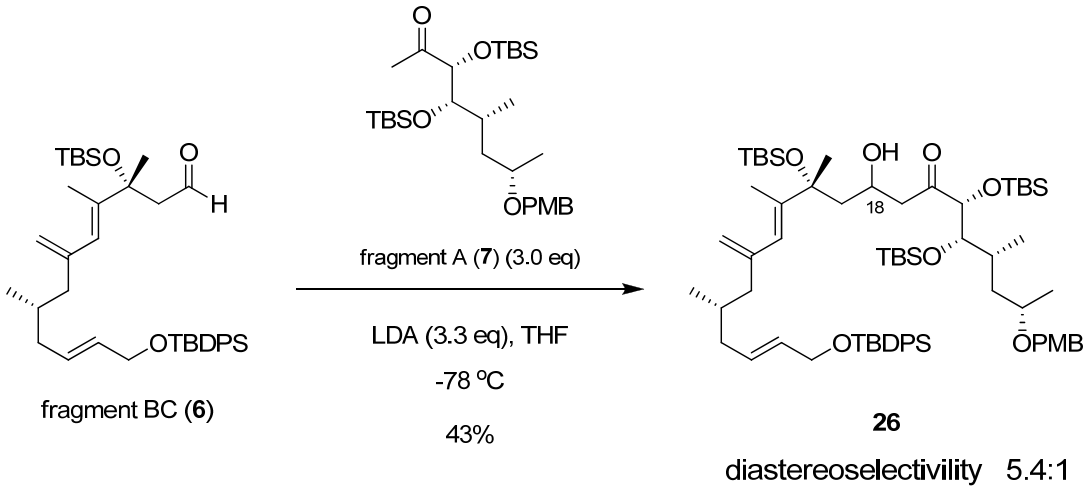
24-(*E*)　　**25**　　fragment BC (**6**)

Scheme 10. Synthesis of fragment BC (**6**). Reagents and conditions: (a) *n*-BuLi, Ph_3PCH_3Br, THF, 0 ºC→rt, 91%; (b) PPTS, CH_2Cl_2/MeOH, 0 ºC, 93%; (c) DMP, CH_2Cl_2, rt, 96%.

第 4 節　アルドール反応

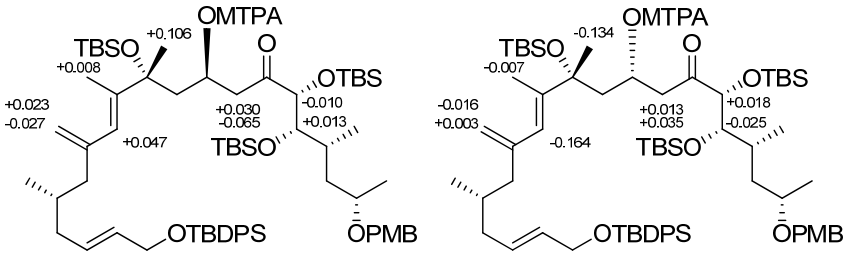
第 1 項　アルドール体の合成及び構造決定

前節においてアルドール前駆体である fragment BC (**6**)の合成を達成したので、fragment A (**7**)とのアルドール反応を検討した。まず、塩基として LDA を用いて、0°C で fragment A (**7**)の脱プロトン化を行った。次に反応系の温度を-78 °C まで下げ、fragment BC (**6**)を滴下したところ、アルドール生成物 **26** を収率 43%、ジアステレオ選択比 5.4:1 で合成することに成功した(Scheme 11)。



Scheme 11

アルドール体 **26** で新たに生じた C_{18} 位の水酸基の絶対立体化学は、新 Mosher 法[30]を用いて決定することとした。まず、両ジアステレオマーをシリカゲルカラムクロマトグラフィーで分割した後、それぞれ(*R*)及び(*S*)-MTPA エステルへと誘導した。この後、両エステル体における ^{1}H-NMR の化学シフト値を比較したところ、Figure 9 に示すような結果が得られた。この結果から、目的とする **26-(*S*)** は minor ジアステレオマーであることが判明した。



26-major (undesired) **26-minor** (desired)

$\Delta\delta$ (ppm)= δ[(*S*)-MTPA]-δ[(*R*)-MTPA]

Figure 9

アルドール反応におけるジアステレオ選択性の発現機構は Figure 10 に示すような遷移状態モデルを用いて説明することができる。まず、fragment A (**7**)と fragment BC (**6**)が有する 2 本の C-O 結合の双極子反発を考慮すると、両結合がアンチペリプラナーの位置関係に存在する model A 及び B が遷移状態として考えられる。そして 2 つの遷移状態モデルのうち、立体的に嵩高い R'基が 6 員環の外側を向く model A が立体化学の観点から有利であるため、主生成物として **26-(*R*)**が得られると予測される。

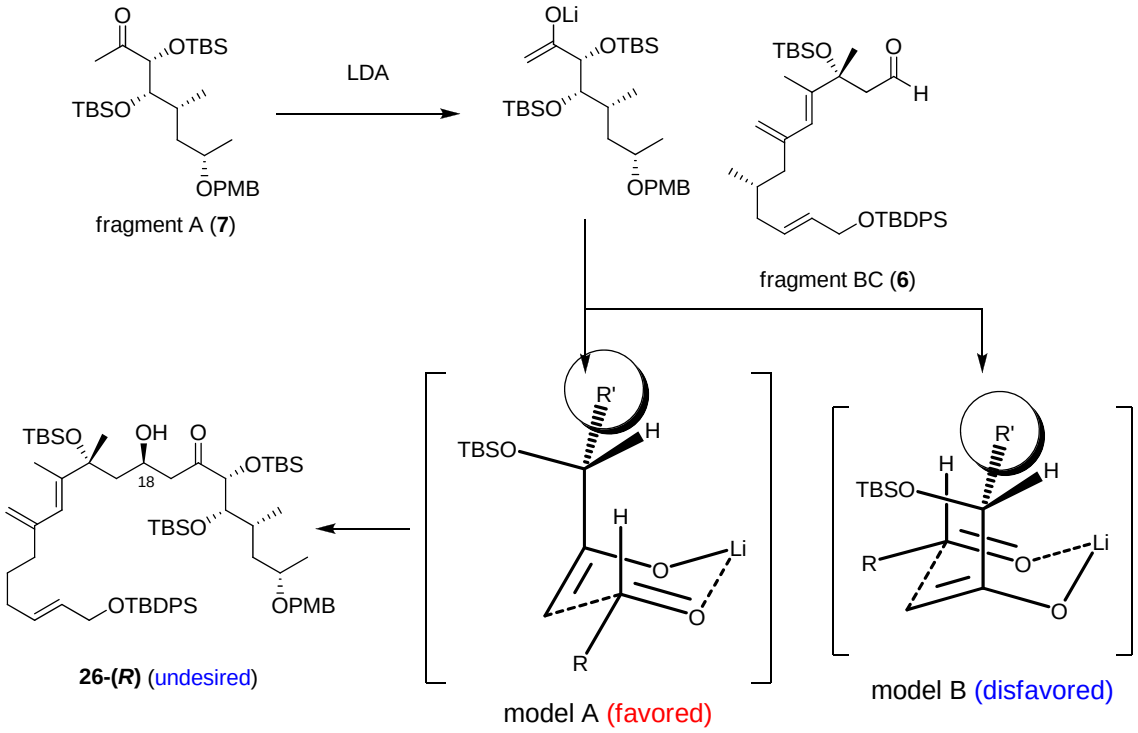


Figure 10

第 2 項　アルドール反応の条件検討

前項において LDA を塩基として用いることでアルドール体 **26** を合成することには成功したが、その収率は 43%と満足のいくものではなかった。これらの原因としては fragment A (**7**)への脱プロトン化が良好に進行していないことが考えられたため、fragment A (**7**)の脱プロトン化の温度を 0 ºC から室温まで昇温し、LHMDS、NaHMDS、KHMDS など種々の塩基を検討した(Table 1)。その結果、NaHMDS、KHMDS を用いた場合は反応が進行しなかったが、LHMDS を用いた際に収率 81%、ジアステレオ選択性 1:4.1 でアルドール生成物 **26** が得られることが分かった(entries 2-4)。続いて、アルドール反応におけるジアステレオ選択性を向上させるために、反応温度の検討を行った。その結果、fragment BC (**6**)を滴下する際の温度が-20 ºC の場合、ジアステレオ選択性は大きく向上し、目的とする **26-(*S*)**が優先的に得られることを見出した(entry 6)。一方で、反応温度が 0 ºC 以上の場合は水酸基の脱離が進行し、副生成物としてエノン体が生じたため、その収率は大きく低下した。

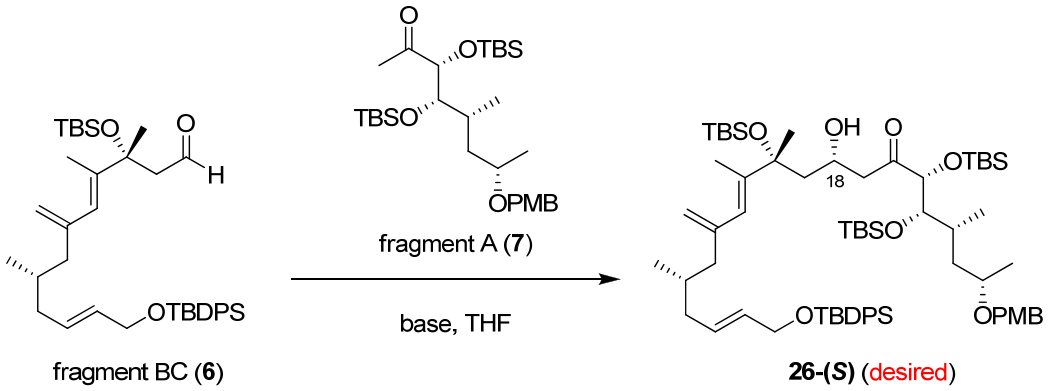


Table 1

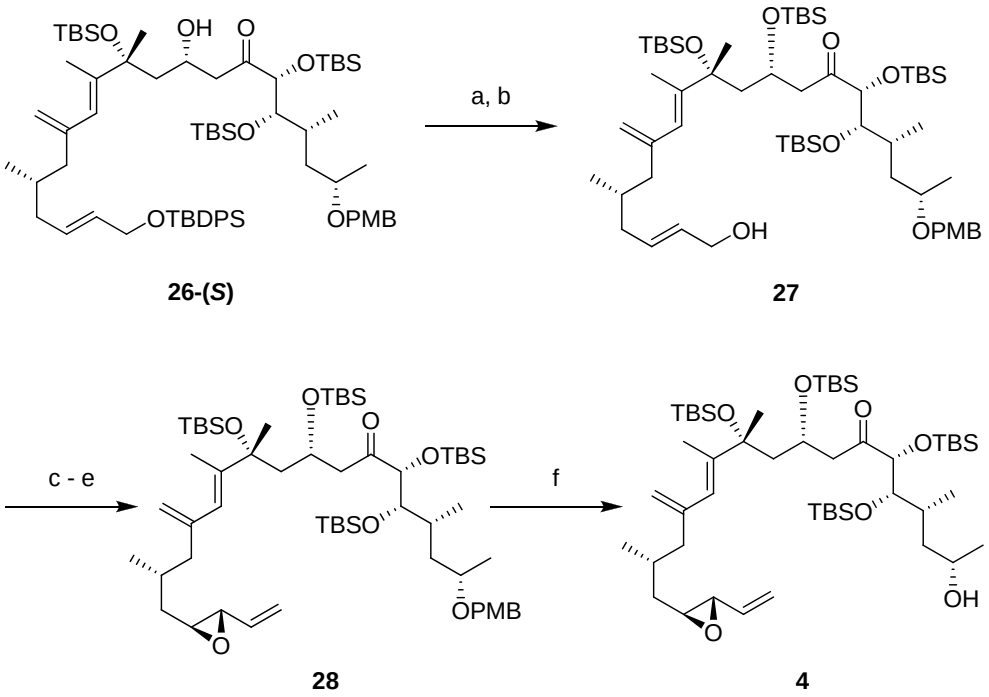
entry	base	temp.(enolate) (ºC)	temp.(reaction) (ºC)	yield (%)	selectivility (*S*:*R*)
1	LDA	0	-78	43	1 : 5.4
2	NaHMDS	r.t.	-78	no reaction	———
3	KHMDS	r.t.	-78	no reaction	———
4	LHMDS	r.t.	-78	81	1 : 4.1
5	LHMDS	r.t.	-40	63	1.3 : 1
6	LHMDS	r.t.	-20	72	2.5 : 1

反応温度が-20 ºC 以上ではジアステレオ選択性がほぼ一定であることを考慮すると、反応温度が上昇すると立体選択性が逆転する理由に関してはアルドール反応における熱力学的支配が強く影響していると推測される。すなわち、反応温度が上昇することで逆アルドール反応が進行し、2 つのジアステレオマーの間に平衡関係が成り立つ。その結果、エネルギー的に安定な構造である *S* 体の方向に平衡が偏り、**26-(*S*)**が優先的に得られると思われる。**26-(*S*)**が **26-(*R*)**よりも熱力学的に安定な理由に関しては、今後、計算科学などを利用することで明らかにしていきたい。

第 5 節　Amphidinolide B の全合成

第 1 項　アリルエポキシド構造の構築

前節のアルドール反応によって得られた **26-(*S*)**に対して、アリルエポキシド構造の導入を行った(Scheme 12)。まず、**26-(*S*)**の 2 級水酸基を TBS 基で保護した後、酢酸・水存在下で TBAF を作用させる[31]ことで TBDPS 基を選択的に脱保護し、アリルアルコール **27** を得た。続いて、化合物 **27** を Sharpless 不斉エポキシ化[32]の条件に付すことでエポキシアルコールを単一で得た後、Dess-Martin 酸化、Wittig 反応の 2 工程を経ることで、アリルエポキシド構造を有する化合物 **28** を高収率で合成することに成功した。最後に PMB 基を DDQ で脱保護することで、fragment ABC (**4**)の合成を達成した。



26-(*S*)　**27**　**28**　**4**

Scheme 12. Synthesis of fragment ABC (**4**). Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 98%; (b) TBAF, AcOH, H_2O, DMF/THF, rt, 79% (89% conv.); (c) Ti(O*i*-Pr)$_4$, TBHP, (+)-DET, MS4A, CH_2Cl_2, -20 ^oC, 84% (92% conv.); (d) DMP, pyridine, 0 ^oC, 97%; (e) NaHMDS, Ph_3PCH_3Br, CH_2Cl_2, 0 ^oC, 98%; (f) DDQ, CH_2Cl_2/buffer, rt, 83%.

第 2 項　エステル化の条件検討

前項で合成した fragment ABC (**4**)と fragment D (**5**)を用いて、山口法によるエステル化[33]を検討した(Table 2)。まず、fragment D (**5**)、Et_3N、2,4,6-trichlorobenzoyl chloride を室温にて撹拌することで酸無水物を発生させた後、fragment ABC (**4**)

と DMAP を加えた(entry 1)。その結果、カップリングは迅速に進行したものの、目的とするエステル体 **29** に加えて、三置換オレフィンの一つが異性化した化合物 **30** が副生成物として得られることが分かった。副反応であるオレフィンの異性化には Figure 11 に示す 2 つの反応経路が考えられる。すなわち、酸無水物を発生させる段階でオレフィンが異性化する route 1 とエステル体 **29** が生成した後にオレフィンが異性化する route 2 である。まず route 1 の経路を想定して、酸無水物の発生温度を下げることでオレフィンの異性化を抑えることを検討した (entries 2, 3)。しかし、反応温度を-20 ºC にまで下げてもオレフィンの異性化を抑えることができず、副生成物 **30** が一定の割合で得られた。そこで、次は route 2 を想定して、fragment ABC (**4**)と DMAP を加える際の反応温度について検討を行った(entry 4)。その結果、反応温度を 0 ºC まで下げた際に、オレフィンの異性化が生じることなく目的物 **29** のみを合成することに成功した。この結果から、エステル体 **29** が生成した後にオレフィンの異性化が進行する route 2 の経路が正しいことが分かった。

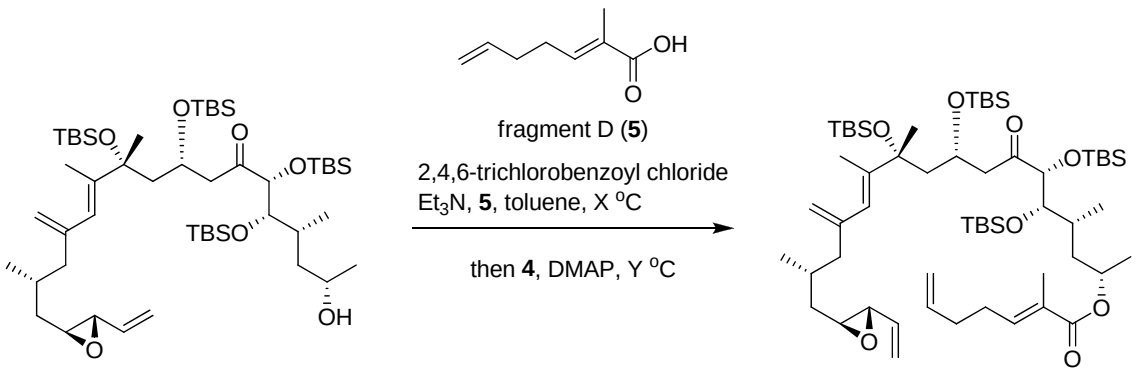
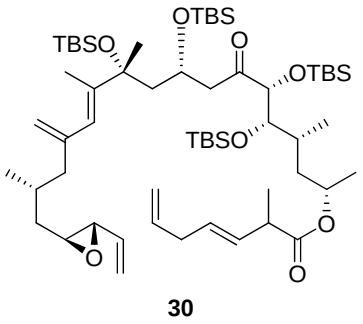


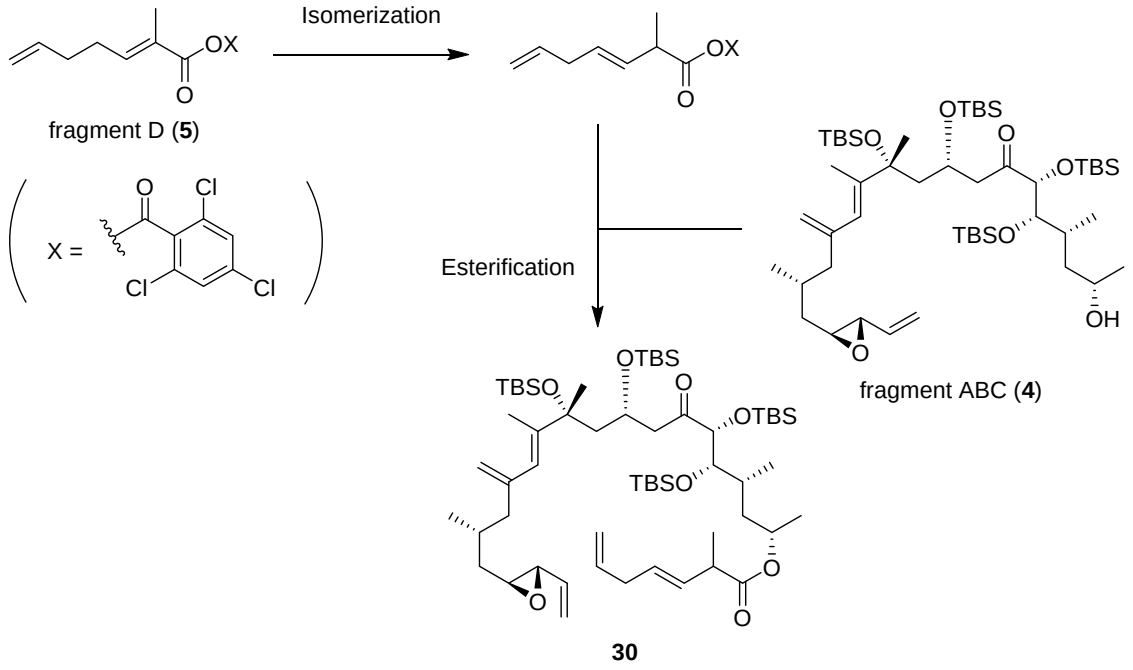
Table 2

entry	temp. (X °C)	temp. (Y °C)	yield (**29**+**30**)	**29** : **30**
1	r.t.	r.t.	65%	3 : 1
2	0	r.t.	88%	2 : 1
3	-20	r.t.	77%	2 : 1
4	0	0	98%	1 : 0



30

route 1



route 2

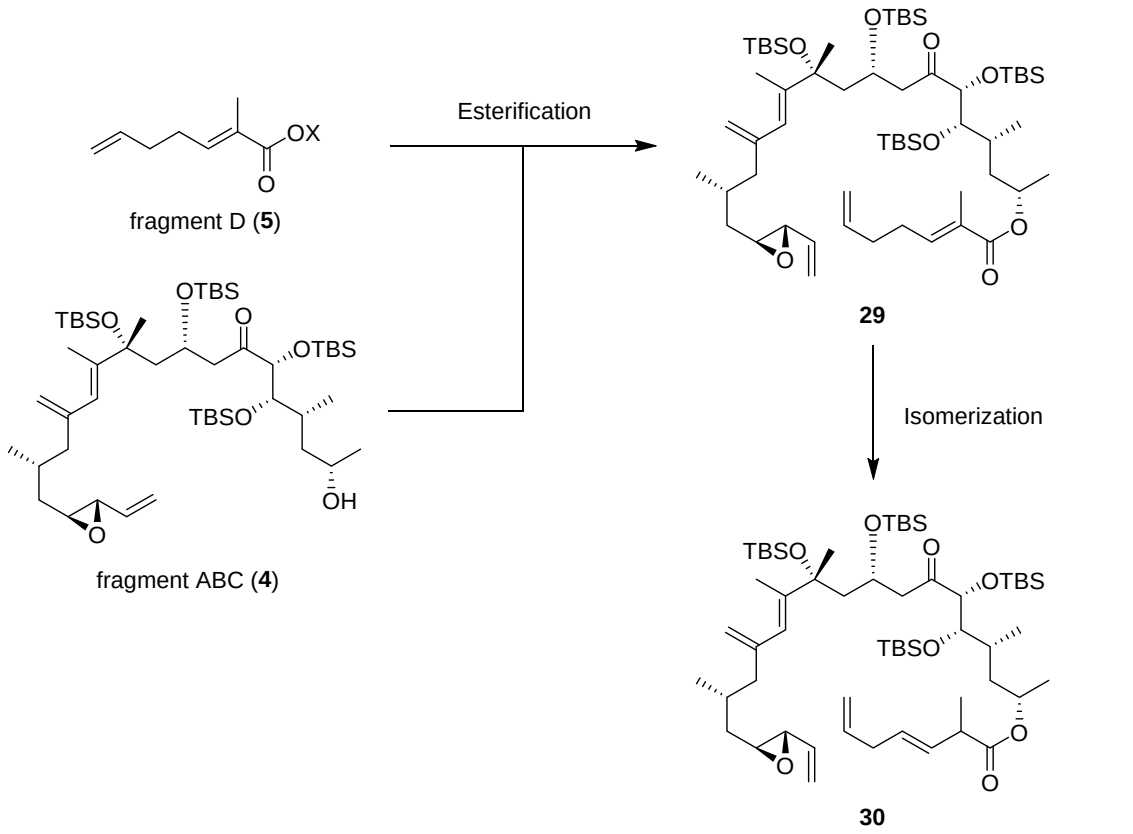
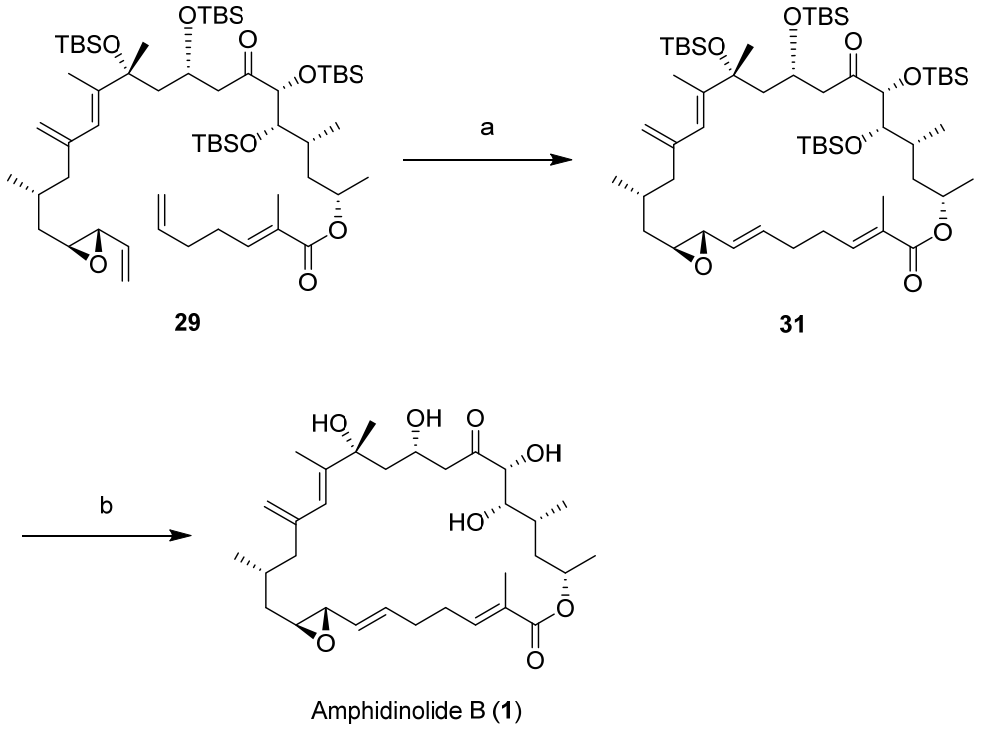


Figure 11

第 3 項　Amphidinolide B の全合成

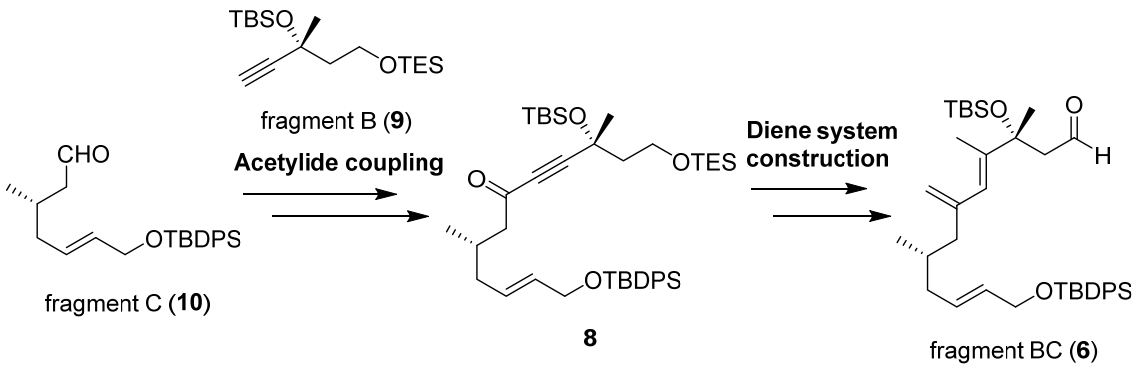
前項でエステル化によって得られた化合物 **29** を用いて、26 員環骨格の構築を行った(Scheme 13)。第二世代 Grubbs 触媒[34]を用いて閉環メタセシス反応を行ったところ、副生成物である *Z* 環化体を得ることなく、目的とする *E* 環化体 **31** のみを高収率で合成することに成功した。最後に、TASF を用いて全ての TBS 基を同時に脱保護することで、amphidinolide B (**1**)の全合成を達成した[35]。合成された **1** のスペクトルデータは天然物と良い一致を示した。



Scheme 13. Total synthesis of amphidinolide B (**1**). Reagents and conditions: (a) Grubbs' 2nd catalyst, benzene, rt, 81%; (b) TASF, THF/DMF, H_2O, rt, 86%

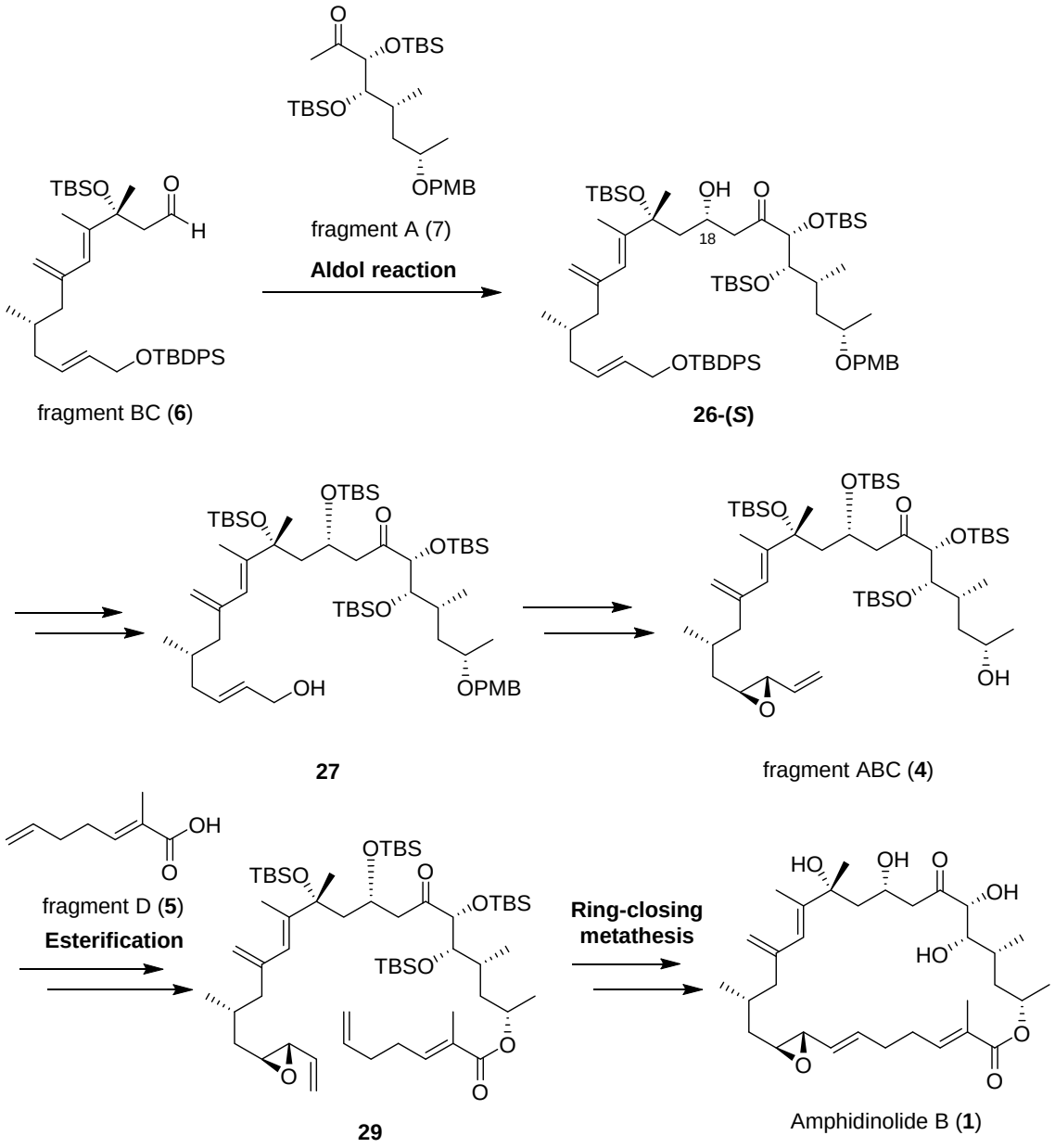
第 6 節　第 2 章まとめ

第 2 章においては、26 員環マクロライド化合物 amphidinolide B (**1**)の合成について述べた。**1** を構成する 4 つの fragment に関しては、高収率で合成することに成功したので、続いて fragment B (**9**)及び C (**10**)のカップリングを行った。まず、**9** のリチウムアセチリドに対して **10** を加えることで両フラグメントをカップリングし、続く TPAP 酸化により **8** を合成した。さらに、Gilman 試薬を用いた 1,4-付加反応、Wittig 反応により本化合物の特徴的構造であるジエン構造を効率的に構築することに成功した。この後、TES 基の脱保護、Dess-Martin 酸化を経て、アルドール前駆体である fragment BC (**6**)を合成した(Scheme 14)。



Scheme 14

続いて、fragment BC (**6**)及び A (**7**)におけるアルドール反応の条件検討を行ったところ、反応温度-20 ºC において LHMDS を用いた際に、収率 74%、ジアステレオ選択比 2.5:1 で目的とするアルドール体 **26-(*S*)**が得られることが分かった。得られた **26-(*S*)**の水酸基を TBS 基で保護した後、TBDPS 基を選択的に除去することでアルコール **27** へと誘導した。さらに、Sharpless の不斉エポキシ化、Dess-Martin 酸化、Wittig 反応、PMB 基の脱保護の 4 工程を経て、アリルエポキシドを有する fragment ABC (**4**)の合成に成功した。続いて、fragment D (**5**)とのエステル化の条件を検討したところ、山口法を用いることで定量的に環化前駆体 **29** が得られることが分かった。最後に、第二世代 Grubbs 触媒を用いた閉環メタセシス反応によって 26 員環骨格を構築した後、TASF を用いて全ての TBS 基を除去することで amphidinolide B (**1**)の全合成を達成した(Scheme 15)。

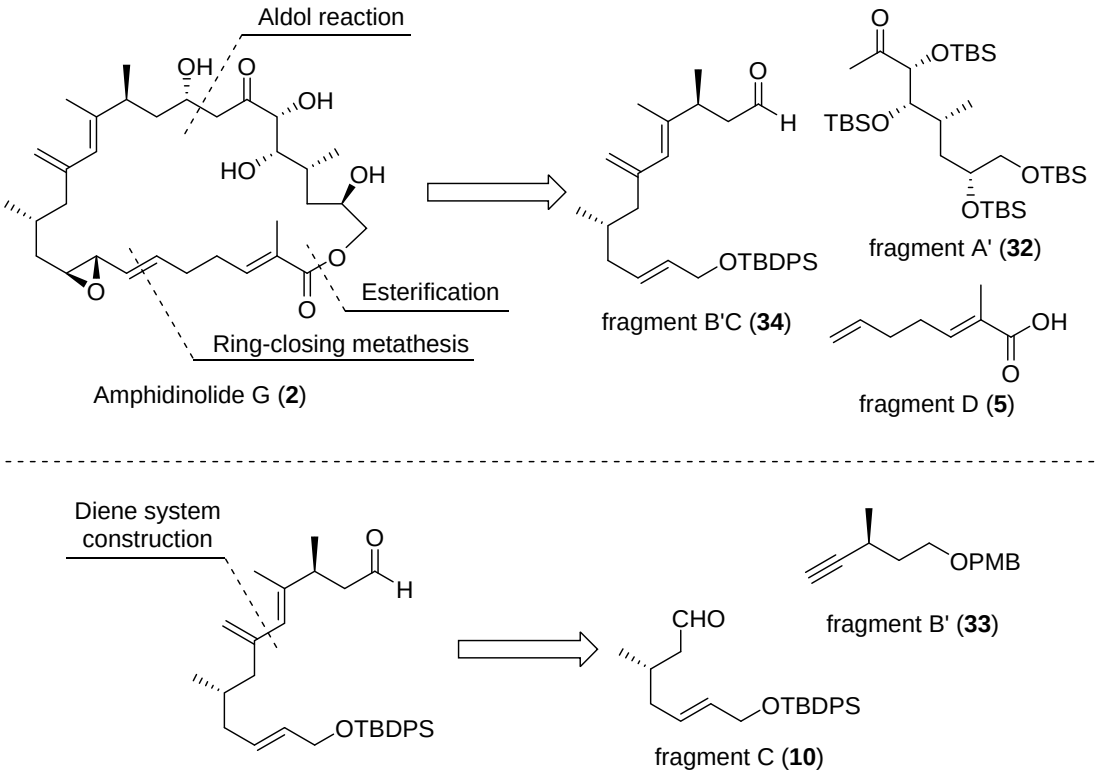

fragment A (7)
Aldol reaction
fragment BC (6)
26-(S)
27
fragment ABC (4)
fragment D (5)
Esterification
Ring-closing metathesis
29
Amphidinolide B (1)

Scheme 15

第 3 章　Amphidinolide G 及び H の合成研究

第 1 節　Amphidinolide G 及び H の合成戦略

前章において amphidinolide B (**1**)の全合成を達成したので、続いて **1** と同様に強力な細胞毒性を有する amphidinolide G (**2**)及び H (**3**)の合成研究に着手した。Amphidinolide G (**2**)及び H (**3**)は構造異性体の関係にあり、穏やかな酸性及び塩基性条件で異性化することが報告されている[12]。そこで、筆者は **2** を合成ターゲットとして選択し、その全合成を達成した後に異性化を行うことで **3** の全合成を達成できるものと考えた。**2** を合成するに当たっては、amphidinolide B (**1**)と同様に収束的な合成経路を用いることとした。すなわち、**2** を構成する炭素骨格を fragment A' (**32**)、B' (**33**)、C (**10**)、D (**5**)の 4 つのフラグメントに分割し、各々を順次連結することで天然物へと誘導できるものと考えた。まず、fragment B' (**33**)及び C (**10**)をアセチリドカップリングで連結し、特徴的なジエン構造を有する fragment B'C (**34**)へと誘導する。さらに、fragment A' (**32**) をアルドール反応で、fragment D (**5**)をエステル化でカップリングした後、閉環メタセシスを用いることで **2** の全合成を達成できるものと考えた(Scheme 16)。

