高立体選択的Diels-Alder反応による
生物活性多環式天然物の不斉全合成研究

Research on Enantioselective Total Synthesis of Bioactive Polycyclic Natural Products via Highly Stereoselective Diels-Alder Reaction

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早稲田大学大学院 先進理工学研究科
化学・生命化学専攻　化学合成法研究

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略語表

Ac	:	acetyl
AIBN	:	2,2'-azobisisobutyronitrile
atm	:	atmosphere
BHT	:	3,5-di-*t*-butyl-4-hydroxytoluene
BMDA	:	bimolecular Diels-Alder
Bn	:	benzyl
Bu	:	butyl
cat.	:	catalytic amount
CBS	:	Corey-Bakshi-Shibata
conv	:	conversion
Cp	:	cyclopentadienyl
Cy	:	cyclohexyl
dba	:	dibenzylideneacetone
dr	:	diastereomeric ratio
DBU	:	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	:	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DEAD	:	diethyl azodicarboxylate
DIAD	:	diisopropyl azodicarboxylate
DIBAL	:	diisobutylaluminum hydride
DIPEA	:	diisopropylethylamine
DMAP	:	4-*N*,*N*-dimethylaminopyridine
DMF	:	*N*,*N*-dimethylformamide
DMP	:	Dess-Martin periodinane
DMSO	:	dimethyl sulfoxide
dppe	:	1,1-bis(diphenylphosphino)ethene
ee	:	enantiomeric excess
Et	:	ethyl
equiv	:	equivalent
FAB	:	fast atom bombardment
HOMO	:	highest occupied molecular orbital
HSPT	:	1-phenyl-1*H*-tetrazole-5-thiol
IMDA	:	intramolecular Diels-Alder
IR	:	infrared spectroscopy
KHMDS	:	potassium bis(trimathylsilyl)amide
KPB	:	potassium phosphate buffer

LDA	:	lithium diisopropylamide
LUMO	:	lowest unoccupied molecular orbital
Me	:	methyl
MOM	:	metoxymethyl
mp	:	melting point
MPM	:	*p*-methoxyphenylmethyl
Ms	:	mesyl
MS	:	molecular sieves
NMR	:	nuclear magnetic resonance
NOE	:	nuclear Overhauser effect
NOESY	:	nuclear Overhauser enhancement spectroscopy
N.R.	:	no reaction
PDC	:	pyridinium dichromate
Ph	:	phenyl
Piv	:	pivaloyl
PPTS	:	pyridinium *p*-toluenesulfonate
PT	:	phenyl tetrazole
quant	:	quantitative
Red-Al	:	sodium bis(2-methoxyethoxy) aluminium hydride
Rf	:	retention factor
rt	:	room temperature
TADA	:	transannular Diels-Alder
TBAF	:	tetrabutylammonium fluoride
TBAI	:	tetrabutylammonium iodide
TBS	:	*t*-butyldimethylsilyl
TEA	:	triethylamine
temp	:	temperature
Tf	:	trifluoromethanesulfonyl
TFA	:	trifluoroacetic acid
THF	:	tetrahydrofuran
TIPS	:	triisopropylsilyl
TMS	:	trimethylsilyl
V-70	:	2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile)

目次

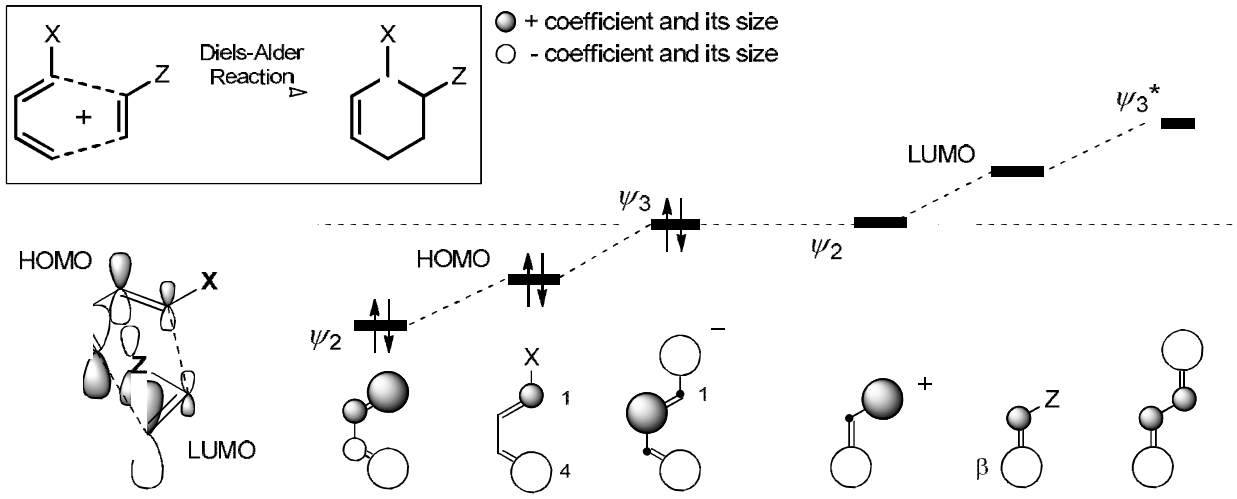
第 1 章　緒論

これまでの創薬においては低分子医薬品の開発が盛んであった。しかし、近年においては医療機関、製薬会社、ベンチャーが抗体医薬、タンパク質間相互作用、遺伝子治療といった領域での医薬品開発に注力してきている。これは低分子医薬品の創製に限界があることが原因として挙げられる。しかしながら抗体医薬、タンパク質間相互作用、遺伝子治療は技術面、コスト面の問題点が多いため、まだ発展途上の段階である。一方、低分子医薬品は合成の簡便さ、コスト面での優位性から開発が比較的容易であるので、今でも限られた創薬範囲の中で、世界中で研究開発が行われている。その戦略の一つとして生物活性を有する天然物からの創薬が挙げられる。近年、創薬における成功確率は安全性、副作用の観点から非常に低くなってきているが、その中で天然物のように複雑な構造をしている化合物、言い換えると sp^3 炭素を構造中に多く含む化合物は毒性が低く医薬品となる確率が高いというデータが示されている。過去にもタキソール、ペニシリン、キニーネ、モルヒネ等、天然物から医薬品となった化合物は多く、また天然物をヒントとした化合物が医薬品となっている例も多い。数多くある疾患の中でがんは未だに安全性の高い新規医薬品が求められている。がん細胞の増殖阻害活性を有する天然物およびその誘導体は抗がん剤となる可能性を秘めているので、その活性を有する天然物、(+)-bucidarasin および(-)-bruceantin の不斉全合成とその後の合成化学的展開により新規抗がん剤を見出すことを最大の目的とした。

(+)-bucidarasin および(-)-bruceantin は不斉中心を含む 6 員炭素環が縮環した骨格をもつため、合成する上で如何に効率良くその 6 員炭素環を構築するかが鍵となる。そこで 6 員環形成に広く活用されている Diels-Alder 反応による標的化合物の不斉全合成を計画した。以下に Diels-Alder 反応の起源と理論について述べる。

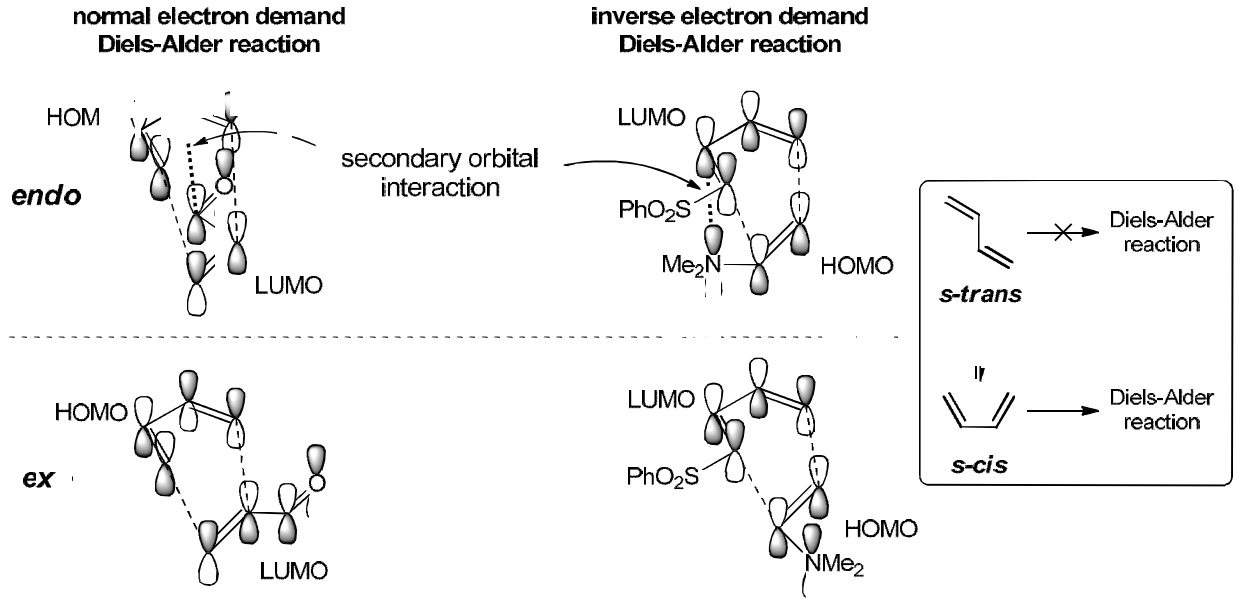
Diels-Alder 反応[1]は、1928 年に Otto Diels と Karl Alder によって発見された 6 員環形成反応である。Diels-Alder 反応は有機化学において基盤となる反応の一つとなっており、現在まで広く研究されている。Woodward-Hoffman 則、フロンティア軌道理論により Diels-Alder 反応の反応機構が合理的に説明され、その後光学活性化合物を与える Diels-Alder 反応の研究が発展した。Diels-Alder 反応を使って光学活性化合物を得ることに注目が集る理由は、反応が簡便でありさらに 4 つまでの新しいキラル中心を作り出すことができるからである。Diels-Alder 反応は、ジエンとジエノフィルによって分子間および分子内で行われる(Figure 1-1)。一般的にはジエンに電子供与基(X:メチル基、アルコキシ基、アミノ基など)が置換した電子豊富なジエンと、ジエノフィルに電子求引基(Z:カルボニル基、シアノ基、ニトロ基、スルホニル基など)が置換した電子不足なジエノフィルが用いられ、フロンティア軌道理論に基づいて考えるとジエンの HOMO(最高被占軌道)とジエノフィルの LUMO(最低空軌道)がエネルギー的に近接し、それらの相互作用によっ

て遷移状態のエネルギーが低下し反応が進行する。このことを考えるとジエンの HOMO、ジエノフィルの LUMO との反応(電子要請型:normal electron demand)だけでなく、ジエンの LUMO、ジエノフィルの HOMO との反応(逆電子要請型:inverse electron demand)も進行することになる。



[1] **Figure 1-1.** sition of Atomic Orbital Coefficients by Substituents of Diene and Dienophile

ジエンは *s-cis* 配座で反応が進行し、遷移状態では軌道間の二次的相互作用(secondary orbital interaction)によってエネルギー的に低下した *endo* 型が優先し反応が進行する(Figure 1-2)。しかしながら必ずしも *endo* 型の遷移状態を経るわけではなく、立体的な環境により *exo* 型が優先されることもある。



[1] **Figure 1-2.** Transit tates of Normal and Inverse Electron D .. nd Diels-Alder Reactions

Diels-Alder 反応の種類として分子間(BMDA)反応、分子内(IMDA)反応[2]、渡環(TADA)反応[3]と多様性があり、その反応機構は電子的および立体的要因により説明できるため、反応の立体選択性が予測しやすい事が特徴として挙げられる

(Figure 1-3)。以下にそれぞれの特徴を挙げる。

分子間 Diels-Alder(BMDA)反応:2 分子の間で反応が行われるためエントロピー変化は負の値を持つ。そのため反応時の活性化エネルギーは増大し、激しい反応条件が求められる。また 2 分子間での反応であるため反応を選択的に行うにはより綿密な分子設計が求められる。しかしながら全合成研究においてはより短工程で収束的な合成経路を計画できる利点がある。

分子内 Diels-Alder(IMDA)反応:1 分子で反応が行われるためエントロピー変化は小さい。従って反応時の活性化エネルギーは小さく、比較的温和な反応条件で済む。

渡環 Diels-Alder(TADA)反応:IMDA 反応の中でも反応点が初めから接近しているためエントロピー変化は極めて小さく、温和な条件でも速く反応が進行する。また、環の立体配座を考えると立体選択的な環構築を設計できる。しかしながら合成においては大員環合成の問題および TADA 反応後の開環反応といった工程が増える欠点がある。

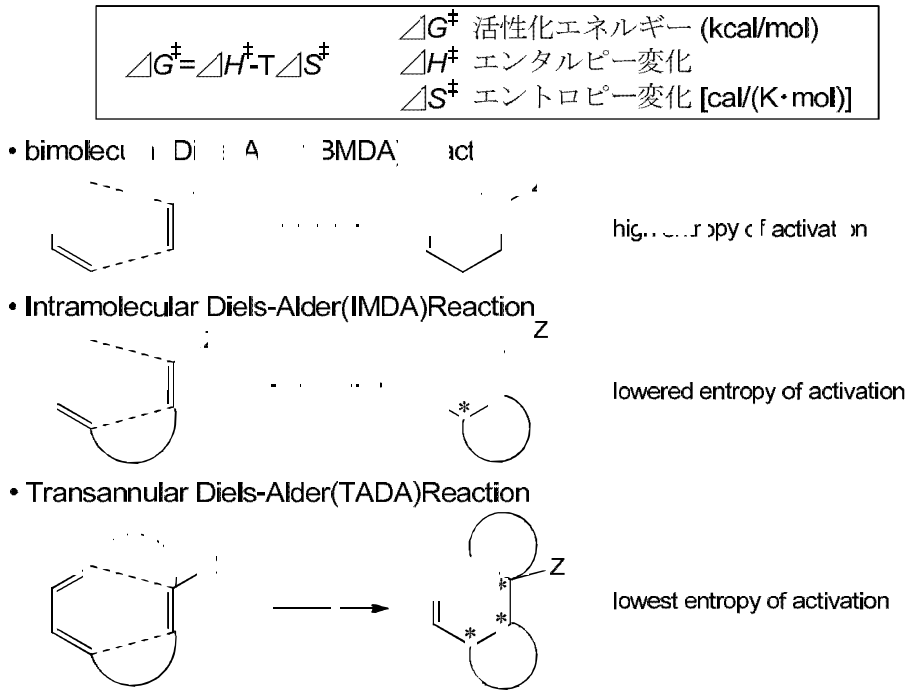
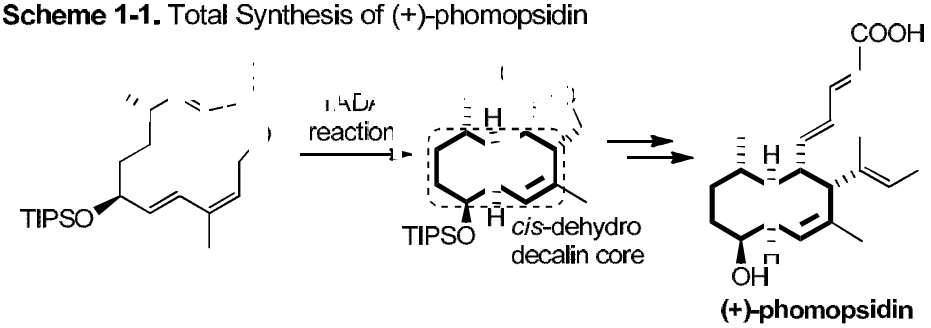