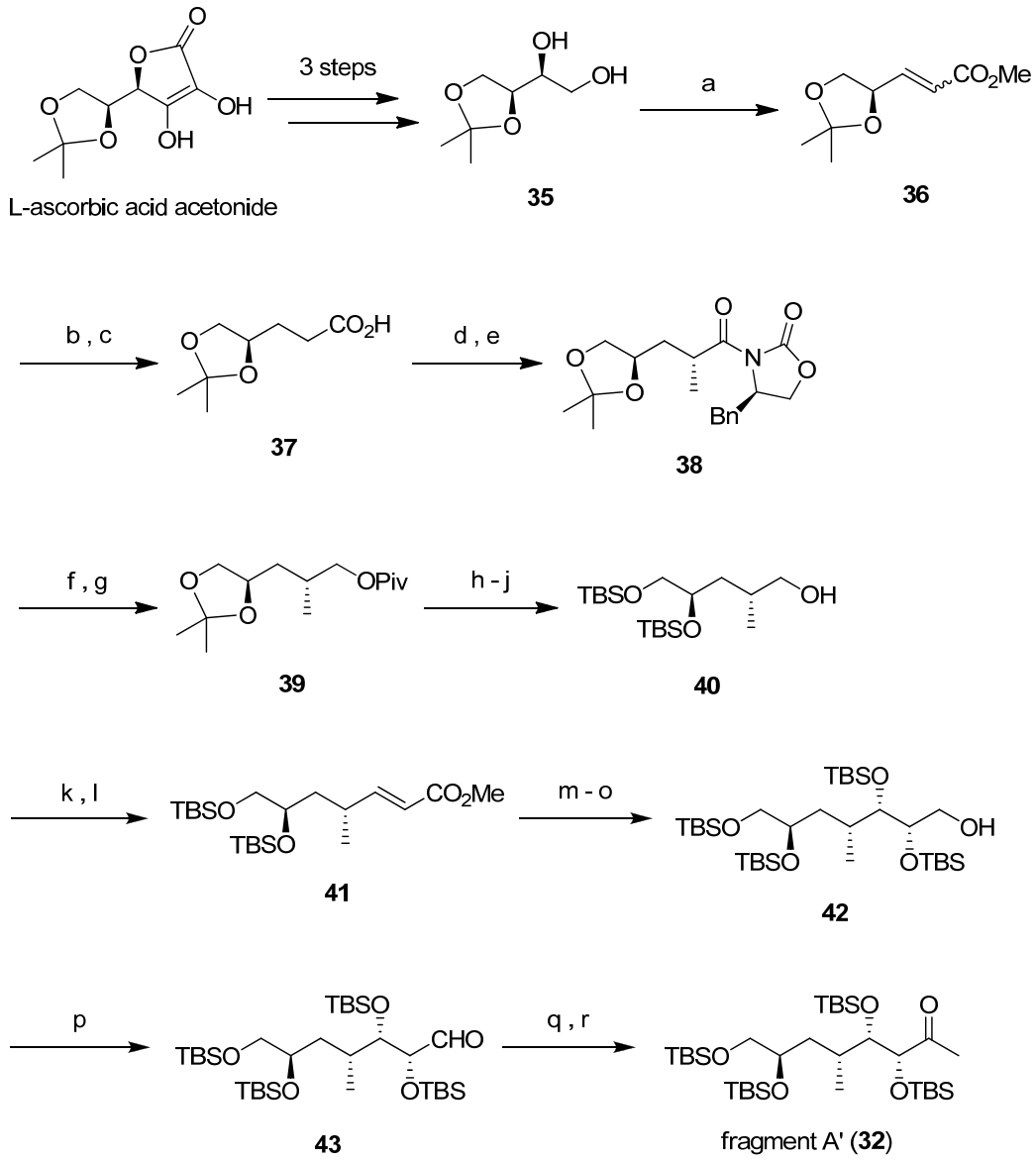

Aldol reaction
OH
O
OH
HO
OH
O
O
O
Esterification
Ring-closing metathesis
Amphidinolide G (2)
O
H
OTBDPS
fragment B'C (34)
O
OTBS
TBSO
OTBS
OTBS
fragment A' (32)
OH
O
fragment D (5)
Diene system construction
O
H
OTBDPS
CHO
OTBDPS
fragment C (10)
OPMB
fragment B' (33)

Scheme 16

第 2 節　Fragment A’及び B’の合成

第 1 項　Fragment A’ の合成

L-アスコルビン酸アセトナイドから 3 工程で得られる既知のジオール **35**[36] を出発原料として、fragment A’ (**32**)の合成を行った。まず、ジオール **35** を酸化的開裂にてアルデヒドへと変換した後、同一容器内で Wittig 試薬を加えることで不飽和エステル **36**(*E*:*Z* = 1:3.2)を得た。さらに、Raney Ni を用いて二重結合を接触還元した後、加水分解によりカルボン酸 **37** へと誘導した。続いて、カルボン酸 **37** と(*R*)-4-benzyl-2-oxazolidinone を縮合した後、Evans の不斉アルキル化反応を用いて C_{23} 位の不斉点を構築することで **38** を単一で得た。次に、$LiBH_4$ による不斉補助基の除去、一級水酸基の Piv 基による保護を経て **39** を合成した。さらに、酸性条件でアセトナイド基を脱保護した後、ジオールを TBS 基で保護し、DIBAL により Piv 基を除去することでアルコール **40** を合成した。得られた **40** の一級水酸基を TEMPO、BAIB によってアルデヒドへと酸化し、Wittig 反応によって不飽和エステル **41** へと変換した。続いて、化合物 **41** を Sharpless 不斉ジヒドロキシル化の条件に付すことでジオールを単一で得た後、TBS 基による保護、DIBAL 還元の 2 工程を経てアルコール **42** を合成した。最後に、**42** の一級水酸基を SO_3・pyr.、DMSO によってアルデヒド **43** へと変換した後、MeLi を用いて増炭して、生じた二級水酸基を TPAP によって酸化することで、18 工程、総収率 48%で fragment A’ (**32**)の合成を達成した(Scheme 17)。また、fragment A’ (**32**)は良い結晶が得られたので、X 線結晶構造解析を用いて望みの立体化学を有していることを確認することができた (Figure 12)。



Scheme 17. Synthesis of fragment A' (**32**). Reagents and conditions: (a) $NaIO_4$, CH_2Cl_2/H_2O, rt then Ph_3PCHCO_2Me, rt; (b) Raney Ni, H_2, EtOH, rt; (c) LiOH, THF/H_2O, 0 °C, 82% (3 steps); (d) PivCl, Et_3N, LiCl, (*R*)-4-Benzyl-2-oxazolidinone, rt, 100%; (e) LHMDS, MeI, THF, -40→-20 °C, 92%; (f) $LiBH_4$, $THF/MeOH/H_2O$, rt; (g) PivCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 92% (2 steps); (h) $TsOH \cdot H_2O$, DMF/H_2O, 30 °C, 50 hPa; (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 92% (2 steps); (j) DIBAL, CH_2Cl_2, -78 °C, 99%; (k) TEMPO, BAIB, CH_2Cl_2, rt; (l) Ph_3PCHCO_2Me, CH_2Cl_2, rt, 92% (2 steps); (m) AD-mix α, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C; (n) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 90% (2 steps); (o) DIBAL, CH_2Cl_2, -78 °C, 95%; (p) SO_3-pyr, DIPEA, DMSO, CH_2Cl_2, rt; (q) MeLi, Et_2O, -78 °C, 99% (2 steps); (r) TPAP, NMO, MS4A, CH_2Cl_2, rt, 97%.

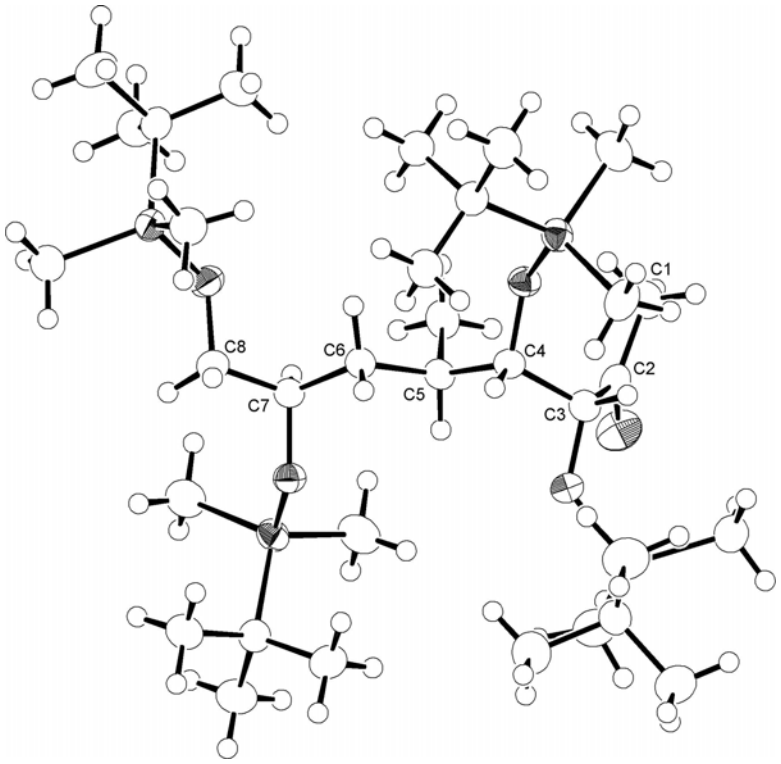
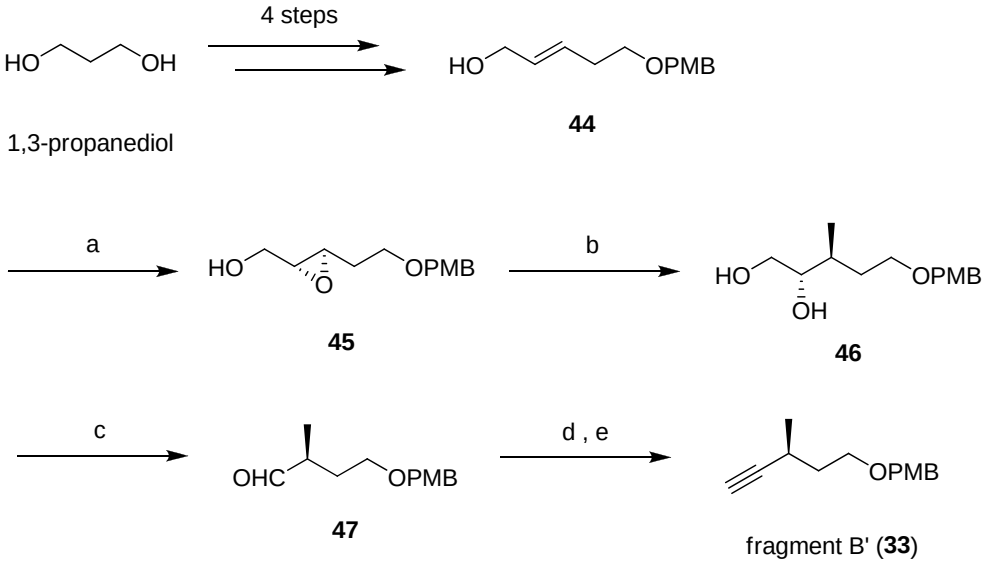


Figure 12

第 2 項　Fragment B’ の合成

1,3-Propanediol から既知の 4 工程で得られるアリルアルコール **44**[37] を出発原料として、fragment B’ (**33**)の合成を行った。まず、**44** に対して(-)-DET を用いて Sharpless 不斉エポキシ化を行ったところ、十分な光学純度で目的のエポキシドを得ることができなかった。そこで様々な酒石酸エステルを用いてエポキシ化の検討を行ったところ、(-)-DIPT を用いた際にエポキシド **45** を収率 91%、光学純度 96% ee で得ることに成功した。続いて $AlMe_3$ を用いてエポキシドを開環することでジオール **46** に誘導した後、ジオールの酸化的開裂を行うことでアルデヒド **47** を合成した。最後に、Corey-Fuchs アルキン合成法を用いてアルデヒドを末端アルキンへと変換することで、5 工程、総収率 51%で fragment B’ (**33**)の合成を達成した(Scheme 18)。

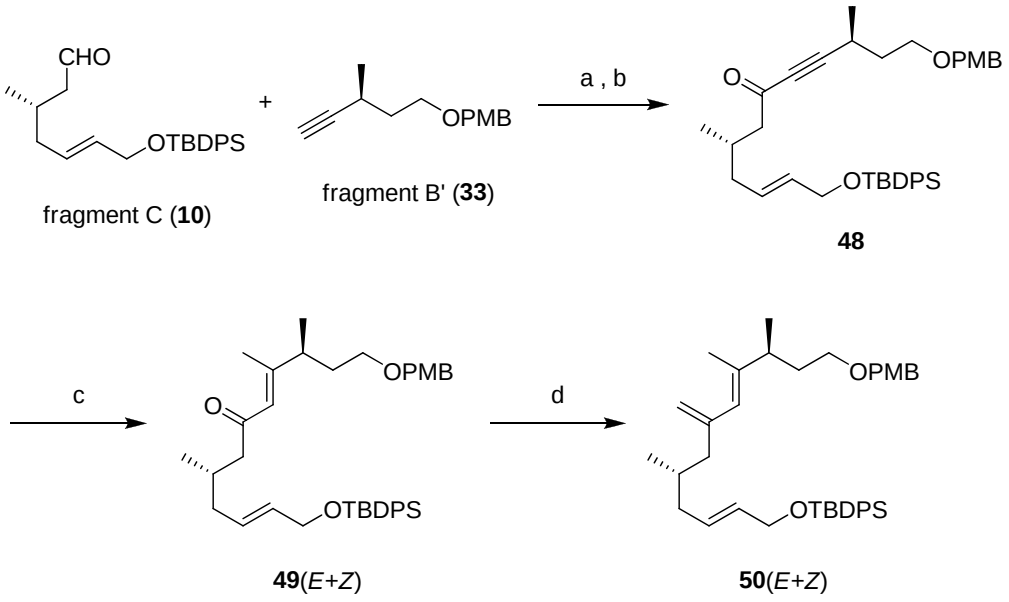


Scheme 18. Synthesis of fragment B' (**33**). Reagents and conditions: (a) Ti(O*i*-Pr)$_4$, TBHP, (-)-DIPT, MS4A, CH_2Cl_2, -20 ^oC, 91%, 96% ee; (b) $AlMe_3$, CH_2Cl_2, 0 ^oC, 72%; (c) $NaIO_4$, THF/H_2O, rt; (d) CBr_4, PPh_3, Et_3N, CH_2Cl_2, 0 ^oC, 90% (2 steps); (e) *n*-BuLi, THF, -78 ^oC, 86%.

第 3 節　Fragment BC の合成

第 1 項　ジエン構造の構築

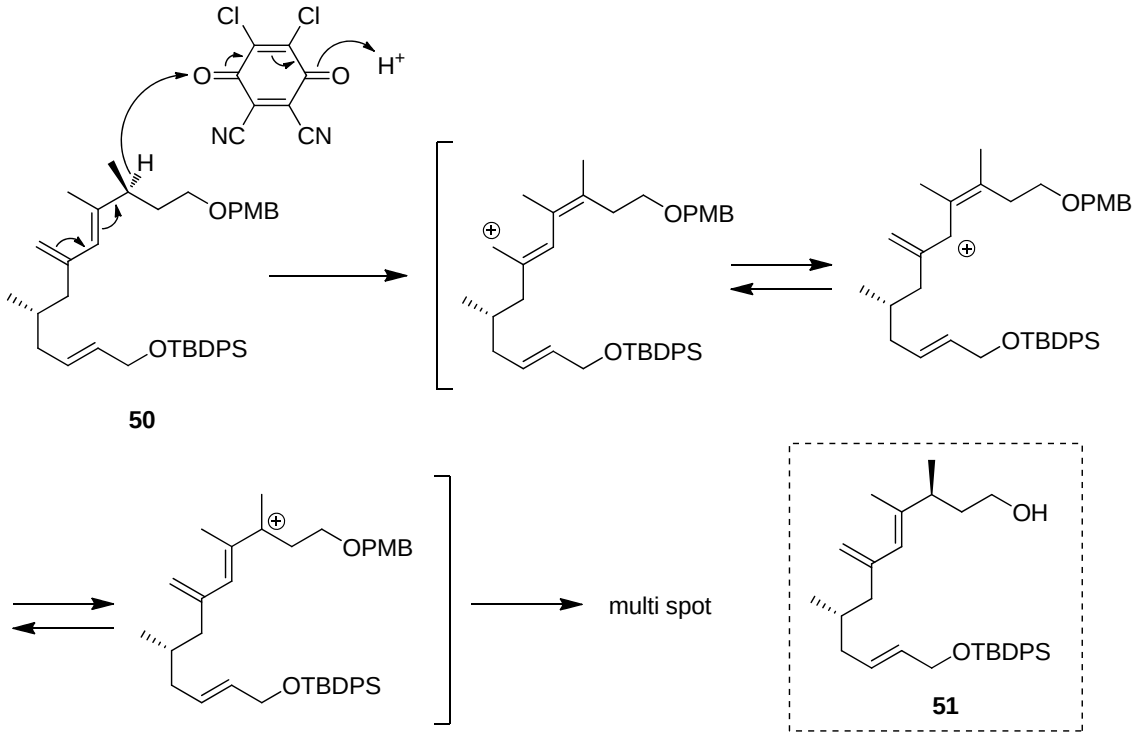
前節で amphidinolide G (**2**)を構成する全てのフラグメントの合成を達成したので、逆合成解析に基づき、fragment B' (**33**)及び C (**10**)のカップリングを行うこととした。まず *n*-BuLi を用いて fragment B' (**33**)からアセチリドを調製した後、fragment C (**10**)のアルデヒドに対して求核付加させることで両フラグメントを結合した。さらに、TPAP 酸化により二級水酸基を酸化することで不飽和ケトン **48** を合成した後、CuCN 及び MeLi から調製した Gilman 試薬を用いて Me 基の 1,4-付加反応を行った。この反応は高収率で進行したが、生成物は *E/Z* 異性体の混合物(*E*:*Z* = 1.5:1)であり、シリカゲルカラムクロマトグラフィーで分離することは困難であった。そこで、これらの混合物を分離することなく Wittig 反応に付し、後の工程において両異性体を分離することにした。すなわち、不飽和ケトン **49** に対して Wittig 反応を行うことで **50** を合成し、特徴的なジエン構造の構築に成功した(Scheme 19)。



Scheme 19. Synthesis of compound **50**. Reagents and conditions: (a) *n*-BuLi, THF, -78→0^{o}C then **10** in THF, rt, 91%; (b) TPAP, NMO, MS4A, CH_2Cl_2, rt, 84%; (c) MeLi, CuCN, Et_2O, -78 →-30 ^{o}C, 84%; (d) *n*-BuLi, Ph_3PCH_3Br, THF, 0 ^{o}C→rt, 98%.

この後、DDQ を用いて PMB 基の脱保護を試みたが、目的とするアルコール **51** の生成は確認できなかった。得られた主生成物の ^{1}H-NMR にはエキソオレフィンのピークが存在しなかったことから、アリル位が DDQ によって酸化された

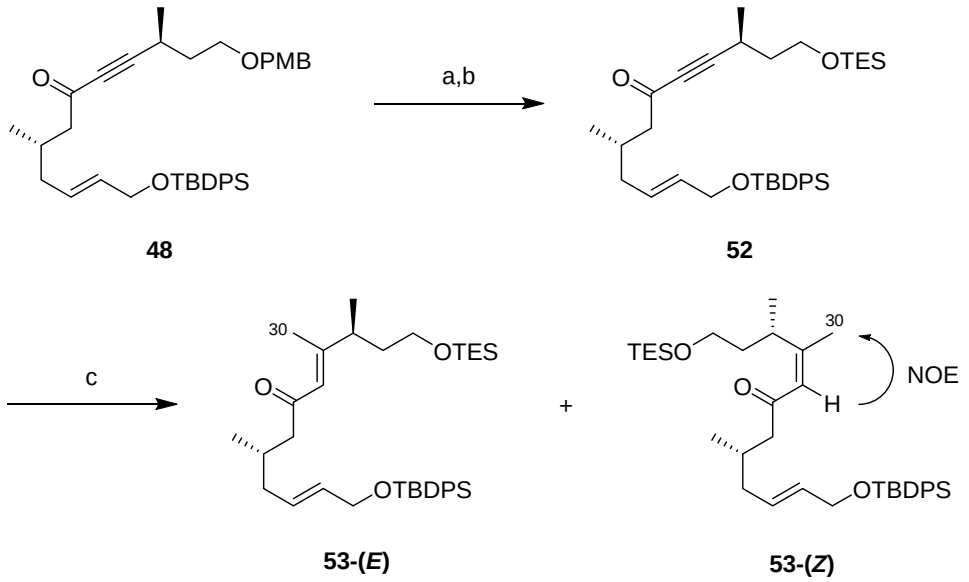
ことでジエンの分解が生じたと考えられる(Scheme 20)。



Scheme 20

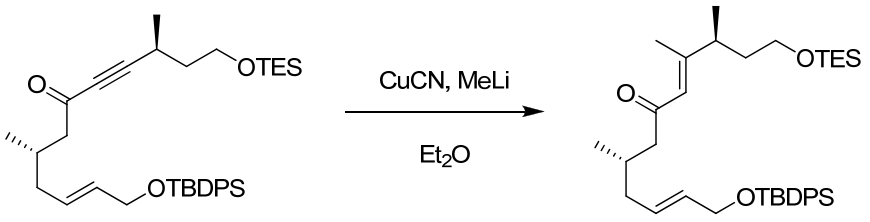
第 2 項　一級水酸基の保護基の変更

そこで、ジエン構造を構築する前に PMB 基を除去し、穏やかな酸性条件で脱保護が可能な TES 基に変換することにした。すなわち、不飽和ケトン **48** の PMB 基を DDQ で除去した後、一級水酸基を TES 基で保護することで **52** を合成した。その後、Gilman 試薬による 1,4-付加反応を同様の条件で行った結果、収率 97%、*E*/*Z* 選択比 2 : 1 でエノン体 **53** を合成することに成功した。*E* 体及び *Z* 体の構造決定に関しては、両異性体をシリカゲルカラムクロマトグラフィーで分割した後、^{13}C-NMR により C_{30} 位の化学シフト値を比較することで決定した。すなわち *E* 体の C_{30} 位のシグナル(16.0 ppm)は、立体障害のために Z 体のシグナル(31.5 ppm)に比べて高磁場にシフトしていることが観測された。また **53-(*Z*)**に関しては、Scheme 21 に示すような NOE 相関が観察されたことからも、その立体化学について決定することができた。



Scheme 21. Synthesis of compound **53**. Reagents and conditions: (a) DDQ, CH_2Cl_2/phosphate buffer, rt, 90%; (b) TESCl, Et_3N, CH_2Cl_2, rt, 93%; (c) MeLi, CuCN, Et_2O, -78 →-30 ^oC, 97% (*E*:*Z*=2:1).

また 1,4-付加反応の幾何選択性が amphidinolide B の合成中間体と比べて低下したことに関しては、三級水酸基の有無が原因として考えられる。すなわち、**52** には三級水酸基が存在しないためにアルキル基の立体障害が低下し、Figure 8 の場合と比べて *cis* 体に平衡が偏ったことで幾何選択性が低下したと考えられる。このように、Gilman 試薬を用いた 1,4-付加反応によってエノン体 **53** を高収率で得ることには成功したが、その *E*/*Z* 選択比に関しては多少の問題点が残った。そこで、*E*/*Z* 選択比の改善を目指して反応温度について更なる検討を行ったところ、-78 ºC から-30 ºC の範囲では Table 3 に示すような結果が得られた。この結果から、グラムスケールの合成においても収率及び *E*/*Z* 選択比の再現性が安定している-78 ºC を最適温度とし、その後の合成へと進むことにした。

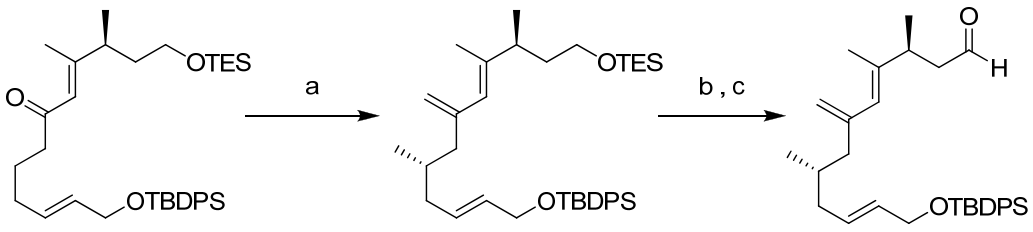


52 **53-(*E*)**

Table 3

entry	temperature	yield	E/Z selectivility
1	-30 ºC	97%	2:1
2	-50 ºC	98%	2:1
3	-78 ºC	96%	2.5:1

続いて、得られた **53-(*E*)**に対して Wittig 反応を行うことでジエン構造を有する **54** を合成した。最後に、PPTS を用いて TES 基を除去した後、一級水酸基を IBX によってアルデヒドへと酸化することで、アルドール前駆体である fragment B'C (**34**)の合成を達成した(Scheme 22)。



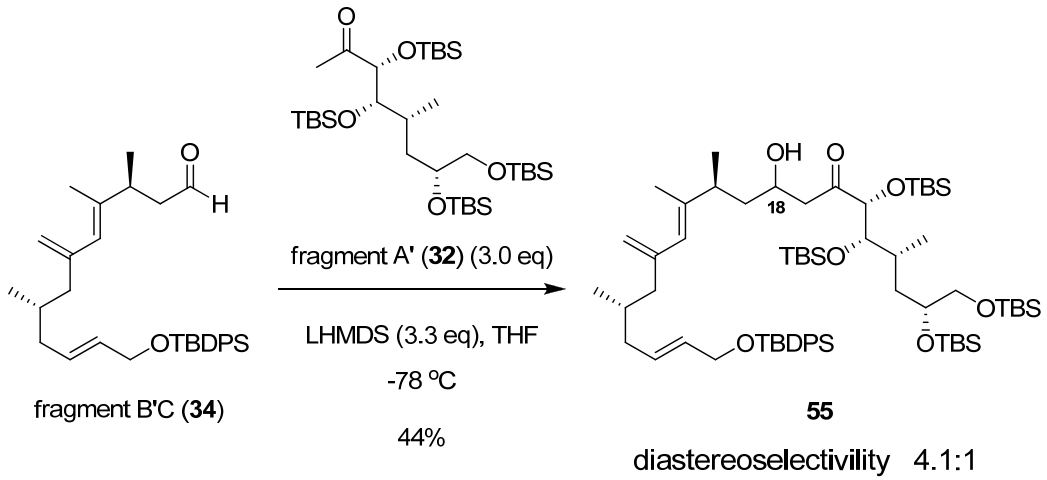
53-(*E*) **54** fragment B'C (**34**)

Scheme 22. Synthesis of fragment B'C (**34**). Reagents and conditions: (a) *n*-BuLi, Ph_3PCH_3Br, THF, 0 ºC→rt, 94%; (b) PPTS, CH_2Cl_2/MeOH, 0 ºC, 93%; (c) IBX, DMSO, rt, 97%.

第 4 節　アルドール反応

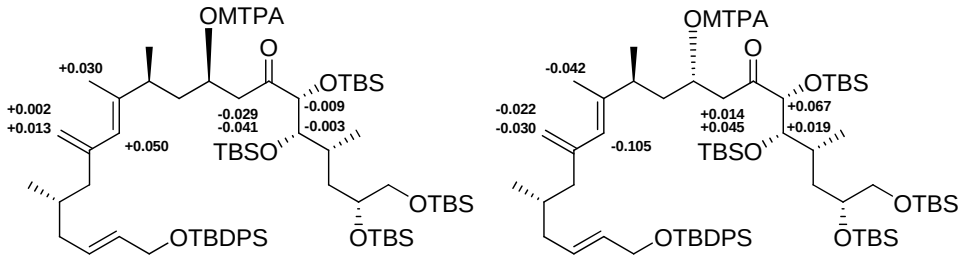
第 1 項　アルドール体の合成及び構造決定

前章でアルドール前駆体である fragment B'C (**34**)の合成を達成したので、アルドール反応を用いて fragment A' (**32**)とのカップリングを行うこととした。まず、amphidinolide B (**1**)の合成研究における検討をもとに、次に示す手順でアルドール反応を行った。まず THF 溶媒中の LHMDS に対して fragment A' (**32**)を滴下した後、0 ºC で 30 分、室温で 1 時間攪拌することでリチウムエノラートを調製した。さらに、-78 ºC においてエノラート溶液に対して fragment B'C (**34**)を滴下することで、アルドール体 **55** を収率 44%、ジアステレオ選択比 4.1:1 で合成することに成功した(Scheme 23)[16i]。



Scheme 23

アルドール体 **55** で新たに生じた C_{18} 位の水酸基の絶対立体化学は、新 Mosher 法を用いて決定することとした。まず、両ジアステレオマーをシリカゲルカラムクロマトグラフィーで分割した後、それぞれ(*R*)及び(*S*)-MTPA エステルへと誘導した。この後、両エステル体における ^{1}H-NMR の化学シフト値を比較したところ、Figure 13 に示すような結果が得られた。この結果から、目的とする **55-(*S*)** は minor ジアステレオマーであることが判明した。



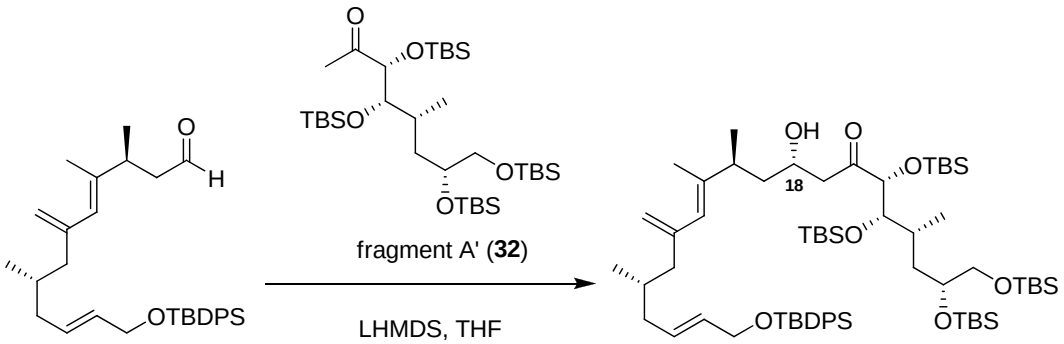
55-major (undesired)　　**55-minor** (desired)

Δδ (ppm)= δ[(*S*)-MTPA]-δ[(*R*)-MTPA]

Figure 13

第 2 項　アルドール反応の条件検討

続いて、アルドール反応におけるジアステレオ選択性を向上させるために、反応温度及び添加剤の検討を行った(Table 4)。その結果、-78 ºC から-10 ºC の範囲では反応温度が上昇するほど、目的物である **55-(*S*)**の収率は向上することが分かった (entries 1-5)。一方、反応温度が 0 ºC 以上の場合は、ジアステレオ選択性は *S* 体優先であるものの、副生成物としてエノン体が生じるため、その収率は低下した。また、リチウムカチオンの捕捉剤として TMEDA を加えた場合、**55-(*S*)** の選択性はわずかに向上したものの、収率は低下するという結果も得られた。



fragment B'C (**34**)

55-(*S*) (desired)

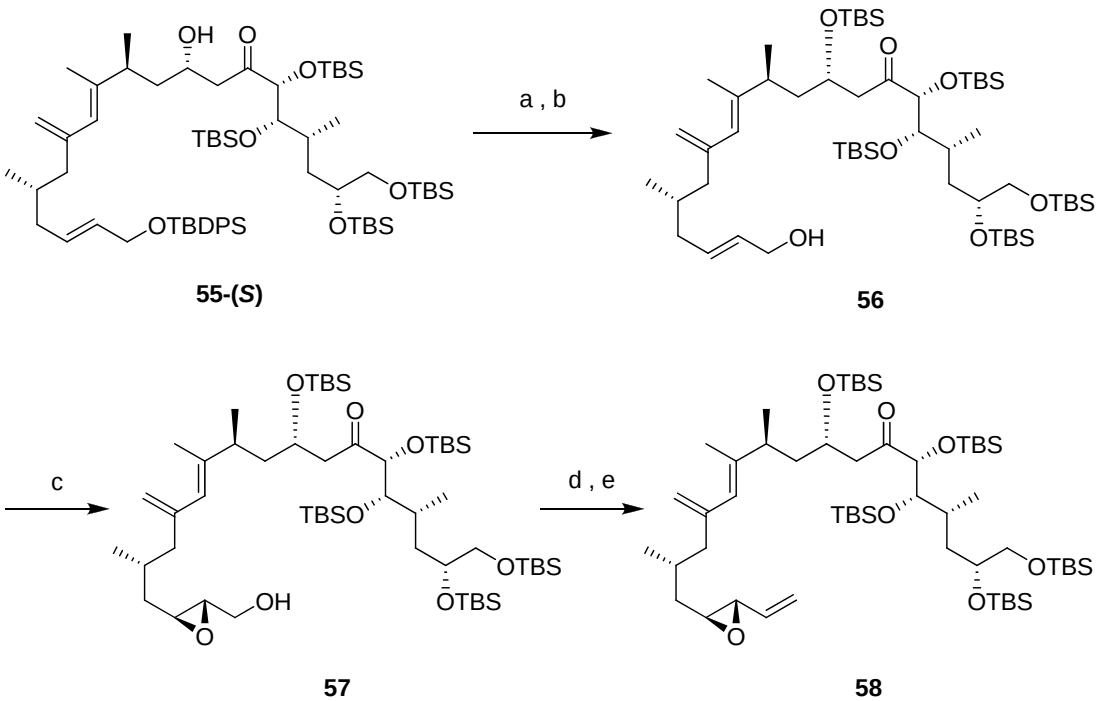
Table 4

entry	additive	temperature (^{o}C)	yield (%)	selectivility (*S*:*R*)
1	none	-78	44	1 : 4.1
2	none	-40	54	1 : 3.5
3	none	-20	74	1 : 1.5
4	none	-10	74	1.3 : 1
5	none	0	50	1.2 : 1
6	TMEDA	-40	36	1 : 2.8

第 5 節　Amphidinolide G の全合成

第 1 項　アリルエポキシド体の合成

前節で合成されたアルドール体 **55-(*S*)**を用いてアリルエポキシド構造の構築を行うこととした。まず、アルドール体 **55-(*S*)**の二級水酸基を TBS 基で保護した後、酢酸-水存在下で TBAF を作用させることで TBDPS 基を選択的に脱保護し、アリルアルコール **56** を合成した。さらに、(+)-DIPT を用いた Sharpless 不斉エポキシ化によって単一でエポキシアルコール **57** へと誘導した後、Dess-Martin 酸化、Wittig 反応の 2 工程を経て、アリルエポキシド構造を有する **58** の合成を達成した(Scheme 24)。この後、fragment D (**5**)とのエステル化を行うためには、**58** が有する 5 つの TBS 基から一級水酸基の TBS 基のみを選択的に除去する必要がある。まず TBAF、HF・pyridine、TASF を用いた条件で脱保護を試みたところ、全ての TBS 基が同時に脱保護されてしまい、目的物の生成は確認できなかった。一方で、PPTS や CSA などのスルホン酸を用いた条件では、ジエン構造の分解反応やアリルエポキシドの開環反応が迅速に進行したため、やはり目的物を得ることはできなかった。



55-(*S*)　**56**　**57**　**58**

Scheme 24. Synthesis of compound **58**. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 98%; (b) TBAF, AcOH, H_2O, DMF/THF, rt, 70% (80% conv.); (c) Ti(O*i*-Pr)$_4$, TBHP, (+)-DIPT MS4A, CH_2Cl_2, -20 ^oC, 67% (73% conv.); (d) DMP, pyridine, CH_2Cl_2, rt, 72%; (e) NaHMDS, Ph_3PCH_3Br, CH_2Cl_2, 0 ^oC, 90%.

第 2 項　一級水酸基を保護する TBS 基の選択的脱保護

前項における脱保護の検討結果から、ジエン構造やアリルエポキシドを有する化合物に対して TBS 基の選択的な脱保護を行うことは困難であるということが分かった。そこで fragment A' (**32**)の段階で一級水酸基の保護基を TBS 基から、穏やかな酸性条件で脱保護が可能である TES 基に変更することで、アルドール反応後の基質においても選択的な脱保護が行えると考えた。以下では、fragment A' (**32**)を基質とした TBS 基の選択的脱保護の検討結果を示す(Table 5)。まず、THF 溶媒下で TBAF を作用させたところ、全ての TBS 基の脱保護が同時に進行した。そこで、entries 1, 2 では反応系に酢酸を加えることで TBAF の反応性を低下させた結果、TBAF:酢酸=1:1 の条件では、16%と低収率ではあるが目的とする一級アルコール **59** が得られた。さらに、entries 3-5 では酸性条件における脱保護について検討を行ったところ、AcOH を用いた条件では反応が進行しなかったが、PPTS や CSA などのスルホン酸を用いた条件では、TBAF を用いた条件と比べて高い選択性で目的の TBS 基の脱保護が進行した。以上の結果から、TBS 基の選択的脱保護にはスルホン酸触媒を用いた条件が適していることが分かり、中でも高い選択性を示した entry 5 の条件を本反応の最適条件とした。その後、得られた **59** の 1 級水酸基を TES 基で保護することでアルドール前駆体 fragment A'' (**60**)を合成した。

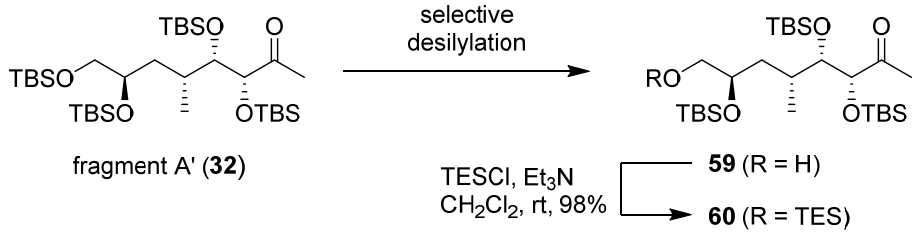
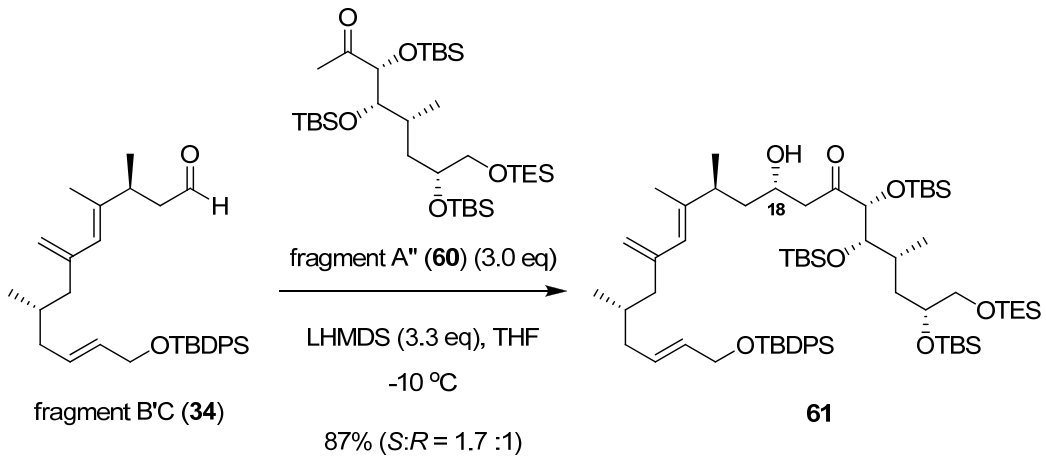


Table 5

entry	regents and conditions	yield
1	TBAF-AcOH (2:1), THF	multi spot
2	TBAF-AcOH (1:1), THF	**59**: 16%, **32**: 53%
3	AcOH-THF-H_2O (3:1:1)	no reaction
4	PPTS (1.0 eq), MeOH-CH_2Cl_2	**59**: 32%, **32**: 44%
5	CSA (50 mol%), MeOH-CH_2Cl_2, 0 °C	**59**: 46%, **32**: 29%

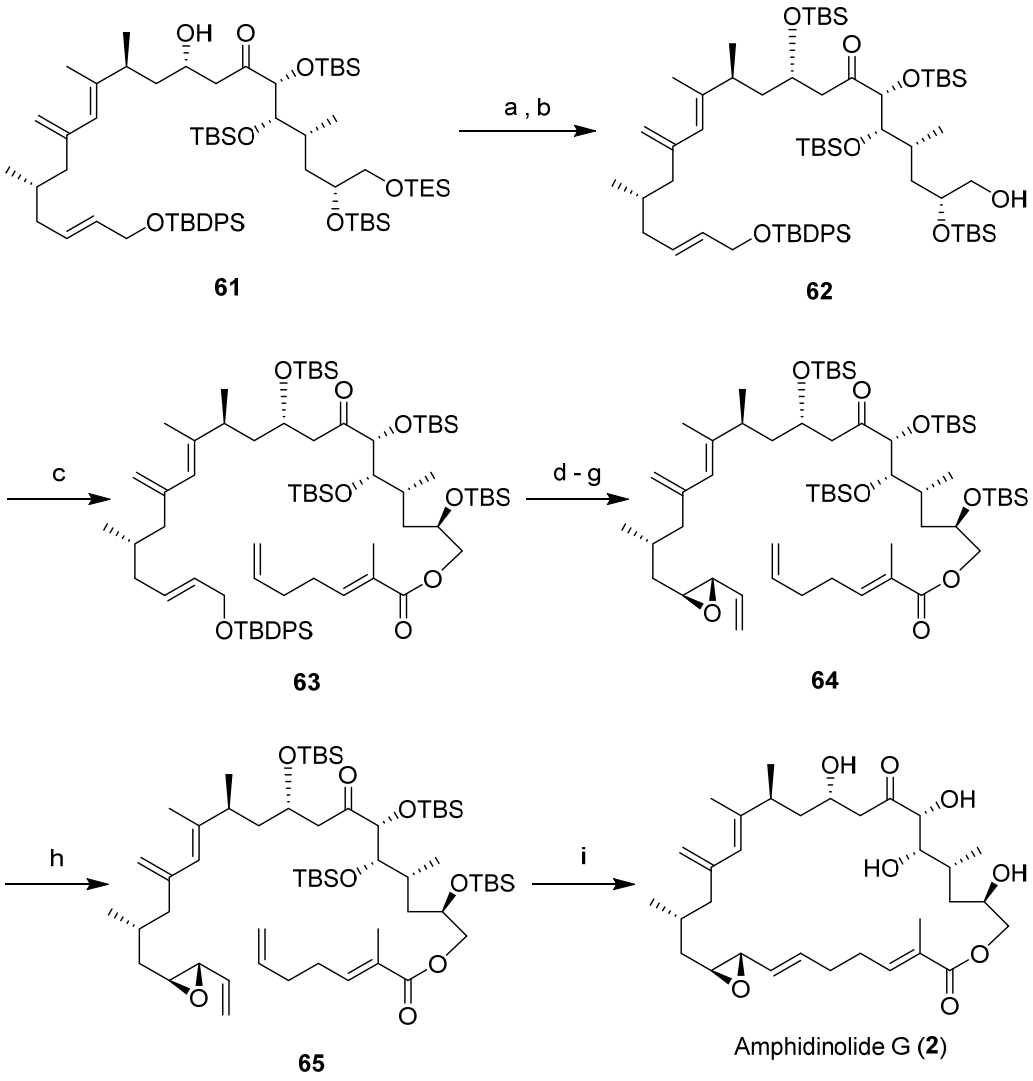
第 3 項　Amphidinolide G の全合成

前項において fragment A’ (**32**)の一級水酸基の保護基を TES 基に変換した fragment A” (**60**)を合成することに成功したので、Table 4 で検討した最適条件を用いて再度アルドール反応を行った。この結果、アルドール反応の収率は以前よりも向上し、収率 87%、ジアステレオ選択性 1.7:1 で目的とする(*S*)-アルドール体 **61** を良好な収率で得ることができた(Scheme 25)。またアルドール体 **61** の C_{18} 位水酸基の絶対立体化学は、前項のアルドール体 **55** と ^{1}H-NMR、^{13}C-NMR を比較することで決定した。



Scheme 25

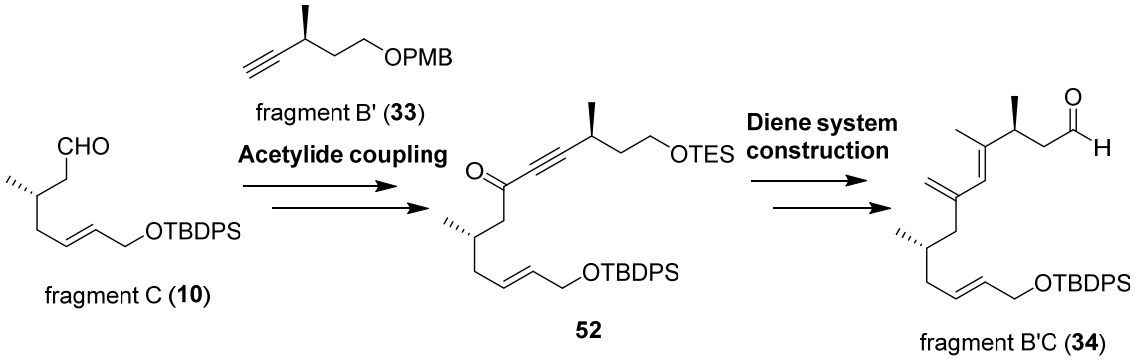
続いて、得られたアルドール体 **61** の水酸基を TBS 基で保護した後、PPTS を用いて酸性条件に付したところ、ジエン構造は分解することなく TES 基のみを選択的に脱保護することに成功した。さらに、得られたアルコール **62** を fragment D (**5**)とのエステル化により **63** へ変換した後、TBDPS 基の脱保護、Sharpless 不斉エポキシ化、Dess-Martin 酸化、Wittig 反応の 4 工程を経てアリルエポキシド構造を有する **64** を合成した。この後、第二世代 Grubbs 触媒を用いた閉環メタセシス反応に **64** を付したところ、反応は *E* 選択的に進行し、27 員環骨格を有する **65** を高収率で得ることに成功した。最後に、TASF を用いて全ての TBS 基を除去することで amphidinolide G (**2**)の全合成を達成した(Scheme 26)。合成された **2** のスペクトルデータは天然物と良い一致を示した。また、amphidinolide G (**2**)から H (**3**)への変換はすでに小林らによって報告されている[13]ため、同時に **3** の形式全合成も達成した。



Scheme 26. Total synthesis of amphidinolide G (**2**). Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, -10 °C, 98%; (b) PPTS, MeOH/CH_2Cl_2, 0 °C, 78%; (c) **5**, Et_3N, 2,4,6-trichlorobenzoyl chlolide, DMAP, toluene, rt, 98%; (d) TBAF, AcOH, H_2O, DMF/THF, rt, 82% (87% conv.); (e) Ti(O*i*-Pr)$_4$, TBHP, (+)-DIPT, MS4A, CH_2Cl_2, -20 °C, 54% (75% conv.); (f) DMP, pyridine, CH_2Cl_2, 0 °C, 91%; (g) NaHMDS, Ph_3PCH_3Br, CH_2Cl_2, 0 °C, 80%; (h) Grubbs' 2nd catalyst, benzene, rt, 95%; (i) TASF, THF/DMF, H_2O, rt, 72%

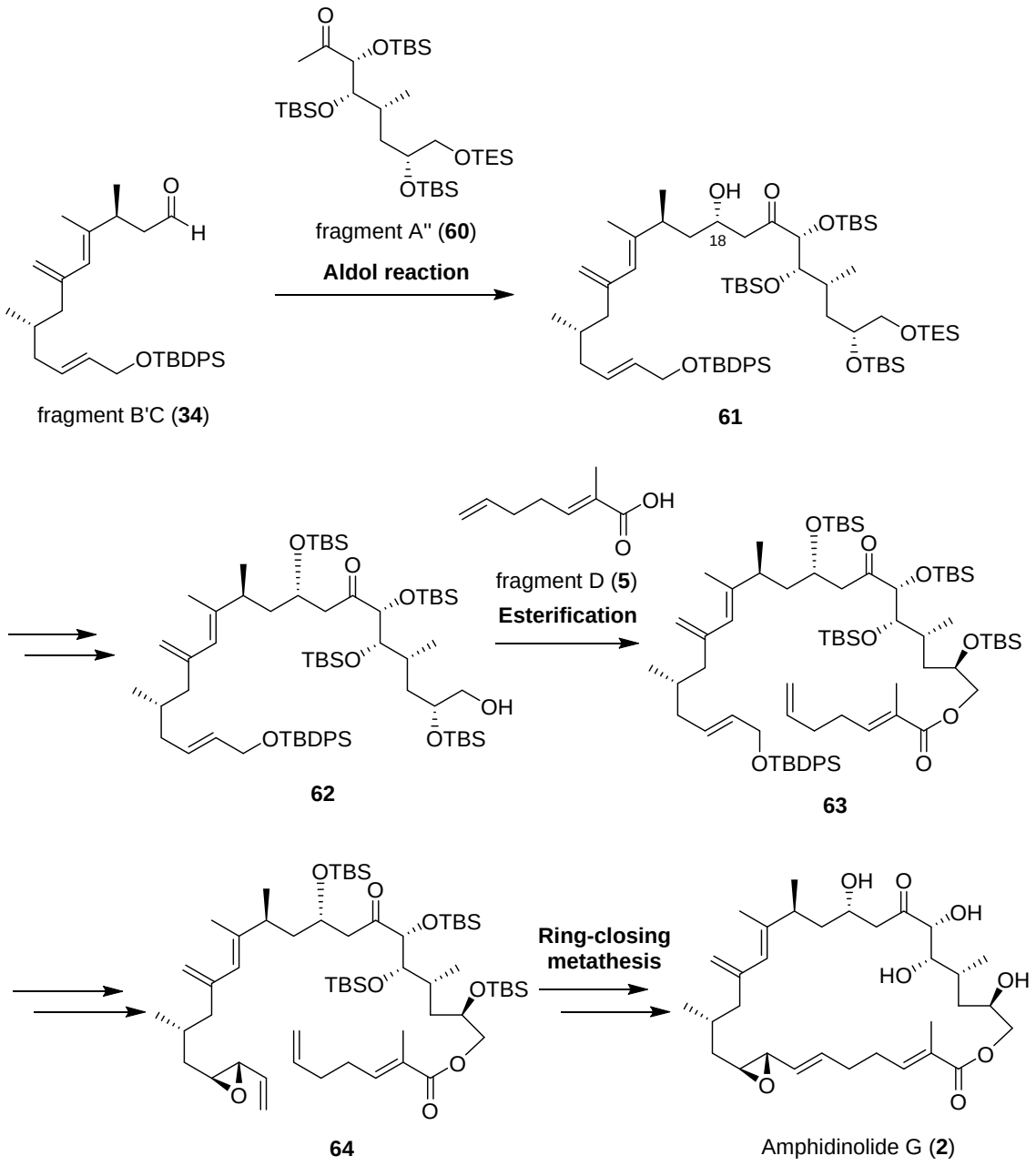
第 6 節　第 3 章まとめ

第 3 章においては、27 員環マクロライド化合物 amphidinolide G (**2**)の合成について述べた。まず、標的化合物の構造に対応した 2 つの fragment A’ (**32**)及び B’ (**33**)を合成した後、アセチリドカップリングを利用することでフラグメント B’ (**33**)及び C (**10**)を結合した。次いで、TPAP 酸化、1,4-付加反応、Wittig 反応の 3 工程を経てジエン構造を構築した後に PMB 基の脱保護を試みたが、ジエン構造の分解が伴い目的物は得られなかった。そこで、PMB 基を TES 基に変更することで **52** へと誘導した後にジエン構造を構築し、続く TES 基の脱保護、IBX 酸化によってアルドール前駆体 **34** を合成した(Scheme 27)。



Scheme 27

続いて、第 2 章におけるアルドール反応の検討で得られた知見をもとに、塩基を LHMDS に固定し、反応温度について検討を行ったところ、反応温度-10 ºC において目的とする(*S*)-アルドール体 **61** を良好な収率で得ることができた(87%, *S*:*R* = 1.7:1)。続いてアルドール体 **61** の水酸基を TBS 基で保護した後、PPTS を用いて TES 基のみを選択的に脱保護することでアルコール **62** を得た。さらに、フラグメント D (**5**)とのエステル化により **63** へ変換した後、Sharpless の不斉エポキシ化、Dess-Martin 酸化、Wittig 反応の 3 工程を経て、アリルエポキシド構造を有する **64** を合成した。最後に、第二世代 Grubbs 触媒を用いた閉環メタセシス反応によって 27 員環骨格を構築した後、TASF を用いて TBS 基を除去することで **2** の全合成を達成した(Scheme 28)[35]。また、amphidinolide G (**2**)から H (**3**)への変換はすでに小林らによって報告されているため、同時に **3** の形式全合成も達成した。


O
OTBS
TBSO
OTES
OTBS
fragment A'' (60)
Aldol reaction
O
H
OTBDPS
fragment B'C (34)
OH
O
18
OTBS
TBSO
OTES
OTBS
OTBDPS
61
OH
O
fragment D (5)
Esterification
OTBS
O
OTBS
TBSO
OH
OTBS
OTBDPS
62
OTBS
O
OTBS
TBSO
OTBS
O
O
OTBDPS
63
Ring-closing metathesis
OTBS
O
OTBS
TBSO
OTBS
O
O
O
64
OH
O
OH
HO
OH
O
O
O
Amphidinolide G (2)

Scheme 28

第 4 章　総括

以上、本研究では海洋生物由来のマクロライド化合物 amphidinolide 類(**1-3**)の合成について述べた。まず amphidinolide B (**1**)の合成研究では、収束型合成に必要な 4 つの fragment を合成した。続いて、アセチリドカップリングにより fragment B (**9**)及び C (**10**)を結合した後、ジエン構造を構築することで fragment BC (**6**)を合成した。さらに、アルドール反応によって fragment A (**7**)を結合することで **26-(*S*)** へと誘導した後、fragment D (**5**)とのエステル化を経て **29** を合成した。最後に、閉環メタセシス反応によって 26 員環構造を構築した後、TBS 基を除去することで **1** の全合成を達成した(Figure 14)。

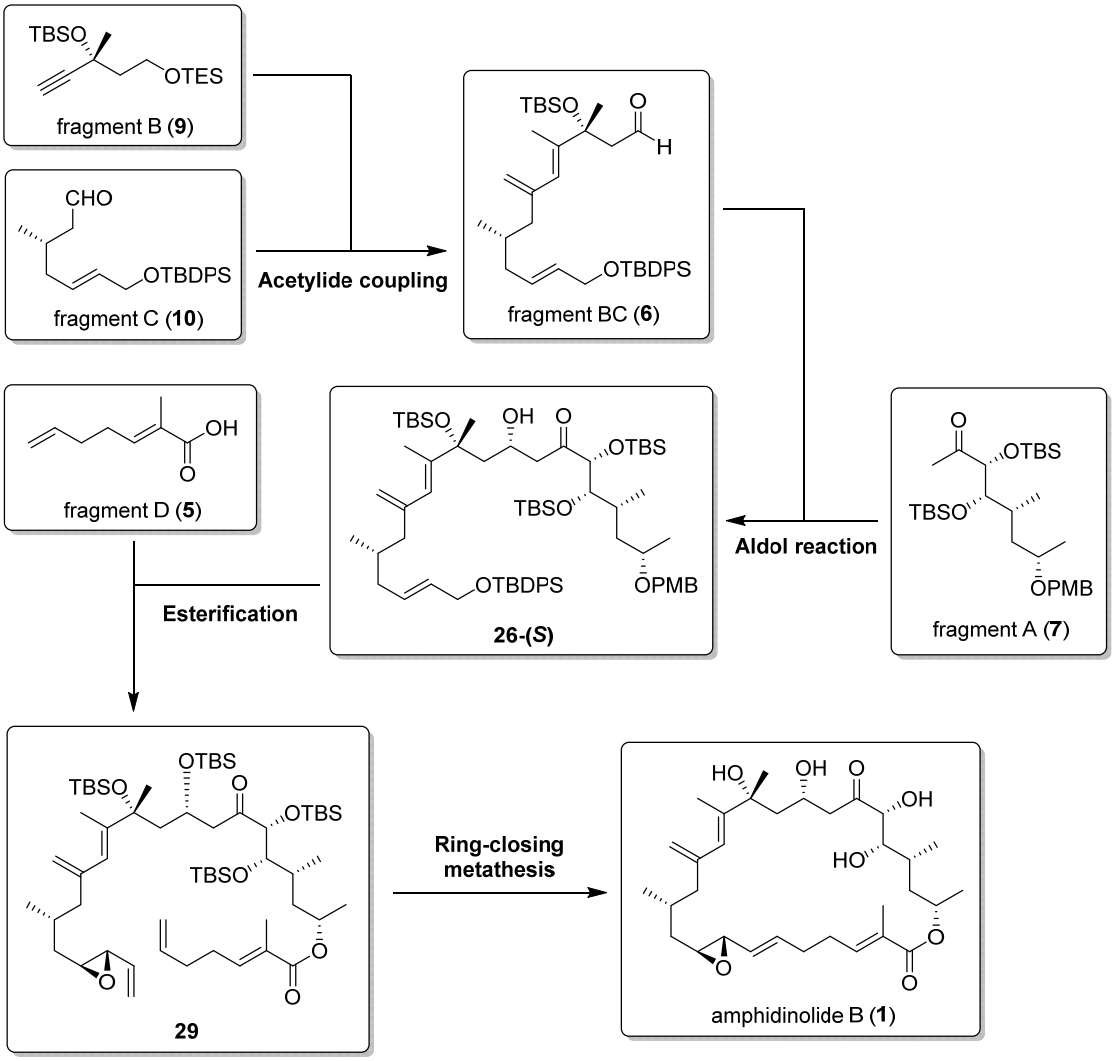


Figure 14

また、amphidinolide G (**2**)及び H (**3**)の合成研究に関しても同様の合成戦略を用いた。すなわち、収束型合成に必要な 4 つの fragment を合成した後、アセチリドカップリングにより fragment B’ (**33**)及び C (**10**)を結合することで fragment B’C (**34**)を合成した。さらに、アルドール反応によって fragment A” (**60**)を結合することで **62** へと誘導した後、fragment D (**5**)とのエステル化を経て **65** を合成した。最後に、閉環メタセシス反応によって 27 員環構造を構築した後、TBS 基を除去することで **2** の全合成を達成した(Figure 15)。また、amphidinolide G (**2**)から H (**3**)への変換はすでに小林らによって報告されているため、同時に **3** の形式全合成も達成した。

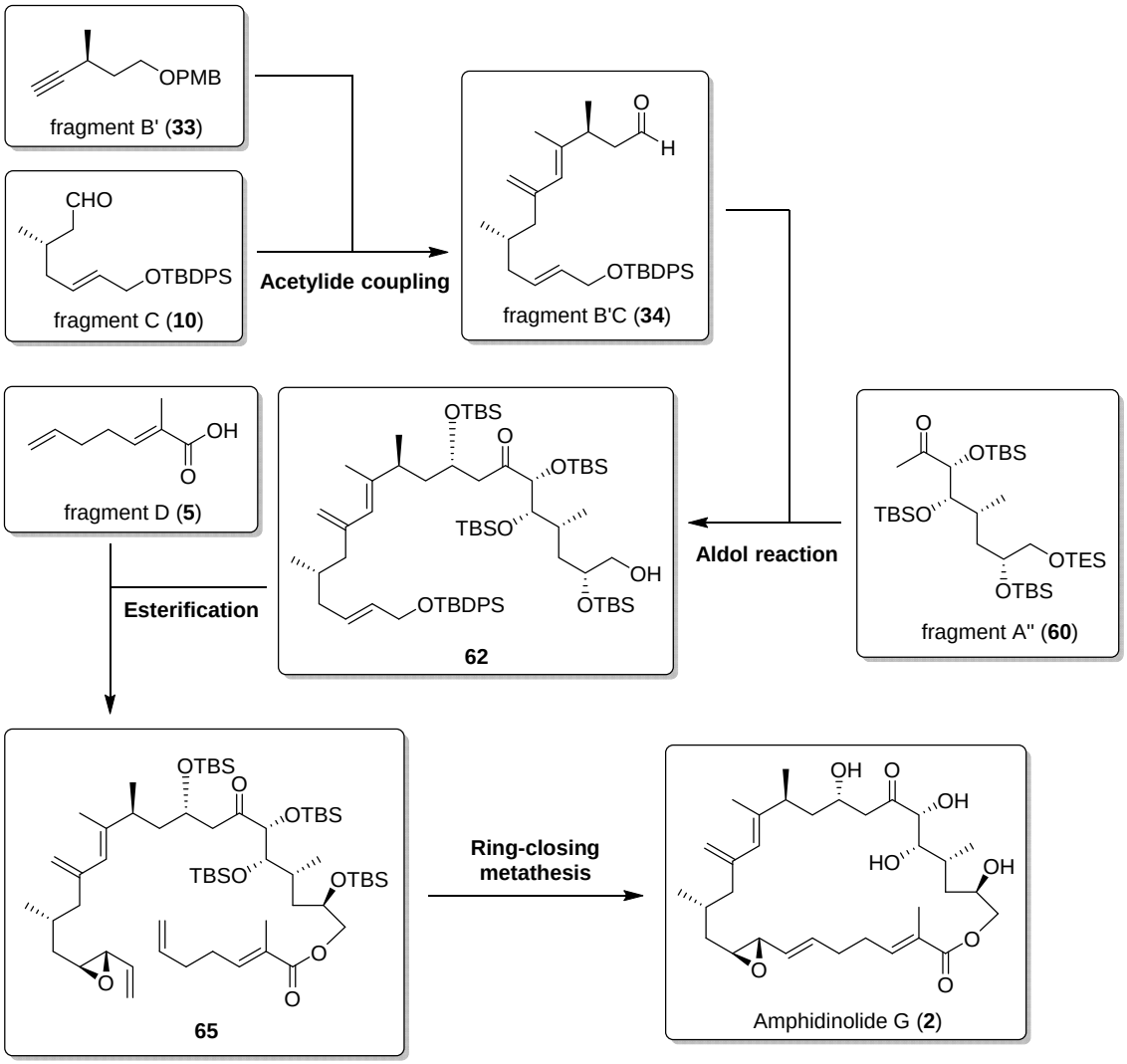


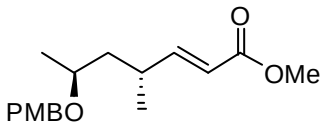
Figure 15

第 5 章　実験の部

General

All reactions were carried out under an argon atmosphere unless otherwise noted. When necessary, solvents were dried prior to use. Dry tetrahydrofuran (THF) and dry diethyl ether (Et_2O) were purchased from Kanto Chemical Co., Inc.. Other anhydrous solvents were also obtained by using an activated commercially available alumina column, and stored over MS4A under an argon atmosphere. Preparative and analytical TLC were carried out using silica gel plates (Kieselgel 60 F_{254}, E. Merck AG, Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection. Kanto Chemical Silica 60N (spherical, neutral, 63-210 μm) was used for column chromatography. Optical rotations were measured on a JASCO DIR-3300 digital polarimeter with a sodium (D line) lamp. IR spectra were recorded on a JASCO Model A-202 spectrophotometer or JASCO FT/IR-4200. ^{1}H-NMR spectra and ^{13}C-NMR spectra were obtained on JEOL JNM-EX270, JEOL JNM-GX400, JEOL JNM-α400, JEOL JNM-AL400 and JEOL JNM-ECX400 spectrophotometers in deuterated solvent ($CDCl_3$, C_6D_6). High-resolution mass spectra were obtained on Waters LCT Premier XE (ESI).

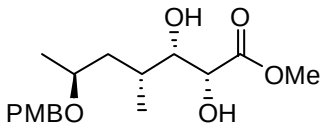
(4*R*,6*S*,*E*)-methyl 6-(4-methoxybenzyloxy)-4-methylhept-2-enoate (13)



To a solution of **12** (2.00 g, 8.57 mmol) in dry CH_2Cl_2 (34 mL) was added DIBAL (1.02 M solution in hexane, 12.6 mL, 12.9 mmol) at -78 °C; the mixture was stirred at the same temperature for 1.5 h. The reaction was quenched by the addition of saturated Rochelle salt aq. at 0 °C. After being stirred at room temperature for 10 h, the resulting slurry was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford a crude aldehyde as a yellow oil, which was used for the following reaction without further purification.

To a solution of the crude aldehyde in CH_2Cl_2 (86 mL) was added Ph_3PCHCO_2Me (7.16 g, 21.4 mmol) at 0 °C; the mixture was stirred at room temperature for 12 h. After the mixture was concentrated *in vacuo*, the residue was purified by silica gel chromatography (EtOAc:toluene, 1:10) to give **13** (1.90 g, 76%) as a colorless oil: $[\alpha]^{23}_D$ +9.00 (*c* 0.99, $CHCl_3$), IR (firm) 1723, 1514, and 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, d, *J* = 6.8 Hz), 1.19 (3H, d, *J* = 5.9 Hz), 1.35 (1H, ddd, *J* = 5.4, 7.8, 15.2 Hz), 1.74 (1H, ddd, *J* = 6.8, 7.8, 15.2 Hz), 2.52 (1H, m), 3.52 (1H, m), 3.71 (3H, s), 3.80 (3H, s), 4.32 (1H, d, *J* = 11.2 Hz), 4.50 (1H, d, *J* = 11.2 Hz), 5.77 (1H, dd, *J* = 1.0, 15.6 Hz), 6.90 (1H, dd, *J* = 7.8, 15.6 Hz), 6.86 (2H, dd, *J* = 2.4, 8.8), and 7.24 (2H, dd, *J* = 2.0, 8.8 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 19.1, 19.7, 33.2, 43.1, 51.4, 55.2, 69.9, 72.0, 113.6, 118.7, 129.1, 130.7, 154.7, 158.9, and 167.1; HRMS (ESI) calcd for $C_{17}H_{24}O_4Na$ $(M+Na)^+$ 315.1572, found *m/z* 315.1552.

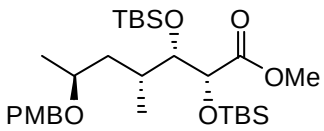
(2*R*,3*S*,4*R*,6*S*)-methyl 2,3-dihydroxy-6-(4-methoxybenzyloxy)-4-methylheptanoate (S-1)



To a solution of AD-mix-α (123 g) in *t*-BuOH (154 mL) and H_2O (154 mL) was added methanesulfoneamide (5.85 g, 61.5 mmol) at room temperature; the mixture was stirred for 30 min. To the mixture was added a solution of **13** (18.0 g, 61.5 mmol) in *t*-BuOH (154 mL) and H_2O (154 mL) at 0 °C; the mixture was stirred at the same temperature for 12 h. The reaction was quenched by the addition of saturated Na_2SO_3 aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine and 2 M HCl aq., dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:1) to give **S-1** (18.1 g, 90%) as a colorless oil: $[\alpha]^{23}_D$ +33.3 (*c* 0.97, $CHCl_3$); IR (film) 3466 and 1742 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.97 (3H, d, *J* = 6.8 Hz), 1.21 (3H, d, *J* = 5.9 Hz), 1.28 (1H, ddd, *J* = 3.0, 8.4, 14.3 Hz), 1.76 (1H, ddd,

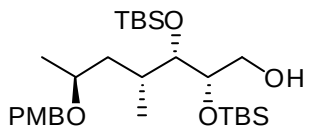
J = 4.5, 9.9, 14.3 Hz), 1.97 (1H, m), 2.57 (1H, d, *J* = 8.2 Hz), 3.14 (1H, d, *J* = 5.4 Hz), 3.58 (1H, m), 3.64 (1H, ddd, *J* = 2.5, 6.8, 8.2 Hz), 3.80 (3H, s), 3.80 (3H, s), 4.27 (1H, dd, *J* = 2.5, 5.4 Hz), 4.32 (1H, d, *J* = 11.2 Hz), 4.56 (1H, d, *J* = 11.2 Hz), 6.87 (2H, d, *J* = 2.1, 6.4 Hz), and 7.25 (2H, dd, *J* = 2.1, 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.6, 20.0, 33.6, 40.9, 52.6, 55.2, 69.9, 71.4, 72.3, 75.9, 113.7, 129.3, 130.4, 159.0, and 174.0; HRMS (ESI) calcd for $C_{17}H_{26}O_6Na$ $(M+Na)^+$ 349.1627, found *m/z* 349.1611.

(2*R*,3*S*,4*R*,6*S*)-methyl 2,3-bis(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyloxy)-4-methylheptanoate (14)



To a solution of **S-1** (1.26 g, 3.86 mmol) in CH_2Cl_2 (39 mL) were added 2,6-lutidine (4.49 mL, 38.6 mmol) and TBSOTf (4.43 mL, 19.3 mmol) at room temperature; the mixture was stirred at the same temperature for 12 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:12) to give **14** (1.88 g, 88%) as a colorless oil: $[\alpha]^{22}_D$ +13.5 (*c* 1.01, $CHCl_3$); IR (film) 1753 and 838 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.02 (3H, s), 0.04 (3H, s), 0.037 (3H, s), 0.042 (3H, s), 0.79 (3H, d, *J* = 6.8 Hz), 0.89 (9H, s), 0.90 (9H, s), 1.18 (3H, d, *J* = 6.1 Hz), 1.26 (1H, ddd, *J* = 4.5, 9.2, 14.0 Hz), 1.73 (1H, ddd, *J* = 5.1, 8.7, 14.0 Hz), 2.00 (1H, m), 3.53 (1H, m), 3.66 (3H, s), 3.71 (1H, dd, *J* = 3.1, 4.6 Hz), 3.79 (3H, s), 4.18 (1H, d, *J* = 4.6 Hz), 4.32 (1H, d, *J* = 11.2 Hz), 4.51 (1H, d, *J* = 11.2 Hz), 6.85 (2H, dd, *J* = 2.1, 6.6 Hz), and 7.24 (2H, dd, *J* = 2.1, 6.6 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -4.8, -4.7, -4.2, -4.1, 14.3, 18.3, 20.0, 25.9, 31.7, 42.4, 51.5, 55.3, 69.8, 72.1, 74.8, 77.7, 113.5, 129.0, 131.1, 158.8, and 172.9; HRMS (ESI) calcd for $C_{29}H_{54}O_6NaSi_2$ $(M+Na)^+$ 577.3357, found *m/z* 577.3351.

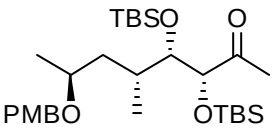
(2*S*,3*S*,4*R*,6*S*)-2,3-bis(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyloxy)-4-methyl heptan-1-ol (15)



To a solution of **14** (1.68 g, 3.03 mmol) in dry CH_2Cl_2 (30 mL) was added DIBAL (1.02M solution in hexane, 8.90 mL, 9.08 mmol) at -78 °C; the mixture was stirred at the same temperature for 1 h. The reaction was quenched by the addition of saturated Rochelle salt aq. at 0 °C. After being stirred at room temperature for 30 min, the resulting slurry was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried

over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:10) to give **15** (1.45 g, 91%) as a colorless oil: $[\alpha]^{21}_D$ +4.68 (*c* 0.99, $CHCl_3$); IR (film) 3468 and 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.08 (3H, s), 0.09 (3H, s), 0.82 (3H, d, *J*= 6.8 Hz), 0.88 (9H, s), 0.90 (9H, s), 1.16 (1H, ddd, *J* = 4.4, 9.8, 13.7 Hz), 1.17 (3H, d, *J* = 5.9 Hz), 1.84 (1H, ddd, *J* = 4.9, 8.8, 13.7 Hz), 2.10 (1H, m), 2.23 (1H, dd, *J* = 5.4, 6.3 Hz), 3.49 (1H, dd, *J* = 3.9, 3.9 Hz), 3.53 (1H, m), 3.63 (1H, m), 3.75-3.82 (2H, m), 3.80 (3H, s), 4.34 (1H, d, *J* = 11.2 Hz), 4.52 (1H, d, *J* = 11.2 Hz), 6.86 (2H, dd, *J* = 2.0, 6.8 Hz), and 7.25 (2H, dd, *J* = 2.0, 6.8 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -4.6, -4.5, -4.2, -4.0, 15.8, 18.1, 18.2, 20.2, 25.87, 25.95, 30.0, 43.3, 55.3, 63.7, 69.8, 71.9, 75.4, 78.5, 113.6, 129.0, 131.1, and 158.8; HRMS (ESI) calcd for $C_{28}H_{54}O_5NaSi_2$ $(M+Na)^+$ 549.3408, found *m/z* 549.3398.

(3*R*,4*S*,5*R*,7*S*)-3,4-bis(*tert*-butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)-5-methyl octan-2-one (7)



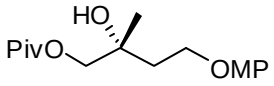
To a solution of **15** (1.73 g, 3.28 mmol) in CH_2Cl_2 (16 mL) and DMSO (16mL) were added DIPEA (5.60 mL, 33.0 mmol) and SO_3-pyr. complex (2.61 g, 16.4 mmol) at 0 ^oC; the mixture was stirred at room temperature for 2.5 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to afford a crude aldehyde as a yellow oil, which was used for the following reaction without further purification.

To a solution of the crude aldehyde in dry Et_2O (33 mL) was added MeLi (1.04 M solution in Et_2O, 3.78 mL, 3.94 mmol) at -78 °C; the mixture was stirred at the same temperature for 12 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:15) to give an alcohol (1.37 g, 77%) as a colorless oil, which was used for the following reaction without further purification.

To a solution of the corresponding alcohol (1.37 g, 2.53 mmol) in CH_2Cl_2 (13 mL) and DMSO (13mL) were added DIPEA (4.30 mL, 25.0 mmol) and SO_3-pyr. (2.01 g, 12.7 mmol) at 0 ^oC; the mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel

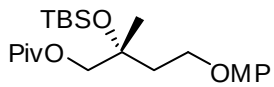
chromatography (EtOAc:hexane, 1:20) to give **7** (1.33 g, 98%) as a colorless oil: $[\alpha]^{22}_{D}$ +1.56 (*c* 1.00, $CHCl_3$); IR (film) 1718 and 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (3H, s), 0.04 (3H, s), 0.065 (3H, s), 0.073 (3H, s), 0.75 (3H, d, *J* = 6.8 Hz), 0.91 (9H, s), 0.92 (9H, s), 1.17 (3H, d, *J* = 5.9 Hz), 1.23 (1H, ddd, *J* = 4.4, 9.3, 13.7 Hz), 1.72 (1H, ddd, *J* = 4.9, 8.8, 13.7 Hz), 2.00 (1H, m), 2.20 (3H, s), 3.50 (1H, m), 3.65 (1H, dd, *J* = 3.4, 4.4 Hz), 3.80 (3H, s), 4.06 (1H, d, *J* = 4.4 Hz), 4.30 (1H, d, *J* = 11.2 Hz), 4.50 (1H, d, *J*= 11.2 Hz), 6.86 (2H, d, *J* = 2.0, 6.8 Hz), and 7.24 (2H, d, *J* = 2.0, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.7, -4.5, -4.0, 14.7, 18.15, 18.19, 19.9, 25.8, 26.0, 28.3, 31.4, 42.4, 55.2, 69.7, 71.9, 78.5, 81.2, 113.6, 129.1, 131.1, 158.9, and 210.1; HRMS (ESI) calcd for $C_{29}H_{54}O_5NaSi_2$ $(M+Na)^+$ 561.3407, found *m/z* 561.3415.

(*R*)-2-hydroxy-4-(4-methoxyphenoxy)-2-methylbutyl pivalate (S-2)



To a solution of **16** (11.8 g, 52.2 mmol) in CH_2Cl_2 (174 mL) and pyridine (348 mL) was added PivCl (19.1 mL, 157 mmol) at 0 °C; the mixture was stirred at room temperature for 4 h. The reaction was quenched by the addition of 6 M HCl aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (acetone:hexane, 1:3) to give **S-2** (15.4 g, 95%) as a colorless oil: $[\alpha]^{23}_{D}$ +7.8 (*c* 1.00, $CHCl_3$); IR (film) 3470, 1728, 1509, 1229, 1152, 1036, and 825 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.23 (9H, s), 1.29 (3H, s), 2.01 (2H, t, *J* = 6.1 Hz), 2.02 (2H, t, *J* = 6.1 Hz), 3.76 (3H, s), 4.04 (2H, s), 4.13 (2H, t, *J* = 6.1 Hz), and 6.83 (4H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 24.7, 27.2, 37.6, 38.9, 55.7, 65.0, 70.6, 71.5, 114.6, 115.3, 152.3, 153.9, and 178.2; HRMS (ESI) calcd for $C_{17}H_{26}O_5Na$ $(M+Na)^+$ 333.1678, found *m/z* 333.1671.