Figure 1-3. Three Types of Diels-Alder Reactions

以上 Diels-Alder 反応の種類と特徴を挙げたが、それぞれに長所と短所があり反応自体に優劣はない。全合成研究を行う上で合成する化合物が有する骨格や骨格上の不斉点および置換基を考慮し、Diels-Alder 反応の種類を選択しなければならない。

当研究室で Diels-Alder 反応を適用し天然物の全合成を達成している[4]ので Scheme 1-1 に示す。

Scheme 1-1. Total Synthesis of (+)-phomopsidin

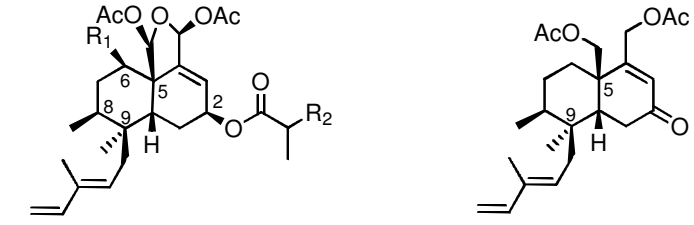


強い微小管重合阻害活性を持つ(+)-phomopsidin は、中心骨格である *cis*-デヒドロデカリン骨格に 6 つの不斉中心を有している。そこで、13 員環マクロラクトンからの TADA 反応によるジアステレオ選択的な *cis*-デヒドロデカリン骨格形成を行なった。そして、続く側鎖部位の導入により、世界初の不斉全合成を達成している。ここで得た知見を活かし、高立体選択的 Diels-Alder 反応による骨格構築を鍵工程とする(+)-bucidarasin A,C および(-)-bruceantin の不斉全合成研究に着手した。

第2章　(-)-bucidarasin Aの不斉全合成

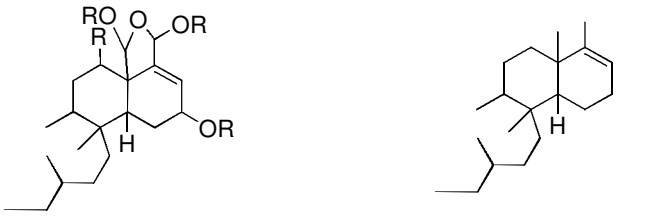
第1節　序論

(+)-bucidarasin A-Dは2002年に*bucida buceras*から単離、構造決定[5]されたclerodane型ジテルペン(Figure 2-1-1)であり、(+)-bucidarasin A-Cはヒト腫瘍細胞に加え、薬剤耐性腫瘍細胞に対しても殺細胞活性を示すことが知られている(KB, A549, IA9, CAKI, HCT-8, MCF-7, HOS, U87-MG, SK-MEL-2等のヒト腫瘍細胞に対してIC_{50}:0.5~1.9 μM)。一方、(+)-bucidarasin Dのみ活性を示さいなことから、(+)-bucidarasin A-Cに共通するビスアセタール構造が生物活性発現に重要な役割を果たしていることが強く示唆されている。構造的特徴としては(+)-bucidarasin A-Cは*cis*-デヒドロデカリンを中心骨格とし、2つの全炭素四級不斉中心(C5, C9位)を含む4連続不斉中心に加え、最大で6つの不斉中心を中心骨格上に有している。その中心骨格には、高度に酸化されたテトラヒドロフラン(THF)環がさらに縮環しており、C9位にはメチル基と(*E*)-3-メチル-2,4-ペンタジエニル基が結合している。



bucidarasin A : R_1 = OH, R_2 = Me
bucidarasin B : R_1 = OH, R_2 = Et
bucidarasin C : R_1 = H, R_2 = Me

bucidarasin D



tricyclic clerodane diterpenes

clerodane diterpenes

Figure 2-1-1. Structures of Bucidarasins A-D, Clerodane and Tricyclic Clerodane Diterpenes

THF環を含む三環式構造をもつ(+)-bucidarasin A-Cに類似のclerodane型ジテルペンは数多く報告されている。その一部をFigure 2-1-2に示すが、未だに全合成の報告例はない。この三環式clerodane型ジテルペンは、新たな抗がん剤のリード化合物となり得る生物活性と複雑な構造を併せ持つため、その初の不斉全合成達成は構造活性相関研究に向けた新規化合物の供給、有機合成化学の発展といった観点から有意義である。また、X線結晶構造解析によって絶対立体配置を決定して

いる化合物はFigure 2-1-2に示す(+)-casearborin Eと(+)-casearin Bの2つしかなく、bucidarasinを含め、数多く存在する三環式clerodane型ジテルペン構造を有する天然物のほとんどが2次元NMRによる相対立体配置のみの決定であり、絶対配置がわかっていない。そこで本研究では、構造活性相関研究に向けたbucidarasin類および類縁体の包括的合成を最終目標とし、最初に(+)-bucidarasin Aの世界初の不斉全合成達成と絶対配置の決定を目的として研究に着手した。

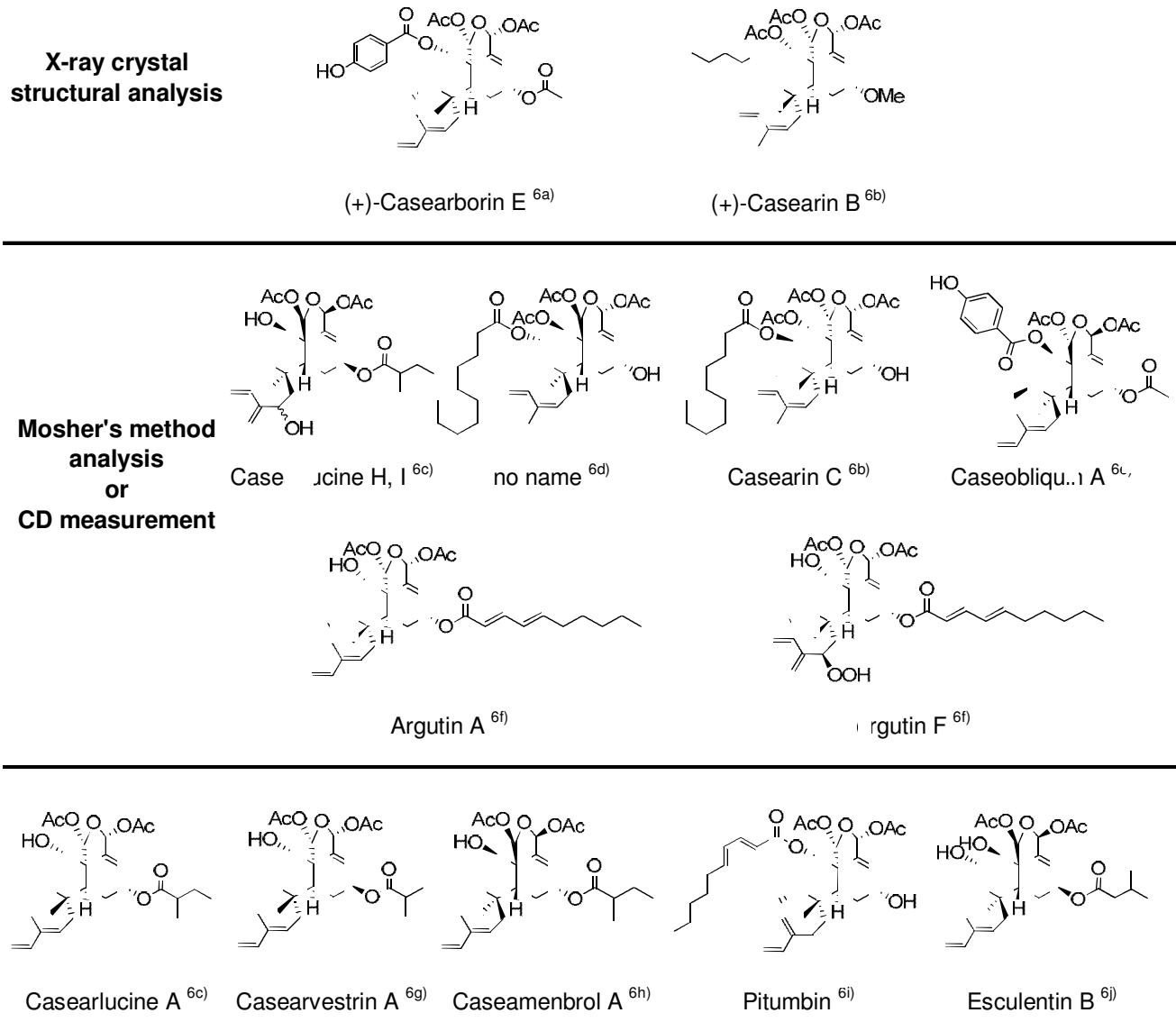
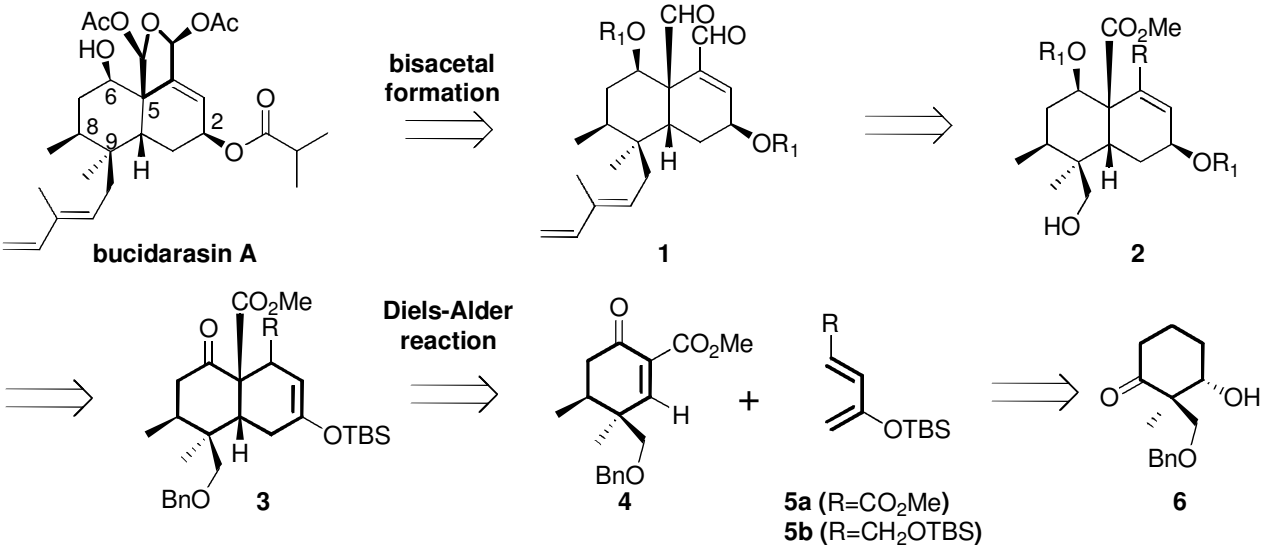


Figure 2-1-2. Tricyclic Clerodane Diterpenes

第2節　合成計画

bucidarasin Aの合成計画をScheme 2-2-1に示す。bucidarasin Aが有するビスアセトキシTHF環は化学的に不安定と考えられるため合成の後半でジアルデヒド**1**から構築、C9位側鎖の(*E*)-3-メチル-2,4-ペンタジエニル側鎖は**2**のヒドロキシメチル基から合成できると考えた。中心骨格である*cis*-デヒドロデカリン骨格はジエノフィル**4**とジエン**5**のBMDA反応により構築できるものとした。この鍵工程では**3**の立体選択的生成が問題である。全炭素四級不斉中心を構築するためにジエノフィル**4**は反応性を高めたα-アルキリデンβ-ケトエステルを設計した。そのジエノフィル**4**は当研究室で開発されたキラルビルディングブロック**6**から合成可能であると考えた。

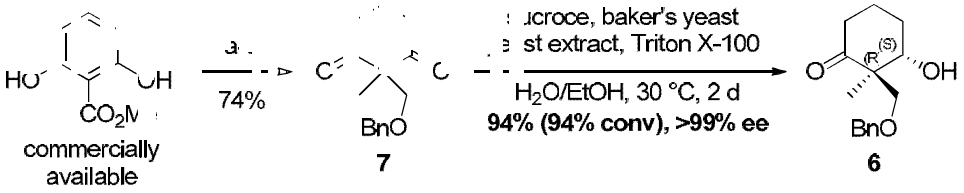
Scheme 2-2-1. Retrosynthetic Analysis toward Total Synthesis of Bucidarasin A



第3節　分子間Diels-Alder反応を用いた中心骨格の合成

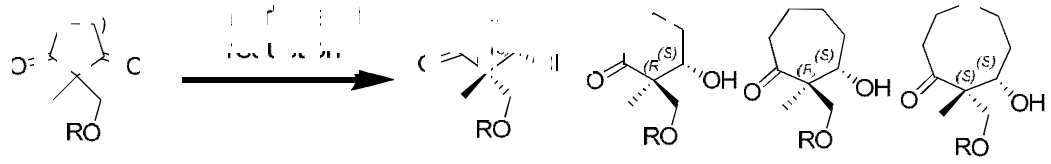
baker's yeastを用いたキラルビルディングブロックの合成法をScheme 2-3-1に示す。当研究室でプロキラルな5~8員シクロアルカンジオンのbaker's yeast還元を行うことで高収率かつ高立体選択的に四級不斉中心の構築に成功している[7]。baker's yeast を用いた還元では一般にPrelog 則[8]に従って、生じる光学活性なアルコールが*S* 配置を与えるような還元体が得られることが知られている。この合成法はスケールアップが可能であり、メチル2,6-ジヒドロキシベンゾエートを出発原料とし5工程で得られるプロキラルなシクロヘキサンジオン**7**を10gのスケールでも高収率かつ高立体選択的に合成することができる。

Scheme 2-3-1. Preparation of Chiral Building Block **6**



Reagents and conditions
(a) $BF_3{\cdot}OEt_2$, MeOH, 3 d, 93%; (b) Na, *t*-BuOH, liq.NH_3, -78 °C, 20 min; MeI, 91%; (c) $LiAlH_4$, Et_2O, 0 °C, 30 min, 96%; (d) BnBr, NaH, TBAI, THF/DMF, 10 h, 92%; (e) 2*M*-HCl/THF, rt, 30 min, 95%.