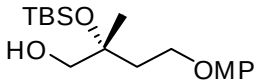
(*R*)-2-(*tert*-butyldimethylsilyloxy)-4-(4-methoxyphenoxy)-2-methylbutyl pivalate (S-3)



To a solution of **S-2** (32.2 g, 104 mmol) in CH_2Cl_2 (1.04 L) were added 2,6-lutidine (50.0 mL, 431 mmol) and TBSOTf (50.0 mL, 218 mmol) at room temperature; the mixture was stirred at the same temperature for 2 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:15) to give **S-3** (43.1 g, 98%) as a colorless oil: $[\alpha]^{22}_{D}$ +1.9 (*c* 1.00, $CHCl_3$); IR (film) 1730, 1509, 1231,

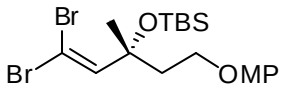
1150, 1041, and 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.12 (6H, s), 0.87 (9H, s), 1.22 (9H, s), 1.32 (3H, s), 1.91-2.11 (2H, m), 3.77 (3H, s), 3.93 (1H, d, *J* = 16.8 Hz), 3.99 (1H, d, *J* = 16.8 Hz), 4.05 (2H, t, *J* = 6.8 Hz), and 6.82 (4H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -1.96, 18.2, 25.78, 25.83, 27.3, 38.9, 39.3, 55.8, 64.4, 70.7, 73.7, 114.5, 115.2, 152.8, 153.5, and 178.0; HRMS (ESI) calcd for $C_{23}H_{41}O_5Si$ $(M+H)^+$ 425.2723, found *m/z* 425.2725.

(*R*)-2-(*tert*-butyldimethylsilyloxy)-4-(4-methoxyphenoxy)-2-methylbutan-1-ol (17)



To a solution of **S-3** (43.1 g, 101 mmol) in dry CH_2Cl_2 (1.04 L) was added DIBAL (1.03 M solution in hexane, 246 mL, 254 mmol) at -78 °C; the mixture was stirred at the same temperature for 2 h. The reaction was quenched by the addition of saturated Rochelle salt aq. at 0 °C. After being stirred at room temperature for 10 h, the resulting slurry was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:8) to give **17** (33.8 g, 97%) as a colorless oil: $[\alpha]^{21}_D$ -11.5 (*c* 1.07, $CHCl_3$); IR (film) 3465, 1509, 1230, 1042, and 834 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.12 (6H, s), 0.88 (9H, s), 1.32 (3H, s), 1.95 (1H, td, *J* = 5.8, 14.3 Hz), 2.07 (1H, ddd, *J* = 5.8, 7.3, 14.3 Hz), 2.30 (1H, dd, *J* = 5.8, 7.9 Hz), 3.41 (1H, dd, *J* = 7.9, 11.0 Hz), 3.47 (1H, dd, *J* = 5.8, 11.0 Hz), 3.77 (3H, s), 3.95-4.13 (2H, m), and 6.83 (4H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -2.00, -1.93, 18.3, 25.6, 25.9, 39.0, 55.7, 64.8, 70.1, 75.4, 114.6, 115.3, 152.5, and 153.7; HRMS (ESI) calcd for $C_{18}H_{32}O_4NaSi$ $(M+Na)^+$ 363.1968, found *m/z* 363.1977.

(*R*)-*tert*-butyl(1,1-dibromo-5-(4-methoxyphenoxy)-3-methylpent-1-en-3-yloxy)dimethylsilane (S-4)

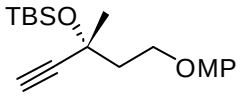


To a solution of **11** (11.1 g, 32.7 mmol) in CH_2Cl_2 (164 mL) and DMSO (164 mL) were added DIPEA (56.0 mL, 327 mmol) and SO_3-pyr. complex (26.0 g, 164 mmol) at 0 °C; the mixture was stirred at the same temperature for 2 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:8) to give the corresponding aldehyde (10.8 g, 98%) as a colorless oil.

To a solution of the aldehyde (10.8 g, 32.0 mmol) in toluene (477 mL) were added Ph_3P (83.8 g, 320 mmol), CBr_4 (53.0 mL, 160 mmol), and Et_3N (44.7 mL, 160 mmol) at

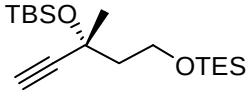
room temperature; the mixture was stirred at the same temperature for 2.5 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography ($CHCl_3$:hexane, 1:5 to 1:2) to give **S-4** (15.5 g, 98%) as a colorless oil: $[\alpha]^{16}_D$ +25.9 (*c* 0.94, $CHCl_3$); IR (film) 1508, 1231, 1042, 1002, and 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.13 (3H, s), 0.14 (3H, s), 0.89 (9H, s), 1.59 (3H, s), 2.08 (1H, ddd, *J* = 5.8, 7.9, 14.0 Hz), 2.39 (1H, ddd, *J* = 6.3, 7.9, 14.0 Hz), 3.78 (3H, s), 3.97-4.14 (2H, m), 6.77 (1H, s), and 6.84 (4H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -2.31, -1.94, 18.3, 25.9, 27.8, 41.2, 55.7, 64.5, 76.5, 86.0, 114.5, 115.3, 145.8, 152.8, and 153.6; HRMS (ESI) calcd for $C_{19}H_{30}O_3NaSiBr_2$ $(M+Na)^+$ 515.0229, found: *m/z* 515.0205.

(*R*)-*tert*-butyl(5-(4-methoxyphenoxy)-3-methylpent-1-yn-3-yloxy)dimethylsilane (18)



To a solution of **S-4** (15.5 g, 31.3 mmol) in dry THF (157 mL) was added EtMgBr (0.96 M solution in THF, 130 mL, 125 mmol) at 0 °C; the mixture was stirred at 0 °C for 2 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C. After being stirred at room temperature for 30 min, the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (acetone:hexane, 1:20) to give **18** (10.0 g, 96%) as a colorless oil: $[\alpha]^{19}_D$ +6.86 (*c* 1.05, $CHCl_3$); IR (film) 3310, 1509, 1232, 1042, and 837 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.20 (6H, s), 0.88 (9H, s), 1.54 (3H, s), 2.10 (1H, td, *J* = 7.4, 13.2 Hz), 2.17 (1H, td, *J* = 7.4, 13.2 Hz), 2.48 (1H, s), 3.77 (3H, s), 4.17 (2H, t, *J* = 7.4 Hz), and 6.84 (4H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -3.1, -2.8, 18.1, 25.8, 31.5, 43.9, 55.8, 65.1, 67.5, 72.5, 87.3, 114.5, 115.2, 152.9, and 153.5; HRMS (ESI) calcd for $C_{19}H_{31}O_3NaSi$ $(M+Na)^+$ 335.2042, found: *m/z* 335.2032.

(*R*)-9,9-diethyl-5-ethynyl-2,2,3,3,5-pentamethyl-4,8-dioxa-3,9-disilaundecane (9)

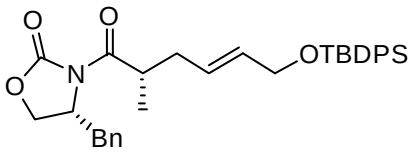


To a solution of **18** (10.0 g, 30.1 mmol) in CH_3CN (321 mL) and H_2O (80 mL) was added CAN (41.2 g, 15.1 mmol) at 0 °C; the mixture was stirred at the same temperature for 10 min. The reaction was quenched by the addition of saturated $NaHCO_3$ aq. at 0 °C. After the mixture was concentrated *in vacuo*, the resulting slurry was extracted with EtOAc. The combined organic layers

were washed with brine and saturated $Na_2S_2O_3$ and $NaHCO_3$ aq., dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:8) to give an alcohol (6.46 g, 94%) as a colorless oil, which was used for the following reaction.

To a solution of the alcohol (5.14 g, 22.5 mmol) in CH_2Cl_2 (225 mL) was added imidazole (9.19 g, 135 mmol) and TESCl (11.3 mL, 67.5 mmol) at 0 °C; the mixture was stirred at room temperature for 2.5 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (benzene:hexane, 1:15) to give **9** (7.32 g, 95%) as a colorless oil: $[\alpha]^{18}_D$ +50.9 (*c* 1.02, $CHCl_3$); IR (film) 3311 and 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.156 (3H, s), 0.159 (3H, s), 6.61 (6H, q, *J* = 7.8 Hz), 0.86 (9H, s), 0.96 (9H, t, *J* = 7.8 Hz), 1.46 (3H, s), 1.90 (1H, td, *J* = 7.3, 13.2 Hz), 1.94 (1H, td, *J* = 7.3, 13.2 Hz), 2.42 (1H, s), 3.83 (1H, dd, *J* = 1.0, 7.3 Hz), and 3.85 (1H, dd, *J* = 1.0, 7.3 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -3.1, -2.8, 4.5, 6.5, 6.91, 6.93, 18.1, 25.7, 31.5, 47.6, 59.6, 67.4, 72.2, and 87.6; HRMS (ESI) calcd for $C_{18}H_{39}O_2Si_2$ $(M+H)^+$ 343.2489, found: *m/z* 343.2491.

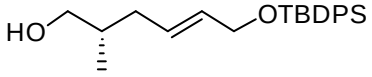
(*R*)-4-Benzyl-3-((*S*,*E*)-6-(*tert*-butyldiphenylsilyloxy)-2-methylhex-4-enoyl)oxazolidin-2-one (21)



To a solution of LHMDS (1.00 M solution in THF, 1.30 mL, 1.30 mmol) was added **19** (0.160 g, 0.686 mmol) in dry THF (1.6 mL) at -40 °C; the resulting mixture was stirred at the same temperature for 30 min. To the mixture was added a solution of **20** (315 mg, 0.722 mmol) in dry THF (20 mL) at -40 °C; the mixture was stirred at -20 °C for 1.5 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:4) to give **21** (0.298 g, 81%) as a colorless oil: $[\alpha]^{24}_D$ -12.7 (*c* 1.02, $CHCl_3$); IR (neat) 2954, 2929, 1780, and 1698 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) *δ* 1.03 (9H, s), 1.18 (3H, d, *J* = 6.8 Hz), 2.24 (1H, m), 2.52 (1H, m), 2.61 (1H, dd, *J* = 10.1, 13.2 Hz), 3.27 (1H, dd, *J* = 3.4, 13.2 Hz), 3.85 (1H, tq, *J* = 6.8, 6.8 Hz), 4.10-4.21 (4H, m) , 4.67 (1H, m), 5.67 (1H, td, *J* = 4.3, 15.3 Hz), 5.70 (1H, td, *J* = 6.4, 15.3 Hz), 7.14-7.19 (2H, m), 7.27-7.41 (9H, m), and 7.64-7.68 (4H, m);

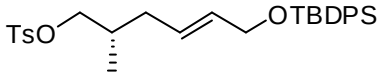
^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 19.3, 26.9, 36.6, 37.6, 38.2, 55.5, 64.4, 66.1, 127.2, 127.4, 127.8, 129.0, 129.5, 129.7, 131.8, 133.8, 133.9, 135.5, 135.6, 135.7, 153.2, and 176.7; HRMS (ESI) calcd for $C_{33}H_{39}NO_4NaSi$ $(M+Na)^+$ 564.2546, found *m/z* 564.2547.

(*S*,*E*)-6-(*tert*-Butyldiphenylsilyloxy)-2-methylhex-4-en-1-ol (S-5)



To a solution of $LiAlH_4$ (0.670 g, 18.0 mmol) in dry THF (40 mL) was added **10** (4.79 g, 8.84 mmol) in dry THF (48 ml) at 0 °C; the mixture was stirred at the same temperature for 1 h. The reaction was quenched by the addition of MeOH and saturated Rochelle salt aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:3) to give **S1** (2.65 g, 81%) as a colorless oil: $[\alpha]^{23}_D$ -0.18 (*c* 1.23, $CHCl_3$); IR (film) 3347, 2930, and 2857 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.90 (3H, d, *J* = 6.8 Hz), 1.06 (9H, s), 1.71 (1H, m), 1.92 (1H, td, *J* = 6.4, 13.5 Hz), 2.15 (1H, td, *J* = 6.4, 13.5 Hz), 3.43 (1H, dd, *J* = 6.1, 10.7 Hz), 3.51 (2H, dd, *J* = 6.1, 10.7 Hz), 4.17 (2H, dd, *J* = 4.5, 1.1 Hz), 5.61 (1H, td, *J* = 4.5, 15.3 Hz), 5.65 (1H, tdd, *J* = 6.4, 1.1, 15.3 Hz), 7.34-7.43 (6H, m), and 7.66-7.70 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 19.4, 27.0, 36.1, 36.3, 64.6, 68.1, 127.7, 129.0, 129.7, 130.6, 133.9, and 135.6; HRMS (ESI) calcd for $C_{23}H_{32}O_2NaSi$ $(M+Na)^+$ 391.2069, found *m/z* 391.2092.

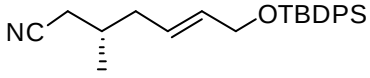
(*S*,*E*)-6-(*tert*-Butyldiphenylsilyloxy)-2-methylhex-4-enyl 4-methylbenzenesulfonate (S-6)



To a solution of **S-5** (2.65 g, 7.19 mmol) in pyridine (24 mL) was added *p*-toluenesulfonyl chloride (5.50 g, 28.8 mmol) at 0 °C; the mixture was stirred at room temperature for 3 h. The reaction was quenched by the addition of 3 M HCl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:4) to give **S-6** (3.76 g, quant.) as a yellow oil: $[\alpha]^{20}_D$ +5.7 (*c* 1.01, $CHCl_3$); IR (film) 2931, 2857, and 1362 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 6.7 Hz), 1.06 (9H, s), 1.81-1.93 (2H, m), 2.08 (1H, m), 2.41 (3H, s), 3.82 (1H, dd, *J* = 5.8, 9.4 Hz), 3.88 (1H, dd, *J* = 5.6, 9.4 Hz), 4.11 (2H, d, *J* = 3.4 Hz), 5.45-5.57 (2H, m), 7.31 (2H, d, *J* = 8.1 Hz), 7.36-7.45 (6H, m), 7.66-7.69 (4H, m), and 7.78 (2H, d, *J* = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 19.3, 21.7, 26.9, 33.0, 35.5, 64.3, 74.5, 127.2, 127.8, 128.0, 129.8, 129.9, 131.6, 133.2, 133.9,

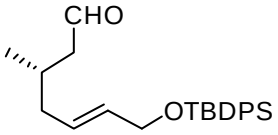
135.6, and 144.8; HRMS (ESI) calcd for $C_{30}H_{39}O_4SSi$ $(M+H)^+$ 523.2338, found *m/z* 523.2331.

(*S*,*E*)-7-(*tert*-Butyldiphenylsilyloxy)-3-methylhept-5-enenitrile (22)



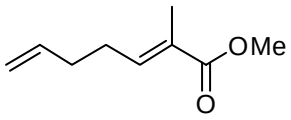
To a solution of **S-6** (3.76 g, 7.19 mmol) in DMSO (36 mL) was added NaCN (1.41 g, 28.8 mmol) at room temperature; the mixture was stirred at 40 ^oC for 6 h. The reaction was quenched by the addition of water at room temperature, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (acetone:hexane, 1:8) to give **22** (2.47 g, 91 %) as a colorless oil: $[\alpha]^{22}_D$ +9.1 (*c* 1.01, $CHCl_3$); IR (film) 2930, 2857, and 2245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (9H, s), 1.08 (3H, *J* = 6.8 Hz), 1.90 (1H, m), 2.10 (2H, t, *J* = 6.3 Hz), 2.17 (1H, dd, *J* = 6.8, 16.6 Hz), 2.28 (1H, dd, *J* = 5.9, 16.6 Hz), 4.20 (2H, d, *J* = 2.9 Hz), 5.55-5.67 (2H, m), 7.37-7.46 (6H, m), and 7.67-7.70 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 19.4, 23.8, 27.0, 30.7, 38.6, 64.2, 118.9, 126.9, 127.8, 129.8, 132.3, 133.9, and 135.7; HRMS (ESI) calcd for $C_{24}H_{32}NOSi$ $(M+H)^+$ 378.2253, found *m/z* 378.2255.

(*S*,*E*)-7-(*tert*-Butyldiphenylsilyloxy)-3-methylhept-5-enal (10)



To a solution of **22** (2.04 g, 5.41 mmol) in dry CH_2Cl_2 (27 mL) was added DIABL (1.02 M solution in hexane, 12.8 mL, 13.1 mmol) at -78 °C; the mixture was stirred at the same temperature for 1 h. The reaction was quenched by the addition of saturated Rochelle salt aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (acetone:hexane, 1:8) to give **10** (2.05 g, 98%) as a colorless oil: $[\alpha]^{21}_D$ -6.6 (*c* 1.01, $CHCl_3$); IR (film) 2958, 2931, 2856, and 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (3H, d, *J* = 6.3 Hz), 1.06 (9H, s), 2.00-2.05 (2H, m), 2.13 (1H, m), 2.19 (1H, ddd, J = 2.4, 7.8, 16.1 Hz), 2.42 (1H, ddd, *J* = 2.0, 4.9, 16.1 Hz), 4.18 (2H, d, *J* = 4.4 Hz), 5.57 (1H, td, *J* = 4.4, 15.1 Hz), 5.63 (1H, m), 7.36-7.45 (6H, m), 7.67-7.70 (4H, m), and 9.75 (1H, t, *J* = 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 20.0, 27.0, 28.4, 39.6, 50.4, 64.5, 127.8, 128.2, 129.8, 131.5, 134.0, 135.7, and 202.8; HRMS (ESI) calcd for $C_{24}H_{32}O_2NaSi$ $(M+Na)^+$ 403.2069, found *m/z* 403.2062.

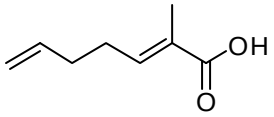
(*E*)-methyl 2-methylhepta-2,6-dienoate (23)



To a suspension of PCC (15.7 g, 72.8 mmol) and Celite (25 g) in CH_2Cl_2 (200 ml) was added a solution of 4-penten-1-ol (4.17 g, 48.4 mmol) in CH_2Cl_2 (50 ml) at 0 °C; the mixture was stirred at room temperature for 4 h. The mixture was diluted by Et_2O and filtered through Celite; the filtrate was concentrated at 40 °C to afford an aldehyde as a yellow oil, which was used for the following reaction without further purification.

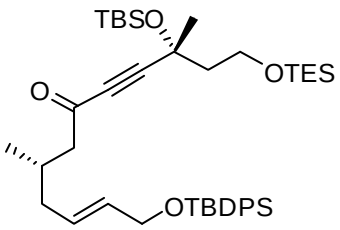
A solution of the aldehyde in benzene (35 ml) was added $Ph_3PC(CH_3)CO_2Me$ (16.9 g, 48.4 mmol) at room temperature for 1 day. After the mixture was concentrated *in vacuo*, the residue was purified by silica gel chromatography (EtOAc:hexane, 1:20) to give **23** (0.73 g, 34%) as a colorless oil: IR (film) 2951, 2931, 2856, and 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (3H, d, *J* = 1.0 Hz), 2.19 (2H, tdd, *J* = 6.3, 6.8, 1.5 Hz), 2.27 (2H, ttd, *J* = 6.8, 6.8, 1.0 Hz), 3.73 (3H, s), 5.00 (1H, dd, *J* = 1.5, 10.2 Hz), 5.05 (1H, dd, *J* = 1.5, 17.1 Hz), 5.81 (1H, tdd, J = 6.3, 10.2, 17.1 Hz), and 6.75 (1H, td, *J* = 1.5, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 28.0, 32.5, 51.7, 115.3, 127.8, 137.4, 141.5, and 168.4; HRMS (ESI) calcd for $C_8H_{12}O_2Na$ $(M+Na)^+$ 163.0735, found *m/z* 163.0751.

(*E*)-2-methylhepta-2,6-dienoic acid (5)



To a solution of **23** (79.2 mg, 0.514 mmol) in THF (4.5 ml) was added 25% NaOH aq. (0.5 ml) at 0 °C; the mixture was stirred at 80 °C for 12 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:5) to give **5** (67.0 mg, 93%) as a colorless oil: IR (film) 3127, 2929, and 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.84 (3H, d, *J* = 1.0 Hz), 2.21 (2H, tdd, *J* = 6.8, 6.3, 1.5 Hz), 2.31 (2H, tdd, *J* = 6.8, 7.3, 1.0 Hz), 5.01 (1H, dd, *J* = 1.5, 10.2 Hz), 5.06 (1H, dd, *J* = 1.5, 17.1 Hz), 5.81 (1H, tdd, *J* = 6.3, 10.2, 17.1 Hz), and 6.91 (1H, td, *J* = 7.3, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 28.3, 32.4, 115.4, 127.3, 137.2, 141.1, and 173.7; HRMS (EI) calcd for $C_8H_{10}O_1$ $(M-H_2O)^+$ 122.0732, found *m/z* 122.0731.

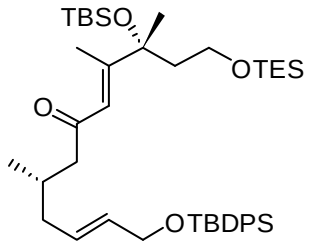
(7*R*,12*S*,*E*)-7-(*tert*-butyldimethylsilyloxy)-3,3-diethyl-7,12,19,19-tetramethyl-18,18-diphenyl-4,17-dioxa-3,18-disilaicos-14-en-8-yn-10-one (8)



To a solution of **9** (0.469 g, 1.37 mmol) in dry THF (2.3 mL) was added *n*-BuLi (1.63M solution in hexane, 0.786 mL, 1.28 mmol) at -78 °C; the mixture was stirred at 0 °C for 40 min. To the mixture was added a solution of **10** (174 mg, 0.458 mmol) in dry THF (2.3 mL) at -78 °C; the mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:15) to give an alcohol (0.319 g, 96%) as a colorless oil.

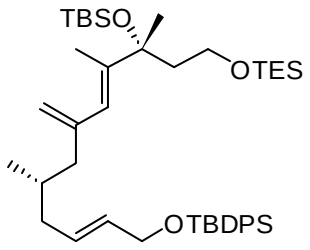
To a solution of the alcohol (0.319 g, 0.441 mmol) in dry CH_2Cl_2 (4.4 mL) were added MS4A (0.220 g), NMO (0.155 g, 1.32 mmol), and TPAP (15.5 mg, 0.0441 mmol) at room temperature; the mixture was stirred at the same temperature for 1 h. After the mixture was concentrated *in vacuo*, the residue was purified by silica gel chromatography (EyOAc:hexane, 1:15) to give **8** (0.267 g, 84%) as a colorless oil: $[\alpha]^{23}_{D}$ +1.55 (*c* 1.01, $CHCl_3$); IR (film) 2210, 1678, and 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.17 (3H, s), 0.18 (3H, s), 0.59 (6H, q, J = 7.8 Hz), 0.87 (9H, s), 0.94 (3H, d, J = 6.8 Hz), 0.95 (9H, t, J = 7.8 Hz), 1.06 (9H, s), 1.51 (3H, s), 1.93-2.04 (3H, m), 2.05 (1H, ddd, J = 6.3, 6.3, 13.7 Hz), 2.17 (1H, m), 2.32 (1H, dd, J = 5.4, 15.6 Hz), 2.55 (1H, dd, J = 5.4, 15.6 Hz), 3.81 (1H, t, J = 8.8 Hz), 3.82 (1H, t, J = 8.8 Hz), 4.17 (2H, d, J = 4.4 Hz), 5.56 (1H, td, J = 3.9, 15.1 Hz), 5.63 (1H, td, J = 6.3, 15.1 Hz), 7.35-7.45 (6H, m), and 7.66-7.69 (4H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ -3.1, -2.8, 4.5, 6.9, 18.1, 19.3, 19.5, 25.6, 26.9, 29.8, 30.8, 39.4, 47.1, 52.0, 59.2, 64.3, 67.7, 83.3, 94.6, 127.5, 127.9, 129.5, 131.2, 133.7, 135.4, and 186.9; HRMS (ESI) calcd for $C_{29}H_{54}O_6Na$ $(M+Na)^+$ 743.4323, found *m/z* 743.4289.

(7*R*,8*E*,12*S*,14*E*)-7-(*tert*-butyldimethylsilyloxy)-3,3-diethyl-7,8,12,19,19-pentamethyl-18,18-diphenyl-4,17-dioxa-3,18-disilaicosa-8,14-dien-10-one (24-(*E*))



To a suspension of CuI (0.620 g, 3.30 mmol) in dry Et_2O (15 mL) was added MeLi (1.09 M solution in hexane, 5.80 mL, 6.40 mmol) at -78 °C; the mixture was stirred at -30 °C for 1 h. To the mixture was added a solution of **8** (0.550 g, 0.760 mmol) in dry THF (3.0 mL) and dry Et_2O (3.0 mL) at -78 °C; the mixture was stirred at -30 °C for 1h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Et_2O:hexane, 1:15) to give **24-(*E*)** (0.450 g, 81%) as a colorless oil: $[\alpha]^{23}_D$ -9.24 (*c* 1.02, $CHCl_3$); IR (film) 1686, and 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.09 (3H, s), 0.15 (3H, s), 0.55 (6H, q, *J* = 7.8 Hz), 0.90 (3H, d, *J* = 6.8 Hz), 0.93 (9H, t, *J* = 7.8 Hz), 0.94 (9H, s), 1.06 (9H, s), 1.40 (3H, s), 1.83 (1H, ddd, *J* = 5.4, 9.8, 13.7 Hz), 1.91-2.06 (4H, m), 2.08 (3H, d, *J* = 1.0 Hz), 2.19 (1H, dd, *J* = 8.3, 14.6 Hz), 2.46 (1H, dd, *J* = 4.9, 14.6 Hz), 3.43 (1H, td, *J* = 9.8, 5.4 Hz), 3.66 (1H, td, *J* = 9.8, 5.4 Hz), 4.16 (2H, d, *J* = 4.4 Hz), 5.56 (1H, td, *J* = 4.4, 15.6 Hz), 5.64 (1H, td, *J* = 6.3, 15.6 Hz), 6.48 (1H, d, *J* = 1.0 Hz), 7.35-7.44 (6H, m), and 7.69 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.9, -1.8, 4.4, 6.8, 15.9, 18.7, 19.3, 19.6, 26.1, 26.9, 27.9, 30.2, 39.7, 43.9, 51.9, 58.9, 64.5, 77.9, 121.2, 127.51, 127.55, 128.7, 129.5, 130.7, 133.7, 135.4, 160.7, and 201.8; HRMS (ESI) calcd for $C_{43}H_{72}O_3NaSi_3$ $(M+Na)^+$ 759.4636, found *m/z* 759.4620.

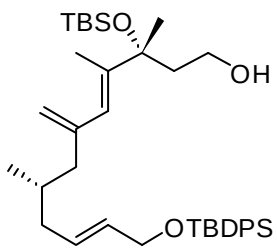
(6*E*,9*S*,12*E*,14*R*)-14-(*tert*-butyldimethylsilyloxy)-18,18-diethyl-2,2,9,13,14-pentamethyl-11-methylene-3,3-diphenyl-4,17-dioxa-3,18-disilaicosa-6,12-diene (25)



To a suspension of Ph_3PCH_3Br (9.63 g, 27.0 mmol) in dry THF (45 mL) was added *n*-BuLi (2.69 M solution in hexane, 9.39 mL, 25.3 mmol) at 0 °C; the mixture was stirred at 0 °C for 30 min. To the mixture was added a solution of **24-(*E*)** (6.21 g, 8.42 mmol) in dry THF (45 mL) at 0 °C; the mixture was stirred at room temperature for 12 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Et_2O:hexane, 1:30) to give **25** (5.61 g, 91%) as a colorless

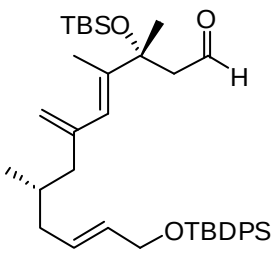
oil: $[\alpha]^{22}_D$ -22.3 (*c* 1.03, $CHCl_3$); IR (film) 1255 and 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (3H, s), 0.11 (3H, s), 0.56 (6H, q, *J* = 7.8 Hz), 0.81 (3H, d, *J* = 6.8 Hz), 0.89 (9H, s), 0.93 (9H, t, *J* = 7.8 Hz), 1.05 (9H, s), 1.37 (3H, s), 1.57 (1H, m), 1.76 (3H, d, *J* = 1.5 Hz), 1.75-1.88 (3H, m), 1.93 (1H, ddd, *J* = 5.4, 10.2, 13.2 Hz), 2.04 (1H, ddd, *J* = 6.8, 6.8, 13.7 Hz), 2.13 (1H, dd, *J* = 5.9, 13.2 Hz), 3.45 (1H, ddd, *J* = 10.2, 10.2, 5.4 Hz), 3.64 (1H, td, *J* = 10.2, 5.4 Hz), 4.16 (2H, d, *J* = 4.4 Hz), 4.78 (1H, s), 4.98 (1H, d, *J* = 1.5 Hz), 5.54 (1H, td, *J* = 4.9, 15.1 Hz), 5.62 (1H, td, *J* = 6.8, 15.1 Hz), 5.90 (1H, s), 7.35-7.44 (6H, m), and 7.69 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -2.1, -1.7, 4.4, 6.9, 14.8, 18.6, 19.3, 26.1, 26.9, 28.1, 31.8, 39.5, 44.2, 45.6, 59.5, 64.6, 77.4, 114.1, 124.5, 127.5, 129.5, 130.2, 133.8, 135.5, 141.9, and 145.1; HRMS (ESI) calcd for $C_{44}H_{74}O_3NaSi_3$ $(M+Na)^+$ 757.4844, found *m/z* 757.4835.

(3*R*,4*E*,8*S*,10*E*)-3-(*tert*-butyldimethylsilyloxy)-12-(*tert*-butyldiphenylsilyloxy)-3,4,8-trimethyl-6-methylenedodeca-4,10-dien-1-ol (S-7)



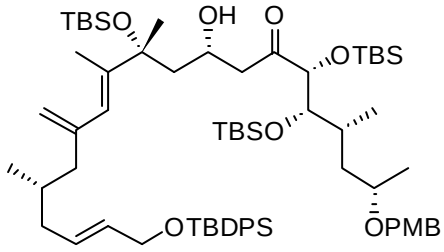
To a solution of **25** (5.61 g, 7.63 mmol) in CH_2Cl_2 (38 mL) and MeOH (38 mL) was added PPTS (0.192 g, 0.763 mmol) at 0 °C; the mixture was stirred at the same temperature for 2 h. The reaction was quenched by the addition of saturated $NaHCO_3$ aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:5) to give **S-5** (4.41 g, 93%) as a yellow oil: $[\alpha]^{22}_D$ -11.6 (*c* 1.07, $CHCl_3$); IR (film) 3366, 2955, 2929, 2857, 1687, and 1617 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.14 (3H, s), 0.82 (3H, d, *J* = 6.8 Hz), 0.90 (9H, s), 1.05 (9H, s), 1.44 (3H, s), 1.59 (1H, m), 1.73 (1H, ddd, *J* = 6.8, 6.8, 14.1 Hz), 1.78 (3H, d, *J* = 1.0 Hz), 1.85 (1H, m), 1.86 (1H, dd, *J* = 8.8, 13.7 Hz), 1.95 (1H, td, *J* = 5.9, 14.1 Hz), 2.05 (1H, td, *J* = 6.3, 14.1 Hz), 2.14 (1H, dd, *J* = 5.9, 13.7 Hz), 2.48 (1H, br), 3.65 (2H, t, *J* = 5.4 Hz), 4.14 (2H, dd, *J* = 1.0, 4.9 Hz), 4.81 (1H, s), 5.01 (1H, t, *J* = 1.0 Hz), 5.54 (1H, d, *J* = 4.9, 15.1 Hz), 5.63 (1H, d, *J* = 6.8, 15.1 Hz), 5.99 (1H, s), 7.35-7.44 (6H, m), and 7.69 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -2.2, -1.7, 14.9, 18.4, 19.2, 19.2, 26.1, 26.8, 27.7, 31.7, 39.4, 43.1, 45.5, 59.8, 64.6, 79.5, 114.5, 125.3, 127.6, 129.4, 129.5, 130.2, 133.8, 135.4, 141.7, and 144.9; HRMS (ESI) calcd for $C_{38}H_{60}O_3NaSi_2$ $(M+Na)^+$ 643.3979, found m/z 643.3998.

(3*R*,4*E*,8*S*,10*E*)-3-(*tert*-butyldimethylsilyloxy)-12-(*tert*-butyldiphenylsilyloxy)-3,4,8-trimethyl-6-methylenedodeca-4,10-dienal (6)



To a solution of **S-7** (0.933 g, 1.50 mmol) in CH_2Cl_2 (15 mL) was added Dess-Martin periodinane (15 wt.% solution in CH_2Cl_2, 4.68 mL, 2.25 mmol) at 0 °C; the mixture was stirred at room temperature for 1.5 h. The reaction was quenched by the addition of saturated $NaHCO_3$ aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:15) to give **6** (0.895 g, 96%) as a colorless oil: $[\alpha]^{22}_D$ -6.6 (*c* 1.01, $CHCl_3$); IR (film) 2955, 2929, 2857, and 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.13 (3H, s), 0.81 (3H, d, *J* = 6.8 Hz), 0.88 (9H, s), 1.05 (9H, s), 1.46 (3H, s), 1.55 (1H, m), 1.82 (3H, d, *J* = 1.2 Hz), 1.85 (1H, dd, *J* = 4.4, 13.2 Hz), 1.86 (1H, m), 2.04 (1H, ddd, *J* = 6.8, 6.8, 13.7 Hz), 2.12 (1H, dd, *J* = 6.3, 13.4 Hz), 2.43 (1H, dd, *J* = 2.9, 15.1 Hz), 2.65 (1H, dd, 2.9, 15.1 Hz), 4.16 (2H, dd, *J* = 1.2, 4.9 Hz), 4.81 (1H, s), 5.01 (1H, dd, *J* = 1.2, 1.2 Hz), 5.53 (1H, td, *J* = 4.9, 15.1 Hz), 5.62 (1H, td, *J* = 6.8, 15.1 Hz), 6.02 (1H, s), 7.35-7.44 (6H, m), 7.66-7.70 (4H, m), and 9.67 (1H, t, *J* = 2.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -2.2, -1.7, 14.8, 18.5, 19.26, 19.29, 26.0, 26.9, 28.0, 31.8, 39.4, 45.3, 54.0, 64.6, 77.1, 114.8, 125.9, 127.51, 127.54, 129.2, 129.5, 130.3, 133.8, 135.4, 140.9, 144.6, and 202.9; HRMS (ESI) calcd for $C_{38}H_{59}O_3Si_2$ $(M+H)^+$ 619.4003, found *m/z* 619.4006.

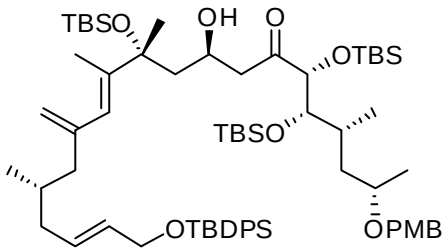
(5*S*,6*R*,9*S*,11*R*,12*E*,16*S*,18*E*)-6,11-bis(*tert*-butyldimethylsilyloxy)-9-hydroxy-5-((2*R*,4*S*)-4-(4-methoxybenzyloxy)pentan-2-yl)-2,2,3,3,11,12,16,23,23-nonamethyl-14-methylene-22,22-diphenyl-4,21-dioxa-3,22-disilatetracosa-12,18-dien-7-one (26-(*S*))



To a solution of LHMDS (1.00 M solution in THF, 2.00 mL, 2.00 mmol) in dry THF (18 mL) was added a solution of **7** (1.00 g, 1.86 mmol) in dry THF (4.0 mL) at -78 °C; the mixture was stirred at the same temperature for 30 min, at 0 °C for 30 min, and at room temperature for 1 h. To the mixture was added a pre-cooled solution of **6** (501 mg, 0.82 mmol) in dry THF (4.0 mL) at -20 °C; the mixture was stirred at the same temperature for 10 min. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by

silica gel column chromatography (MTBE:hexane, 1:40) and gel permeation chromatography (JAIGEL-1H, $CHCl_3$, flow rate 3.5 mL/min, UV detection at 254 nm) to give **26-(*S*)** (504 mg, 53%) as a colorless oil: $[\alpha]^{22}_D$ -13.3 (*c* 1.00, $CHCl_3$); IR (film) 3505, 2955, 2929, 1719, and 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.02 (3H, s), 0.04 (6H, s), 0.08 (3H, s), 0.09 (3H, s), 0.11 (3H, s), 0.71 (3H, d, *J* = 6.7 Hz), 0.81 (3H, d, *J* = 6.5 Hz), 0.88 (9H, s), 0.89 (9H, s), 0.93 (9H, s), 1.05 (9H, s), 1.15 (3H, d, *J* = 6.1 Hz), 1.18 (1H, ddd, *J* = 4.5, 9.0, 13.7 Hz), 1.48 (1H, m), 1.50 (3H, s), 1.59 (1H, m), 1.70 (1H, ddd, *J* = 5.2, 8.1, 13.7 Hz), 1.79 (3H, d, *J* = 0.9 Hz), 1.84 (1H, dd, *J* = 4.7, 13.7 Hz), 1.79-1.90 (2H, m), 1.94-2.09 (2H, m), 2.13 (1H, dd, *J* = 6.1 Hz, 13.7 Hz), 2.60 (1H, dd, *J* = 5.6 Hz, 17.5 Hz), 2.85 (1H, dd, *J* = 6.5 Hz, 17.5 Hz), 3.48 (1H, m), 3.53 (1H, d, *J* = 1.6 Hz), 3.64 (1H, dd, *J* = 3.8 Hz, 4.5 Hz), 3.79 (3H, s), 4.14 (1H, d, *J* = 4.5 Hz), 4.16 (2H, dd, *J* = 0.9 Hz, 4.7 Hz), 4.31 (1H, m), 4.31 (1H, d, *J* = 11.7 Hz), 4.48 (1H, d, *J* = 11.7 Hz), 4.80 (1H, s), 4.99 (1H, dd, *J* = 0.9 Hz), 5.54 (1H, td, *J* = 4.7 Hz, 15.3 Hz), 5.64 (1H, td, *J* = 7.0, 15.3 Hz), 5.89 (1H, s), 6.85 (2H, dd, *J* = 2.0, 6.7 Hz), 7.24 (2H, dd, *J* = 1.8, 6.7 Hz), 7.34 (6H, m), and 7.69 (4H, m); ^{13}C NMR (100 MHz, C_6D_6) δ -4.6, -4.2, -4.1, -3.7, -2.3, -1.5, 14.2, 15.3, 15.6, 18.5, 18.6, 18.8, 19.6, 20.2, 26.2, 26.3, 26.4, 27.1, 27.2, 32.1, 32.3, 39.9, 42.4, 45.8, 48.6, 54.8, 65.0, 65.3, 69.9, 71.6, 79.3, 79.6, 82.1, 114.0, 115.1, 125.7, 129.5, 130.0, 131.1, 131.8, 134.3, 136.0, 143.4, 145.3, 159.6, and 209.7; HRMS (ESI) calcd for $C_{67}H_{112}O_8NaSi_4$ $(M+Na)^+$ 1179.7332, found *m/z* 1179.7335.

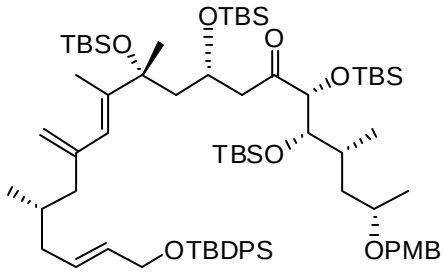
(5*S*,6*R*,9*R*,11*R*,12*E*,16*S*,18*E*)-6,11-bis(*tert*-butyldimethylsilyloxy)-9-hydroxy-5-((2*R*, 4*S*)-4-(4-methoxybenzyloxy)pentan-2-yl)-2,2,3,3,11,12,16,23,23-nonamethyl-14-methylene-22,22-diphenyl-4,21-dioxa-3,22-disilatetracosa-12,18-dien-7-one (26-(*R*))



$[\alpha]^{18}_D$ -18.8 (*c* 1.00, $CHCl_3$); IR (film) 3502, 2956, 2930, 1719, and 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.02 (3H, s), 0.03 (3H, s), 0.08 (3H, s), 0.09 (3H, s), 0.13 (3H, s), 0.16 (3H, s), 0.70 (3H, d, *J* = 6.8 Hz), 0.82 (3H, d, *J* = 6.8 Hz), 0.89 (9H, s), 0.90 (9H, s), 0.95 (9H, s), 1.06 (9H, s), 1.16 (3H, d, *J* = 5.9 Hz), 1.18 (1H, ddd, *J* = 4.9, 8.3, 13.7 Hz), 1.54-1.68 (2H, m), 1.59 (3H, s), 1.70 (1H, ddd, *J* = 5.9, 7.8, 13.7 Hz), 1.78 (3H, d, *J* = 1.0 Hz), 1.81-1.92 (3H, m), 1.95-2.09 (2H, m), 2.14 (1H, dd, *J* = 6.3 Hz, 13.7 Hz), 2.58 (1H, dd, *J* = 5.4 Hz, 16.6 Hz), 2.82 (1H, dd, *J* = 7.3 Hz, 16.6 Hz), 3.49 (1H, m), 3.66 (1H, dd, *J* = 2.9 Hz, 4.9 Hz), 3.76 (1H, s), 3.80 (3H, s), 4.08 (1H, m), 4.16 (2H, d, *J* = 4.9 Hz), 4.22 (1H, d, *J* = 4.9 Hz), 4.33 (1H, d, *J* = 11.2 Hz), 4.48 (1H, d, *J* = 11.2 Hz), 4.83 (1H, s), 5.00 (1H, d, *J* = 2.0 Hz),

5.54 (1H, td, *J* = 4.9 Hz, 15.1 Hz), 5.63 (1H, td, *J* = 6.8, 15.1 Hz), 6.02 (1H, s), 6.86 (2H, dd, *J* = 2.0, 6.8 Hz), 7.25 (2H, dd, *J* = 2.0, 6.8 Hz), 7.40 (6H, m), and 7.69 (4H, m); ^{13}C NMR (100 MHz, C_6D_6) δ -4.9, -4.3, -4.1, -3.7, -1.7, -1.2, 15.3, 15.6, 18.56, 18.60, 19.6, 19.7, 20.2, 26.3, 26.42, 26.44, 27.1, 28.4, 32.0, 32.3, 40.0, 42.4, 45.8, 48.1, 48.7, 54.8, 65.0, 67.1, 69.9, 72.0, 79.5, 81.2, 82.6, 114.0, 115.0, 126.2, 129.4, 129.8, 130.0, 131.0, 131.9, 134.3, 136.0, 141.2, 145.5, 159.6, and 209.6; HRMS (ESI) calcd for $C_{67}H_{112}O_8NaSi_4$ $(M+Na)^+$ 1179.7332, found *m/z* 1179.7328.

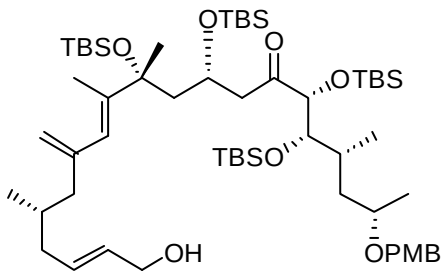
(5*S*,6*R*,9*S*,11*R*,12*E*,16*S*,18*E*)-6,9,11-tris(*tert*-butyldimethylsilyloxy)-5-((2*R*,4*S*)-4-(4-methoxybenzyloxy)pentan-2-yl)-2,2,3,3,11,12,16,23,23-nonamethyl-14-methylene-22,22-diphenyl-4,21-dioxa-3,22-disilatetracosa-12,18-dien-7-one (S-8)



To a solution of **26-(*S*)** (1.20 g, 1.04 mmol) in CH_2Cl_2 (10 mL) were added 2,6-lutidine (0.720 mL, 6.20 mmol) and TBSOTf (0.710 mL, 3.10 mmol) at room temperature; the mixture was stirred at the same temperature for 1 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:20) to give **S-8** (1.29 g, 98%) as a colorless oil: $[\alpha]^{22}_D$ -39.2 (*c* 1.01, $CHCl_3$); IR (film) 3423, 2955, 2929, and 1718 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.14 (3H, s), 0.15 (6H, s), 0.20 (3H, s), 0.22 (9H, s), 0.26 (3H, s), 0.98 (3H, d, *J* = 6.8 Hz), 0.98 (3H, d, *J* = 6.8 Hz), 1.03 (9H, s), 1.04 (9H, s), 1.05 (9H, s), 1.06 (9H, s), 1.16 (3H, d, *J* = 5.9 Hz), 1.21 (9H, s), 1.34 (1H, ddd, *J* = 3.9, 9.8, 13.7 Hz), 1.58 (3H, s), 1.84 (1H, m), 1.88-2.01 (4H, m), 2.12 (3H, s), 2.07-2.22 (2H, m), 2.30 (1H, dd, *J* = 5.4, 13.2 Hz), 2.33 (1H, m), 3.00 (1H, dd, *J* = 6.8 Hz, 17.6 Hz), 3.12 (1H, dd, *J* = 5.4 Hz, 17.6 Hz), 3.37 (3H, s), 3.54 (1H, m), 3.85 (1H, dd, *J* = 4.4, 4.4 Hz), 4.12 (1H, t, *J* = 4.4 Hz), 4.15 (2H, dd, *J* = 1.0, 4.9 Hz), 4.27 (1H, d, *J* = 11.7 Hz), 4.30 (1H, d, *J* = 4.4 Hz), 4.51 (1H, m), 4.51 (1H, d, *J* = 11.7 Hz), 5.14 (1H, s), 5.16 (1H, s), 5.65 (1H, td, *J* = 4.9, 15.1 Hz), 5.83 (1H, td, *J* = 6.8, 15.1 Hz), 6.02 (1H, s), 6.89 (2H, dd, *J* = 2.0, 6.8 Hz), 7.25 (6H, m), 7.30 (2H, dd, *J* = 2.0, 6.8 Hz), and 7.69 (4H, m); ^{13}C NMR (100 MHz, C_6D_6) δ -4.5, -4.3, -4.04, -3.97, -3.6, -3.5, -2.2, -1.3, 15.1, 15.7, 18.3, 18.58, 18.6, 18.8, 19.4, 19.6, 20.3, 26.3, 26.37, 26.41, 26.5, 27.1, 32.0, 32.1, 40.1, 42.9, 46.0, 49.8, 50.7, 54.8, 64.9, 66.4, 70.0, 71.8, 78.3, 79.4, 82.3, 114.0, 1115.6, 126.4, 128.6, 129.4, 129.5, 130.0, 131.0, 131.9, 134.4, 136.0, 143.0, 145.2, 159.6, and 208.0; HRMS (ESI) calcd for $C_{73}H_{126}O_8NaSi_5$ $(M+Na)^+$

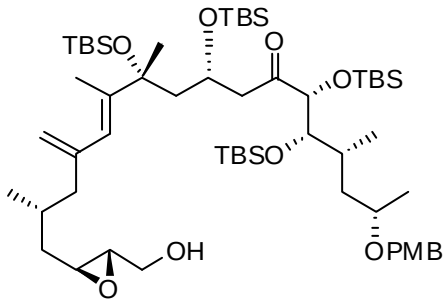
1293.8197, found *m/z* 1293.8162.

(5*S*,6*R*,9*S*,11*R*)-6,9-bis(*tert*-butyldimethylsilyloxy)-11-((*S*,2*E*,8*E*)-10-hydroxy-6-methyl-4-methylenedeca-2,8-dien-2-yl)-5-((2*R*,4*S*)-4-(4-methoxybenzyloxy)pentan-2-yl)-2,2,3,3,11,13,13,14,14-nonamethyl-4,12-dioxa-3,13-disilapentadecan-7-one (27)



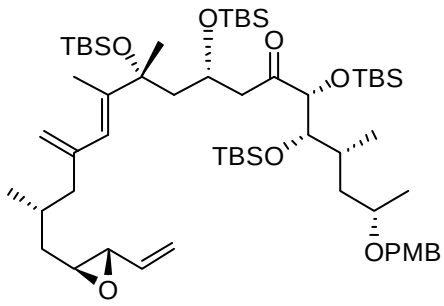
To a solution of **S-8** (1.30 g, 1.02 mmol) in DMF (14 mL) were added a solution of TBAF (1.0M solution in THF, 0.510 mL, 0.510 mmol), AcOH (29.0 μL, 0.510 mmol) and H_2O (46.0 μL, 2.50 mmol) in THF (4.6 mL) at 0 °C; the mixture was stirred at the same temperature for 4 h. The reaction was quenched by the addition of water at 0 °C, and the resulting slurry was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:10) and gel permeation chromatography (JAIGEL-1H, $CHCl_3$, flow rate 3.5 mL/min, UV detection at 254 nm) to give **27** (0.840 g, 79%) as a yellow oil, along with the recovered **S-8** (0.150 g, 12%): $[\alpha]^{22}_D$ -36.0 (*c* 0.56, $CHCl_3$); IR (film) 3505, 2929, 2857, and 1718 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.15 (9H, s), 0.19 (3H, s), 0.215 (3H, s), 0.223 (6H, s), 0.26 (3H, s), 0.97 (3H, d, *J* = 6.3 Hz), 0.98 (3H, d, *J* = 6.8 Hz), 1.03 (9H, s), 1.04 (9H, s), 1.05 (9H, s), 1.06 (9H, s), 1.18 (3H, d, *J* = 5.9 Hz), 1.34 (1H, ddd, *J* = 3.4, 9.8, 13.7 Hz), 1.57 (3H, s), 1.81 (1H, m), 1.85-1.99 (4H, m), 2.09 (3H, s), 2.10 (1H, dd, *J* = 4.9, 13.7 Hz), 2.18 (1H, m), 2.28 (1H, dd, *J* = 5.9, 13.7 Hz), 2.34 (1H, m), 3.03 (1H, dd, *J* = 7.3, 17.6 Hz), 3.12 (1H, dd, *J* = 5.4, 17.6 Hz), 3.36 (3H, s) 3.54 (1H, m), 3.84 (1H, dd, *J* = 4.4, 4.4 Hz), 3.94-3.98 (2H, m), 4.27 (1H, d, *J* = 11.7 Hz), 4.30 (1H, d, *J* = 4.9 Hz), 4.48 (1H, m), 4.52 (1H, d, *J* = 11.7 Hz), 5.12 (1H, s), 5.13 (1H, s), 5.63 (1H, td, *J* = 5.4, 15.1 Hz), 5.72 (1H, td, *J* = 6.8, 15.1 Hz), 6.01 (1H, s), 6.90 (2H, d, *J* = 8.3 Hz), and 7.31 (2H, d, *J* = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.6, -4.44, -4.39, -4.0, -3.7, -2.6, -1.7, 14.5, 15.2, 17.9, 18.3, 18.4, 19.2, 19.9, 25.9, 26.0, 26.1, 28.1, 30.9, 31.5, 39.6, 42.5, 45.5, 49.9, 50.0, 55.3, 63.8, 65.7, 69.6, 71.9, 77.8, 78.6, 81.5, 113.6, 115.0, 125.6, 128.3, 129.1, 130.5, 131.2, 131.7, 142.5, 144.8, 158.9, and 208.2; HRMS (ESI) calcd for $C_{57}H_{108}O_8NaSi_4$ $(M+Na)^+$ 1055.7019, found *m/z* 1055.6996.

(5*S*,6*R*,9*S*,11*R*)-6,9-bis(*tert*-butyldimethylsilyloxy)-11-((*R*,*E*)-7-((2*S*,3*S*)-3-(hydroxy methyl)oxiran-2-yl)-6-methyl-4-methylenehept-2-en-2-yl)-5-((2*R*,4*S*)-4-(4-methoxy benzyloxy)pentan-2-yl)-2,2,3,3,11,13,13,14,14-nonamethyl-4,12-dioxa-3,13-disilape ntadecan-7-one (S-9)



To a suspension of Ti(O*i*-Pr)$_4$ (19.5 mg, 0.0690 mmol) and MS4A in dry CH_2Cl_2 (2.0 mL) was added a solution of (+)-DIPT (16.0 mg, 0.0690 mmol) in dry CH_2Cl_2 (0.2 mL) at - 40 °C; the mixture was stirred at -30 °C for 30 min. To the mixture were added TBHP (5.50 M solution in decane, 125 μL, 0.690 mmol) and a solution of **27** (71.0 mg, 0.0690 mmol) in dry CH_2Cl_2 (3.0 mL) at -30 °C for 30 min. The reaction was quenched by the addition of saturated (+)-tartaric acid aq. at 0 °C, and the resulting slurry was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:6) to give **S-9** (61.0 mg, 84%) as a colorless oil, along with the recovered **27** (6.4 mg, 9.0%): $[\alpha]^{22}_D$ -25.1 (*c* 1.00, $CHCl_3$); IR (film) 3505, 2928, and 1724 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.15 (6H, s), 0.16 (3H, s), 0.20 (3H, s), 0.23 (9H, s), 0.26 (3H, s), 0.97 (3H, d, *J* = 6.3 Hz), 0.98 (3H, d, *J* = 6.8 Hz), 1.04 (9H, s), 1.047 (9H, s), 1.053 (9H, s), 1.06 (9H, s), 1.17 (3H, d, *J* = 5.9 Hz), 1.20 (1H, m), 1.33 (1H, m), 1.57 (3H, s), 1.66 (1H, ddd, J = 4.4, 6.3, 13.7 Hz), 1.88-2.02 (4H, m), 2.10 (3H, s), 2.10 (1H, dd, *J* = 4.9, 12.7 Hz), 2.26 (1H, dd, *J* = 5.4 Hz, 12.7 Hz), 2.34 (1H, m), 2.65 (1H, ddd, *J* = 2.0, 2.9, 4.4 Hz), 2.93 (1H, td, *J* = 5.9, 2.0 Hz), 3.03 (1H, dd, *J* = 6.8, 17.6 Hz), 3.13 (1H, dd, *J* = 5.4, 17.6 Hz), 3.37 (3H, s), 3.39 (1H, m), 3.50-3.59 (2H, m), 3.84 (1H, dd, *J* = 4.4, 4.4 Hz), 4.27 (1H, d, *J* = 11.7 Hz), 4.30 (1H, d, *J* = 4.9 Hz), 4.49 (1H, m), 4.52 (1H, d, *J* = 11.7 Hz), 5.10 (1H, s), 5.13 (1H, s), 6.01 (1H, s), 6.90 (2H, d, *J* = 8.8 Hz), and 7.31 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ -4.5, -4.2, -4.0, -3.9, -3.6, -3.4, -2.2, -1.2, 14.4, 15.2, 15.7, 18.3, 18.6, 18.8, 19.8, 20.3, 23.2, 26.3, 26.37, 26.43, 26.4, 26.5, 28.6, 29.9, 30.3, 32.0, 32.4, 39.2, 43.0, 46.5, 49.9, 50.6, 50.8, 54.5, 54.8, 59.0, 62.0, 66.5, 70.0, 71.8, 78.5, 79.4, 82.3, 114.1, 115.8, 126.2, 129.5, 131.8, 143.1, 144.9, 159.6, and 208.3; HRMS (ESI) calcd for $C_{57}H_{108}O_9NaSi_4$ $(M+Na)^+$ 1071.6968, found *m/z* 1071.6954.

(5*S*,6*R*,9*S*,11*R*)-6,9-bis(*tert*-butyldimethylsilyloxy)-5-((2*R*,4*S*)-4-(4-methoxybenzyloxy)pentan-2-yl)-2,2,3,3,11,13,13,14,14-nonamethyl-11-((*R*,*E*)-6-methyl-4-methylene-7-((2*S*,3*S*)-3-vinyloxiran-2-yl)hept-2-en-2-yl)-4,12-dioxa-3,13-disilapentadecan-7-one (28)

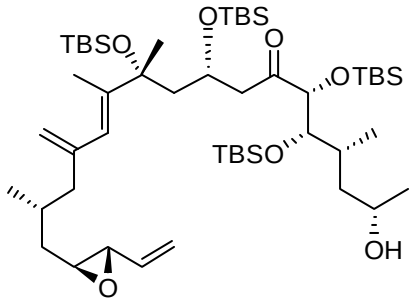


To a solution of **S-9** (12.5 mg, 0.0119 mmol) in CH_2Cl_2 (1.0 mL) was added pyridine (50.0 μL, 0.620 mmol) and Dess-Martin periodinane (15 wt.% solution in CH_2Cl_2, 500 μL, 0.240 mmol) at 0 °C; the mixture was stirred at the same temperature for 18 h. The reaction was quenched by the addition of saturated $NaHCO_3$ aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:12) to give an aldehyde as a colorless oil.

To a suspension of Ph_3PCH_3Br (94.0 mg, 0.264 mmol) in dry THF (1.5 mL) was added NaHMDS (1.0M solution in THF, 0.250 mL, 0.250 mmol) at 0 °C; the mixture was stirred at the same temperature for 1 h. To the mixture was added a solution of the aldehyde (12.2 mg, 0.0116 mmol) in dry THF (1.0 mL) at 0 °C; the mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:15) to give **28** (11.9 mg, 95%) as a colorless oil: $[\alpha]^{22}_D$ -32.1 (*c* 0.80, $CHCl_3$); IR (film) 2928 and 1716 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.14 (3H, s), 0.156 (3H, s), 0.159 (3H, s), 0.20 (3H, s), 0.22 (9H, s), 0.25 (3H, s), 0.97 (3H, d, *J* = 6.3 Hz), 0.98 (3H, d, *J* = 6.8 Hz), 1.03 (9H, s), 1.04 (9H, s), 1.05 (9H, s), 1.06 (9H, s), 1.17 (3H, d, *J* = 5.9 Hz), 1.23 (1H, ddd, *J* = 5.9, 8.3, 13.7 Hz), 1.57 (3H, s), 1.67 (1H, ddd, *J* = 4.4, 5.9, 13.7 Hz), 1.88-2.00 (4H, m), 2.10 (3H, s), 2.25 (1H, m), 2.33 (1H, m), 2.82 (1H, td, *J* = 5.9, 2.0 Hz), 2.96 (1H, dd, *J* = 2.0 Hz, 7.3 Hz), 3.00 (1H, dd, *J* = 6.8, 18.1 Hz), 3.13 (1H, dd, *J* = 5.4, 18.1 Hz), 3.37 (3H, s), 3.54 (1H, m), 3.85 (1H, t, *J* = 4.4 Hz), 4.27 (1H, d, *J* = 11.7 Hz), 4.29 (1H, dd, *J* = 4.4, 4.4 Hz), 4.49 (1H, m), 4.52 (1H, d, *J* = 11.7 Hz), 5.05 (1H, dd, *J* = 1.5, 10.3 Hz), 5.10 (1H, s), 5.14 (1H, s), 5.33 (1H, dd, *J* = 1.5, 17.6 Hz), 5.57 (1H, ddd, *J* = 7.3, 10.3, 17.6 Hz), 6.01 (1H, s), 6.90 (2H, d, *J* = 8.8 Hz), and 7.31 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ -4.5, -4.3, -4.0, -3.6, -3.5, -2.2, -1.3, 15.1, 15.6, 18.2, 18.57, 18.59, 18.8, 19.7, 20.3, 26.3, 26.35, 26.41, 26.5, 28.6, 29.9,

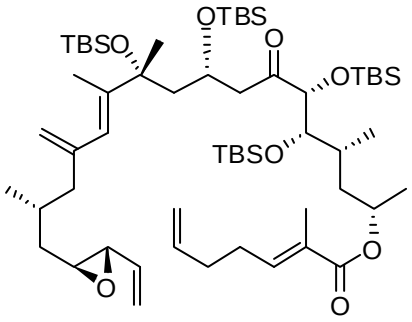
31.9, 39.6, 43.0, 46.5, 49.7, 50.6, 54.8, 59.0, 66.4, 70.0, 71.7, 78.4, 79.3, 82.2, 114.0, 115.7, 118.0, 126.1, 129.4, 137.0, 143.1, 144.8, 159.6, and 208.0; HRMS (ESI) calcd for $C_{58}H_{108}O_8NaSi_4$ $(M+Na)^+$ 1067.7019, found *m/z* 1067.7045.

(5*S*,6*R*,9*S*,11*R*)-6,9-bis(*tert*-butyldimethylsilyloxy)-5-((2*R*,4*S*)-4-hydroxypentan-2-yl)-2,2,3,3,11,13,13,14,14-nonamethyl-11-((*R*,*E*)-6-methyl-4-methylene-7-((2*S*,3*S*)-3-vinyloxiran-2-yl)hept-2-en-2-yl)-4,12-dioxa-3,13-disilapentadecan-7-one (4)



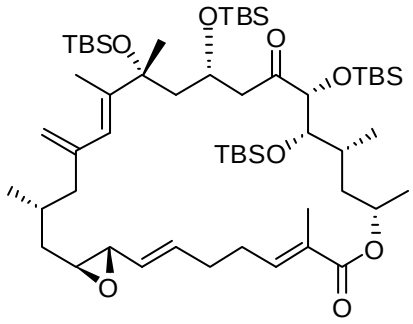
To a solution of **28** (28.5 mg, 0.027 mmol) in CH_2Cl_2 (2.0 mL), H_2O (0.40 mL), and pH 7 phosphate buffer (4.0 mL) was added DDQ (18.0 mg, 0.0790 mmol) at 0 °C; the mixture was stirred at room temperature for 30 min. The reaction mixture was filtered through Celite, and the resulting slurry was washed with saturated $NaHCO_3$ aq. and extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:12) to give **4** (20.7 mg, 83%) as a colorless oil; $[\alpha]^{22}_D$ -50.6 (*c* 0.80, $CHCl_3$); IR (film) 2928, 1717, 1472, 1255, 835, and 773 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.127 (3H, s), 0.131 (3H, s), 0.15 (3H, s), 0.19 (3H, s), 0.21 (6H, s), 0.23 (3H, s), 0.25 (3H, s), 0.97 (3H, d, *J* = 6.3 Hz), 0.98 (3H, d, *J* = 6.8 Hz), 1.03 (9H, s), 1.045 (18H, s), 1.05 (9H, s), 1.11 (3H, d, *J* = 5.9 Hz), 1.13 (1H, m), 1.20 (1H, ddd, *J* = 5.9, 8.3, 13.7 Hz), 1.56 (3H, s), 1.69 (1H, ddd, *J* = 4.4, 5.9, 13.7 Hz), 1.89 (1H, ddd, *J* = 3.9, 9.8, 13.7 Hz), 1.93-2.02 (3H, m), 2.07 (1H, dd, *J* = 5.4, 13.7 Hz), 2.07 (3H, s), 2.15 (1H, m), 2.23 (1H, m), 2.84 (1H, td, *J* = 5.9, 1.5 Hz), 2.97 (1H, dd, *J* = 1.5, 7.3 Hz), 2.99 (1H, dd, *J* = 6.8, 18.0 Hz), 3.15 (1H, dd, *J* = 5.4, 18.0 Hz), 3.72 (1H, m), 3.76 (1H, dd, *J* = 4.4, 5.4 Hz), 4.34 (1H, d, *J* = 4.4 Hz), 4.48 (1H, tt, *J* = 5.9, 5.9 Hz), 5.05 (1H, dd, *J* = 1.5, 10.2 Hz), 5.09 (1H, s), 5.13 (1H, s), 5.33 (1H, dd, *J* = 1.5 Hz, 17.6 Hz), 5.58 (1H, ddd, *J* = 7.3, 10.2, 17.6 Hz), and 6.00 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.0, -4.7, -4.5, -4.4, -4.1, -3.9, -2.6, -1.6, 14.6, 16.3, 17.8, 18.2, 18.4, 19.4, 24.6, 25.8, 26.0, 26.1, 26.1, 28.2, 29.5, 32.5, 39.1, 43.7, 46.0, 50.1, 50.5, 59.1, 59.3, 65.3, 65.8, 77.8, 78.5, 81.9, 115.3, 125.5, 135.9, 142.6, 144.2, and 208.6; HRMS (ESI) calcd for $C_{50}H_{100}O_7NaSi_4$ $(M+Na)^+$ 947.6444, found *m/z* 947.6450.

(*E*)-((2*S*,4*R*,5*S*,6*R*,9*S*,11*R*,16*R*,*E*)-5,6,9,11-tetrakis(*tert*-butyldimethylsilyloxy)-4,11,12,16-tetramethyl-14-methylene-7-oxo-17-((2S,3S)-3-vinyloxiran-2-yl)heptadec-12-en-2-yl) 2-methylhepta-2,6-dienoate (29)



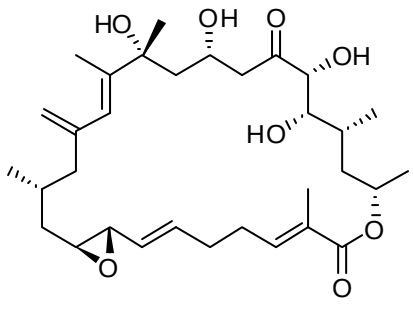
To a solution of **5** (85.7 mg, 0.612 mmol) in toluene (7.8 mL) were added 2,4,6-trichlorobenzoyl chloride (95.7 μL, 0.612 mmol) and Et_3N (84.8 μL, 0.612 mmol) at 0 °C; the mixture was stirred at the same temperature for 2.5 h. To the mixture was added a solution of **4** (31.3 mg, 0.0338 mmol) in toluene (5.2 mL) and DMAP (74.7 mg, 0.612 mmol); the mixture was stirred at 0 ^oC for 2 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:25) to give **29** (34.5 mg, 98%) as a colorless oil; $[\alpha]^{22}_D$ -26.9 (*c* 0.50, $CHCl_3$); IR (film) 2928, 1717, 1472, 1255, 835, and 773 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.15 (9H, s), 0.18 (3H, s), 0.19 (3H, s), 0.21 (3H, s), 0.23 (3H, s), 0.26 (3H, s), 0.96 (3H, d, *J* = 5.8 Hz), 1.03-1.07 (3H, m), 1.02 (9H, s), 1.03 (9H, s), 1.041 (9H, s), 1.044 (9H, s), 1.27 (3H, d, *J* = 6.3 Hz), 1.17-1.36 (2H, m), 1.45 (1H, ddd, *J* = 4.3, 8.5, 13.7 Hz), 1.55 (3H, s), 1.66 (1H, ddd, *J* = 4.3, 5.4, 13.5 Hz), 1.90 (3H, s), 1.90-2.05 (8H, m), 2.06 (3H, s), 2.13 (1H, m), 2.23 (1H, m) 2.81 (1H, td, *J* = 5.6, 1.3 Hz), 2.96 (1H, dd, *J* = 1.3, 7.6 Hz), 2.98 (1H, dd, *J* = 6.3, 18.0 Hz), 3.10 (1H, dd, *J* = 5.4, 18.0 Hz), 3.89 (1H, dd, *J* = 4.3, 4.3 Hz), 4.31 (1H, d, *J* = 4.5 Hz), 4.47 (1H, tt, *J* = 5.6, 5.6 Hz), 4.95 (1H, d, *J* = 1.3, 10.3 Hz), 4.98 (1H, dd, *J* = 1.3, 16.2 Hz), 5.06 (1H, dd, *J* = 1.5, 10.3 Hz), 5.10 (1H, s), 5.12 (1H, s), 5.32 (1H, dd, *J* = 1.5, 17.3 Hz), 5.36 (1H, m), 5.56 (1H, ddd, *J* = 7.6, 10.3, 17.3 Hz), 5.68 (1H, ddd, *J* = 6.3. 10.3, 16.2 Hz), 5.99 (1H, s), and 6.96 (1H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ -4.6, -4.5, -4.1, -4.0, -3.6, -2.2, -1.3, 1.4, 12.9, 15.2, 16.1, 18.2, 18.5, 18.6, 18.8, 19.7, 21.1, 26.2, 26.3, 26.4, 26.5, 28.4, 28.7, 29.9, 30.2, 32.2, 32.9, 39.6, 41.6, 46.4, 50.3, 50.7, 59.0, 59.1, 66.3, 68.7, 78.4, 78.7, 82.1, 115.3, 115.7, 118.1, 126.2, 129.1, 136.9, 137.8, 141.1, 143.0, 144.9, 167.4, and 207.7; HRMS (ESI) calcd for $C_{58}H_{110}O_8NaSi_4$ $(M+Na)^+$ 1069.7176, found *m/z* 1069.7146.

(1*S*,2*E*,6*E*,10*S*,12*R*,13*S*,14*R*,17*S*,19*R*,20*E*,24*R*,26*S*)-13,14,17,19-tetrakis(*tert*-butyldimethylsilyloxy)-7,10,12,19,20,24-hexamethyl-22-methylene-9,27-dioxabicyclo[24.1.0]heptacosa-2,6,20-triene-8,15-dione (31)



To a solution of **29** (1.90 mg, 1.81 μmol) in benzene (2.0 mL) was added Grubbs 2nd generation catalyst (0.160 mg, 0.190 μmol) at room temperature; the mixture was stirred at the same temperature for 18 h. The reaction was quenched by the addition of DMSO (12.0 μL, 1.69 mmol); the mixture was stirred overnight. The crude product was purified by Florisil chromatography (EtOAc:hexane, 1:10) to give **31** (1.5 mg, 81%) as a colorless oil: $[\alpha]^{22}_{D}$ -32.8 (*c* 0.61, $CHCl_3$); IR (film) 2929, 1706, 1472, 1255, 835, and 774 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.11 (3H, s), 0.14 (3H, s), 0.16 (3H, s), 0.18 (3H, s), 0.19 (3H, s), 0.21 (3H, s), 0.22 (3H, s), 0.28 (3H, s), 0.99-1.08 (6H, m), 1.02 (9H, s), 1.05 (9H, s), 1.06 (18H, s), 1.26 (3H, d, *J* = 6.3 Hz), 1.19-1.36 (2H, m), 1.48 (3H, s), 1.61 (1H, m), 1.76 (1H, td, *J* = 4.9, 13.7 Hz), 1.90 (3H, s), 1.95 (3H, s), 1.89-2.06 (7H, m), 2.22 (1H, m), 2.38 (1H, m), 3.06-3.15 (4H, m), 3.85 (1H, dd, *J* = 4.4, 4.4 Hz), 4.31 (1H, d, *J* = 4.4 Hz), 4.33 (1H, m), 5.00 (1H, s), 5.08 (1H, s), 5.31 (1H, m), 5.31 (1H, dd, *J* = 7.3, 15.6 Hz), 5.76 (1H, td, *J* = 5.9, 15.6 Hz), 6.03 (1H, s), and 6.90 (1H, m); ^{13}C NMR (100 MHz, C_6D_6) δ -4.4, -4.2, -3.7, -3.63, -3.57, -2.0, -1.2, 1.3, 12.9, 14.8, 15.8, 18.2, 18.5, 18.6, 18.9, 20.1, 21.2, 26.28, 26.32, 26.4, 26.7, 27.7, 29.1, 30.0, 30.2, 31.4, 32.0, 40.1, 41.4, 46.8, 49.7, 58.8, 60.0, 66.6, 68.4, 78.9, 79.2, 82.2, 115.8, 126.4, 129.3, 130.4, 133.6, 140.3, 142.5, 145.1, 167.4, and 207.4; HRMS(ESI) calcd for $C_{56}H_{106}O_8NaSi_4$ $(M+Na)^+$ 1041.6863, found *m/z* 1041.6859.

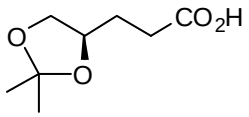
Amphidinolide B (1)



To a solution of **31** (7.80 mg, 7.70 μmol) in dry THF (1.4 mL) was added a solution of TASF (63.0 mg, 0.230 mmol) in dry DMF (0.50 mL) and H_2O (10 μl) at 0 °C; the mixture was stirred at room temperature for 1 h. The mixture was purified by Florisil chromatography (EtOAc:hexane, 1:1) to give **1** (3.7 mg, 86%) as a white solid: $[\alpha]^{23}_{D}$ -57.7 (*c* 0.20, $CHCl_3$); IR (film) 3433, 3359, 2924, 1705, 1472, 1262, and 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, *J* = 6.5 Hz), 1.00 (3H, d, *J* = 6.7 Hz), 1.25 (1H, m), 1.27 (1H, m), 1.27 (3H, d, *J* = 6.1 Hz), 1.40 (1H, s), 1.41 (3H, s), 1.48 (1H, ddd, *J* = 2.9,

10.5, 13.7 Hz), 1.63 (1H, m), 1.75 (1H, dd, *J* = 5.4, 14.4 Hz), 1.82 (3H, s), 1.82 (3H, s), 1.83 (1H, m), 1.92 (1H, m), 1.93 (1H, dd, *J* = 6.5, 14.6 Hz), 2.12 (1H, m), 2.13 (1H, m), 2.17 (1H, dd, *J* = 4.9, 13.2 Hz), 2.20 (1H, m), 2.37 (1H, m), 2.41 (1H, m), 2.78 (1H, dd, *J* = 3.1, 16.2 Hz), 2.86 (1H, dd, *J* = 7.4, 16.2 Hz), 2.92 (1H, td, *J* = 2.5, 8.5 Hz), 3.13 (1H, dd, *J* = 2.2, 8.5 Hz), 3.17 (1H, d, *J* = 10.1 Hz), 3.70 (1H, ddd, *J* = 1.6, 8.5, 10.1 Hz), 3.87 (1H, d, *J* = 5.2 Hz), 3.91 (1H, d, *J* = 3.4 Hz), 4.18 (1H, m), 4.32 (1H, dd, *J* = 1.8, 5.2 Hz), 4.81 (1H, s), 5.02 (1H, s), 5.05 (1H, m), 5.14 (1H, dd, *J* = 8.5, 15.5 Hz), 5.91 (1H, ddd, *J* = 4.9, 8.5, 15.5 Hz), 5.96 (1H, s), and 6.75 (1H, ddd, *J* = 1.3, 5.8, 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 15.0, 15.6, 18.1, 20.9, 26.7, 28.3, 29.1, 30.8, 33.2, 39.3, 39.4, 45.2, 45.9, 46.9, 59.3, 60.1, 66.6, 68.3, 75.6, 75.9, 77.7, 114.8, 124.3, 128.3, 128.4, 135.4, 139.9, 143.1, 144.3, 167.7, and 212.4; HRMS (ESI) calcd for $C_{32}H_{50}O_8Na$ $(M+Na)^+$ 585.3411, found *m/z* 585.3403.

(*R*)-3-(2,2-Dimethyl-1,3-dioxolan-4-yl)propanoic acid (37)



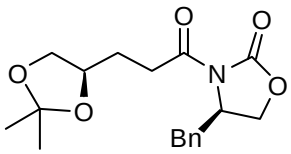
To a solution of $NaIO_4$ (3.78 g, 17.7 mmol) in a 2:1 mixture of CH_2Cl_2-H_2O (90 mL) was added the **35** (1.91 g, 11.8 mmol) at 0 °C; the mixture was stirred at room temperature for 1.5 h. To the mixture was added Ph_3PCHCO_2Me (7.89 g, 23.6 mmol) at 0 °C; the mixture was stirred at room temperature overnight. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:3) to give an unsaturated ester (1.84 g, 84%) as a colorless oil.

The ester (1.02 g, 5.48 mmol) was dissolved in EtOH (55 mL). The mixture was stirred at room temperature in the presence of Raney Ni W-4 overnight under a hydrogen atmosphere. The Raney Ni W-4 was removed by filtration, and the filtrate was concentrated at 110 °C to afford a saturated ester as a crude oil.