Table 2-3-1. Baker's Yeast Reduction of Prochiral Diketones

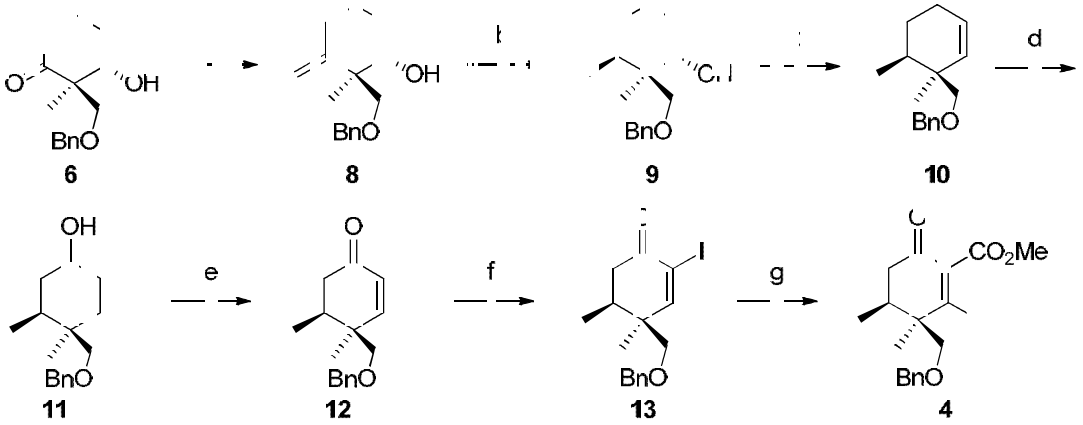


entry	substrate	yield (%)	ee (%)
1	n = 1, R = Bn	90 (85% conv)	>99
[redacted]			
3	n = 3, R = Bn	91	>99
4	n = 3, R = Piv	95	>99
5	n = 4, R = Piv	93 (86% conv)	>99

このようにして得られたキラルビルディングブロック**6**を用いて合成を進めることとした。Wittig反応はレトロアルドール反応を防ぐために低温で行った。次のCrabtree触媒を用いた水素添加反応[9]は、水酸基のdirecting effect により高立体選択的にC8位に当たる不斉炭素を構築できた。続く脱水反応は当初、水酸基をメシル体へと変換後、crudeで塩基性条件下、脱水反応を行なったが(Table 2-3-2, entry 1)、反応時間が長く原料が消失しないこと、また収率が安定しないことから他の条件での検討を行うこととした。脱離能の高いトリフラートで反応を行なったところ低温で反応が進行し目的物が得られたが、トリフラート体が不安定であるた

めか副生成物も複数確認され収率は中程度であった。Entry 3に示すオキシ塩化リンを用いたところ、原料は消失し副生成物の確認も見られなかったが、収率は50%程度であった。これは中間体で反応が停止し、後処理で目的物が得られているためと判断し、entry 4に示すように加熱したところ、高収率で再現良く目的物を得ることができた。二酸化セレンによるアリル位の酸化は検討の結果、ギ酸を用いた反応条件[10]が最も良いことがわかった。水酸基をPDC酸化することでエノン**12**を得、ケトンのα位をヨウ素化し、Pdを用いた一酸化炭素挿入反応によりDA反応前駆体であるジエノフィル**4**を合成した。

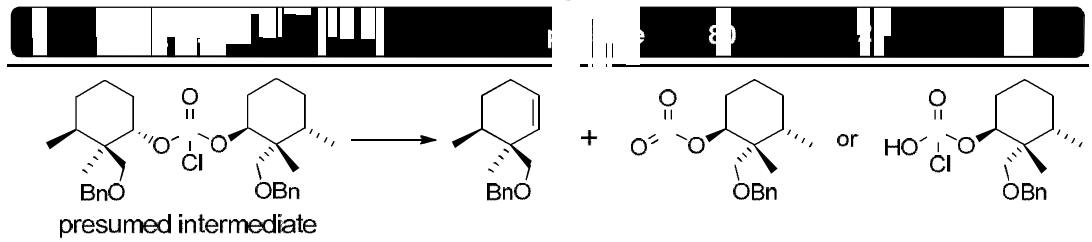
Scheme 2-3-2. Synthesis of the Dienophile of the Diels-Alder Reaction



Reagents and conditions
(a) PPh_3CH_3Br, *n*-BuLi, -30 ºC, 18 h, 91% (90% conv); (b) H_2, Crabtree's reagent, $(CH_2Cl)_2$, 80 ºC, 14 h, 92%; (c) $POCl_3$, pyridine, 80 ºC, 21 h, 98%; (d) SeO_2, dioxane/HCOOH, 80 ºC, 3 d; then NH_4OH, 65%; (e) PDC, MS4Å, CH_2Cl_2, rt, 3 h, 86%; (f) I_2, DMAP, CCl_4/pyridine, 50 ºC, 1 d, 98%; (g) CO, $Pd(PPh_3)_4$, TEA, THF/MeOH, 55 ºC, 8 h, 98%.

Table 2-3-2. Dehydration of **9**

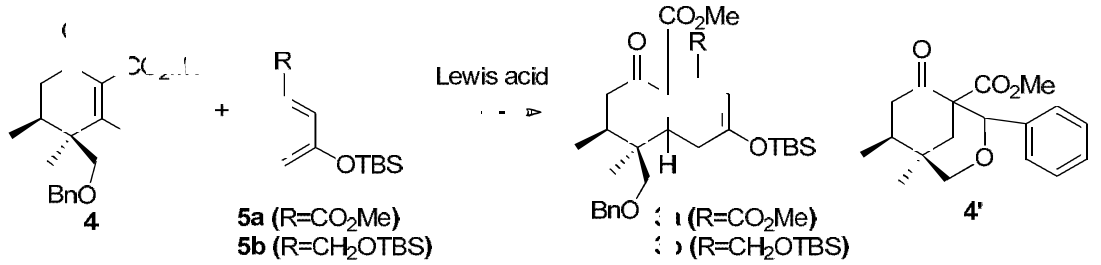
		solvent	temp (°C)	time (h)	yield (%)
1	[illegible]	THF	rt	0.5	
	2) DBU (3.0)	toluene	reflux	72	77-96
2	Tf_2O (1.5), pyridine (10.0)	CH_2Cl_2	0	1.5	65
3	$POCl_3$ (3.5)	pyridine	rt	11	52



鍵反応である**4**を用いたBMDA反応では、生成物が後の工程で変換しやすくなるように、まずエステル基を有するジエン**5a**[11]を検討した。Table 2-3-3, entry 1,2に示す条件では加熱しても目的物は得られず、**4**に存在するベンジル位水素原子が1,5-ヒドリドシフトし、環化した化合物**4'**を主生成物として得る結果となった。低温での反応が求められたのでジエンのHOMOのエネルギー準位がより高い**5b**[11]

を用いることとした。Entry 3~8に示すように種々のLewis酸を検討したところ、$SnCl_4$、-60℃という条件で中程度ではあるが反応が進行することが分かった。

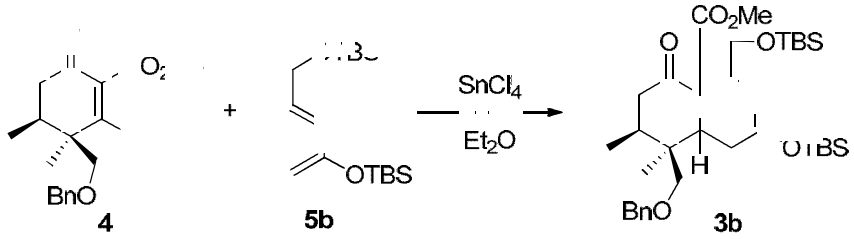
Table 2-3-3. BMDA Reaction of **4** with **5**



entry	Lewis acid (equiv)	diene (equiv)	solvent	temp (°C)	time (h)	yieid (%)
1	$ZnCl_2$ (1.5)	**5a** (1.5)	toluene	60	10	**4'** 73
2	$SnCl_2$ (1.5)	**5a** (1.5)	toluene	50	24	**4'** 40
3	$ZnCl_2$ (1.0)	**5b** (2.0)	THF	rt	24	N.R.
4	BF_3·Et_2O (1.0)	**5b** (3.0)	Et_2O	rt	24	N.R.
5	$TiCl_4$ (1.0)	**5b** (5.0)	Et_2O	-50	24	N.R.
6	$EtAlCl_2$ (1.0)	**5b** (5.6)	Et_2O	-40	48	**3b** 14 (77% conv)
7	$FeCl_3$ (1.0)	**5b** (8.6)	Et_2O	-40	48	**3b** 64 (29% conv)
[redacted]						

次に$SnCl_4$を用いたBMDA反応の最適化を行うこととした(Table 2-3-4)。0℃で反応を行うと速やかに進行するものの、その立体選択性は3/2と低いものであった。-60℃で反応を行うと中程度の変換率ではあるが立体選択性は9/1と良好な選択性で目的物を得た。この条件でスケールを上げて反応を行なった所、収率の再現が取れず反応を繰り返し行わないとentry 2と同程度の収率にはならなかった。これは$SnCl_4$ がEt_2Oと反応してしまいLewis酸として機能しなくなっていることが原因と考えられる。そこで最適化を行った結果、entry 4に示すように反応溶液の濃度を上げることで$SnCl_4$ を0.1 等量に制限しても反応は再現性良く進行し目的物を得ることができた。ここで得られた2つのジアステレオマー混合物は分離困難であったため次の工程で分離することとした。

Table 2-3-4. Optimization of the BMDA Reaction of **4** with **5b**



4 **5b** **3b**

entry	**4**	**5b** (equiv)	$SnCl_4$ (equiv)	solvent	temp (°C)	time (h)	yield (%)
1	50 mg	2.0	1.0	Et_2O (0.05 M)	0	0.3	85 (dr = 3/2) [c]
2	50 mg	2.0	1.0	Et_2O (0.05 M)	-60	1	82 (71% conv) (dr = 9/1) [c]
[a] 3	500 mg	2.0	1.0	Et_2O (0.05 M)	-60	1	85 (82% conv) (dr = 91) [c]
[redacted]							

a) The same operation was repeated three times after work-up.

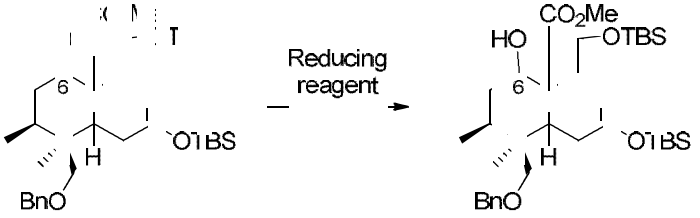
b) The same operation was repeated once more after work-up.

c) Dr was determined by ^1H NMR.

第4節　分子間Diels-Alder反応の選択性解析

BMDA反応で得られた環化体の立体構造を解析するためにC6位ケトンの還元を行なった(Table 2-4-1)。Entry4,5に示すようにDIBAL-Hを用いた還元が最も効果的であったが、さらに選択性を向上できないかentry 6~9に示すアルミニウムヒドリドを用いて検討を行なった。$LiAlH_4$やAlH_3は反応性が高すぎるために反応系が複雑化した。DIBAL-Hのようにアルミニウムに嵩高い置換基を有する還元剤を用いればより選択性が向上できると考え、Red-Alや$LiAl(O\textit{t}\text{-}Bu)_3H$を用い検討したが反応が殆ど進行しなかった。これらの結果からやはり還元剤はDIBAL-Hが最も効果的であることがわかった。DIBAL還元により得られたジアステレオマー**14A**,**14B**,**14C**をそれぞれシリカゲルカラムクロマトグラフィーにより分離することができた。その全てをNOESY測定により構造決定を試みたがシリルエノールエーテルのためか、**14A**と**14B**は測定中に分解したため、解析するには至らなかった。しかしながら**14C**はNOESY測定の結果、その相関からFigure 2-4-1に示す立体配置を有する構造であることが示唆された。そこでこの**14C**を利用し**14A**,**14B**の立体を決定することとした。

Table 2-4-1. Reduction of C6 Ketone



3b (*d.r.* = 9:1)　　**14** (A,B,C)

entry	reagent (equiv)	solvent	temp (°C)	time (h)	result (**14A/14B/14C**)
1	$NaBH_4$ (excess)	EtOH	rt	96	4.5/4.5/1
2	$LiBH_4$ (excess)	THF	0	9	4.5/4.5/1
3	DIBAL-H (3.0)	toluene	-78	0.1	6/3/1
[illegible]	[illegible]	Et_2O	[illegible]	[illegible]	[illegible]
6	$LiAlH_4$ (excess)	Et_2O	-78	0.1	multi spots [a]
7	$LiAlH_4$ (10), $AlCl_3$ (10)	Et_2O	-20	1	decomposition
8	Red-Al (5.0)	THF	rt	24	almost N.R. [b]
9	$LiAl(O\textit{t}\text{-}Bu)_3H$ (excess)	THF	60	24	N.R.

a) There were several spots including **14**.
b) Some high polar components appeared on the TLC.

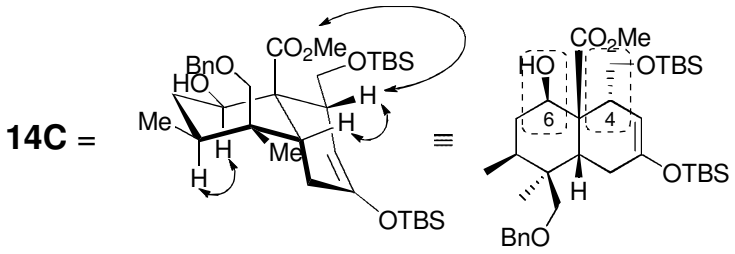
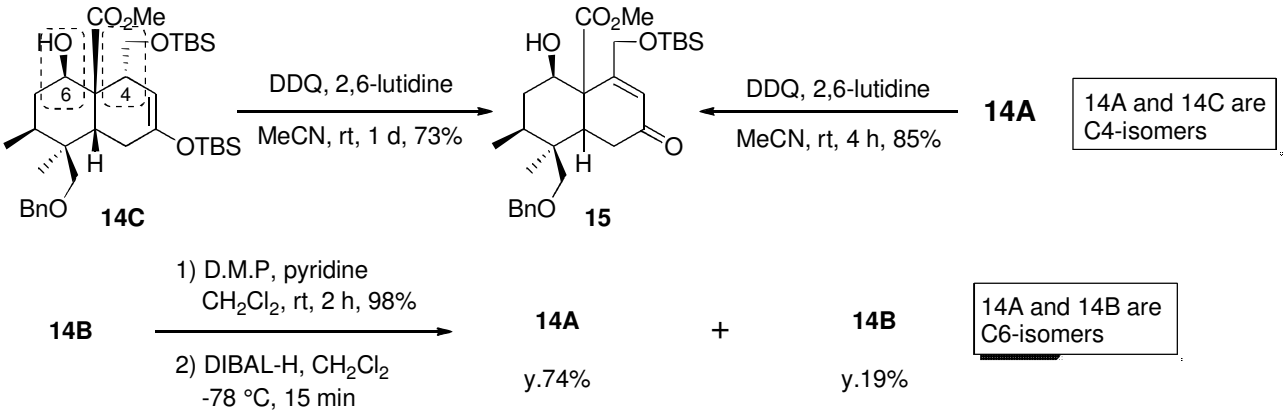


Figure 2-4-1. NOE Correlations in the NOESY Spectrum of **14C**

DDQ[12]を用いて**14C**をエノンに変換した。この化合物は**14A**から同様にして得たエノンと一致したことから**14A**と**14C**はC4位の異性体であることが明らかとなった。次に**14B**の水酸基を酸化し再度DIBAL還元したところ**14A**と**14B**が得られたことから**14A**と**14B**はC6位の異性体であることが明らかとなり、**14A**と**14B**はFigure 2-4-2に示す立体配置を有することが示唆された。これらの結果をまとめるとBMDA反応は*exo*/*endo*が9/1の比で進行したことがわかり、そのmajor体のケトンの還元は4/1の比で、minor体の還元は単一のジアステレオマーとして反応が進行したことが推測された。これはTable 2-3-4に示したBMDA反応でbucidarasinの骨格形成に関しては選択性を発現させる必要性はないことが示された。ただ、その他の天然物合成に適用することを考えると高立体選択的に骨格構築を行う価値はあると考えている。