To a solution of the ester in THF (17 mL) was added 1.5 M LiOH aq. (17 mL) at 0 °C; the mixture was stirred at the same temperature for 3 h. The mixture was acidified to pH 4 with 10% citric acid aq., and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give **37** (0.935 g, 98% in 2 steps) as a colorless oil: $[\alpha]^{20}_D$ +2.1 (*c* 1.01, $CHCl_3$); IR (film) 2987 and 1712 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) *δ* 1.33 (3H, s), 1.39 (3H, s), 1.79-1.93 (2H, m), 2.40-2.55 (2H, m), 3.55 (1H, dd, *J* = 6.8, 8.3 Hz), 4.04 (1H, dd, *J* = 6.4, 8.3 Hz), 4.13 (1H, m), and 10.9 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 25.7, 27.0, 28.6, 30.3, 69.1, 74.9, 109.3, and 179.1; HRMS

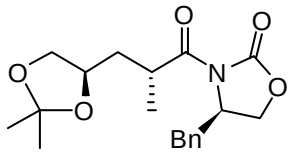
(ESI) calcd for $C_8H_{15}O_4$ $(M+H)^+$ 175.0970, found *m/z* 175.0968.

(*R*)-4-Benzyl-3-(3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoyl)oxazolidin-2-one (S-10)



To a solution of **37** (18.0 g, 0.103 mol) in dry THF (965 mL) were added Et_3N (44.4 mL, 0.321 mol) and PivCl (18.9 mL, 0.155 mol) at 0 °C; the mixture was stirred at room temperature for 2 h. To the mixture were added LiCl (21.9 g, 0.517 mol) and (*R*)-4-benzyl-2-oxazolidinone (27.5 g, 0.155 mol); the mixture was stirred at room temperature overnight. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:3) to give **S-10** (34.2 g, 100%) as a colorless oil: $[\alpha]^{18}_D$ -42.4 (*c* 1.01, $CHCl_3$); IR (film) 2984, 2933, 1782, and 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.42 (3H, s), 1.96 (2H, m), 2.78 (1H, dd, *J* = 9.8, 13.2 Hz), 3.07 (2H, t, *J* = 7.8 Hz), 3.30 (1H, dd, *J* = 3.4, 13.2 Hz), 3.60 (1H, dd, *J* = 6.8, 7.8 Hz), 4.08 (1H, dd, *J* = 5.9, 7.8 Hz), 4.16-4.23 (3H, m), 4.67 (1H, m), and 7.20-7.36 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 27.1, 28.3, 32.1, 38.0, 55.3, 66.4, 69.3, 75.0, 109.2, 127.5, 129.1, 129.5, 135.4, 153.6, and 172.8; HRMS (ESI) calcd for $C_{18}H_{23}NO_5Na$ $(M+Na)^+$ 356.1474, found *m/z* 356.1489.

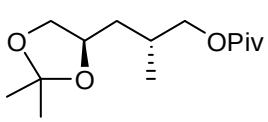
(*R*)-4-Benzyl-3-((*R*)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylpropanoyl)oxazolidin-2-one (38)



To a solution of LHMDS (1.00 M solution in THF, 54.0 mL, 54.0 mmol) was added **S-10** (8.96 g, 26.9 mmol) in dry THF (220 mL) at -40 °C; the mixture was stirred at the same temperature for 1 h. To the mixture was added MeI (22.7 mL, 0.365 mol) at the same temperature; the mixture was stirred at -20 °C for 4 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:3) to give **38** (8.45 g, 92%) as needles from EtOAc-hexane; mp 93-93.5 °C: $[\alpha]^{21}_D$ -65.4 (*c* 1.02, $CHCl_3$); IR (film) 2983, 2936, 2876, 1780, and 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, d, *J* = 7.3 Hz), 1.30 (3H, s), 1.36 (3H, s), 1.66 (1H, ddd, *J* = 4.4, 5.4, 13.7 Hz), 2.05 (1H,

ddd, J = 8.3, 8.8, 13.7 Hz), 2.79 (1H, dd, J = 9.8, 13.2 Hz), 3.26 (1H, dd, J = 3.4, 13.2 Hz), 3.50 (1H, dd, J = 7.3, 7.8 Hz), 3.99 (1H, m), 4.03 (1H, dd, J = 5.9, 7.8 Hz), 4.14-4.20 (3H, m), 4.66 (1H, m), and 7.21-7.36 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 25.8, 27.0, 34.8, 38.2, 38.3, 55.6, 66.2, 69.7, 74.4, 109.1, 127.5, 129.1, 129.6, 135.5, 153.5, and 177.2; HRMS (ESI) calcd for $C_{19}H_{26}NO_5$ $(M+H)^+$ 348.1811, found *m/z* 348.1805.

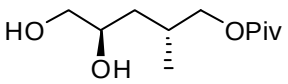
(*R*)-3-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-methylpropyl pivalate (39)



To a solution of **38** (10.8 g, 31.1 mmol) in a 4:4:1 mixture of THF-MeOH-H_2O (306 mL) was added $LiBH_4$ (3.01 g, 0.124 mol) at 0 °C; the mixture was stirred at room temperature for 5 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:1) to give an alcohol as a colorless oil.

To a solution of the alcohol in CH_2Cl_2 (125 mL) were added Et_3N (17.2 mL, 0.124 mol), DMAP (0.760 g, 6.22 mmol) and PivCl (11.4mL, 93.3 mmol) at 0 ^{o}C; the mixture was stirred at room temperature overnight. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:10) to give **39** (7.37g, 92% in 2 steps) as a colorless oil: $[\alpha]^{20}_D$ -10.0 (*c* 1.00, $CHCl_3$); IR (film) 2979, 2937, 2876, and 1730 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.97 (3H, d, J = 6.8 Hz), 1.19 (9H, s), 1.33 (3H, s), 1.33 (1H, m), 1.38 (3H, s) 1.69 (1H, ddd, J = 5.2, 8.5, 13.7 Hz), 2.01 (1H, m), 3.48 (1H, t, J = 7.5 Hz), 3.84-3.99 (2H, m), 4.05 (1H, dd, J = 5.9, 7.8 Hz), and 4.18 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9, 25.9, 27.2, 27.4, 30.3, 37.7, 39.0, 69.3, 70.0, 74.0, 108.9, and 178.6; HRMS (ESI) calcd for $C_{14}H_{26}O_4Na$ $(M+Na)^+$ 281.1729, found *m/z* 281.1723.

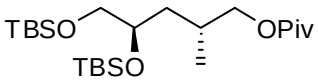
(2*R*,4*R*)-4,5-Dihydroxy-2-methylpentyl pivalate (S-11)



To a solution of **39** (15.6 g, 60.4 mmol) in a 5:1 mixture of DMF-H_2O (360 mL) was added TsOH·H_2O (11.5 g, 60.5 mmol) at 0 ^{o}C; the mixture was stirred at 30 °C under 50 hPa for 22 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with Et_2O three times. The combined organic layers were washed with brine,

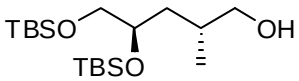
dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:1) to give **S-11** as a colorless oil: $[\alpha]^{21}_D$ +4.1 (*c* 1.00, $CHCl_3$); IR (film) 3422, 2963, and 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, d, *J* = 6.4 Hz), 1.15-1.26 (10H, m), 1.52 (1H, *J* = 4.9, 9.3, 14.2 Hz), 2.06 (1H, m), 3.45 (1H, dd, *J* = 7.8, 10.8 Hz), 3.66 (1H, dd, *J* = 2.9, 10.8 Hz), 3.83 (1H, m), 3.93 (1H, dd, *J* = 6.4, 10.7 Hz), and 4.00 (1H, dd, *J* = 5.9, 10.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 27.3, 29.7, 36.7, 39.0, 67.4, 69.6, 70.0, and 178.9; HRMS (ESI) calcd for $C_{11}H_{22}O_4Na$ $(M+Na)^+$ 241.1419, found *m/z* 241.1416.

(2*R*,4*R*)-4,5-Bis(*tert*-butyldimethylsiloxy)-2-methylpentyl pivalate (S-12)



To a solution of **S-11** in CH_2Cl_2 (530 mL) were added 2,6-lutidine (24.4 mL, 0.211 mol) and TBSOTf (30.3 mL, 0.132 mol) at 0 °C; the mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:40) to give **S-12** (24.7 g, 92% in 2 steps) as a colorless oil: $[\alpha]^{20}_D$ +27.1 (*c* 1.00, $CHCl_3$); IR (film) 2957 and 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (6H, s), 0.06 (6H, s), 0.88 (9H, s), 0.89 (9H, s), 0.93 (3H, d, *J* = 6.8 Hz), 1.20 (9H, s), 1.35-1.49 (2H, m), 2.01 (1H, m), 3.37 (1H, dd, *J* = 6.8, 9.8 Hz), 3.50 (1H, dd, *J* = 4.9, 9.8 Hz), 3.72 (1H, m), and 3.90 (2H, d, *J* = 5.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.2, -5.2, -4.7, -3.9, 16.7, 18.2, 18.5, 26.0, 26.1, 27.4, 29.0, 38.5, 39.0, 68.0, 69.9, 71.0, and 178.7; HRMS (ESI+) calcd for $C_{23}H_{51}O_4Si_2$ $(M+H)^+$ 447.3326, found *m/z* 447.3322.

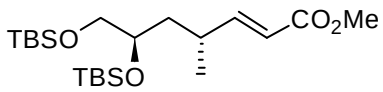
(2*R*,4*R*)-4,5-Bis(*tert*-butyldimethylsiloxy)-2-methylpentan-1-ol (40)



To a solution of **S-12** (11.9 g, 26.6 mmol) in CH_2Cl_2 (51 mL) was added DIBAL-H (1.04 M solution in hexane, 51.0 mL, 53.1 mmol) at -78 °C; the mixture was stirred at the same temperature for 3.5 h. The reaction was quenched by the addition of saturated Rochelle salt aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:10) to give **40** (9.51 g, 99%) as a colorless oil: $[\alpha]^{20}_D$ +27.2 (*c* 1.00, $CHCl_3$); IR (film) 3399, 2929, 2858, and 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.07 (6H, s), 0.88 (9H, s), 0.89 (9H, s), 0.93 (3H, d, *J* = 6.8 Hz), 1.39 (1H, ddd, *J* = 3.9, 8.3, 13.7 Hz), 1.47 (1H,

ddd, J = 4.4, 8.3, 13.7 Hz), 1.85 (1H, m), 3.38 (1H, dd, J = 6.8, 9.8 Hz), 3.46 (2H, t, J = 4.9 Hz), 3.56 (1H, dd, J = 4.9, 9.8 Hz), and 3.76 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.1, -5.0, -4.4, -3.8, 17.2, 18.4, 18.6, 26.1, 26.2, 32.2, 38.5, 68.0, 69.2, and 71.5; HRMS (ESI) calcd for $C_{18}H_{43}O_3Si_2$ $(M+H)^+$ 363.2751, found *m/z* 363.2751.

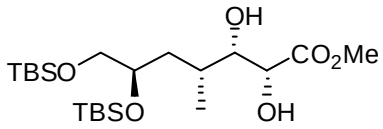
(4*R*,6*R*,*E*)-Methyl 6,7-bis(*tert*-butyldimethylsiloxy)-4-methylhept-2-enoate (41)



To a solution of **40** (2.55 g, 7.03 mmol) in CH_2Cl_2 (70 mL) were added TEMPO (0.110 g, 0.704 mmol) and iodobenzene diacetate (4.53 g, 14.1 mmol) at 0 °C; the mixture was stirred at room temperature for 6 h. After the mixture was concentrated *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc:hexane, 1:30) to give an aldehyde as a colorless oil.

To a solution of the aldehyde in CH_2Cl_2 (70 mL) was added Ph_3PCHCO_2Me (11.8 g, 35.2 mmol) at 0 °C; the mixture was stirred at room temperature for 12 h. After the mixture was concentrated *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc:hexane, 1:30) to give **41** (2.69 g, 92% in 2 steps) as a colorless oil: $[\alpha]^{21}_D$ +6.2 (*c* 1.02, $CHCl_3$); IR (film) 2955, 2930, 2858, and 1729 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.06 (6H, s), 0.88 (9H, s), 0.89 (9H, s), 1.02 (3H, d, J = 6.6 Hz), 1.46-1.60 (2H, m), 2.52 (1H, tq, J = 6.9, 6.9 Hz), 3.36 (1H, dd, J = 6.3, 9.9 Hz), 3.53 (1H, dd, J = 5.2, 9.9 Hz), 3.66 (1H, m), 3.71 (3H, s) 5.87 (1H, d, J = 15.7 Hz), and 6.92 (1H, dd, J = 7.3, 15.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.2, -5.2, -4.7, -3.9, 18.2, 18.5, 18.9, 26.0, 26.1, 32.5, 40.8, 51.6, 67.7, 71.0, 118.9, 155.5, and 167.5; HRMS (ESI) calcd for $C_{21}H_{45}O_4Si_2$ $(M+H)^+$ 417.2856, found *m/z* 417.2848.

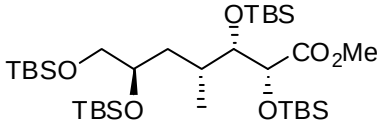
(2*R*,3*S*,4*R*,6*R*)-Methyl 6,7-bis(*tert*-butyldimethylsiloxy)-2,3-dihydroxy-4-methylheptanoate (S-13)



To a solution of AD-mix α (61.5 g) in a 1:1 mixture of *t*-BuOH-H_2O (150 mL) were added methane sulfonamide (2.79 g, 29.3 mmol) at room temperature, and the mixture was stirred for 30 min. To the mixture was added a solution of **41** (12.2 g, 29.3 mmol) in a 1:1 mixture of *t*-BuOH-H_2O (150 mL) at 0 °C; the mixture was stirred at the same temperature for 1 day. The reaction was quenched by the addition of saturated $Na_2S_2O_3$ aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:10) to give **S-13** (11.9 g, 90%) as a colorless oil:

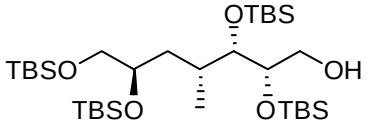
$[\alpha]^{21}_D$ +24.8 (*c* 1.02, $CHCl_3$); IR (film) 3466, 2954, 2929, and 1743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.08 (6H, s), 0.88 (9H, s), 0.89 (9H, s), 1.01 (3H, d, *J* = 6.8 Hz), 1.42-1.54 (2H, m), 1.97 (1H, m), 2.20 (1H, d, *J* = 8.3 Hz), 2.96 (1H, d, *J* = 5.4 Hz), 3.38 (1H, dd, *J* = 6.8, 10.3 Hz), 3.56 (1H, dd, *J* = 5.4, 10.3 Hz), 3.62 (1H, ddd, *J* = 2.4, 6.8, 8.3 Hz), 3.74 (1H, m), 3.82 (3H, s), and 4.28 (1H, dd, *J* = 2.4, 5.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.2, -5.2, -4.7, -3.9, 15.3, 18.3, 18.5, 26.0, 26.1, 32.4, 38.1, 52.9, 68.0, 71.2, 71.5, 76.7, and 174.6; HRMS (ESI) calcd for $C_{21}H_{46}O_6NaSi_2$ $(M+Na)^+$ 473.2731, found *m/z* 473.2732.

(5*R*,6*S*,7*R*,9*R*)-Methyl 6,9-bis(*tert*-butyldimethylsiloxy)-2,2,3,3,7,12,12,13,13-nonamethyl-4,11-dioxa-3,12-disilatetradecane-5-carboxylate (S-14)



To a solution of **S-13** (3.21 g, 7.12 mmol) in CH_2Cl_2 (72 mL) were added 2,6-litidine (6.60 mL, 28.5 mmol) and TBSOTf (6.55 mL, 28.5 mmol) at 0 °C; the mixture was stirred at room temperature for 1 day. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:50) to give **S-14** (4.85 g, quant.) as a colorless oil: $[\alpha]^{21}_D$ +17.5 (*c* 1.02, $CHCl_3$); IR (film) 2929, 2858, and 1756 cm^{-1} ;^1H NMR (400 MHz, $CDCl_3$) δ 0.02-0.07 (24H, m), 0.82 (3H, d, *J* = 7.3 Hz), 0.87 (9H, s), 0.88 (9H, s), 0.89 (9H, s), 0.90 (9H, s), 1.37 (1H, ddd, *J* = 3.4, 9.8, 13.2 Hz), 1.56 (1H, ddd, *J* = 2.9, 11.7, 13.2 Hz), 2.00 (1H, m), 3.33 (1H, dd, *J* = 6.3, 9.8 Hz), 3.54 (1H, dd, *J* = 4.9, 9.8 Hz), 3.67 (3H, s), 3.67 (1H, m), 3.70 (1H, dd, *J* = 2.4, 4.9 Hz), and 4.18 (1H, d, *J* = 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.2, -5.2, -4.7, -4.6, -4.5, -4.0, -4.0, -3.8, 13.2, 18.3, 18.4, 18.5, 18.5, 26.1, 26.1, 26.2, 31.1, 40.1, 51.6, 68.4, 71.1, 75.2, 79.0, and 173.2; HRMS (ESI) calcd for $C_{33}H_{74}O_6Si_4Na$ $(M+Na)^+$ 701.4460, found *m/z* 701.4445.

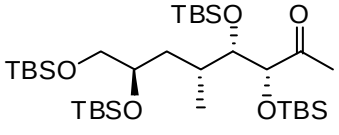
(2*S*,3*S*,4*R*,6*R*)-2,3,6,7-Tetrakis(*tert*-butyldimethylsiloxy)-4-methylheptan-1-ol (42)



To a solution of **S-14** (0.113 g, 0.166 mmol) in CH_2Cl_2 (1.7 mL) was added DIBAL-H (1.03 M solution in hexane, 0.970 mL, 0.999 mmol) at -78 °C; the mixture was stirred at the same temperature for 3 h. The reaction was quenched by the addition of saturated Rochelle salt aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried

over anhydrous Na_2SO_4, and concentrated *in vacuo*. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:30) to give **42** (0.104 g, 95%) as a colorless oil: $[\alpha]^{23}_D$ +7.4 (*c* 1.00, $CHCl_3$); IR (film) 3486, 2955, 2930, and 2858 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.06 (6H, s), 0.07 (3H,s), 0.09 (6H, s), 0.10 (3H, s), 0.87 (3H, d, J = 6.3 Hz), 0.87 (9H, s), 0.88 (9H, s), 0.89 (9H, s), 0.90 (9H, s), 1.46-1.50 (2H, m), 2.14 (1H, m), 2.22 (1H, t, J = 5.8 Hz), 3.30 (1H, dd, J = 6.8, 9.8 Hz), 3.50 (1H, t, J = 3.9 Hz), 3.54 (1H, dd, J = 4.9, 9.8 Hz), 3.62 (1H, m), 3.68 (1H, m), and 3.75-3.81 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.2, -4.6, -4.6, -4.5, -4.2, -4.0, -4.0, 14.9, 18.2, 18.2, 18.3, 18.5, 26.0, 26.0, 26.1, 26.1, 29.1, 40.9, 63.8, 68.3, 70.9 75.7, and 79.5; HRMS (ESI) calcd for $C_{32}H_{75}O_5Si_4Na$ $(M+Na)^+$ 651.4692, found *m/z* 651.4676.

(3*R*,4*S*,5*R*,7*R*)-3,4,7,8-Tetrakis(*tert*-butyldimethylsiloxy)-5-methyloctan-2-one (32)



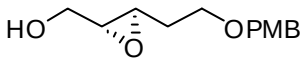
To a solution of **42** (0.104 g, 0.16 mmol) in CH_2Cl_2 (0.80 mL) and DMSO (0.80 mL) were added DIPEA (0.274 mL, 1.59 mmol) and SO_3-pyr. complex (0.126 g, 0.796 mmol) at 0 °C; the mixture was stirred at room temperature for 2.5 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:60) to give an aldehyde as a colorless oil.

To a solution of the aldehyde in Et_2O (1.6 mL) was added MeLi (1.09 M solution in hexane, 0.175 mL, 0.191 mmol) at -78 °C; the mixture was stirred at the same temperature for 5 h. To the mixture was added MeLi (0.117 mL, 0.128 mmol) and stirring was continued for 4 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:60) to give an alcohol (0.104 g, 99% in 2 steps) as a colorless oil.

To a solution of the alcohol (62.8 mg, 0.0944 mmol) in CH_2Cl_2 (0.85 mL) were added MS4A (47.3 mg), NMO (97%, 33.2mg, 0.284 mmol) and TPAP (3.3 mg, 9.5 μmol) at room temperature; the mixture was stirred at room temperature for 1 h. After the mixture was concentrated *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc:hexane, 1:60) to give **32** (60.8 mg, 97%) as cubic crystals from

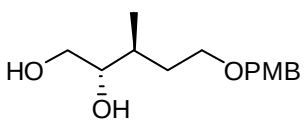
MeOH; mp 75-75.5 °C: $[\alpha]^{23}_D$ +6.3 (*c* 1.01, $CHCl_3$); IR (film) 2952, 2929, 2858, and 1725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02-0.06 (18H, m), 0.08 (3H, s), 0.10 (3H, s), 0.78 (3H, d, *J* = 8.8 Hz), 0.87 (9H, s), 0.88 (9H, s), 0.91 (9H, s), 0.93 (9H, m), 1.36 (1H, ddd, *J* = 2.9, 9.8, 13.7 Hz), 1.54 (1H, ddd, *J* = 2.5, 11.7, 13.7 Hz), 2.01 (1H, m), 2.19 (3H, s), 3.32 (1H, dd, *J* = 6.3, 9.8 Hz), 3.54 (1H, dd, *J* = 4.9, 9.8 Hz), 3.62-3.68 (2H, m), and 4.06 (1H, d, *J* = 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.2, -5.2, -4.7, -4.5, -4.2, -4.0, -3.6, 13.6, 18.2, 18.4, 18.5, 26.1, 26.1, 26.2, 28.2, 30.6, 40.3, 68.3, 70.9, 79.8, 81.6, and 209.9; HRMS (ESI) calcd for $C_{33}H_{74}O_5Si_4Na$ $(M+Na)^+$ 685.4511, found *m/z* 685.4508.

((2*R*,3*R*)-3-(2-(4-Methoxybenzyloxy)ethyl)oxiran-2-yl)methanol (45)



To a suspension of Ti(O*i*-Pr)$_4$ (1.71 mL, 5.84 mmol) and MS4A (7.0 g) in CH_2Cl_2 (30 mL) was added (-)-DIPT (1.35 g, 5.76 mmol) at -40 °C; the mixture was stirred at -30 °C for 30 min. To the mixture was added TBHP (5.50 M solution in decane, 5.90 mL, 32.0 mmol) at -30 °C; the mixture was stirred at the same temperature for 30 min. To the mixture was added a solution of **44** (2.56 g, 11.5 mmol) in CH_2Cl_2 (30 mL) at -30 °C; the mixture was stirred at -20 °C for 20 h. The reaction was quenched by the addition of tartaric acid and ferric sulfate heptahydrate aq. at 0 °C, and the resulting slurry was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:1) to give **45** (2.49 g, 91%, 96% ee) as a colorless oil: $[\alpha]^{22}_D$ +24.5 (*c* 1.08, $CHCl_3$); IR (film) 3463, 2932, 2864, 1614, and 1516 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.75-1.99 (2H, m), 2.97 (1H, td, *J* = 2.5, 4.3 Hz), 3.10 (1H, ddd, *J* = 2.5, 4.3, 6.3 Hz), 3.58 (2H, t, *J* = 6.6 Hz), 3.62 (1H, dd, *J* = 4.3, 12.5 Hz), 3.81 (3H, s), 3.91 (1H, dd, *J* = 2.5, 12.5 Hz), 4.45 (2H, s), and 6.89 (2H, d, *J* = 8.7 Hz), 7.26 (2H, d, *J* = 8.7 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 32.3, 53.9, 55.5, 58.5, 61.8, 66.7, 72.9, 113.9, 129.3, and 159.2; HRMS (ESI) calcd for $C_{13}H_{18}O_4Na$ $(M+Na)^+$ 261.1103, found *m/z* 261.1106.

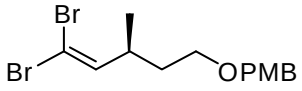
(2*S*,3*S*)-5-(4-Methoxybenzyloxy)-3-methylpentane-1,2-diol (46)



To a solution of **45** (6.06 g, 25.4 mmol) in dry CH_2Cl_2 (130 mL) was added $AlMe_3$ (1.03 M solution in hexane, 110 mL, 113 mmol) at 0 °C; the mixture was stirred at room temperature for 16 h. The mixture was diluted with Et_2O (120 mL) and water (4.0 mL) at 0 °C, and stirring was continued vigorously at room temperature until a white gel was

generated. To the mixture were added 4 M NaOH aq. (6.0 mL) and water (6.0 mL); the mixture was stirred vigorously at room temperature until a white solid was generated. The mixture was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 3:2) to give **46** (4.67 g, 72%) as a colorless oil: $[\alpha]^{22}_D$ -2.8 (*c* 1.14, $CHCl_3$); IR (film) 3376, 2932, 2872, 1614, and 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, d, J = 6.3 Hz), 1.62-1.80 (3H, m), 2.40 (1H, dd, J = 3.9, 5.9 Hz), 3.40-3.52 (3H, m), 3.58 (1H, ddd, J = 3.9, 6.3, 9.3 Hz), 3.63-3.69 (2H, m), 3.80 (3H, s), 4.42 (2H, s), 6.88 (2H, d, J = 8.8 Hz), and 7.24 (2H, d, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 33.4, 34.5, 55.4, 65.1, 68.0, 73.0, 76.0, 114.0, 129.5, 129.9, and 159.4; HRMS (ESI) calcd for $C_{14}H_{22}O_4Na$ $(M+Na)^+$ 277.1416, found *m/z* 277.1420.

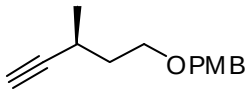
(*S*)-1-((5,5-Dibromo-3-methylpent-4-enyloxy)methyl)-4-methoxybenzene (S-15)



To a solution of $NaIO_4$ (1.60 g, 7.50 mmol) in a 1:1 mixture of THF-H_2O (40 mL) was added a solution of **46** (1.39 g, 5.47 mmol) in THF (20 mL); the mixture was stirred at room temperature for 10 min. To the mixture was added a 2:1 mixture of benzene-Et_2O (75 mL), and the organic layer was washed with water, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. A crude aldehyde was obtained, and immediately used for the next reaction without further purification.

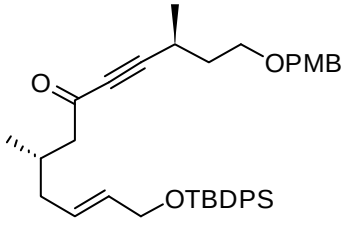
To a solution of CBr_4 (7.80 g, 16.0 mmol) in dry CH_2Cl_2 (20 mL) was added a solution of Ph_3P (12.4 g, 33.0 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C; the mixture was stirred at the same temperature for 10 min. To the mixture was added a solution of the crude aldehyde in dry CH_2Cl_2 (30 mL) at 0 ^oC; the mixture was stirred at the same temperature for 30 min. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:4) to give **S-15** (2.36 g, 90% in 2 steps) as a colorless oil: $[\alpha]^{22}_D$ +22.4 (*c* 1.01, $CHCl_3$); IR (film) 2960, 2932, 2864, 1614, and 1514 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, d, J = 6.8 Hz), 1.51-1.74 (2H, m), 2.67 (1H, m), 3.37-3.49 (2H, m), 3.81 (3H, s), 4.42 (2H, s), 6.20 (2H, d, J = 9.8 Hz), 6.88 (2H, d, J = 8.8 Hz), and 7.27 (2H, d, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 35.8, 36.2, 55.5, 67.9, 72.9, 87.9, 113.9, 129.4, 130.6, 143.8, and 159.1; HRMS (ESI) calcd for $C_{14}H_{18}O_2NaBr_2$ $(M+Na)^+$ 398.9571, found *m/z* 398.9553.

(*S*)-1-Methoxy-4-((3-methylpent-4-ynyloxy)methyl)benzene (33)



To a solution of **S-15** (45.1 mg, 0.119 mmol) in dry THF (1.0 mL) was added *n*-BuLi (1.57M solution in hexane, 0.230 mL, 0.360 mmol) at -78 ^{o}C; the mixture was stirred at the same temperature for 30 min. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:7) to give **7** (22.4 mg, 86%) as a colorless oil: $[\alpha]^{22}_{D}$ +56.7 (*c* 0.81, $CHCl_3$); IR (film) 3300, 2936, 2864, 2112, 1614, and 1514 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.20 (3H, d, *J* = 6.9 Hz), 1.65-1.82 (2H, m), 2.03 (1H, d, *J* = 2.3 Hz) 2.66 (1H, m), 3.59 (2H, t, *J* = 6.1 Hz), 3.80 (3H, s), 4.44 (2H, s), 6.88 (2H, d, *J* = 8.7 Hz), and 7.27 (2H, d, *J* = 8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 22.8, 36.8, 55.4, 67.9, 68.6, 72.9, 88.7, 113.9, 129.4, 130.8, and 159.3; HRMS (ESI) calcd for $C_{14}H_{19}O_2$ $(M+H)^+$ 219.1385, found *m/z* 219.1382.

(3*S*,8*S*,*E*)-12-(*tert*-Butyldiphenylsiloxy)-1-(4-methoxybenzyloxy)-3,8-dimethyldodec-10-en-4-yn-6-one (48)

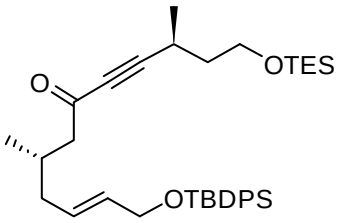


To a solution of **33** (4.02 g, 18.4 mmol) in dry THF (160 mL) was added *n*-BuLi (1.57 M solution in hexane, 10.4 mL, 16.3 mmol) at -78 °C; the mixture was stirred at 0 °C for 30 min. To the mixture was added a solution of **10** (2.69 g, 7.07 mmol) in dry THF (20 mL) at 0 °C; the mixture was stirred at the same temperature overnight. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (acetone:hexane, 1:5) to give an alcohol as a colorless oil.

To a solution of the alcohol in CH_2Cl_2 (70 mL) were added MS4A (5.2 g), NMO (97%, 2.50 g, 21.3 mmol) and TPAP (0.250 g, 0.711 mmol) at room temperature; the mixture was stirred at room temperature for 3 h. After the mixture was concentrated *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc:hexane, 1:5) to give **48** (3.54 g, 84% in 2 steps) as a colorless oil: $[\alpha]^{22}_{D}$ +28.5 (*c* 1.00, $CHCl_3$); IR (film) 2931, 2209, 1671, and 1512 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.92 (3H, d, *J* = 6.4 Hz), 1.05 (9H, s), 1.22 (3H, d, *J* = 6.9 Hz), 1.69-1.83 (2H, m), 1.90-2.09 (2H, m), 2.16 (1H, m), 2.28 (1H, dd, *J* = 8.2, 15.5 Hz), 2.51 (1H, dd, *J* = 5.3, 15.5 Hz), 2.84 (1H,

tq, J = 6.9, 6.9 Hz), 3.55 (2H, t, J = 6.1 Hz), 3.79 (3H, s), 4.16 (2H, d, J = 3.5 Hz), 4.42 (2H, s), 5.50-5.69 (2H, m), 6.87 (2H, d, J = 8.9 Hz), 7.24 (2H, d, J = 8.9 Hz), 7.33-7.45 (6H, m), and 7.65-7.70 (4H, m); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.5, 19.7, 20.2, 23.3, 27.1, 30.1, 36.3, 39.5, 52.4, 55.4, 64.6, 67.5, 72.9, 97.5, 113.9, 127.7, 128.3, 129.3, 129.6, 130.4, 131.2, 133.8, 135.6, 159.2, and 188.0; HRMS (ESI) calcd for $C_{38}H_{48}O_4SiNa$ $(M+Na)^+$ 619.3220, found *m/z* 619.3213.

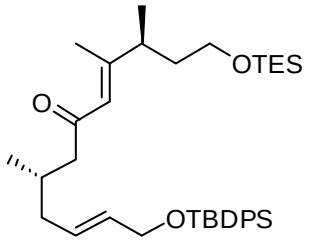
(7*S*,12*S*,*E*)-3,3-Diethyl-7,12,19,19-tetramethyl-18,18-diphenyl-4,17-dioxa-3,18-disilaicos-14-en-8-yn-10-one (52)



To a solution of **48** (1.52 g, 2.55 mmol) in CH_2Cl_2 (20 mL) and pH 7 phosphate buffer (5.0 mL) was added DDQ (1.40 g, 6.17 mmol) at 0 °C; the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered through Celite, and the resulting slurry was washed with saturated $NaHCO_3$ aq. and extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:3) to give an alcohol (1.10 g, 90%) as a colorless oil.

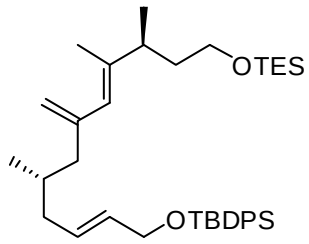
To a solution of the alcohol (18.9 mg, 0.0396 mmol) in CH_2Cl_2 (1.0 mL) were added Et_3N (49 μL, 0.352 mmol) and TESCl (38 μL, 0.232 mmol) at 0 °C; the mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:40) to give **52** (21.7 mg, 93%) as a colorless oil: $[\alpha]^{23}_D$ +43.7 (*c* 0.52, $CHCl_3$); IR (film) 2955, 2874, 2209, and 1673 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.60 (6H, q, J = 7.9 Hz), 0.91-1.00 (12H, m), 1.06 (9H, s), 1.24 (3H, d, J = 6.8 Hz), 1.70 (3H, td, J = 6.1, 6.8 Hz), 1.90-2.10 (2H, m), 2.18 (1H, m), 2.30 (1H, dd, J = 8.2, 15.3 Hz), 2.54 (1H, dd, J = 5.4, 15.3 Hz), 2.83 (1H, tq, J = 6.8, 6.8 Hz), 3.71 (2H, t, J = 6.1 Hz), 4.17 (2H, d, J = 3.3 Hz), 5.50-5.68 (2H, m), 7.33-7.46 (6H, m), and 7.65-7.71 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.5, 6.9, 19.4, 19.6, 20.1, 22.7, 27.0, 30.0, 39.1, 39.5, 52.4, 60.3, 64.5, 81.4, 97.8, 127.8, 128.4, 129.7, 131.3, 134.0, 135.7, and 188.2; HRMS (ESI) calcd for $C_{36}H_{54}O_3Si_2Na$ $(M+Na)^+$ 613.3509, found *m/z* 613.3504.

(7*S*,8*E*,12*S*,14*E*)-3,3-Diethyl-7,8,12,19,19-pentamethyl-18,18-diphenyl-4,17-dioxa-3,18-disilaicosa-8,14-dien-10-one (53-(*E*))



To a suspension of CuCN (0.146 g, 1.47 mmol) in dry Et_2O (11 mL) was added MeLi (1.12 M solution in Et_2O, 2.55 mL, 2.86 mmol) at -78 °C; the mixture was stirred at -30 °C for 1 h. To the mixture was added a solution of **52** (43.4 mg, 0.0734 mmol) in dry Et_2O (4.0 mL) at -78 °C; the mixture was stirred stirring at the same temperature for 1 h. The reaction mixture was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:50) to give a 2.5:1 mixture of **53-(*E*)** and **53-(*Z*)** (43.6 mg, 98%). The product was purified by flash silica gel column chromatography (EtOAc:hexane, 1:50) to give **53-(*E*)** as a colorless oil: $[\alpha]^{23}_D$ -3.0 (*c* 0.67, $CHCl_3$); IR (film) 2956, 1684, and 1614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.58 (6H, q, *J* = 7.8 Hz), 0.90 (3H, d, *J* = 6.3 Hz), 0.95 (9H, t, *J* = 7.8 Hz), 1.06 (9H, s), 1.06 (3H, d, *J* = 6.8 Hz), 1.55 (1H, m), 1.70 (1H, m), 1.93 (1H, ddd, *J* = 1.0, 6.8, 13.7 Hz), 2.00-2.13 (2H, m), 2.08 (3H, s), 2.19 (1H, dd, *J* = 8.3, 15.1 Hz), 2.36 (1H, tq, *J* = 6.8, 6.8 Hz), 2.43 (1H, dd, *J* = 5.4, 15.1 Hz), 3.54 (2H, dt, *J* = 2.0, 6.8 Hz), 4.17 (2H, dd, *J* = 1.0, 4.9 Hz), 5.52-5.68 (2H, m), 6.05 (1H, s), 7.35-7.45 (6H, m), and 7.66-7.71 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 4.5, 6.9, 16.2, 19.3, 19.4, 19.8, 27.0, 30.0, 37.8, 39.7, 40.6, 51.4, 60.9, 64.6, 123.2, 127.8, 129.0, 129.7, 130.9, 134.0, 135.7, 162.3, and 201.5; HRMS (ESI) calcd for $C_{37}H_{58}O_3Si_2Na$ $(M+Na)^+$ 629.3822, found *m/z* 629.3812.