Scheme 2-4-1. Structure Elucidation of **14A** and **14B**



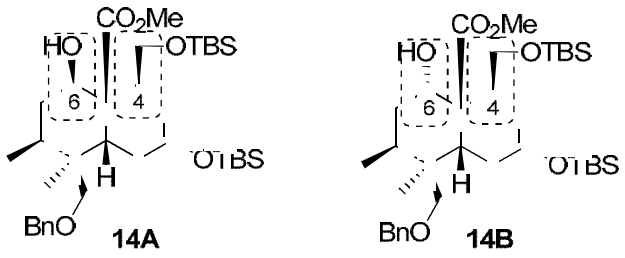


Figure 2-4-2. Proposed Structures of **14A** and **14B**

BMDA反応時の**4**の立体配座はFigure 2-4-3に示す2通りのhalf-chair-likeな立体配座が考えられるが、2つのメチル基がpseudo equatorialに位置する配座がエネル

ギー的に安定だと考えられる。そしてBMDA反応は予想通りベンジルオキシメチル基による立体障害を避けるように*Re*面で立体選択的に進行し、縮環部位に関して所望の立体配置を有する化合物のみを与えたと考えられる。序論で述べたように立体選択的な骨格構築を行うためには綿密な分子設計が求められる**4**と**5b**のBMDA反応においては予想通り、期待した立体配置を持つ生成物を得ることができた。収束的な合成であるため比較的短工程でC5位全炭素四級不斉中心を含む骨格構築に成功したと言える。

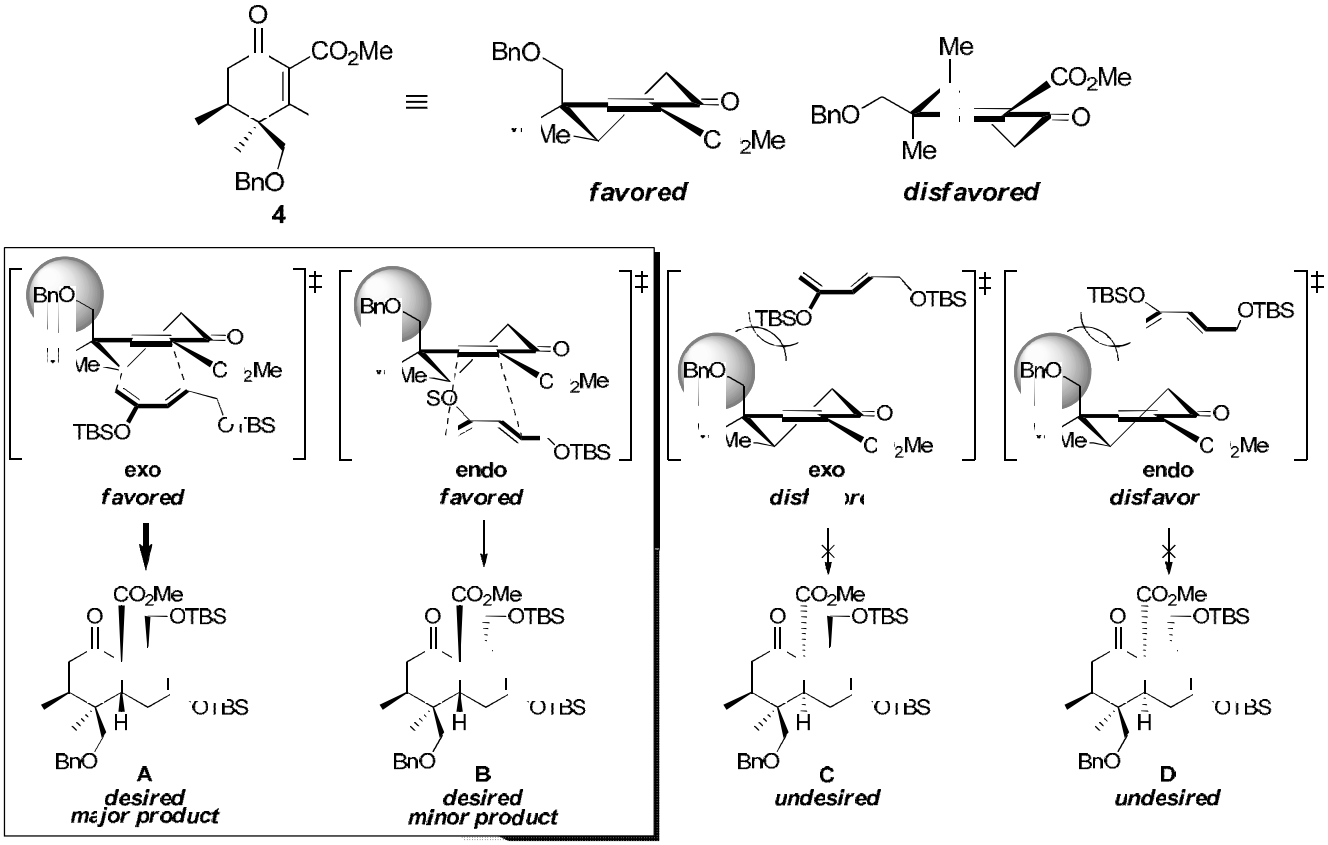


Figure 2-4-3. Proposed Mechanism of the BMDA Reaction

C6位ケトンの還元では、**3b**の配座異性体としてFigure 2-4-4に示すようなAおよびBの2種類の配座異性体が考えられるが、C4位置換基(-CH_2OTBS基)の立体障害により選択性が大きく発現していることに加え、**3b**minor体の還元で得られた**14C**がFigure 2-4-1に示すNOEが観測されていることから、縮環部位のエステル基およびベンジルオキシメチル基はaxial位に位置する立体配座Aで反応が進行していることが予想される。**3b**major体の還元では$NaBH_4$のような立体的に小さい還元剤を用いるとconvexおよびconcave面の両方から還元が進行し1/1のジアステレオ比であった(Figure 2-4-4)。一方、DIBAL-Hのようなルイス酸性のある還元剤を用いると、非極性溶媒であるtoluene中で反応を行うと選択性が低下することから、カルボニル基の炭素がカチオン性をもち、sp^2平面からずれ、ヒドリドがC5位エステル基およびC7位axial水素の立体障害を避けたconcave面からのaxial攻撃が優先し、4/1の

ジアステレオ比で所望の立体配置を有する還元体を与えたと推測している。また、**3b**minor体の還元ではC4位置換基(-CH_2OTBS基)の立体障害も加わり、単一の生成物を与えたと考えられる(Figure 2-4-5)。

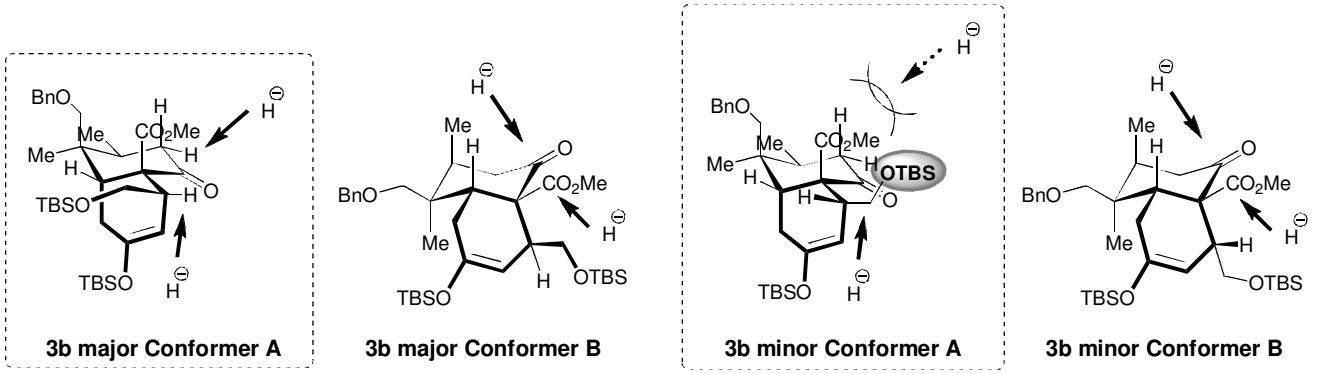


Figure 2-4-4. Proposed Mechanism of Reduction of Ketone **3b** using $NaBH_4$

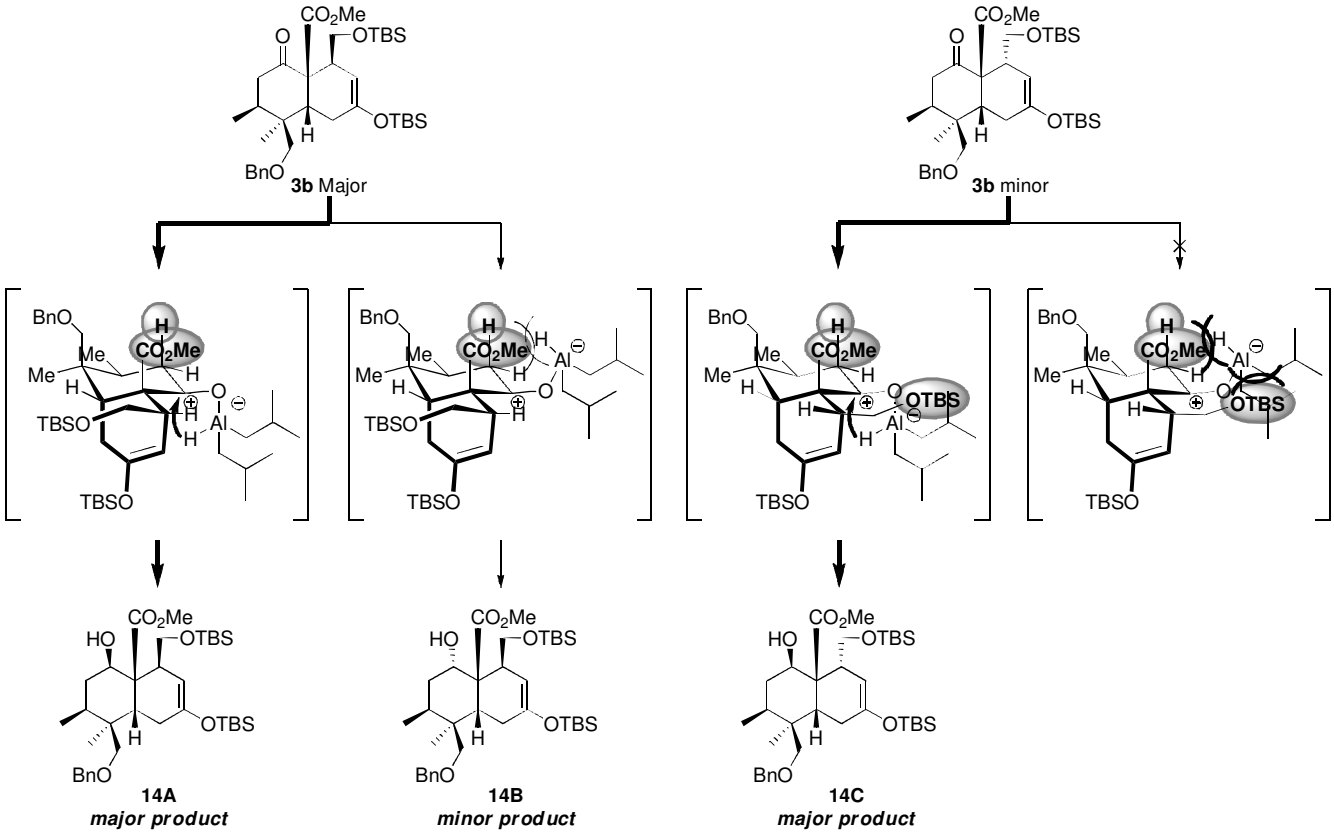
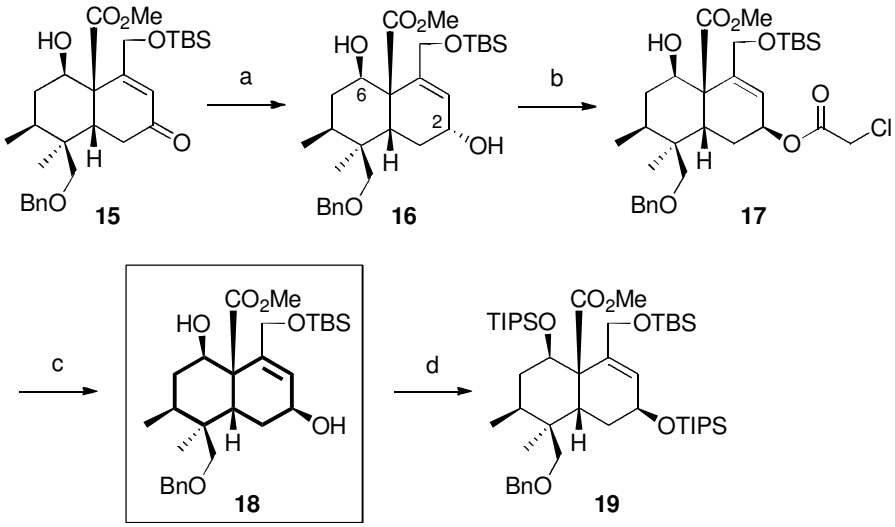


Figure 2-4-5. Proposed Mechanism of Reduction of Ketone **3b** using DIBAL-H

第5節　C9位(*E*)-3-メチル-2,4-ペンタジエニル側鎖合成

エノン**15**の1,2還元はconvex面からの攻撃が進行し**16**を立体選択的に与えたため、クロロ酢酸を用いてC2位水酸基を光延反転することでbucidarasinの*cis*-デヒドロデカリン骨格上に存在する不斉炭素を全て構築することに成功した(Scheme 2-5-1)。この時C6位の水酸基は立体障害により反応しなかったと考えられる。**18**の2つの水酸基をTIPS基で保護し**19**を得た。

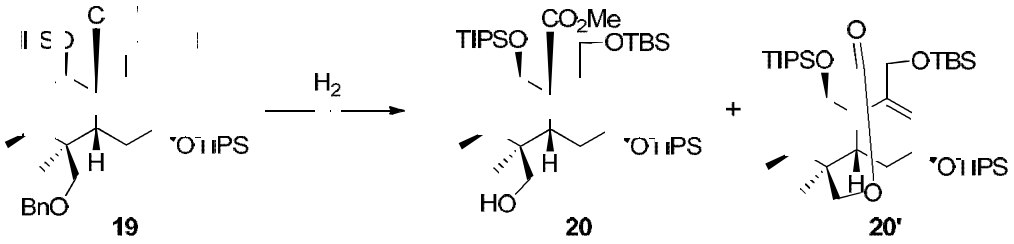
Scheme 2-5-1. Construction of *cis*-Dehydrodecalin Core



Reagents and conditions
(a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH/CH_2Cl_2, 0 °C, 30 min, 97%; (b) DIAD, PPh_3, α-chloroacetic acid, toluene, rt, 15 min; (c) K_2CO_3, MeOH, 0 °C, 30 min, 92% (2 steps); (d) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 12 h, 90%

水素添加条件によるBn基の脱保護を行なった(Table 2-5-1)。Merck社のPd/Cを用いるとMeOH溶媒では反応系が複雑になったがEtOAc溶媒では目的物を主生成物として得た。しかし、副生成物としてラクトン体**20'**が得られた。これはエステル基とヒドロキシメチル基が1,3-diaxialの位置に存在し、接近している為と考えられる。0℃では若干ながら単離収率が向上したのでラクトン化は精製中ではなく、反応中に進行していることが示唆された。水素添加反応に使用するPd/Cはサプライヤーの違いでpHが異なる事が知られている[13]。Pd/C製造の原料である$PdCl_2$の残存量に起因しており、それが原因でラクトン体**20'**が得られてきていると考え、Aldrich社のPd/Cに変更してみたところ収率が向上した。しかしながら完全にラクトン体**20'**の抑制は出来なかった。そこでPerlmann触媒に変更したところラクトン体**20'**の生成を大幅に抑制し、さらに系中にアルミナを添加することによりラクトン体**20'**の生成を完全に抑制することができた。