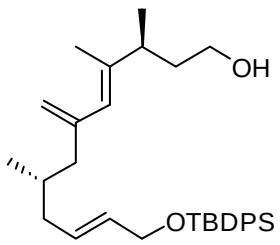
(6*E*,9*S*,12*E*,14*S*)-18,18-Diethyl-2,2,9,13,14-pentamethyl-11-methylene-3,3-diphenyl-4,17-dioxa-3,18-disilaicosa-6,12-diene (54)



To a suspension of Ph_3PCH_3Br (0.375 g, 1.05 mmol) in dry THF (9.0 mL) was added *n*-BuLi (1.66 M solution in hexane, 0.590 mL, 0.979 mmol) at 0 °C; the mixture was stirred at the same temperature for 30 min. To the mixture was added a solution of **53-(*E*)** (47.6 mg, 0.0784 mmol) in dry THF (3.0 mL) at 0 °C; the mixture was stirred at room temperature for 1 day. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The

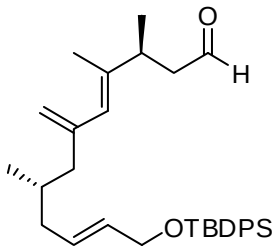
residue was purified by silica gel column chromatography (EtOAc:hexane, 1:80) to give **54** (44.6 mg, 94%) as a colorless oil: $[\alpha]^{23}_{D}$ -4.2 (*c* 1.00, $CHCl_3$); IR (film) 2955 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.57 (6H, q, *J* = 7.9 Hz), 0.82 (3H, d, *J* = 7.0 Hz), 0.94 (9H, t, *J* = 7.9 Hz), 1.02 (3H, d, *J* = 4.7 Hz), 1.05 (9H, s), 1.47-1.69 (3H, m), 1.71 (3H, d, *J* = 1.1 Hz), 1.77-1.89 (2H, m), 2.03 (1H, td, *J* = 6.7, 13.7 Hz), 2.10 (1H, dd, *J* = 6.3, 13.7 Hz), 2.27 (1H, tq, *J* = 7.0, 7.0 Hz), 3.52 (1H, t, *J* = 7.0 Hz), 4.16 (2H, dd, *J* = 0.9, 4.4 Hz), 4.79 (1H, d, *J* = 1.3 Hz), 5.00 (1H, d, *J* = 1.3 Hz), 5.53 (1H, td, *J* = 4.7, 15.0 Hz), 5.55 (1H, s), 5.63 (1H, td, *J* = 7.0, 15.0 Hz), 7.34-7.44 (6H, m), and 7.67-7.71 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 4.5, 7.0, 14.2, 19.3, 19.4, 20.0, 27.0, 31.9, 38.0, 39.5, 40.1, 45.5, 61.6, 64.8, 114.3, 125.6, 127.7, 129.7, 129.7, 130.4, 134.1, 135.7, 142.2, and 145.1; HRMS (ESI) calcd for $C_{37}H_{58}O_3Si_2Na$ $(M+H)^+$ 605.4210, found *m/z* 605.4207.

(3*S*,4*E*,8*S*,10*E*)-12-(*tert*-Butyldiphenylsilyloxy)-3,4,8-trimethyl-6-methylenedodeca-4,10-dien-1-ol (S-16)



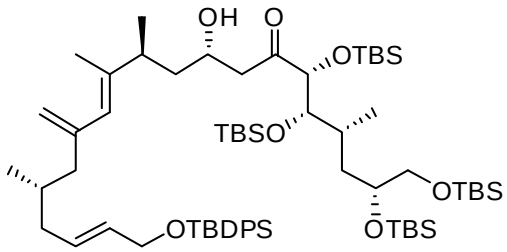
To a solution of **54** (21.7 mg, 0.0359 mmol) in CH_2Cl_2 (0.18 mL) and MeOH (0.18 mL) was added PPTS (1.8 mg, 7.14 μmol) at 0 °C; the mixture was stirred at the same temperature for 2 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:5) to give **S-16** (16.3 mg, 93%) as a colorless oil: $[\alpha]^{22}_{D}$ -3.5 (*c* 1.00, $CHCl_3$); IR (film) 3420, 2928, and 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, d, *J* = 6.5 Hz), 1.03-1.06 (12H, m), 1.53-1.62 (2H, m), 1.67 (1H, m), 1.73 (3H, d, *J* = 1.3 Hz), 1.80-1.89 (2H, m), 2.04 (1H, m), 2.11 (1H, dd, *J* = 6.3, 13.5 Hz), 2.33 (1H, m), 3.59 (1H, t, *J* = 6.7 Hz), 4.17 (2H, dd, *J* = 1.1, 4.9 Hz), 4.81 (1H, dd, *J* = 1.1, 2.5 Hz), 4.98 (1H, t, *J* = 1.1 Hz), 5.54 (1H, td, *J* = 4.9, 15.3 Hz), 5.59-5.69 (2H, m), 7.35-7.45 (6H, m), and 7.67-7.71 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 14.1, 19.4, 19.4, 20.0, 27.0, 32.0, 37.7, 39.4, 40.5, 45.4, 61.7, 64.8, 114.6, 126.0, 127.7, 129.7, 129.7, 130.3, 134.0, 135.7, 142.2, and 144.9; HRMS (ESI) calcd for $C_{37}H_{58}O_3Si_2Na$ $(M+H)^+$ 491.3345, found *m/z* 491.3347.

(3*S*,4*E*,8*S*,10*E*)-12-(*tert*-Butyldiphenylsilyloxy)-3,4,8-trimethyl-6-methylenedodeca-4,10-dienal (34)



To a solution of **S-16** (0.148 g, 0.302 mmol) in DMSO (6.0 mL) was added IBX (0.253 g, 0.903 mmol) at 0 °C; the mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of water at 0 °C, and the resulting slurry was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc:hexane, 1:8) to give **34** (0.144 g, 98%) as a colorless oil: $[\alpha]^{22}_{D}$ -2.8 (*c* 0.89, $CHCl_3$); IR (film) 2962, 2928, 2856, and 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, d, *J* = 6.3 Hz), 1.05 (9H, s), 1.10 (3H, d, *J* = 7.3 Hz), 1.55 (1H, m), 1.76 (3H, d, *J* = 1.5 Hz), 1.79-1.88 (2H, m), 2.02 (1H, td, *J* = 6.8, 13.7 Hz), 2.09 (1H, dd, *J* = 6.3, 13.7 Hz), 2.34 (1H, ddd, *J* = 2.4, 7.3, 16.1 Hz), 2.52 (1H, ddd, *J* = 2.4, 6.8, 16.1 Hz), 2.77 (1H, tq, *J* = 6.8, 6.8 Hz), 4.17 (2H, d, *J* = 4.4 Hz), 4.80 (1H, s), 4.98 (1H, s), 5.49-5.68 (2H, m), 5.63 (1H, s), 7.34-7.44 (6H, m), 7.66-7.71 (4H, m), and 9.68 (1H, t, *J* = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 15.1, 19.4, 19.8, 27.0, 31.9, 38.0, 39.4, 42.2, 45.2, 49.0, 64.7, 114.9, 126.3, 127.7, 129.6, 129.7, 130.4, 134.1, 135.7, 140.6, 144.6, and 202.5; HRMS (ESI) calcd for $C_{37}H_{58}O_3Si_2Na$ $(M+H)^+$ 489.3189, found *m/z* 489.3189.

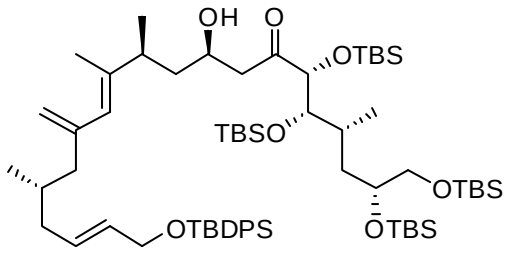
(6*R*,8*R*,9*S*,10*R*,13*S*,15*S*,16*E*,20*S*,22*E*)-6,9,10-Tris(*tert*-butyldimethylsiloxy)-13-hydroxy-2,2,3,3,8,15,16,20,27,27-decamethyl-18-methylene-26,26-diphenyl-4,25-dioxa-3,26-disilaoctacosa-16,22-dien-11-one (55-(*S*))



To a solution of LHMDS (1.00 M solution in THF, 0.800 mL, 0.800 mmol) in dry THF (2.0 mL) was added a solution of **32** (0.486 g, 0.733 mmol) in dry THF (3.0 mL) at -78 °C; the mixture was stirred at the same temperature for 30 min, at 0 °C for 30 min, and at room temperature for 1 h. To the mixture was added a solution of **34** (0.134 g, 0.274 mmol) in dry THF (3.0 mL) at -10 °C; the mixture was stirred at the same temperature for 5 min. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography

(Et_2O:hexane, 1:40) and gel permeation chromatography (JAIGEL-1H, $CHCl_3$, flow rate 3.5 mL/min, UV detection at 254 nm) to give a 1.3:1 mixture of **55-(*S*)** and **55-(*R*)** (0.233 g, 74%, retention time: 42.0 min). The product was purified by silica gel column chromatography (Wako gel C-300, MTBE:hexane, 1:30) to give **55-(*S*)** as a colorless oil: $[\alpha]^{22}_D$ +10.7 (*c* 0.99, $CHCl_3$); IR (film) 3464, 2955, 2929, 2858, and 1712 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.09 (9H, s), 0.17 (6H, s), 0.18 (3H, s), 0.19 (3H, s), 0.22 (3H, s), 0.91 (3H, d, *J* = 6.8 Hz), 0.99 (9H, s), 1.02 (9H, s), 1.05 (3H, m), 1.05 (9H, s), 1.05 (9H, s), 1.09 (3H, d, *J* = 6.8 Hz), 1.20 (9H, m), 1.46 (1H, ddd, *J* = 4.4, 8.3, 13.7 Hz), 1.80 (3H, d, *J* = 1.0 Hz), 1.65-1.93 (6H, m), 2.08 (1H, td, *J* = 6.8, 13.7 Hz), 2.19 (1H, dd, *J* = 6.4, 13.7 Hz), 2.37 (1H, m), 2.63 (1H, tq, *J* = 6.8, 6.8 Hz), 2.81 (1H, dd, 2.9, 18.1 Hz), 2.99 (1H, dd, *J* = 8.8, 18.1 Hz), 3.13 (1H, d, *J* = 2.5 Hz), 3.53 (1H, dd, *J* = 6.8, 9.8 Hz), 3.72 (1H, dd, *J* = 4.4, 9.8 Hz), 3.87 (1H, m), 3.88 (1H, dd, *J* = 2.9, 4.9 Hz), 4.22 (2H, dd, *J* = 1.0, 4.9 Hz), 4.29 (1H, m), 4.34 (1H, d, *J* = 4.9 Hz), 4.95 (1H, d, *J* = 1.9 Hz), 5.06 (1H, d, *J* = 1.9 Hz), 5.62 (1H, td, *J* = 4.9, 15.1 Hz), 5.72 (1H, td, *J* = 6.8, 15.1 Hz), 5.78 (1H, s), 7.23-7.28 (6H, m), and 7.80-7.84 (4H, m); ^{13}C NMR (100 MHz, C_6D_6) *δ* -5.2, -4.7, -4.3, -4.3, -4.2, -3.9, -3.5, 14.2, 14.9, 18.5, 18.5, 18.6, 19.2, 19.5, 19.6, 26.2, 26.3, 27.1, 30.8, 32.1, 39.7, 40.0, 40.7, 42.6, 45.6, 48.2, 65.0, 66.1, 68.6, 71.3, 80.3, 81.7, 114.8, 125.8, 128.6, 129.7, 130.0, 130.9, 134.4, 136.0, 143.4, 145.1, and 211.8; HRMS (ESI) calcd for $C_{71}H_{133}O_7Si_6Na$ $(M+Na)^+$ 1173.7622, found *m/z* 1173.7616.

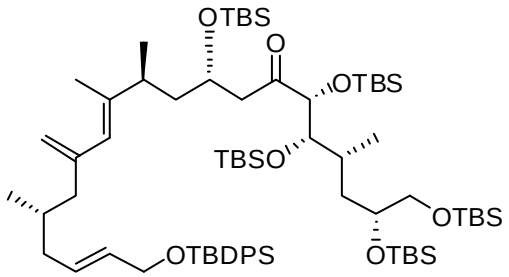
(6*R*,8*R*,9*S*,10*R*,13*R*,15*S*,16*E*,20*S*,22*E*)-6,9,10-Tris(*tert*-butyldimethylsilyloxy)-13-hydroxy-2,2,3,3,8,15,16,20,27,27-decamethyl-18-methylene-26,26-diphenyl-4,25-dioxa-3,26-disilaoctacosa-16,22-dien-11-one (55-(*R*))



$[\alpha]^{23}_D$ -8.1 (*c* 1.01, $CHCl_3$); IR (film) 3434, 2954, 2930, 2858, 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (3H, s), 0.04 (6H, s), 0.05 (3H, s), 0.05 (3H, s), 0.06 (3H, s), 0.11 (3H, s), 0.15 (3H, s), 0.72 (3H, d, *J* = 6.7 Hz), 0.83 (3H, d, *J* = 6.7 Hz), 0.88 (9H, s), 0.89 (9H, s), 0.91 (9H, s), 0.95 (9H, s), 1.03 (3H, d, *J* = 7.0 Hz), 1.06 (9H, s), 1.31 (1H, m), 1.69 (3H, d, *J* = 1.1 Hz), 1.36-1.75 (4H, m), 1.85 (1H, dd, *J* = 7.9, 13.5 Hz), 1.86 (1H, m), 2.10 (1H, dd, *J* = 6.3, 13.5 Hz), 2.01-2.13 (2H, m), 2.42 (1H, dd, *J* = 9.6, 18.4 Hz), 2.45 (1H, m), 2.98 (1H, dd, *J* = 2.0, 13.5 Hz), 3.15 (1H, s), 3.32 (1H, dd, *J* = 6.7, 9.9 Hz), 3.55 (1H, dd, *J* = 4.9, 9.9 Hz), 3.64 (1H, m), 3.65 (1H, dd, *J* = 2.5, 5.2 Hz), 3.96 (1H, m), 4.09 (1H, d, *J* = 4.9 Hz), 4.18 (2H, d, *J* = 4.9 Hz), 4.80 (1H, d, *J* = 2.0 Hz), 4.96 (1H, d,

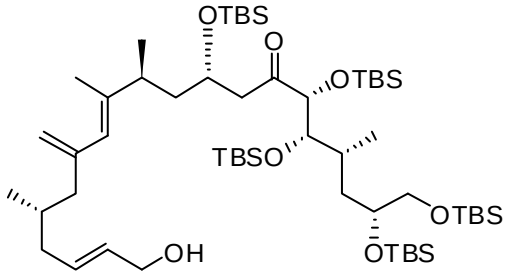
J = 2.0 Hz), 5.55 (1H, td, *J* = 4.9, 15.3 Hz), 5.64 (1H, td, *J* = 7.0, 15.3 Hz), 5.65 (1H, s), 7.35-7.43 (6H, m), 7.68-7.71 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.2, -5.2, -5.0, -4.5, -4.4, -4.0, -3.6, 13.3, 13.9, 18.2, 18.3, 18.4, 18.5, 19.4, 19.4, 20.1, 26.0, 26.1, 26.2, 27.0, 29.7, 31.8, 39.4, 39.6, 40.8, 41.7, 45.3, 47.7, 64.8, 65.8, 68.1 70.9, 80.0, 81.2, 114.4, 126.5, 127.7, 127.7, 128.5, 129.7, 130.4, 134.1, 135.7, 141.5, 145.0, 212.4; ESIMS calcd for $C_{71}H_{133}O_7Si_6Na$ $(M+Na)^+$ 1173.7622, found *m/z* 1173.7610.

(6*R*,8*R*,9*S*,10*R*,13*S*,15*S*,16*E*,20*S*,22*E*)-6,9,10,13-Tetrakis(*tert*-butyldimethylsilyloxy) -2,2,3,3,8,15,16,20,27,27-decamethyl-18-methylene-26,26-diphenyl-4,25-dioxa-3,26-disilaoctacosa-16,22-dien-11-one (S-17)



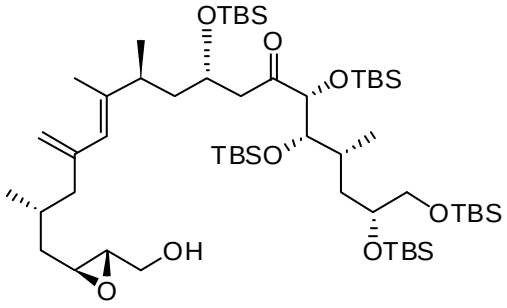
To a solution of **55-(*S*)** (56.0 mg, 0.0486 mmol) in CH_2Cl_2 (0.50 mL) were added 2,6-lutidine (0.170 mL, 1.50 mmol) and TBSOTf (0.110 mL, 0.490 mmol) at 0 ^oC; the mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 ^oC, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (Et_2O:hexane, 1:100) to give **S-17** (60.2 mg, 98%) as a colorless oil. $[\alpha]^{24}_D$ -12.3 (*c* 0.99, $CHCl_3$); IR (neat) 2955, 2929, 2858, 1721, 1472, 1462, 1254, 1113, 836, and 775 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.09 (6H, s), 0.12 (3H, s), 0.17 (6H, s), 0.19 (3H, s), 0.20 (3H, s), 0.21 (3H, s), 0.22 (3H, s), 0.24 (3H, s), 0.93 (3H, d, *J* = 6.8 Hz), 0.98 (9H, s), 1.02-1.06 (3H, m), 1.02 (9H, s), 1.04 (9H, s), 1.06 (9H, s), 1.06 (9H, s), 1.18 (3H, m), 1.20 (9H, m), 1.87 (3H, s), 1.65-1.97 (7H, m), 2.12 (1H, m), 2.19 (1H, dd, *J* = 6.4, 13.2 Hz), 2.41 (1H, m), 2.56 (1H, se, *J* = 6.8 Hz), 2.90 (1H, dd, 6.8, 18.1 Hz), 3.21 (1H, dd, *J* = 5.4, 18.1 Hz), 3.54 (1H, dd, *J* = 6.8, 9.8 Hz), 3.73 (1H, dd, *J* = 4.9, 9.8 Hz), 3.85-3.98 (2H, m), 4.23 (2H, d, *J* = 4.9 Hz), 4.32 (1H, d, *J* = 4.4 Hz), 4.49 (1H, m), 5.00 (1H, s), 5.08 (1H, s), 5.63 (1H, td, *J* = 4.9, 15.6 Hz), 5.75 (1H, td, *J* = 6.8, 15.6 Hz), 5.84 (1H, s), 7.23-7.27 (6H, m), and 7.79-7.85 (4H, m); ^{13}C NMR (98.5 MHz, C_6D_6) δ -5.2, -4.7. -4.5, -4.3, -4.3, -4.1, -4.0, -3.9, -3.7, 14.4, 15.1, 18.3, 18.4, 18.5, 18.5, 18.6, 19.3, 19.5, 19.5, 26.2, 26.2, 26.3, 27.0, 30.6, 32.1, 39.7, 39.8, 40.9, 44.0, 45.7, 49.1, 64.9, 66.8, 68.6, 71.3, 80.3, 81.9, 114.8, 125.7, 128.5, 129.6, 129.9, 130.9, 134.3, 136.0, 143.1, 145.1, 207.8; HRMS (ESI) calcd for $C_{71}H_{133}O_7Si_6Na$ $(M+Na)^+$ 1265.8667, found m/z 1265.8656.

(5*S*,8*R*,9*S*,10*R*,12*R*)-8,9,12-Tris(*tert*-butyldimethylsilyloxy)-5-((2*S*,3*E*,7*S*,9*E*)-11-hydroxy-2,3,7-trimethyl-5-methyleneundeca-3,9-dienyl)-2,2,3,3,10,15,15,16,16-nonamethyl-4,14-dioxa-3,15-disilaheptadecan-7-one (56)



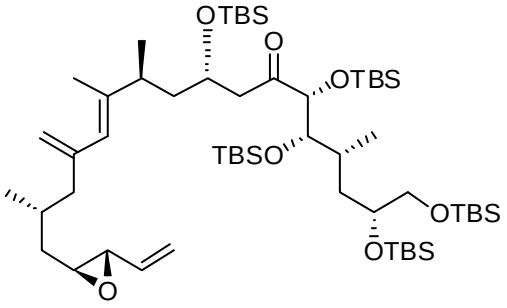
To a solution of **S-17** (0.136 g, 0.107 mmol) in DMF (1.1 mL) was added a 1:1:5 mixture of TBAF-AcOH-H_2O (0.100 M solution in THF, 0.537 mL, 0.0537 mmol) at room temperature; the mixture was stirred at room temperature for 3.5 h. The reaction was quenched by the addition of water at 0 ^oC, and the resulting slurry was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (Et_2O:hexane, 1:10) and GPC to give **56** (76.5 mg, 70%) as a colorless oil, along with the recovered **S-17** (18.2 mg, 13%). $[\alpha]^{23}_D$ -17.0 (*c* 1.01, $CHCl_3$); IR (neat) 3351, 2955, 2929, 2858, 1719, 1472, 1462, 1255, 1114, 1076, 836, and 775 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.10 (6H, s), 0.13 (3H, s), 0.18 (3H, s), 0.19 (3H, s), 0.20 (3H, s), 0.22 (3H, s), 0.23 (3H, s), 0.23 (3H, s), 0.25 (3H, s), 0.92 (3H, d, *J* = 6.3 Hz), 0.99 (9H, s), 1.04 (9H, s), 1.05-1.07 (3H, m), 1.06 (9H, s), 1.07 (9H, s), 1.07 (9H, s), 1.18 (3H, d, *J* = 6.8 Hz), 1.87 (3H, d, *J* = 1.0 Hz), 1.66-1.96 (7H, m), 2.10 (1H, td, *J* = 5.4, 13.7 Hz), 2.18 (1H, dd, *J* = 5.9, 13.2 Hz), 2.43 (1H, m), 2.54 (1H, se, *J* = 6.8 Hz), 2.89 (1H, dd, *J* = 6.8, 18.0 Hz), 3.21 (1H, dd, *J* = 5.4, 18.0 Hz), 3.54 (1H, dd, *J* = 6.8, 9.8 Hz), 3.74 (1H, dd, *J* = 4.9, 9.8 Hz), 3.87-3.95 (4H, m), 4.32 (1H, d, *J* = 4.9 Hz), 4.49 (1H, m), 5.00 (1H, s), 5.08 (1H, s), 5.52-5.66 (2H, m), and 5.83 (1H, s); ^{13}C NMR (98.5 MHz, C_6D_6) *δ* -5.2, -4.7. -4.5, -4.3, -4.3, -4.1, -4.0, -3.9, -3.7, 14.4, 15.0, 18.3, 18.4, 18.5, 18.5, 18.6, 19.4, 19.5, 26.2, 26.3, 26.3, 30.6, 32.1, 39.8, 39.9, 40.9, 44.0, 45.8, 49.0, 63.5, 66.8, 68.6, 71.3, 80.3, 81.9, 114.8, 125.8, 130.4, 131.7, 143.0, 145.1, and 208.0; HRMS (ESI) calcd for $C_{55}H_{115}O_7Si_5Na$ $(M+Na)^+$ 1027.7489, found m/z 1027.7495.

(5*S*,8*R*,9*S*,10*R*,12*R*)-8,9,12-Tris(*tert*-butyldimethylsilyloxy)-5-((2*S*,7*R*,*E*)-8-((2*S*,3*S*)-3-(hydroxymethyl)oxiran-2-yl)-2,3,7-trimethyl-5-methyleneoct-3-enyl)-2,2,3,3,10,15,15,16,16-nonamethyl-4,14-dioxa-3,15-disilaheptadecan-7-one (57)



To a suspension of Ti(O*i*-Pr)$_4$ (0.100 M solution in CH_2Cl_2, 0.112 mL, 0.0112 mmol) and MS4A (44.8 mg) in CH_2Cl_2 (0.20 mL) was added (+)-DIPT (0.120 M solution in CH_2Cl_2, 0.112 mL, 0.0134 mmol) at -20 ^oC; the mixture was stirred at the same temperature for 30 min. To the suspension was added TBHP (5.50 M solution in decane, 30.5 μL, 0.168 mmol) at -20 ^oC; the mixture was stirred at the same temperature for 30 min. To the suspension was added a solution of **56** (11.5 mg, 0.0112 mmol) in CH_2Cl_2 (0.50 mL) at -20 ^oC; the mixture was stirred at the same temperature for 6 h. The reaction was quenched by the addition of saturated tartaric acid aq. at 0 ^oC, and the resulting slurry was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc:hexane, 1:3) to give **57** (7.80 mg, 67%) as a colorless oil, along with the recovered **56** (1.00 mg, 9%). $[\alpha]^{22}_D$ -21.9 (*c* 1.01, $CHCl_3$); IR (neat) 2955, 2929, 2857, 1718, 1472, 1254, 1108, 1073, 836, and 775 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.10 (6H, s), 0.14 (3H, s), 0.18 (3H, s), 0.19 (3H, s), 0.20 (3H, s), 0.22 (3H, s), 0.23 (6H, s), 0.26 (3H, s), 0.91 (3H, d, *J* = 6.8 Hz), 0.99 (9H, s), 1.04 (9H, s), 1.05-1.08 (3H, m), 1.06 (9H, s), 1.07 (9H, s), 1.08 (9H, s), 1.18 (3H, d, *J* = 6.8 Hz), 1.59 (1H, ddd, *J* = 4.9, 6.3, 13.7 Hz), 1.65-1.89 (6H, m), 1.86 (3H, s), 1.95 (1H, dd, *J* = 7.8, 13.2 Hz), 2.14 (1H, dd, *J* = 6.3, 13.2 Hz), 2.43 (1H, m), 2.51-2.61 (2H, m), 2.83 (1H, dt, *J* = 2.0, 5.9 Hz), 2.90 (1H, dd, *J* = 6.8, 18.0 Hz), 3.23 (1H, dd, *J* = 5.4, 18.0 Hz), 3.35 (1H, m), 3.55 (1H, dd, *J* = 6.3, 9.8 Hz), 3.55 (1H, m), 3.74 (1H, dd, *J* = 4.9, 9.8 Hz), 3.87-3.94 (2H, m), 4.33 (1H, d, *J* = 4.4 Hz), 4.47 (1H, m), 4.98 (1H, s), 5.05 (1H, s), and 5.81 (1H, s); ^{13}C NMR (98.5 MHz, C_6D_6) *δ* -5.2, -4.7. -4.5, -4.3, -4.3, -4.1, -4.0, -3.9, -3.7, 14.4, 15.0, 18.3, 18.4, 18.5, 18.6, 19.3, 19.7, 26.2, 26.3, 26.3, 29.9, 30.7, 39.0, 39.9, 40.9, 43.9, 46.3, 48.9, 54.3, 58.8, 61.9, 66.9, 68.6, 71.3, 80.2, 81.9, 114.9, 125.6, 143.3, 144.7, and 208.0; HRMS (ESI) calcd for $C_{55}H_{114}O_8Si_5Na$ $(M+Na)^+$ 1065.7258, found m/z 1065.7263.

(5*S*,8*R*,9*S*,10*R*,12*R*)-8,9,12-Tris(*tert*-butyldimethylsilyloxy)-2,2,3,3,10,15,15,16,16-nonamethyl-5-((2*S*,7*R*,*E*)-2,3,7-trimethyl-5-methylene-8-((2*S*,3*S*)-3-vinyloxiran-2-yl)oct-3-enyl)-4,14-dioxa-3,15-disilaheptadecan-7-one (58)

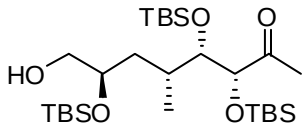


To a solution of **57** (13.3 mg, 0.0127 mmol) in CH_2Cl_2 (0.80 mL) was added pyridine (51.4 μL, 0.638 mmol) and Dess-Martin periodinane (54.1 mg, 0.128 mmol) at 0 °C; the mixture was stirred at the same temperature for 2.5 h. The reaction was quenched by the addition of saturated $NaHCO_3$ aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$ five times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc:hexane, 1:5) to give the corresponding aldehyde (9.30 mg, 70%) as a colorless oil.

To a solution of Ph_3PCH_3Br (52.5 mg, 0.147 mmol) in THF (0.70 mL) was added NaHMDS (1.00 M solution in THF, 73.5 μL, 0.0735 mmol) at 0 °C; the mixture was stirred at the same temperature for 30 min. To the mixture was added a solution of the aldehyde (5.10 mg, 4.90 μmol) in THF (0.80 mL) at 0 °C; the mixture was stirred at the same temperature for 30 min. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc:hexane, 1:15) to give **58** (4.60 mg, 90%) as a colorless oil. $[\alpha]^{23}_{D}$ -18.4 (*c* 1.01, $CHCl_3$); IR (neat) 2955, 2929, 2857, 1721, 1463, 1254, 1110, 1072, 836, and 775 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.10 (6H, s), 0.14 (3H, s), 0.18 (3H, s), 0.19 (3H, s), 0.19 (3H, s), 0.22 (3H, s), 0.23 (6H, s), 0.26 (3H, s), 0.92 (3H, d, *J* = 6.3 Hz), 0.99 (9H, s), 1.04 (9H, s), 1.06-1.08 (3H, m), 1.06 (9H, s), 1.07 (9H, s), 1.08 (9H, s), 1.18 (3H, d, *J* = 6.8 Hz), 1.62 (1H, ddd, *J* = 4.4, 6.3, 13.7 Hz), 1.66-1.91 (6H, m), 1.85 (3H, d, *J* = 1.0 Hz), 1.96 (1H, dd, *J* = 7.8, 13.2 Hz), 2.14 (1H, dd, *J* = 6.3, 13.2 Hz), 2.43 (1H, m), 2.55 (1H, se, *J* = 6.8 Hz), 2.75 (1H, dt, *J* = 2.0, 5.9 Hz), 2.90 (1H, dd, *J* = 6.8, 18.0 Hz), 2.93 (1H, dd, *J* = 7.8 Hz), 3.20 (1H, dd, *J* = 5.4, 18.0 Hz), 3.54 (1H, dd, *J* = 6.8, 9.8 Hz), 3.74 (1H, dd, *J* = 4.9, 9.8 Hz), 3.87-3.95 (2H, m), 4.34 (1H, d, *J* = 4.9 Hz), 4.47 (1H, m), 4.98 (1H, s), 5.04 (1H, s), 5.05 (1H, dd, *J* = 1.5, 10.3 Hz), 5.31 (1H, dd, *J* = 1.5, 17.1 Hz), 5.55 (1H, ddd, *J* = 7.3, 10.3, 17.1 Hz), and 5.81 (1H, s); ^{13}C NMR (98.5 MHz, C_6D_6) *δ* -5.2, -4.6. -4.5, -4.3, -4.3, -4.0, -4.0, -3.9, -3.7, 14.4, 15.0, 18.3, 18.4, 18.5, 18.6, 19.3, 19.6, 26.2, 26.3, 26.3, 29.9, 30.7, 39.3, 39.9, 40.8, 43.9, 46.3, 48.8, 58.9, 59.0, 66.9, 68.6, 71.3,

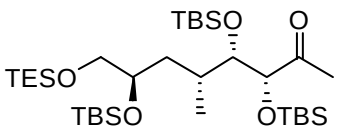
80.2, 81.9, 114.9, 117.9, 125.5, 136.9, 143.3, 144.7, and 207.8; HRMS (ESI) calcd for $C_{56}H_{114}O_7Si_5Na$ $(M+Na)^+$ 1061.7309, found m/z 1061.7300.

(3*R*,4*S*,5*R*,7*R*)-3,4,7-tris(*tert*-butyldimethylsilyloxy)-8-hydroxy-5-methyloctan-2-one (59)



To a solution of **32** (37.5 mg, 0.0565 mmol) in MeOH (0.80 mL) and CH_2Cl_2 (0.40 mL) was added CSA (6.6 mg, 0.028 mmol) at 0 °C; the mixture was stirred at the same temperature for 1.5 h. The reaction was quenched by the addition of saturated $NaHCO_3$ aq. at 0 °C, and the resulting slurry was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:15) to give **59** (14.2 mg, 46%) as a colorless oil, along with the recovered **32** (10.8 mg, 29%): $[\alpha]^{21}_D$ -17.3 (*c* 1.00, $CHCl_3$); IR (film) 3510, 2954, 2931, 2859, and 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (3H, s), 0.04 (3H, s), 0.065 (3H, s), 0.073 (3H, s), 0.08 (3H, s), 0.10 (3H, s), 0.81 (3H, d, *J* = 6.8 Hz), 0.88 (9H, s), 0.91 (9H, s), 0.92 (9H, s), 1.28 (1H, ddd, *J* = 4.4, 10.2, 13.7 Hz), 1.73 (1H, ddd, *J* = 4.4, 8.8, 13.7 Hz), 1.85 (1H, br), 1.90 (1H, m), 2.04 (3H, s), 3.42 (1H, dd, *J* = 4.4 Hz, 11.2 Hz), 3.55 (1H, dd, *J* = 4.4, 11.2 Hz), 3.63 (1H, dd, *J* = 3.9, 4.4 Hz), 3.77 (1H, tt, *J* = 4.4, 4.4 Hz), and 4.09 (1H, d, *J* = 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.0, -4.7, -4.5, -3.9, 14.5, 18.0, 18.2, 25.9, 26.0, 28.4, 30.8, 38.7, 66.9, 70.6, 79.1, 81.3, and 209.6; HRMS (ESI) calcd for $C_{27}H_{60}O_5NaSi_3$ $(M+Na)^+$ 571.3646, found *m/z* 571.3651.

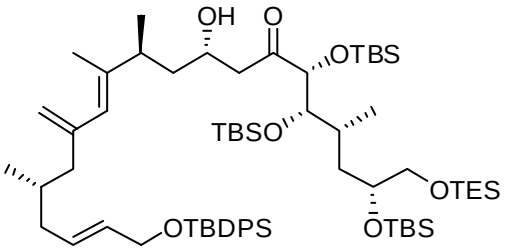
(3*R*,4*S*,5*R*,7*R*)-3,4,7-tris(*tert*-butyldimethylsilyloxy)-5-methyl-8-(triethylsilyloxy)octan-2-one (60)



To a solution of **59** (1.01 g, 1.84 mmol) in CH_2Cl_2 (19 mL) were added Et_3N (2.03 mL, 14.7 mmol) and TESCl (1.23 mL, 7.34 mmol) at 0 °C; the mixture was stirred at room temperature for 1.5 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with $CHCl_3$ three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:50) to give **60** (1.19 g, 98%) as a colorless oil: $[\alpha]^{25}_D$ +2.4 (*c* 1.00, $CHCl_3$); IR (film) 2955, 2932, 2859, and 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.04 (6H, s), 0.05 (3H, s), 0.08 (3H, s), 0.09 (3H, s), 0.79 (3H, d, *J* = 6.8 Hz), 0.86 (9H, s), 0.91 (9H, s), 0.92 (9H, s), 0.94 (9H, t, *J* = 7.8 Hz), 1.36 (1H, ddd, *J* = 2.9,

9.8, 13.7 Hz), 1.73 (1H, ddd, *J* = 2.4, 11.7, 13.7 Hz), 2.01 (1H, m), 2.20 (3H, s), 3.30 (1H, dd, *J* = 6.3 Hz, 9.8 Hz), 3.52 (1H, dd, *J* = 5.4, 9.8 Hz), 3.63 (1H, dd, *J* = 2.9, 4.9 Hz), 3.66 (1H, m), and 4.09 (1H, d, *J* = 4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.9, -4.72, -4.68, -4.4, -4.2, -3.8, 4.3, 6.8, 13.5, 18.1, 18.2, 25.9, 25.9, 26.0, 28.1, 30.5, 40.0, 67.7, 70.9, 79.6, 81.4, and 209.7; HRMS (ESI) calcd for $C_{18}H_{39}O_2Si_2$ $(M+H)^+$ 343.2489, found *m/z* 343.2491.

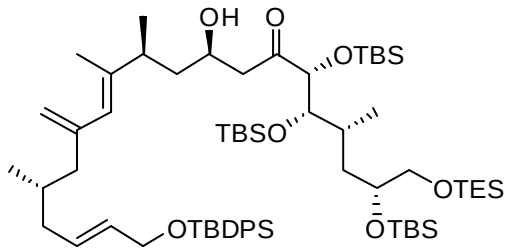
(6*R*,8*R*,9*S*,10*R*,13*S*,15*S*,16*E*,20*S*,22*E*)-6,9,10-tris(*tert*-butyldimethylsilyloxy)-3,3-diethyl-13-hydroxy-8,15,16,20,27,27-hexamethyl-18-methylene-26,26-diphenyl-4,25-dioxa-3,26-disilaoctacosa-16,22-dien-11-one (61)



To a solution of LHMDS (1.00 M solution in THF, 3.70 mL, 3.70 mmol) in dry THF (7.0 mL) was added a solution of **60** (2.20 g, 3.32 mmol) in dry THF (13 mL) at -78 °C; the mixture was stirred at 0 °C for 30 min and at room temperature for 1 h. To the mixture was added a pre-cooled solution of **34** (0.547 g, 1.12 mmol) in dry THF (13.1 mL) at -10 °C; the mixture was stirred at the same temperature for 20 min. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc there times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (MTBE:hexane, 1:40) and gel permeation chromatography (JAIGEL-1H, $CHCl_3$, flow rate 3.5 mL/min, UV detection at 254 nm) to give **61** (0.705 g, 55%) as a colorless oil: $[\alpha]^{21}_D$ +10.2 (*c* 0.99, $CHCl_3$); IR (film) 2955, 2929, 2857 and 1718 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.09 (3H, s), 0.16 (3H, s), 0.17 (3H, s), 0.19 (3H, s), 0.20 (3H, s), 0.21 (3H, s), 0.62 (6H, q, *J* = 7.8 Hz), 0.91 (3H, d, *J* = 6.8 Hz), 1.02 (9H, t, *J* = 7.8 Hz), 1.02 (9H, s), 1.01-1.06 (3H, m), 1.05 (9H, s), 1.05 (9H, s), 1.09 (3H, d, *J* = 6.8 Hz), 1.20 (9H, s), 1.45 (1H, ddd, *J* = 4.4, 8.3, 13.7 Hz), 1.80 (3H, d, *J* = 1.0 Hz), 1.66-1.89 (5H, m),1.99 (1H, dd, *J* = 7.8, 13.7 Hz) 2.08 (1H, td, *J* = 6.8, 13.7 Hz), 2.16 (1H, dd, *J* = 6.3, 13.7 Hz), 2.37 (1H, m), 2.63 (1H, qt, *J* = 6.8, 6.8 Hz), 2.80 (1H, dd, *J* = 2.4, 18.0 Hz), 2.99 (1H, dd, *J* = 9.3, 18.0 Hz), 3.14 (1H, d, *J* = 2.4 Hz), 3.54 (1H, dd, *J* = 6.3, 9.8 Hz), 3.72 (1H, dd, *J* = 5.4, 9.8 Hz), 3.87 (1H, dd, *J* = 3.4, 4.9 Hz), 3.91 (1H, m), 4.21 (2H, dd, *J* = 1.0, 4.9 Hz), 4.29 (1H, m), 4.33 (1H, d, *J* = 4.9 Hz), 4.95 (1H, d, *J* = 2.0 Hz), 5.06 (1H, d, *J* = 2.0 Hz), 5.61 (1H, td, *J* = 4.9, 15.1 Hz), 5.72 (1H, td, *J* = 6.8, 15.1 Hz), 5.77 (1H, s), 7.26 (6H, m), and 7.82 (4H, m); ^{13}C NMR (100 MHz, C_6D_6) δ -4.7, -4.32, -4.27, -4.2, -3.8, -3.6, 4.8, 7.1, 14.3, 18.49, 18.54, 18.6, 19.2,

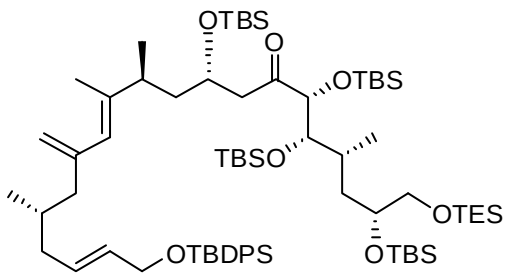
19.5, 26.2, 26.31, 26.33, 27.1, 31.0, 32.1, 39.7, 40.0, 40.5, 42.7, 45.6, 48.2, 65.0, 66.0, 68.3, 71.5, 80.2, 81.7, 114.8, 125.8, 128.6, 129.7, 130.0, 130.9, 134.4, 136.0, 143.4, 145.1, and 211.8; HRMS (ESI+) calcd for $C_{65}H_{118}O_7NaSi_5$ $(M+Na)^+$ 1173.7622, found *m/z* 1173.7600.