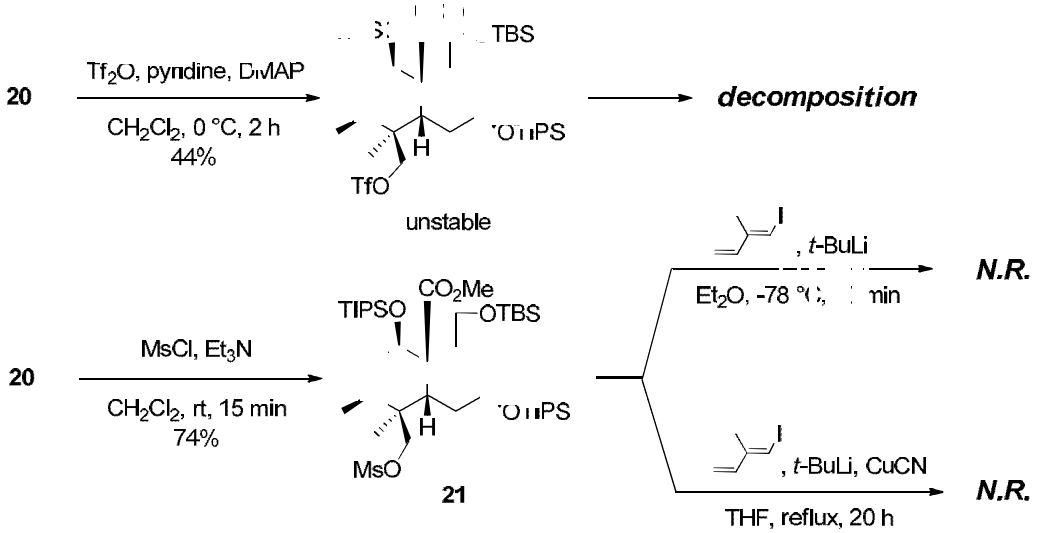
Table 2-5-1. Deprotection of Benzyl Group



entry	reagent	solvent	temp (°C)	time (min)	results
1	Pd/C [Merck]	MeOH	rt	15	multi spots
2	Pd/C [Merck]	EtOAc	rt	15	**20** 51% **20'** 39%
3	Pd/C [Merck]	EtOAc	0	30	**20** 60% **20'** 30%
4	Pd/C [Aldrich]	EtOAc	0	30	**20** 75% **20'** 22%
5	$Pd(OH)_2$/C [Aldrich]	EtOAc	0	30	**20** 95% **20'** trace

得られた水酸基を脱離基とし、S_N2反応によりペンタジエニル基の導入を試みた(Scheme 2-5-2)。水酸基をトリフラート化すると反応は進行するものの単離するとすぐに分解してしまった。メシル体**21**は単離できたので文献既知であるヨードジエンとの反応を行ったが、立体障害の大きいネオペンチル位における反応のためか求核置換反応及びカップリング反応は全く進行しなかった。

Scheme 2-5-2. S_N2 Alkylation with Iododiene



次に**20**をアルデヒド**22**へと変換し求核付加反応を試みた。ヨードジエン由来の有機リチウムは速やかに反応し、**23**を得ることができたが、**23**と生じた水酸基が分子内のエステルと反応したラクトン**24**との分離が困難であったため、**23**と**24**の混合物に塩基を作用させラクトン体**24**を得た。このラクトン体**24**のPdを用いた還元反応[14]を行なったところ(Table 2-5-2)、所望の**25**は得られずにジエンが内部に異性化した**25'**が得られる結果となった。多置換オレフィンの方が安定と考えられ、

異性化を完全に抑制し、**25**を得るのは困難と判断し、これ以上の条件検討は行わないこととした。

Scheme 2-5-3. Nucleophilic Addition with Iododiene

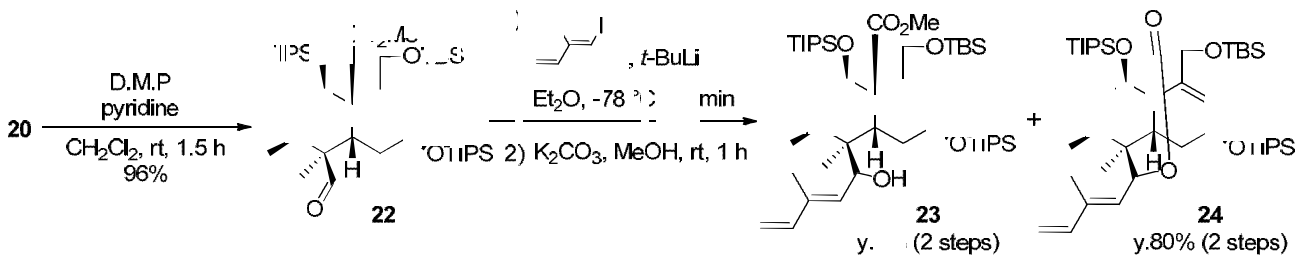
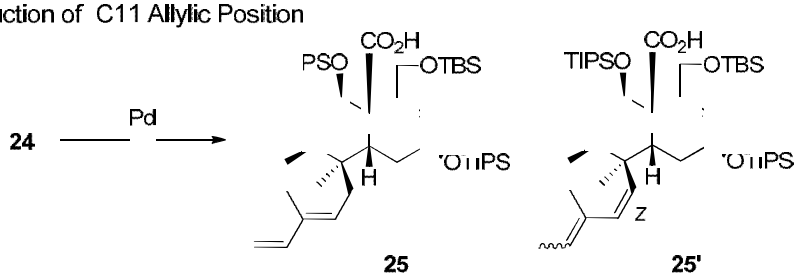


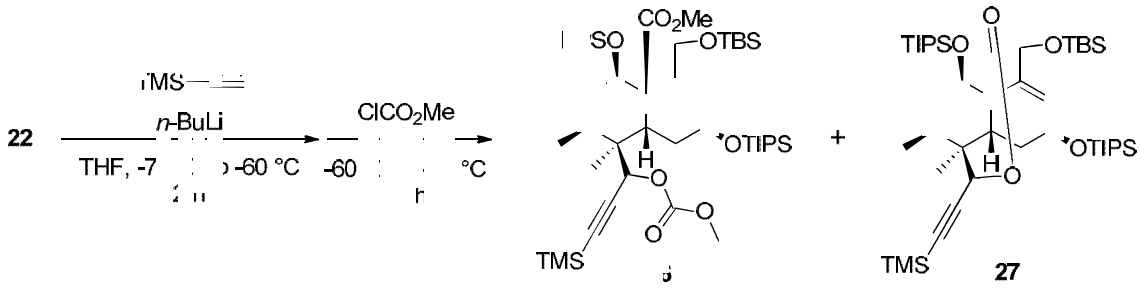
Table 2-5-2. Reduction of C11 Allylic Position



entry	reagent (equiv)	solvent	temp (°C)	time (h)	yield (%)
1	$Pd_2(dba)_3$ (0.2), dppe (0.4), $HCOONH_4$ (10.0)	1,4-dioxane	70	3	**25'** 60 (*E*/*Z* mixture)
2	$Pd(PPh_3)_4$ (0.2), $LiBH_4$ (10.0)	MeOH/THF(1/1)	0	0.5	**25'** 100 (*E*/*Z* mixture)

アルデヒド**22**への求核付加反応は速やかに進行することが分かったので次に、アセチレンを導入しジエンへの変換を試みた。TMSアセチリドを**22**へ付加させ生じたアルコキシドをクロロギ酸メチルで捕捉することでカルボネート**26**を得た。ラクトン体**27**が副生成物として得られたが下記に示すTable 2-5-3, entry 2の条件がその生成を最も抑制した。

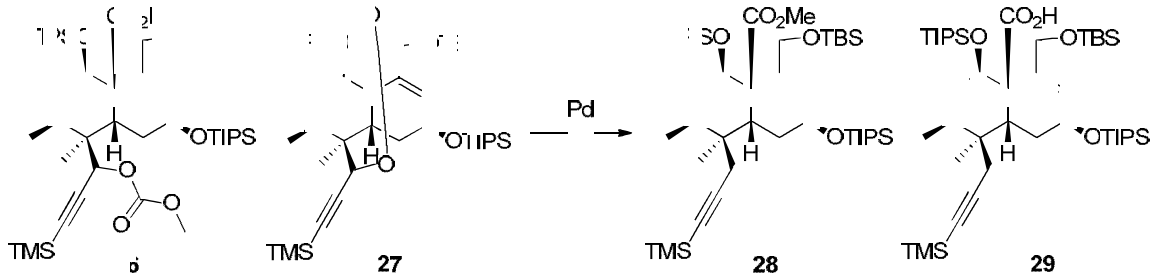
Table 2-5-3. Nucleophilic Addition with TMS Acetylene



entry	reagent (equiv)	results
1	TMS acetylene (3.0), *n*-BuLi (2.0), $ClCO_2Me$ (5.0)	**26** 39% **27** 60%
[illegible]		
3	TMS acetylene (8.0), *n*-BuLi (6.0), $ClCO_2Me$ (15.0)	**26** 57% **27** 32%
4	TMS acetylene (10.0), *n*-BuLi (8.0), $ClCO_2Me$ (20.0)	**26** 49% **27** 47%

続くギ酸還元[14]はTable 2-5-4, entry1に示す条件で高収率で目的物**28**を与えた。ラクトン体**27**も同様にギ酸還元を試みたが目的とする**29**は得られなかった。

Table 2-5-4. Pd-Catalyzed Reduction of **26** and **27** with Formic Acid



y	substrate	reag equiv)	solv t	temp (°C	me (h)	esults
		n-Bu_3P (0.4), $HCOONH_4$ (10.0)				
2	**27**	$Pd(OAc)_2$ (0.2), *n*-Bu_3P (0.4), $HCOONH_4$ (10.0)	THF	60	24	N.R.
3	**27**	$Pd(OAc)_2$ (0.2), *n*-Bu_3P (0.4), $HCOONH_4$ (10.0)	DMF	80	24	N.R.

脱TMS後、生じた末端アルキンをメチル化し、ヒドロメタル化を行った(Table 2-5-5, entry 1)が反応はほとんど進行しなかった。Entry 2の条件では反応が非常に遅くスズヒドリドから生じた水素による副生成物も得られた。そこでentry 3では溶媒に希釈したスズヒドリドをシリンジポンプを用い長時間かけて滴下した。その後ヨウ素化すると原料が多く残るが極僅かに目的物と思われる化合物が原料との混合物として得られた。しかし、これはNMRよりアルケン内部がヨウ素化されたものであることが示唆された(Scheme 2-5-5)。この結果からアルキンのヒドロメタル化は位置選択性に問題があることが分かった。

Scheme 2-5-4. Synthesis of **31**

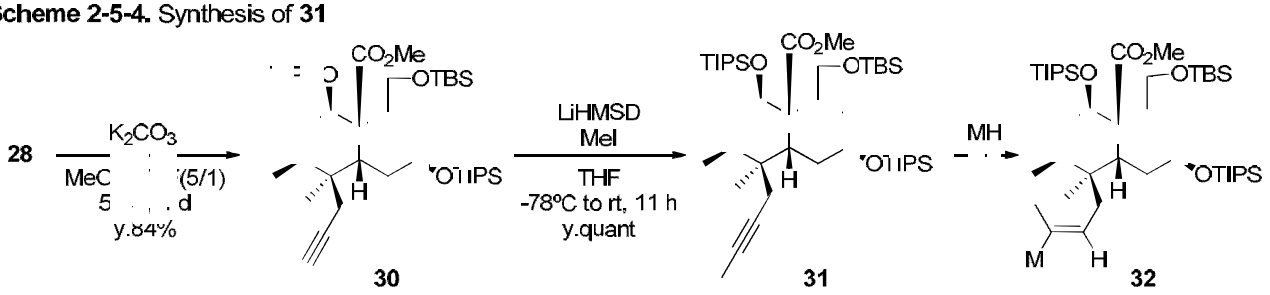
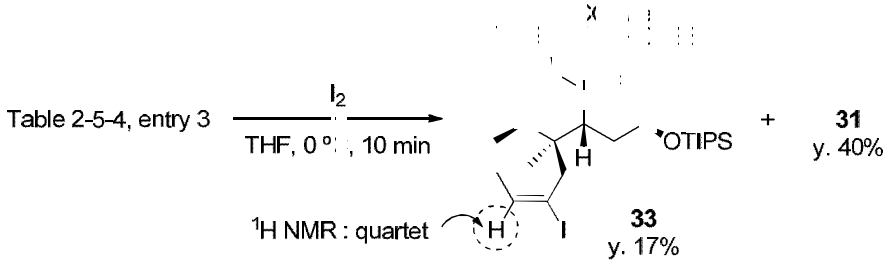


Table 2-5-5. Hydrometalation of **31**

r		solvent	temp (°C)	time (h)	results
	d(PPh_3)$_2$$Cl_2$ (0.1), *n*-Bu_3SnH (2.0)	THF	50	24	N.R.
[15] 2	$Pd(OAc)_2$ (0.1), PCy3 (0.2), *n*-Bu_3SnH (4.0)	hexane	rt	24	**31** + many spots
3	$Pd(OAc)_2$ (0.1), PCy3 (0.2), *n*-Bu_3SnH (4.0)	hexane	rt	[a] 17	**31** + 2 spots
4	AIBN (0.1), *n*-Bu_3SnH (10.0)	toluene	100	12	N.R.
5	Bu_3(Bu)SnCuLi·LiCN (3.0)	THF	rt	24	N.R.
6	$ZrCp_2HCl$ (5.0 eq.)	THF	70	24	N.R.

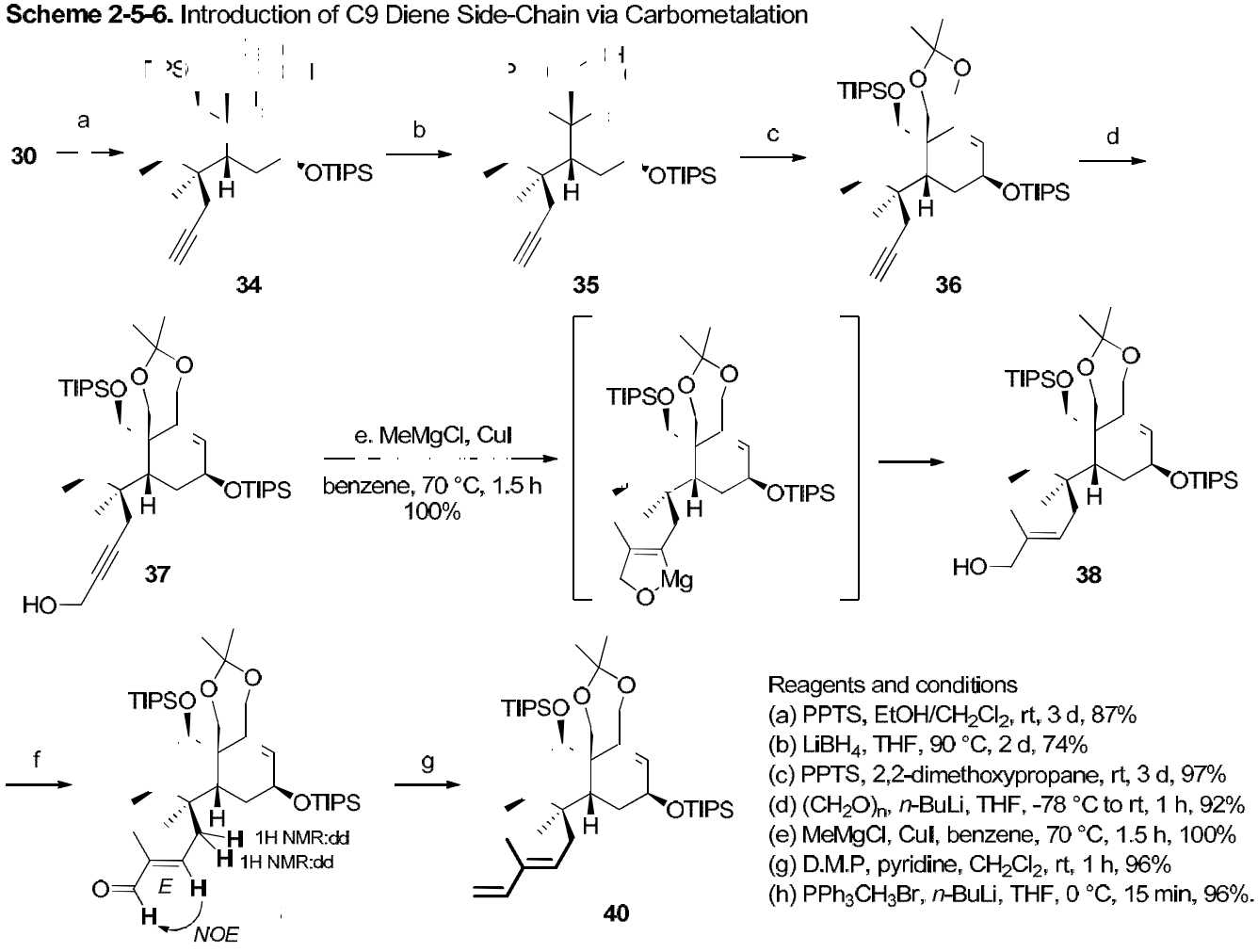
a) *n*-BuSnH was added dropwise over 3 h via syringe pomp at rt.

Scheme 2-5-5. Estimated Structure of Hydrometalated Compound



アルキン**30**のTBS基を除去し、**34**とした後、メチルエステルを還元してジオール**35**へと変換した。続くジオールの保護は2,2-ジメトキシプロパンを溶媒とすることで反応が高収率で進行した。末端アルキンをパラホルムアルデヒドと反応させプロパルギルアルコール体**37**へ変換した。この水酸基を足がかりとし、MeMgCl, CuIを用いた条件[16]でカルボメタル化を行うことでMe基が導入された(*E*)-アリルアルコール体をScheme 2-5-6に示す反応機構で立体選択的に高収率で得ることが出来た。続く酸化、Wittig反応の2工程によりbucidarasin が有するC9位側鎖である(*E*)-3-メチル-2,4-ペンタジエニル基を構築することに成功した。

Scheme 2-5-6. Introduction of C9 Diene Side-Chain via Carbometalation



Reagents and conditions
(a) PPTS, EtOH/CH_2Cl_2, rt, 3 d, 87%
(b) $LiBH_4$, THF, 90 °C, 2 d, 74%
(c) PPTS, 2,2-dimethoxypropane, rt, 3 d, 97%
(d) $(CH_2O)_n$, *n*-BuLi, THF, -78 °C to rt, 1 h, 92%
(e) MeMgCl, CuI, benzene, 70 °C, 1.5 h, 100%
(g) D.M.P, pyridine, CH_2Cl_2, rt, 1 h, 96%
(h) PPh_3CH_3Br, *n*-BuLi, THF, 0 °C, 15 min, 96%.

第6節　(-)-bucidarasin Aの不斉全合成

C9位側鎖の構築に成功したので、**40**からアセトナイドの脱保護、続いてジオールのSwern酸化を行うことでジアルデヒド体**42**を合成し、ビスアセトキシ基を有するテトラヒドロフラン環構築の検討を行った。Table 2-6-1, entry 1の条件ではTLC上で痕跡量の目的物と思われるスポットが確認できたため、entry 2では触媒量の硫酸[17]を添加し反応が加速されないか試みたが、酸性が強すぎるためか原料が分解してしまった。Entry 2の条件にAcONaを加えると反応が進行したことからentry 3に示す最適化した条件で再現性良く単一の生成物として目的物を得ることができた。Entry 4に示すAc_2Oを添加しない条件では全く反応が進行しないことからオキソニウム中間体経由ではなく、Scheme 2-6-1に示すようなヘミアセタールを中間体として経由する反応機構が考えられる。またこの反応は、熱力学支配で進行し、生成物のエネルギー的な安定性によって立体選択性が発現していると考えられる。

Scheme 2-6-1. Synthesis of the THF Ring Bearing *cis*-Acetoxy Groups

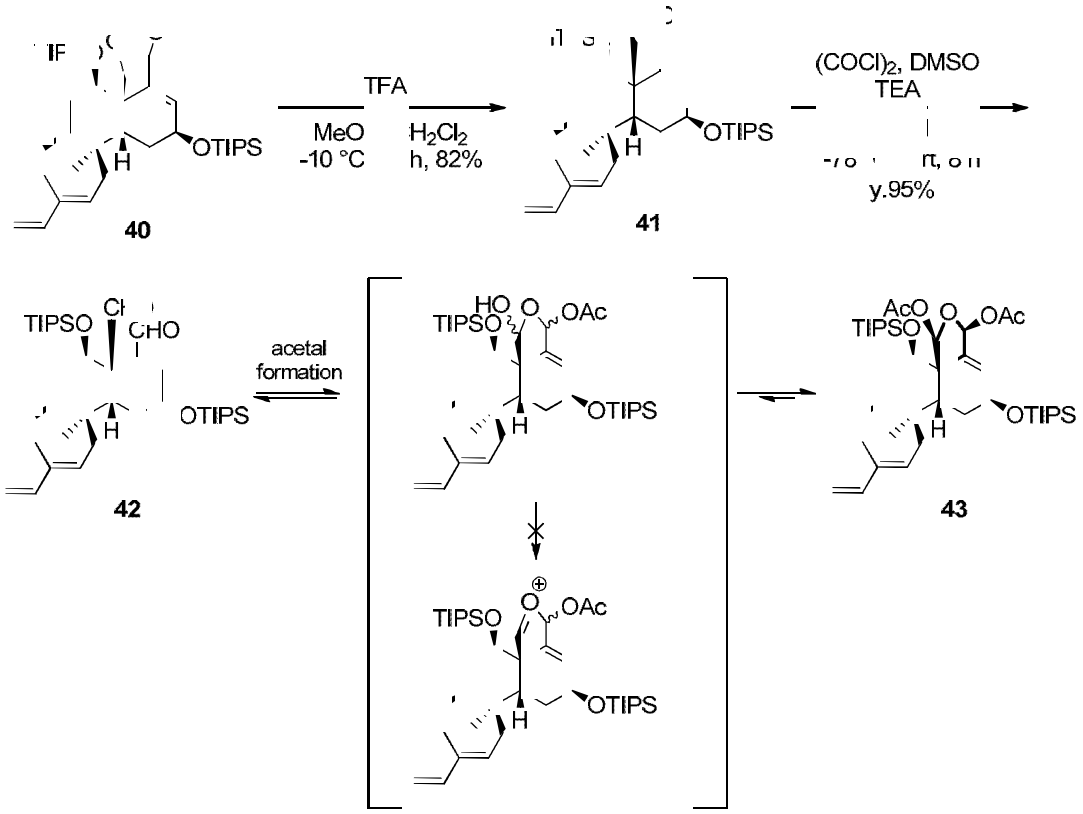
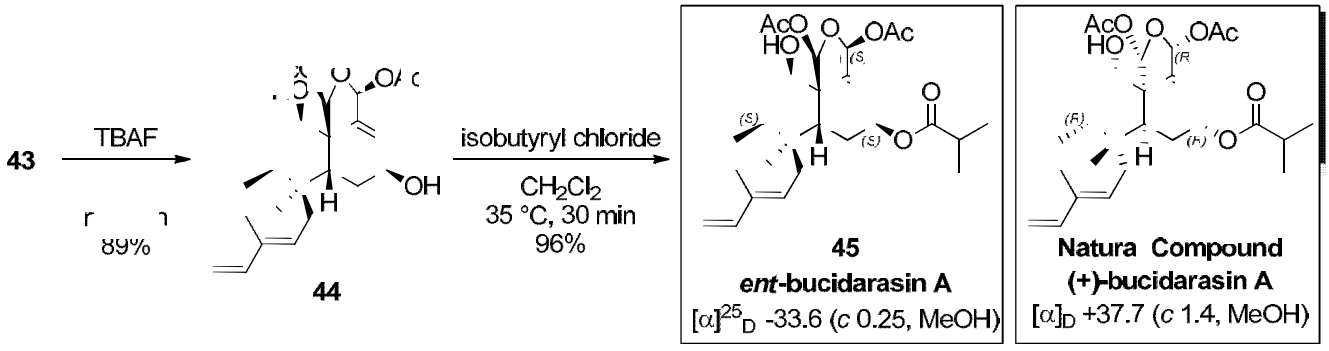


Table 2-6-1. Formation of the THF Ring Bearing *cis*-Acetoxy Groups

entry	reagent (equiv)	solvent	temp (°C)	time (h)	results
1	none	$AcOH/Ac_2O$(3/2)	70	72	trace
2	c.H_2SO_4 (cat.)	$AcOH/Ac_2O$ (4/1)	rt	0.5	decomposition
[illegible]	[illegible] c.H_2SO_4 (3.0)	[illegible]	[illegible]	[illegible]	[illegible]
4	NaOAc (5.0), c.H_2SO_4 (3.0)	AcOH	rt	48	N.R.

最後に得られた**43**のTIPS基を脱保護しアリル位水酸基を選択的にアシル化することでbucidarasin Aを合成した。合成化合物の旋光度を測定したところ天然物との符号は逆であったことから天然体はScheme 2-6-2に示す絶対配置を持つことが証明された。

Scheme 2-6-2. Total Synthesis of (-)-Bucidarasin A

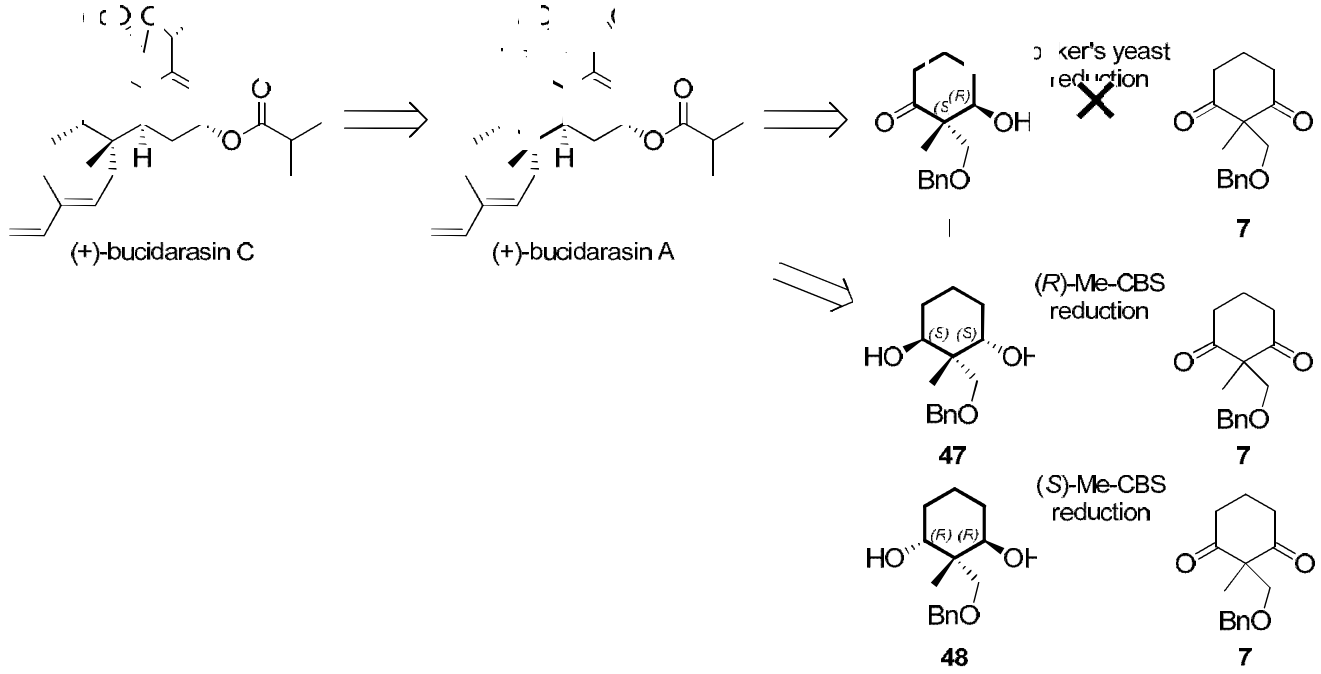


第 3 章　(+)-bucidarasin A および C の不斉全合成

第 1 節　合成計画

天然体の bucidarasin の絶対立体配置が明らかとなったので改めて天然型 bucidarasin A および C の全合成に着手した。(+)-bucidarasin C は(+)-bucidarasin A の C6 位水酸基をデオキシ化することで合成できると考えた。第 2 章で説明した (-)-bucidarasin A の不斉全合成はシクロヘキサンジオンを baker's yeast 還元したキラルビルディングブロック **6** を利用している。天然体である(+)-bucidarasin A を合成するために必要な逆の鏡像異性体を合成できる baker's yeast は存在しないため、如何にして必要なキラルビルディングブロックを合成するかが問題となる。そこで当研究室で開発された CBS 還元を用いて合成できるキラルビルディングブロック **47** および **48** を活用することとした。

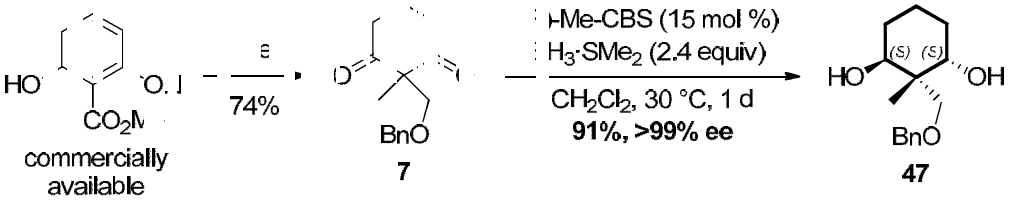
Scheme 3-1-1. Retrosynthetic Analysis toward Total Synthesis of (+)-Bucidarasins A and C



第 2 節　(*R*)-Me-CBS 触媒を用いたエナンチオマー中間体の合成

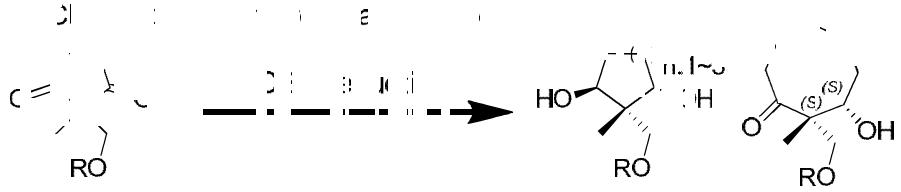
(*R*)-Me-CBS 触媒 [18a]を用いたキラルビルディングブロックの合成法を Scheme 3-1-2 に示す。当研究室でプロキラルな 5~8 のシクロアルカンジオンの CBS 還元を行うことで高収率かつ高立体選択的に四級不斉中心を含むキラルビルディングブロックの構築に成功している [7b]。CBS 還元の反応機構は、Corey らによって詳細に検討され解明されている [18b]。この合成法は生成物を大量に供給可能であり、メチル-2,6-ジヒドロキシベンゾエートを出発原料とし 5 工程で得られるプロキラルなシクロヘキサンジオン **7** を 10g のスケールでも高収率で合成することができる。

Scheme 3-2-1. Preparation of Chiral Building Block



Reagents and conditions
(a) BF_3·OEt_2, MeOH, 3 d, 93%; (b) Na, *t*-BuOH, liq.NH_3, -78 °C, 20 min; MeI, 91%; (c) $LiAlH_4$, Et_2O, 0 °C, 30 min, 96%; (d) BnBr, NaH, TBAI, THF/DMF, 10 h, 92%; (e) 2*M*·HCl/THF, rt, 30 min, 95%.