(6*R*,8*R*,9*S*,10*R*,13*R*,15*S*,16*E*,20*S*,22*E*)-6,9,10-tris(*tert*-butyldimethylsilyloxy)-3,3-diethyl-13-hydroxy-8,15,16,20,27,27-hexamethyl-18-methylene-26,26-diphenyl-4,25-dioxa-3,26-disilaoctacosa-16,22-dien-11-one (S-18)



$[\alpha]^{19}_D$ -6.5 (*c* 1.00, $CHCl_3$); IR (film) 2955, 2930, 2858 and 1712 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.08 (3H, s), 0.16 (3H, s), 0.17 (3H, s), 0.19 (3H, s), 0.20 (3H, s), 0.21 (3H, s), 0.63 (6H, q, *J* = 7.8 Hz), 0.94 (3H, d, *J* = 6.8 Hz), 1.02 (9H, t, *J* = 7.8 Hz), 1.02 (9H, s), 1.02-1.06 (6H, m), 1.05 (9H, s), 1.07 (9H, s), 1.21 (9H, s), 1.51-1.70 (3H, m), 1.71-1.86 (2H, m), 1.78 (3H, d, *J* = 1.0 Hz), 1.90 (1H, dd, *J* = 7.8, 13.2 Hz), 2.10 (1H, td, *J* = 6.8, 13.2 Hz), 2.22 (1H, dd, *J* = 6.3, 13.2 Hz), 2.35 (1H, m), 2.66 (1H, dd, *J* = 9.3, 17.6 Hz), 2.73 (1H, m), 3.07 (1H, dd, *J* = 2.4, 17.6 Hz), 3.07 (1H, s), 3.53 (1H, dd, *J* = 6.3, 9.8 Hz), 3.74 (1H, dd, *J* = 5.4, 9.8 Hz), 3.87 (1H, dd, *J* = 2.9, 4.9 Hz), 3.91 (1H, m), 4.22 (1H, m), 4.24 (2H, d, *J* = 4.9 Hz), 4.30 (1H, d, *J* = 4.9 Hz), 4.99 (1H, d, *J* = 2.0 Hz), 5.09 (1H, d, *J* = 2.0 Hz), 5.65 (1H, td, *J* = 4.9, 15.1 Hz), 5.78 (1H, td, *J* = 7.3, 15.1 Hz), 5.87 (1H, s), 7.26 (6H, m), and 7.83 (4H, m); ^{13}C NMR (100 MHz, C_6D_6) δ -4.8, -4.3, -4.22, -4.21, -3.8, -3.5, 4.8, 7.2, 13.8, 13.9, 18.49, 18.53, 18.6, 19.5, 19.7, 20.4, 26.2, 26.4, 27.1, 30.7, 32.2, 39.8, 40.0, 40.7, 42.4, 45.6, 47.9, 65.0, 66.2, 68.3, 71.4, 80.2, 82.0, 114.7, 127.1, 128.6, 129.8, 130.0, 130.9, 134.4, 136.0, 141.6, 145.3, and 211.7; HRMS (ESI+) calcd for $C_{65}H_{118}O_7NaSi_5$ $(M+Na)^+$ 1173.7622, found *m/z* 1173.7618.

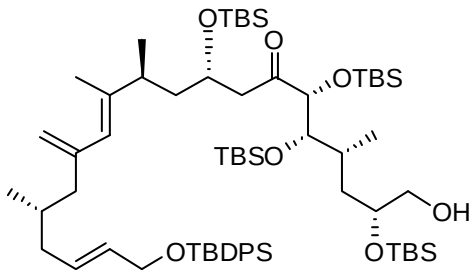
(6*R*,8*R*,9*S*,10*R*,13*S*,15*S*,16*E*,20*S*,22*E*)-6,9,10,13-tetrakis(*tert*-butyldimethylsilyloxy)-3,3-diethyl-8,15,16,20,27,27-hexamethyl-18-methylene-26,26-diphenyl-4,25-dioxa-3,26-disilaoctacosa-16,22-dien-11-one (S-19)



To a solution of **61** (0.144 g, 0.125 mmol) in CH_2Cl_2 (6.1 mL) were added 2,6-lutidine (0.220 mL, 1.90 mmol) and TBSOTf (0.140 mL, 0.630 mmol) at -10 °C; the mixture was stirred at the same temperature for 1 h. The reaction was quenched by the addition of

saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (Et_2O:hexane, 1:60) to give **S-18** (0.155 g, 98%) as a colorless oil: $[\alpha]^{20}_D$ -16.8 (*c* 1.02, $CHCl_3$); IR (film) 2957, 2933, 2890, and 1720 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.13 (3H, s), 0.18 (3H, s), 0.20 (3H, s), 0.21 (3H, s), 0.22 (3H, s), 0.23 (6H, s), 0.25 (3H, s), 0.63 (6H, q, *J* = 7.8 Hz), 0.98 (3H, d, *J* = 6.8 Hz), 0.94 (3H, d, *J* = 6.8 Hz), 1.01 (6H, t, *J* = 7.8 Hz), 1.03-1.08 (3H, m), 1.03 (9H, s), 1.05 (9H, s), 1.07 (9H, s), 1.08 (9H, s), 1.19 (3H, d, *J* = 6.8 Hz), 1.20 (9H, s), 1.67-1.85 (6H, m), 1.87 (3H, s), 1.94 (1H, dd, *J* = 8.3, 13.7 Hz), 2.13 (1H, m), 2.19 (1H, dd, *J* = 6.3, 13.7 Hz), 2.42 (1H, m), 2.56 (1H, qt, *J* = 6.8, 6.8 Hz), 2.89 (1H, dd, *J* = 6.8, 18.0 Hz), 3.20 (1H, dd, *J* = 5.4, 18.0 Hz), 3.54 (1H, dd, *J* = 6.3, 9.8 Hz), 3.74 (1H, dd, *J* = 5.4, 9.8 Hz), 3.90 (1H, dd, *J* = 3.9, 3.9 Hz), 3.93 (1H, m), 4.23 (1H, d, *J* = 4.9 Hz), 4.32 (1H, d, *J* = 4.4 Hz), 4.49 (1H, tt, *J* = 5.8, 5.8 Hz), 5.00 (1H, d, *J* = 1.5 Hz), 5.09 (1H, d, *J* = 1.5 Hz), 5.64 (1H, td, *J* = 4.9, 15.1 Hz), 5.75 (1H, td, *J* = 6.8, 15.1 Hz), 5.84 (1H, s), 7.25-7.27 (6H, m), and 7.81-7.84 (4H, m); ^{13}C NMR (100 MHz, C_6D_6) δ -4.6, -4.4, -4.3, -4.0, -3.9, -3.81, -3.76, -3.6, 4.8, 7.2, 14.5, 15.1, 18.3, 18.5, 18.6, 18.7, 19.4, 19.5, 19.6, 26.3, 26.4, 27.1, 30.8, 32.1, 39.8, 39.9, 40.7, 44.1, 45.7, 49.1, 65.0, 66.9, 68.4, 71.6, 80.3, 82.0, 114.8, 125.8, 128.6, 129.7, 130.0, 131.0, 134.4, 136.0, 143.1, 145.2, and 207.9; HRMS (ESI) calcd for $C_{71}H_{132}O_7NaSi_6$ $(M+Na)^+$ 1287.8486, found *m/z* 1287.8497.

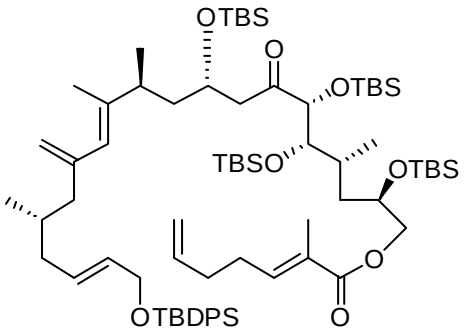
(5*R*,7*R*,8*S*,9*R*,12*S*,14*S*,15*E*,19*S*,21*E*)-8,9,12-tris(*tert*-butyldimethylsilyloxy)-5-(hydroxymethyl)-2,2,3,3,7,14,15,19,26,26-decamethyl-17-methylene-25,25-diphenyl-4,24-dioxa-3,25-disilaheptacosa-15,21-dien-10-one (62)



To a solution of **S-18** (0.320 g, 0.253 mmol) in MeOH (11 mL) and CH_2Cl_2 (5.5 mL) was added PPTS (0.159 g, 0.633 mmol) at 0 °C; the mixture was stirred at the same temperature for 4 h. The reaction was quenched by the addition of saturated $NaHCO_3$ aq. at 0 °C, and the resulting slurry was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:30) to give **62** (0.226 g, 78%) as a colorless oil: $[\alpha]^{23}_D$ -24.9 (*c* 0.99, $CHCl_3$); IR (film) 3485, 2952, 2929, 2893, and 1720 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 0.10 (3H, s), 0.11 (3H, s), 0.14 (3H, s), 0.16 (3H, s), 0.19 (3H, s), 0.20 (3H, s), 0.23 (3H, s), 0.24 (3H, s), 0.94 (3H, d, *J* = 6.5 Hz),

1.01-1.05 (3H, m), 1.01 (9H, s), 1.03 (9H, s), 1.04 (9H, s), 1.05 (9H, s), 1.19 (3H, d, *J* = 6.7 Hz), 1.20 (9H, s), 1.42 (1H, ddd, *J* = 3.4, 10.3, 13.9 Hz), 1.68-1.97 (6H, m), 1.88 (3H, d, *J* = 1.3 Hz), 1.94 (1H, dd, *J* = 8.1, 13.9 Hz), 2.14 (1H, m), 2.20 (1H, dd, *J* = 6.3, 13.5 Hz), 2.26 (1H, m), 2.56 (1H, qt, *J* = 6.7, 6.7 Hz), 2.88 (1H, dd, *J* = 7.0, 18.0 Hz), 3.18 (1H, dd, *J* = 5.2 Hz, 18.0 Hz), 3.40 (1H, dd, *J* = 4.9, 10.8 Hz), 3.48 (1H, dd, *J* = 4.3, 10.8 Hz), 3.77 (1H, tt, *J* = 4.7 Hz), 3.85 (1H, dd, *J* = 4.0, 4.0 Hz), 4.23 (2H, dd, *J* = 0.9, 4.9 Hz), 4.32 (1H, d, *J* = 4.3 Hz), 4.49 (1H, tt, *J* = 5.2, 6.7 Hz), 5.00 (1H, d, *J* = 2.0 Hz), 5.09 (1H, d, *J* = 2.0 Hz), 5.64 (1H, td, *J* = 4.9, 15.3 Hz), 5.76 (1H, td, *J* = 7.2, 15.3 Hz), 5.84 (1H, s), 7.27 (6H, m), and 7.83 (4H, m); ^{13}C NMR (100 MHz, C_6D_6) δ -4.6, -4.4, -4.3, -4.2, -4.1, -4.0, -3.9, -3.7, 15.1, 15.3, 18.3, 18.4, 18.5, 18.6, 19.4, 19.51, 19.54, 26.21, 26.24, 26.27, 26.33, 27.1, 31.1, 32.1, 39.4, 39.8, 39.8, 44.1, 45.7, 49.3, 65.0, 66.9, 67.4, 71.4, 79.8, 82.1, 114.8, 125.8, 128.6, 129.7, 130.0, 131.0, 134.4, 136.0, 143.1, 145.2, and 208.0; HRMS (ESI) calcd for $C_{65}H_{118}O_7NaSi_5$ $(M+Na)^+$ 1173.7622, found *m/z* 1173.7610.

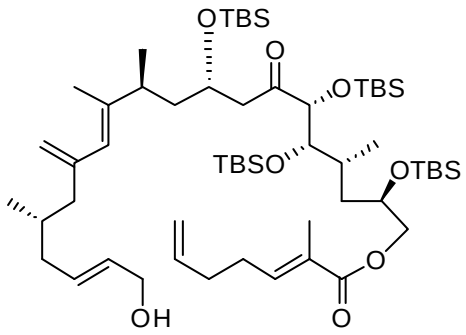
(*E*)-((2*R*,4*R*,5*S*,6*R*,9*S*,11*S*,12*E*,16*S*,18*E*)-2,5,6,9-tetrakis(*tert*-butyldimethylsilyloxy)-20-(*tert*-butyldiphenylsilyloxy)-4,11,12,16-tetramethyl-14-methylene-7-oxoicosa-12, 18-dienyl) 2-methylhepta-2,6-dienoate (63)



To a solution of **5** (99.7 mg, 0.711 mmol) in toluene (7.3 mL) was added 2,4,6-trichlorobenzoyl chloride (0.111 mL, 0.712 mmol) and Et_3N (98.6 μL, 0.712 mmol) at 0 °C; the mixture was stirred at the same temperature for 10 min. To the mixture was stirred a solution of **62** (84.5 mg, 0.0733 mmol) in toluene (7.3 mL) and DMAP (87.0 mg, 0.712 mmol) at 0 °C; the mixture was stirred at room temperature for 1.5 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:40) to give **63** (91.9 mg, 98%) as a colorless oil: $[\alpha]^{24}_D$ -20.5 (*c* 0.98, $CHCl_3$); IR (film) 2955, 2929, 2895, and 1716 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.11 (3H, s), 0.13 (3H, s), 0.16 (3H, s), 0.18 (3H, s), 0.20 (6H, s), 0.23 (3H, s), 0.24 (3H, s), 0.94 (3H, d, *J* = 6.8 Hz), 1.00 (3H, d, *J* = 6.8 Hz), 1.03 (9H, s), 1.036 (9H, s), 1.042 (9H, s), 1.05 (9H, s), 1.20 (3H, d, *J* = 6.8 Hz), 1.21 (9H, s), 1.54 (1H, ddd, *J* = 2.9, 11.2, 13.7 Hz), 1.68-2.04 (10H, m), 1.88 (3H, s), 1.88 (3H, s), 2.14

(1H, m), 2.20 (1H, dd, *J* = 6.3, 13.7 Hz), 2.35 (1H, m), 2.56 (1H, qt, *J* = 6.8, 6.8 Hz), 2.89 (1H, dd, *J* = 6.8, 18.0 Hz), 3.18 (1H, dd, *J* = 5.4, 18.0 Hz), 3.85 (1H, dd, *J* = 3.9, 3.9 Hz), 4.06 (1H, m), 4.16 (1H, dd, *J* = 4.9, 11.2 Hz), 4.23 (2H, d, *J* = 4.9 Hz), 4.29 (1H, dd, *J* = 5.4, 11.2 Hz), 4.31 (1H, d, *J* = 4.4 Hz), 4.49 (1H, tt, *J* = 5.4, 6.3 Hz), 4.97 (1H, dd, *J* = 1.5, 10.2 Hz), 5.00 (1H, dd, *J* = 1.5, 17.1 Hz), 5.00 (1H, d, *J* = 2.0 Hz), 5.09 (1H, d, *J* = 2.0 Hz), 5.61-5.75 (2H, m), 5.74 (1H, td, *J* = 6.8, 15.1 Hz), 5.84 (1H, s), 6,96 (1H, td, *J* = 6.3, 1.5 Hz) 7.24-7.27 (6H, m), and 7.81-7.84 (4H, m); ^{13}C NMR (100 MHz, C_6D_6) δ -4.6, -4.4, -4.32, -4.29, -4.1, -4.0, -3.9, -3.7, 12.8, 14.6, 15.2, 18.3, 18.4, 18.5, 18.6, 19.4, 19.5, 19.6, 26.21, 26.24, 26.26, 26.34, 27.1, 28.3, 31.0, 32.1, 32.9, 39.75, 39.84, 40.5, 44.1, 45.7, 49.3, 65.0, 67.0, 68.6, 69.3, 80.0, 82.0, 114.8, 115.5, 125.8, 128.5, 129.7, 130.0, 131.0, 134.4, 136.0, 137.7, 141.7, 143.1, 145.2, 167.5, and 207.8; HRMS(ESI) calcd for $C_{73}H_{128}O_8NaSi_5$ $(M+Na)^+$ 1295.8353, found *m/z* 1295.8352.

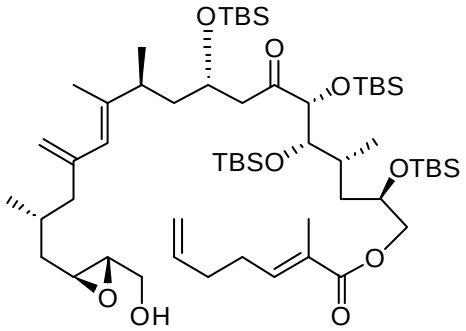
(*E*)-((2*R*,4*R*,5*S*,6*R*,9*S*,11*S*,12*E*,16*S*,18*E*)-2,5,6,9-tetrakis(*tert*-butyldimethylsilyloxy)-20-hydroxy-4,11,12,16-tetramethyl-14-methylene-7-oxoicosa-12,18-dienyl) 2-methylhepta-2,6-dienoate (S-20)



To a solution of **63** (0.119 g, 0.0933 mmol) in DMF (0.94 mL) was added a solution of TBAF (1.0M solution in THF, 46.7 μL, 0.047 mmol), AcOH (2.70 μL, 0.0470 mmol) and H_2O (4.20 μL 0.240 mmol) in THF (0.42 mL) at 0 °C; the mixture was stirred at room temperature for 5 h. The reaction was quenched by the addition of water at 0 °C, and the resulting slurry was extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:8) and gel permeation chromatography (JAIGEL-1H, $CHCl_3$, flow rate 3.5 mL/min, UV detection at 254 nm) to give **S-19** (79.5 mg, 82%) as a yellow oil, along with the recovered **63** (6.50 mg, 4.3%): $[\alpha]^{22}_D$ -26.6 (*c* 0.98, $CHCl_3$); IR (film) 3411, 2954, 2929, 2897, and 1715 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.12 (3H, s), 0.14 (3H, s), 0.16 (3H, s), 0.18 (3H, s), 0.19 (3H, s), 0.21 (3H, s), 0.23 (3H, s), 0.24 (3H, s), 0.92 (3H, d, *J* = 6.8 Hz), 1.01 (3H, d, *J* = 6.8 Hz), 1.035 (9H, s), 1.039 (9H, s), 1.047 (9H, s), 1.053 (9H, s), 1.18 (3H, d, *J* = 6.8 Hz), 1.55 (1H, ddd, *J* = 2.9, 11.2, 13.7 Hz), 1.68-1.89 (5H, m), 1.87 (3H, s), 1.88 (3H, s), 1.92 (1H, dd, *J* = 7.8, 13.2 Hz), 1.99-2.03 (4H, m), 2.10 (1H, ddd, *J* = 5.4, 5.4, 13.2 Hz), 2.18 (1H, dd, *J* = 5.9, 13.2 Hz),

2.36 (1H, m), 2.54 (1H, qt, *J* = 6.8, 6.8 Hz), 2.88 (1H, dd, *J* = 6.8, 18.0 Hz), 3.19 (1H, dd, *J* = 5.4, 18.0 Hz), 3.86 (1H, dd, *J* = 3.9, 3.9 Hz), 3.93 (2H, m), 4.07 (1H, m), 4.17 (1H, dd, *J* = 4.9, 11.2 Hz), 4.23 (1H, dd, *J* = 5.4, 11.2 Hz), 4.31 (1H, d, *J* = 4.4 Hz), 4.47 (1H, tt, *J* = 5.9, 5.9 Hz), 4.98 (1H, dd, *J* = 1.5, 10.2 Hz), 4.99 (1H, dd, *J* = 1.5, 17.1 Hz), 5.00 (1H, d, *J* = 2.0 Hz), 5.08 (1H, d, *J* = 2.0 Hz), 5.53-5.73 (3H, m), 5.83 (1H, s), and 6,96 (1H, td, *J* = 5.9, 1.5 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ -4.6, -4.5, -4.32, -4.27, -4.1, -4.0, -3.9, -3.6, 12.8, 14.6, 15.1, 18.3, 18.4, 18.5, 18.6, 19.4, 19.5, 26.21, 26.23, 26.25, 26.3, 28.3, 31.0, 32.1, 32.9, 39.9, 40.4, 44.0, 45.8, 49.1, 63.6, 66.9, 68.6, 69.3, 80.0, 81.9, 114.8, 115.5, 125.8, 128.5, 128.6, 130.4, 131.7, 137.7, 141.7, 143.1, 145.2, 167.6, and 208.0; HRMS (ESI) calcd for $C_{57}H_{111}O_8Si_4$ $(M+H)^+$ 1035.7356, found *m/z* 1035.7371.

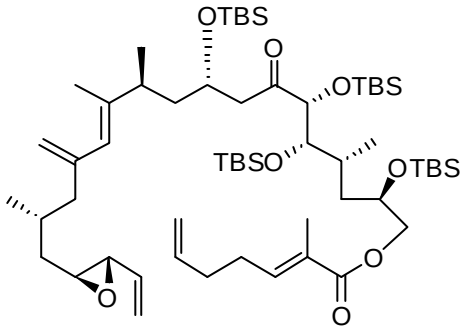
(*E*)-((2*R*,4*R*,5*S*,6*R*,9*S*,11*S*,16*R*,*E*)-2,5,6,9-tetrakis(*tert*-butyldimethylsilyloxy)-17-((2*S*,3*S*)-3-(hydroxymethyl)oxiran-2-yl)-4,11,12,16-tetramethyl-14-methylene-7-oxoheptadec-12-enyl) 2-methylhepta-2,6-dienoate (S-21)



To a solution of Ti(O*i*-Pr)$_4$ (25.0 mg, 0.088 mmol) and MS4A in dry CH_2Cl_2 (0.85 mL) was added a solution of (+)-DET (21.9 mg, 0.106 mmol) in dry CH_2Cl_2 (0.40 mL) at - 40 °C; the mixture was stirred at -30°C for 30 min, To the mixture was added TBHP (5.50 M solution in decane 0.241 mL, 1.32 mmol) and a solution of **S-19** (91.3 mg, 0.0880 mmol) in dry CH_2Cl_2 (1.2 mL) at the same temperature; the mixture was stirred at – 20 °C for 30 min. The reaction was quenched by the addition of saturated (+)-tartaric acid aq. at 0 °C, the resulting slurry was extracted with Et_2O three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:6) to give **S-20** (49.6 mg, 54%) as a colorless oil, along with the recovered **S-19** (25.7 mg, 28%): $[\alpha]^{22}_D$ -26.6 (*c* 0.98, $CHCl_3$); IR (film) 3411, 2954, 2929, 2897, and 1715 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.13 (3H, s), 0.14 (3H, s), 0.17 (3H, s), 0.187 (3H, s), 0.194 (3H, s), 0.21 (3H, s), 0.22 (3H, s), 0.25 (3H, s),), 0.91 (3H, d, *J* = 6.8 HZ), 1.01-1.03 (3H, m), 1.03 (9H, s), 1.04 (9H, s), 1.05 (9H, s), 1.06 (9H, s), 1.19 (3H, d, *J* = 6.8 Hz), 1.51-1.61 (2H, m), 1.68-1.89 (4H, m), 1.85 (3H, s), 1.88 (3H, s), 1.95 (1H, dd, *J* = 7.8, 13.2 Hz), 1.99-2.03 (4H, m), 2.14 (1H, dd, *J* = 6.3, 13.2 Hz), 2.36 (1H, m), 2.52-2.61 (2H, m), 2.83 (1H, td, 5.4, 2 Hz), 2.90 (1H, dd, *J* = 6.8, 17.6 Hz), 3.17 (1H, dd, *J* = 5.4, 17.6 Hz), 3.36 (1H, dd *J* = 2.9, 12.2 Hz), 3.55 (1H,

dd, *J* = 2.4, 12.2 Hz), 3.88 (1H, dd, *J* = 3.9, 3.9 Hz), 4.08 (1H, m), 4.18 (1H, dd, *J* = 4.9, 11.2 Hz), 4.29 (1H, dd, *J* = 5.9, 112 Hz), 4.33 (1H, d, *J* = 4.4 Hz), 4.47 (1H, tt, *J* = 5.9, 5.9 Hz), 4.98 (1H, d, *J* = 2 Hz), 4.95-5.03 (2H, m), 5.00 (1H, d, *J* = 2 Hz), 5.67 (1H, tdd, *J* = 6.3, 10.2, 17.1 Hz), 5.81 (1H, s), and 6.96 (1H, td, *J* = 5.9, 1.5 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ -4.6, -4.5, -4.3, -4.2, -4.1, -4.0, -3.97, -3.7, 12.8, 14.6, 15.1, 18.3, 18.4, 18.6, 18.6, 19.4, 19.7, 26.2, 26.3, 28.3, 30.0, 31.1, 32.9, 39.0, 39.9, 40.4, 43.9, 46.4, 48.9, 54.4, 58.9, 62.0, 67.0, 68.6, 69.3, 79.8, 81.9, 115.0, 115.5, 125.6, 128.5, 128.6, 137.7, 141.8, 143.3, 144.8, 167.6, and 208.0; HRMS (ESI) calcd for $C_{57}H_{110}O_9NaSi_4$ $(M+Na)^+$ 1073.7125, found *m/z* 1073.7115.

(*E*)-((2*R*,4*R*,5*S*,6*R*,9*S*,11*S*,16*R*,*E*)-2,5,6,9-tetrakis(*tert*-butyldimethylsilyloxy)-4,11,12,16-tetramethyl-14-methylene-7-oxo-17-((2*S*,3*S*)-3-vinyloxiran-2-yl)heptadec-12-enyl) 2-methylhepta-2,6-dienoate (64)

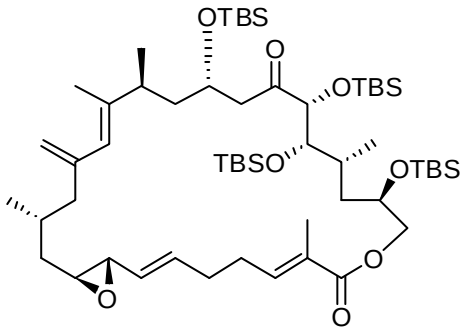


To a solution of **S-20** (7.70 mg, 7.32 μmol) in CH_2Cl_2 (0.55 mL) was added pyridine (30 μL, 0.37 mmol) at 0 °C and Dess-Martin periodinane (15 wt. % solution in CH_2Cl_2, 0.23 mL, 0.110 mmol) at 0 °C; the mixture was stirred at the same temperature for 4 h. The reaction was quenched by the addition of 2-propanol (2.5 mL) at 0 °C; the mixure was stirred at room temperature for 1 h. The crude product was purified by Florisil chromatography (EtOAc:hexane, 1:8) to give an aldehyde (7.00 mg, 91%) as a colorless oil.

To a solution of Ph_3PCH_3Br (95.4 mg, 0.267 mmol) in dry THF (0.80 mL) was added NaHMDS (1.0M solution in THF, 0.20 mL, 0.20 mmol) at 0 °C; the mixture was stirred at 0 °C for 1 h. To the mixture was added a solution of the aldehyde (3.50 mg, 3.33 μmol) in dry THF (1.6 mL) at 0 °C; the mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of saturated NH_4Cl aq. at 0 °C, and the resulting slurry was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (EtOAc:hexane, 1:15) to give **64** (2.80 mg, 80%) as a colorless oil: $[\alpha]^{22}_D$ -23.6 (*c* 0.96, $CHCl_3$); IR (film) 2954, 2928, 2856, and 1714 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.13 (3H, s), 0.15 (3H, s), 0.17 (3H, s), 0.19 (3H, s), 0.20 (3H, s), 0.21 (3H, s), 0.23 (3H, s), 0.26 (3H, s), 0.92 (3H, d, *J* = 6.8 Hz), 1.02 (3H, d, *J* = 6.8 Hz), 1.04 (9H, s), 1.05 (9H, s), 1.062 (9H, s), 1.064 (9H, s), 1.19 (3H, d, *J* = 6.8 Hz), 1.52-1.64 (2H, m), 1.69-1.89 (4H, m), 1.86 (3H, s), 1.89 (3H, s), 1.96 (1H, dd,

J = 7.8, 13.2 Hz), 1.94-2.04 (4H, m), 2.14 (1H, dd, *J* = 6.3, 13.2 Hz), 2.37 (1H, m), 2.57 (1H, qt, *J* = 6.8, 6.8 Hz), 2.75 (1H, td, *J* = 5.9, 2.0 Hz), 2.91 (1H, dd, *J* = 6.8, 17.6 Hz), 2.93 (1H, dd, *J* = 2.0, 7.3 Hz), 3.17 (1H, dd, *J* = 4.8, 17.6 Hz), 3.89 (1H, dd, *J* = 3.9, 3.9 Hz), 4.08 (1H, m), 4.18 (1H, dd, *J* = 4.9, 11.2 Hz), 4.30 (1H, dd, *J* = 5.4, 11.2 Hz), 4.34 (1H, d, *J* = 4.4 Hz), 4.46 (1H, tt, *J* = 5.9, 5.9 Hz), 4.96-5.06 (4H, m), 5.06 (1H, dd, *J* = 1.5, 10.2 Hz), 5.32 (1H, dd, *J* = 1.5, 17.1 Hz), 5.55 (1H, ddd, *J* = 7.3, 10.2, 17.1 Hz), 5.68 (1H, tdd, *J* = 6.3, 10.2, 17.1 Hz) 5.81 (1H, s), and 6,97 (1H, td, *J* = 5.9, 1.4 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ -4.6, -4.5, -4.3, -4.2, -4.1, -4.0, -3.9, -3.7, 12.8, 14.7, 15.1, 18.3, 18.4, 18.55, 18.64, 19.4, 19.7, 26.2, 26.26, 26.34, 28.3, 30.0, 31.2, 32.9, 39.4, 39.9, 40.4, 43.9, 46.4, 48.9, 59.0, 59.1, 67.1, 68.6, 69.3, 79.8, 82.0, 115.0, 115.5, 118.0, 125.6, 128.6, 136.9, 137.7, 141.7, 143.3, 144.8, 167.5, and 207.9; HRMS (ESI) calcd for $C_{58}H_{110}O_8NaSi_4$ $(M+Na)^+$ 1069.7176, found *m/z* 1069.7192.

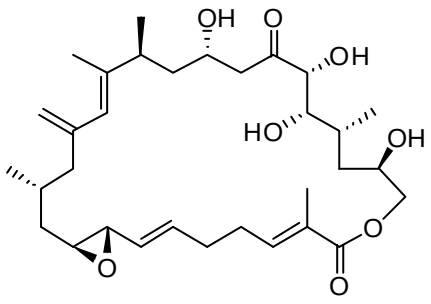
(1*S*,2*E*,6*E*,11*R*,13*R*,14*S*,15*R*,18*S*,20*S*,21*E*,25*R*,27*S*)-11,14,15,18-tetrakis(*tert*-butyldimethylsilyloxy)-7,13,20,21,25-pentamethyl-23-methylene-9,28-dioxabicyclo[25.1.0]octacosa-2,6,21-triene-8,16-dione (65)



To a solution of **64** (8.30 mg, 7.92 μmol) in benzene (8.3 mL) was added Grubbs 2nd catalyst (0.670 mg, 0.790 μmol) at room temperature; the mixture was stirred at the same temperature for 3 h. The reaction was quenched by the addition of DMSO (45.0 μL, 0.63 mmol); the mixture was stirred overnight. The crude solution was purified by Florisil chromatography (EtOAc:hexane, 1:15) to give **65** (7.70 mg, 95%) as a colorless oil: $[\alpha]^{22}_D$ -19.1 (*c* 0.82, $CHCl_3$); IR (film) 2955, 2929, 2856, and 1715 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.14 (3H, s), 0.15 (3H, s), 0.17 (3H, s), 0.19 (3H, s), 0.206 (3H, s), 0.209 (3H, s), 0.22 (3H, s), 0.24 (3H, s), 0.97 (3H, d, *J* = 6.5 Hz), 1.025 (9H, s), 1.026 (9H, s), 1.069 (9H, s), 1.072 (9H, s), 1.11 (3H, d, *J* = 5.4 Hz), 1.13 (3H, d, *J* = 5.6 Hz), 1.22 (1H, ddd, *J* = 5.1, 9.0, 13.7 Hz), 1.57 (1H, ddd, *J* = 4.7, 6.5, 13.7 Hz), 1.62-1.77 (2H, m), 1.78-1.85 (2H, m), 1.83 (3H, d, *J* = 1.1 Hz), 1.87 (3H, d, *J* = 1.1 Hz), 1.95 (1H, dd, *J* = 8.8, 13.2 Hz), 1.95-2.00 (4H, m), 2.14 (1H, dd, *J* = 5.8, 13.0 Hz), 2.46 (1H, m), 2.55 (1H, qt, *J* = 7.0, 7.0 Hz), 2.81 (1H, ddd, *J* = 1.8, 5.2, 6.5 Hz), 2.97 (1H, dd, *J* = 1.8, 7.9 Hz), 2.98 (1H, dd, *J* = 5.4, 17.3 Hz), 3.11 (1H, dd, *J* = 5.6, 17.3 Hz), 3.89 (1H, dd, *J* = 3.8, 3.8 Hz), 4.14 (1H, m), 4.32 (1H, m), 4.34 (1H, d, *J* = 4.3 Hz), 4.36 (1H, dd, *J* = 4.5, 10.5 Hz), 4.96 (1H, d, *J* = 2.2 Hz), 5.04 (1H, d, *J* = 2.2 Hz), 5.68 (1H, td, *J* = 5.8, 15.5 Hz) 5.78 (1H, s), and 6,89 (1H, m); ^{13}C NMR (100 MHz, C_6D_6) δ -4.5, -4.22,

-4.16, -4.14, -4.08, -4.0, -3.9, -3.5, 12.9, 14.5, 15.0, 18.4, 18.6, 18.7, 19.6, 20.0, 26.3, 27.1, 29.9, 30.7, 30.9, 39.8, 40.3, 41.6, 42.6, 46.3, 47.0, 58.8, 59.3, 67.6, 68.7, 69.1, 79.7, 81.6, 115.2, 125.7, 128.6, 130.3, 133.5, 140.9, 142.5, 144.6, 167.2, and 208.6; HRMS (ESI) calcd for $C_{56}H_{106}O_8NaSi_4$ $(M+Na)^+$ 1041.6863, found *m/z* 1041.6881.

Amphidinolide G (2)



To a solution of **65** (2.0 mg, 2.0 μmol) in dry THF (0.40 mL) was added a solution of TASF (16.2 mg, 0.0589 mmol) in dry DMF (0.15 mL) and H_2O (3.0 μl) at 0 °C; the mixture was stirred at room temperature for 2 h. The crude product was purified by Florisil chromatography (EtOAc:hexane, 8:1) to give **2** (0.80 mg, 72%) as a white solid: $[\alpha]^{22}_D$ -57.1 (*c* 0.082, $CHCl_3$); IR (film) 3433, 3359, 2924, 1705, 1472, 1262, and 1118 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, *J* = 6.5 Hz), 1.06 (3H, d, *J* = 6.7 Hz), 1.11 (3H, d, *J* = 6.7 Hz), 1.19 (1H, ddd, *J* = 3.1, 8.5, 13.7 Hz), 1.40 (1H, ddd, *J* = 2.2, 5.5, 14.1 Hz), 1.43 (1H, m), 1.48 (1H, m), 1.63 (1H, m), 1.74 (3H, d, *J* = 1.1 Hz), 1.83 (1H, m), 1.84 (3H, d, *J* = 1.1 Hz,), 1.88 (1H, m), 2.04 (1H, m), 2.11 (1H, m), 2.15-2.43 (6H, m), 2.68 (1H, d, *J* = 5.2 Hz), 2.68 (1H, d, *J* = 6.7 Hz), 2.94 (1H, ddd, *J* = 2.2, 2.2, 8.5 Hz), 3.05 (1H, dd, *J* = 2.2, 8.5 Hz), 3.11 (1H, d, *J* = 2.5 Hz), 3.44 (1H, d, *J* = 7.9 Hz), 3.91 (1H, m), 3.94 (1H, m), 3.97 (1H, m), 4.14 (1H, dd, *J* = 3.1, 11.4 Hz), 4.23 (1H, dd, *J* = 3.4, 11.4 Hz), 4.30 (1H, d, *J* = 3.6 Hz), 4.32 (1H, d, *J* = 11.4 Hz), 4.35 (1H, dd, *J* = 1.8, 3.6 Hz), 4.82 (1H, s), 4.99 (1H, s), 5.20 (1H, dd, *J* = 8.5, 15.5 Hz), 5.52 (1H, s), 5.84 (1H, ddd, *J* = 4,7, 8.8, 15.5 Hz), and 6.71 (1H, td, *J* = 6.3, 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 12.8, 18.0, 18.2, 20.6, 27.1, 29.3, 31.0, 36.3, 37.0, 39.9, 40.4, 40.8, 44.1, 46.8, 59.3, 59.8, 66.6, 68.7, 69.1, 74.3, 77.8, 114.9, 125.8, 128.2, 128.8, 135.8, 141.1, 141.7, 143.9, 167.8, and 211.5; HRMS(ESI) calcd for $C_{32}H_{50}O_8Na$ $(M+Na)^+$ 585.3403, found *m/z* 585.3414.

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