Ta

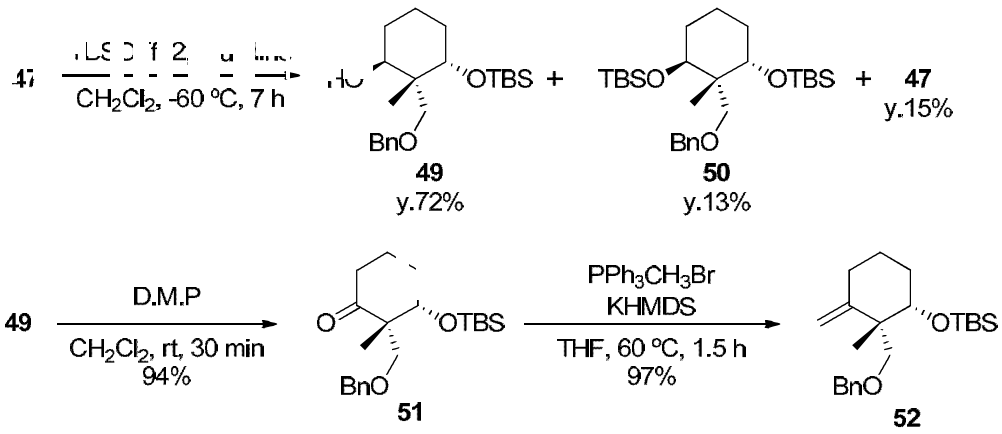


entry	substrate	yield (%	ee (%)
1	n = 1, R = Bn	91	>99
[redacted]			
3	n = 3, R = Piv	84	>99
4	n = 4, R = Piv	73	88

このようにして得られたキラルビルディングブロック **47** の 2 つの水酸基を片方のみ保護できないか試みた。TBSCl を用いると加熱条件下でも反応は遅く、TLC でモノ TBS 化された 2 つのスポットが検出され、且つ非常に分離困難な状況だったため反応性を高めた TBSOTf を用いて反応を試みることにした。TBSOTf を用いると非常に反応が早く、ジ TBS 化された **50** が主生成物として得られてきたので、低温下で溶媒に希釈した TBSOTf をシリンジポンプを用い長時間かけて滴下したところ、モノ TBS 化された **49** を主生成物として得ることができた。Figure 3-2-1 に示す **47** と **49** の NOESY 測定によりベンジルオキシメチル基と *cis* の関係にある axial 位を占める水酸基が TBS 化されたことが示唆された。立体的に嵩高

い置換基が axial 位を占めるのは不安定と予想されるが、この反応は速度論支配と考えられ、equatorial 側水酸基はベンジルオキシメチル基により遮蔽されており、axial 側水酸基が優先して反応したと考えられる(Figure 3-2-2)。得られた **49** の水酸基を酸化、Wittig 反応の 2 工程によりオレフィン **52** へと誘導し水素添加反応の検討を行なった。

Scheme 3-2-2. Synthesis of **52**



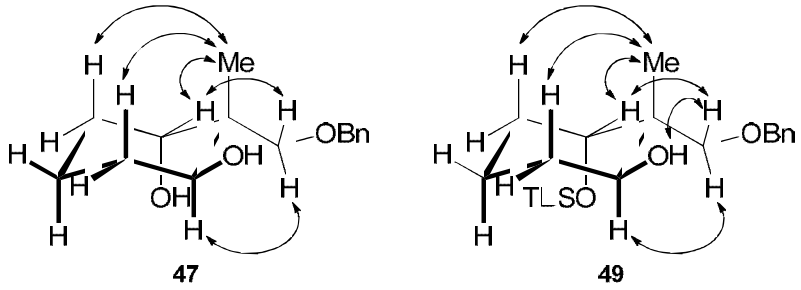


Figure 3-2-1. NOE Correlations in the NOESY Spectrum of **47** and **49**

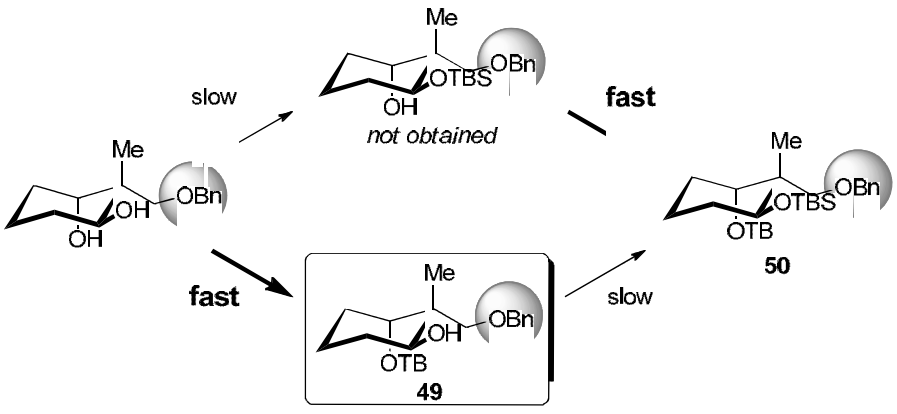
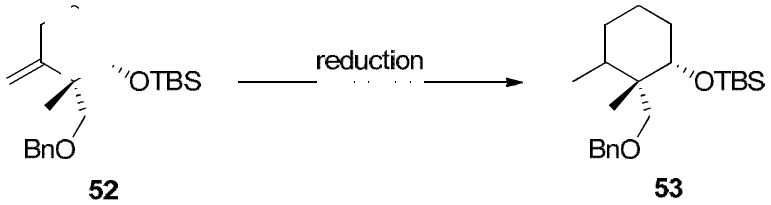


Figure 3-2-2. TBS Protection of Hydroxyl Group by Kinetic Control

Wilkinson 触媒を用いた水素添加反応[19]を Table 3-2-1 に示す。室温では非常に反応が遅いので(entry 1)、60℃で反応を行なったところ短時間でおよそ 5.5/1 のジアステレオ比で還元が進行した(entry 2)。立体選択性向上を期待し entry 3 に示す

ように4日間かけて35℃で反応を行なったが立体選択性の向上は見られなかった。触媒を Rh/Al_2O_3 に変更すると反応は速やかに進行するものの、およそ3/1のジアステレオ比となり、立体選択性が下がる結果であった。Entry 2の条件を採用し合成を進めていくこととし、この段階でのジアステレオマーの分離は困難であったが、脱シリル化することでそれぞれのジアステレオマーの分離に成功し、(+)-bucidarasinのC8位に相当する不斉炭素を構築できた。オキシ塩化リンによる脱水反応で、非天然体合成に使用した **10** とのエナンチオマーである **10'** を合成することができた。

Table 3-2-1. Reduction of **52**

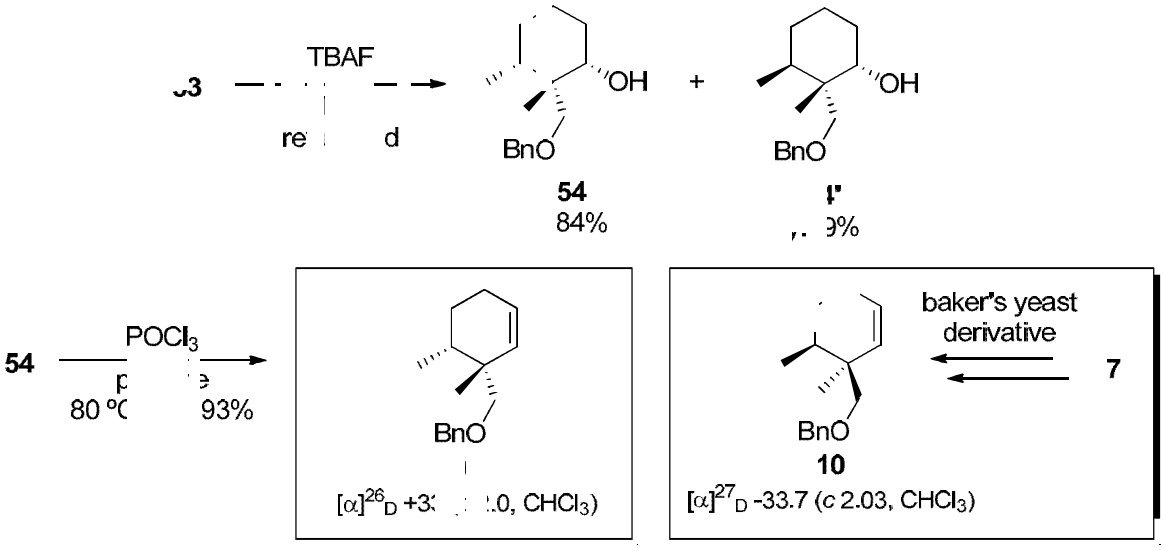


52 **53**

entry	reagent (equiv)	solvent	temp (℃)	time (h)	results
1	H_2, Wilkinson reagent (0.4)	benzene	rt	96	almost N.R.
[illegible]					
3	H_2, Wilkinson reagent (0.4)	benzene	35	96	97% (dr = 5.5/1) [a]
4	Wilkinson reagent (0.4), Et_3SiH (excess)	THF	50	24	N.R.
6	H_2, Rh/Al_2O_3 (cat.)	benzene	rt	1	quant (dr = 3/1) [a]
7	H_2, Rh/Al_2O_3 (cat.)	benzene/hexane (3/1)	0	1	quant (dr = 3/1) [a]

a) Dr was determined by ^1H NMR.

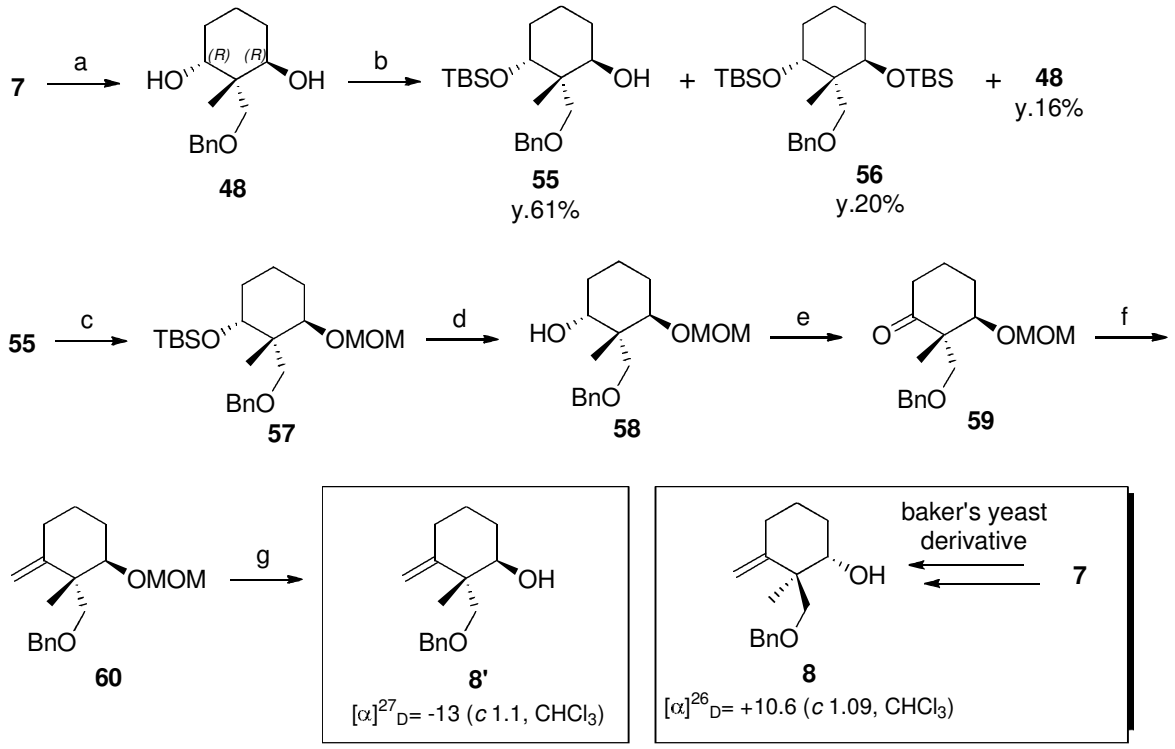
Scheme 3-2-1. Synthesis of the Enantiomer of **10**



第 3 節　(*S*)-Me-CBS 触媒を用いたエナンチオマー中間体の合成

第 2 節の合成法と同様に(*S*)-Me-CBS 触媒を用いて高収率かつ高立体選択的にキラルビルディングブロック **48** を合成した。TBS 化、MOM 化、脱 TBS 化の 3 工程で **58** を合成し、水酸基の酸化、Wittig 反応の 2 工程によりオレフィン **60** へと誘導した。**60** を脱 MOM 化することで、非天然体合成に使用した **8** のエナンチオマーである **8'**を合成することができた。

Scheme 3-3-1. Synthesis of the Enantiomer of **8**

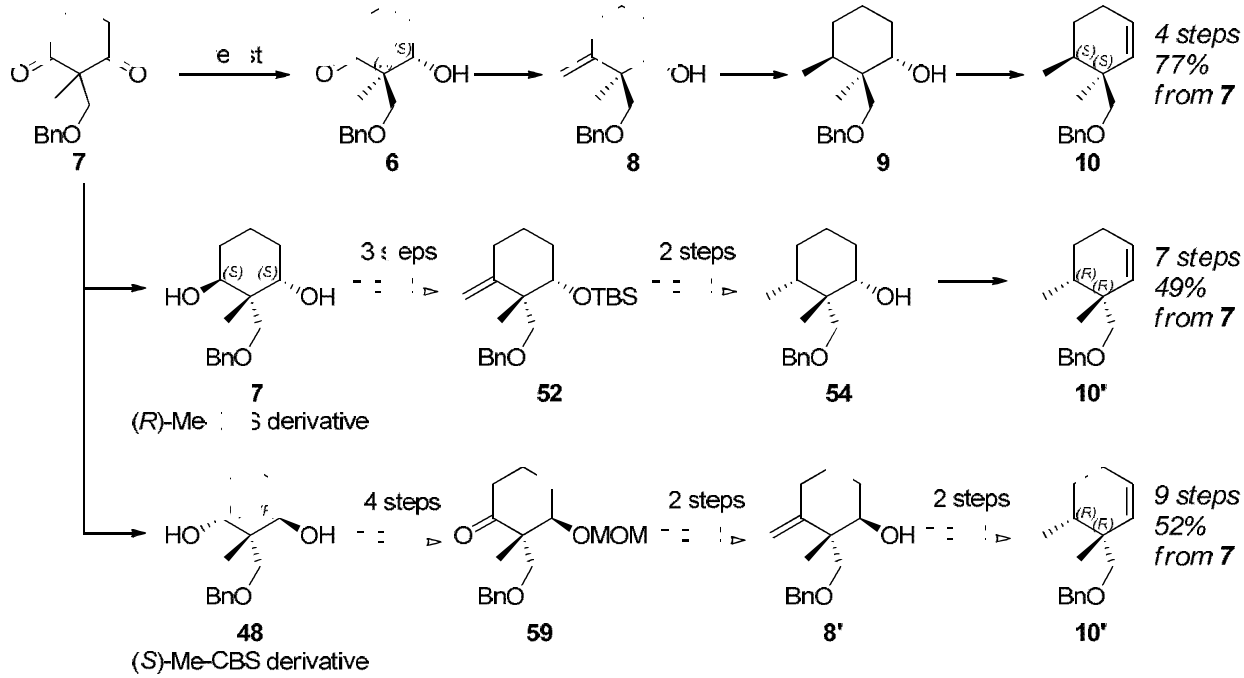


Reagents and conditions
(a) (*S*)-Me-CBS, BH_3·SMe_2, CH_2Cl_2, 30 ºC, 1 d, 94%, >99% ee, (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, -60 ºC, 7 h; (c) MOMCl ,DIPEA, NaI, CH_2Cl_2, 35 ºC, rt, 99%, (d) TBAF, THF, 50 ºC, 5 h, 93%, (e) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, rt, 30 min, 100%, (f) PPh_3CH_3Br, KHMDS, THF, rt, 1 h, 97%, (g) 5*M*·HCl, EtOH, 50 ºC, 12 h, 94%.

以上をまとめた合成法を Scheme 3-3-2 に示す。

第 2 章第 3 節に示した合成法では **7** から baker's yeast 還元を含む 4 工程で収率 77%で **10** を合成している。それに対して第 3 章第 2 節に示した合成法では **7** から CBS 還元を含む 7 工程で収率 52%で **10'**を合成した。本節に示した合成法では **7** から CBS 還元を含む 9 工程で収率 52%で **10'**を合成した(**8'**→**10'**は第 2 章第 3 節の収率で計算している)。以上のようにシクロヘキサンジオンを原料とし(*R*)または(*S*)-Me-CBS 触媒を用いて還元することで高収率かつ高立体選択的にキラルビルディングブロックを合成し、(+)-bucidarasin A 合成に可能な中間体 **10'**の合成に成功した。

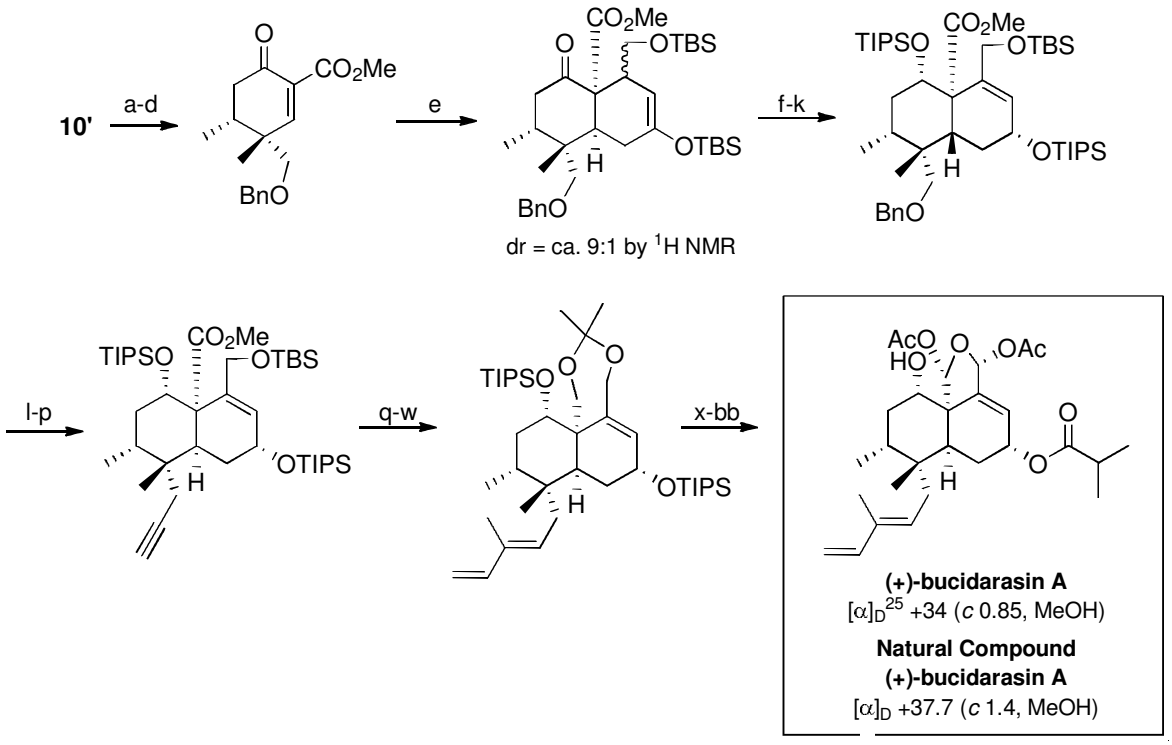
Scheme 3-3-2. Synthesis of the Enantiomer of **10** via CBS Reduction



第 4 節　(+)-bucidarasin A の不斉全合成

中間体 **10'**の合成に成功したので(-)-bucidarasin A の合成と同様の操作で(+)-bucidarasin A の合成に成功した。合成品と天然物のすべてのスペクトルデータは完全に一致した。この(+)-bucidarasin A の不斉全合成は三環式 clerodane 型ジテルペン構造を有する天然物の初の不斉全合成である。

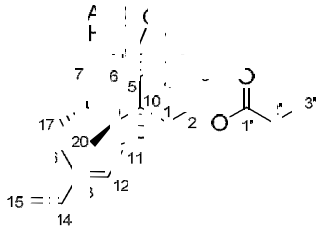
Scheme 3-4-1. Total Synthesis of (+)-Bucidarasin A



Reagents and conditions

(a) SeO_2, dioxane/HCOOH, 80 °C, 3 d; then NH_4OH, 56%; (b) PDC, MS4Å, CH_2Cl_2, rt, 3 h, 81%; (c) I_2, DMAP, CCl_4/pyridine, 50 °C, 1 d, 94%; (d) CO, $Pd(PPh_3)_4$, TEA, THF/MeOH, 55 °C, 8 h, 92%; (e) **5b**, $SnCl_4$, Et_2O, -60 °C, 17 h, 95%; (f) DIBAL-H, CH_2Cl_2, -78 °C, 30 min, 79% (separate diastereomers); (g) DDQ, 2,6-lutidine, MeCN, rt, 1 h, 78%, (h) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH/CH_2Cl_2, 0 °C, 30 min, 92%; (i) DIAD, PPh_3, α-chloroacetic acid, toluene, rt, 15 min; (j) K_2CO_3, MeOH, 0 °C, 30 min, 86% (2 steps); (k) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 12 h, 82%; (l) H_2, $Pd(OH)_2$/C, Al_2O_3, AcOEt, 0 °C, 30 min; (m) D.M.P., pyridine, CH_2Cl_2, rt, 1.5 h, 96% (2 steps); (n) TMS acetylene, *n*-BuLi, THF, -60 °C; then methyl chloroformate, -10 °C, 76%, (o) $Pd(OAc)_2$, $^nBu_3P$, $HCOONH_4$, THF, 60 °C, 2 d, 89%; (p) K_2CO_3, MeOH/THF, 50 °C, 1 d, quant; (q) PPTS, EtOH/CH_2Cl_2, rt, 3 d, 87%; (r) $LiBH_4$, THF, 90 °C, 2 d, 91%; (s) PPTS, 2,2-dimethoxypropane, rt, 3 d, 89%; (t) $(CH_2O)_n$, *n*-BuLi, THF, -78 °C to rt, 1 h, 88%; (u) MeMgCl, CuI, benzene, 70 °C, 1.5 h, 100%; (v) D.M.P, pyridine, CH_2Cl_2, rt, 1 h, 96%; (w) PPh_3CH_3Br, *n*-BuLi, THF, 0 °C, 15 min, 100%; (x) TFA, MeOH/CH_2Cl_2, -10 °C, 18 h, 73%; (y) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, rt, 8 h, 95%; (z) NaOAc, c.H_2SO_4, AcOH/Ac_2O, rt, 2 d, 71%; (aa) TBAF, THF, rt, 1.5 h, 85%; (bb) isobutyryl chloride, TEA, CH_2Cl_2, 35 °C, 30 min, 98%.

Table 3-4-1. Comparison of NMR Data for Natural and Synthetic (+)-Bucidarasin A

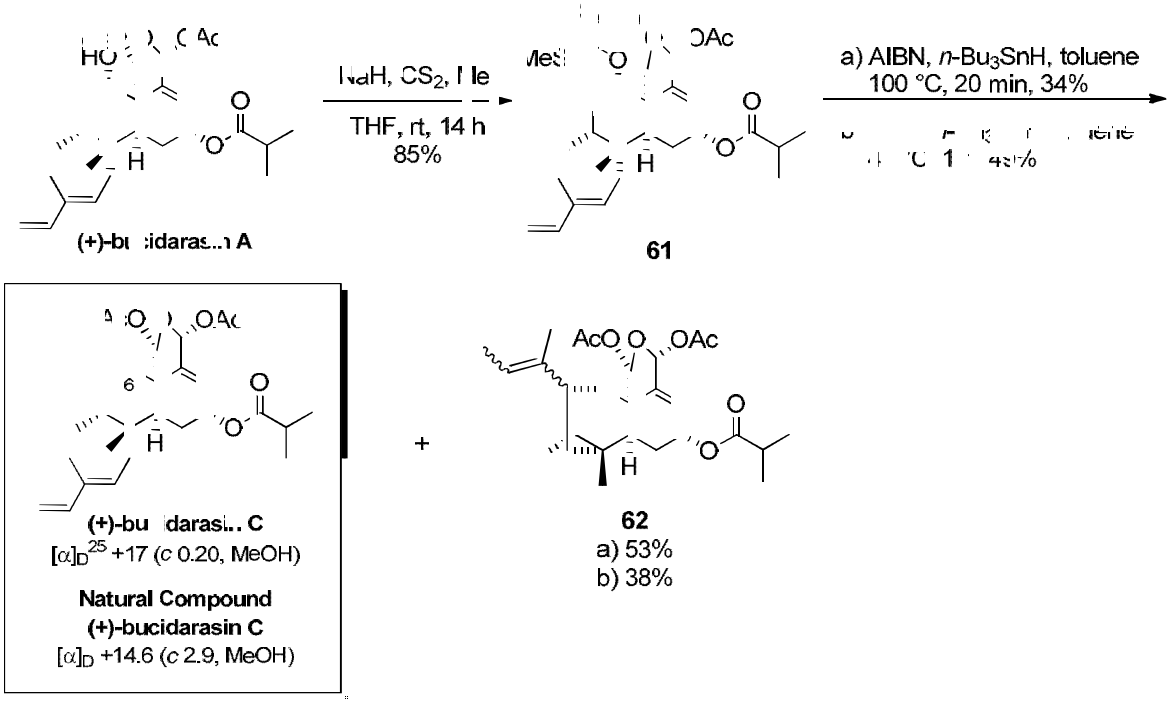


	Natural Compound		Synthetic Compound	
	^{1}H δ (multi, *J* [Hz])	^{13}C δ	^{1}H δ (multi, *J* [Hz])	^{13}C δ
1	[illegible]	[illegible]	[illegible]	[illegible]
2	[illegible]	[illegible]	[illegible]	[illegible]
3	[illegible]	12[illegible]	[illegible]	12[illegible]
4		145.3		145.2
5		53.6	3.80 (1H, ddd, J = 12.4, 9.6, 3.7 Hz)	53.5
6	3.80 (1H, d, *J*=9.2 Hz) *mistake*	72.8	1.68 (3H, m)	72.8
7	1.62, 1.75 (2H, m)	37.6	1.77 (1H, m)	37.5
8	1.77 (1H, m)	36.7		36.7
9		37.4	2.36 (1H, dd, J = 11.4, 5.5 Hz)	37.3
10	2.36 (1H, dd, *J*=12.5, 5.2 Hz)	36.8	1.68 (1H, m), 2.24 (1H, dd, J = 16.5, 7.8 Hz)	36.8
11	1.66 (1H, m), 2.23 (1H, dd, *J*=16.5, 8.2 Hz)	30.3	5.37 (1H, m)	30.3
12	5.38 (1H, br d)	129.0		129.0
13		135.7	6.27 (1H, dd, J = 17.4, 10.5 Hz)	135.7
14	6.27 (1H, dd, *J*=17.3, 10.5 Hz)	141.2	4.93 (1H, d, J = 10.5 Hz), 5.10 (1H, d, J = 17.4 Hz)	141.2
15	4.93 (1H, d, *J*=10.5 Hz), 5.09 (1H, d, *J*=17.3 Hz)	111.1	1.66 (3H, s)	111.1
16	1.67 (1H, s)	12.0	0.93 (3H, d, J = 6.9 Hz)	12.0
17	0.93 (1H, s)	15.6	6.73 (1H, dd, J = 1.4, 1.4 Hz)	15.6
18	6.73 (1H, t, *J*=1.5 Hz)	95.6	6.51 (1H, s)	95.6
19	6.52 (1H, s)	97.0	0.81 (3H, s)	96.9
20	0.81 (1H, s)	25.0		25.0
1'		176.5	2.64 (1H, qq, J = 6.9, 6.9 Hz)	176.5
2'	2.64 (1H, m)	34.1	1.20 (3H, d, J = 6.9 Hz), 1.22 (3H, d, J = 6.9 Hz)	34.0
3'	1.21 (3H, d, *J*=7.0 Hz), 1.22 (3H, d, *J*=7.0 Hz)	18.7, 19.1	1.94 (3H, s)	18.7, 19.2
18-Acetyl Me	1.95 (3H, s)	21.6		21.6
18-CO		169.4	2.10 (3H, s)	169.4
19-Acetyl Me	2.10 (3H, s)	21.2		21.2
19-CO		170.2		170.2

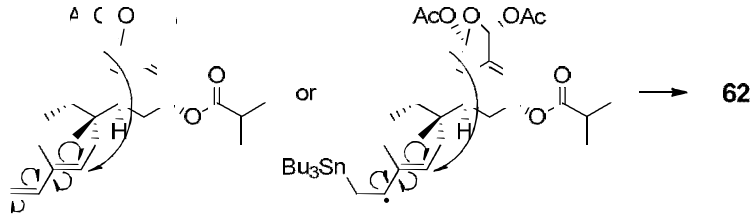
第 5 節　(+)-bucidarasin C の不斉全合成

(+)-bucidarasin A の C6 位の水酸基をキサンテート **61** へと変換後、AIBN を用いて Barton-McCombie デオキシ化[20a]を行うと 34%の収率ではあるが (+)-bucidarasin C の合成に成功した(Scheme 3-5-1)。Scheme 3-5-2 に示すように副生成物として C6 位に生じたラジカルが C9 位側鎖ジエン部位と反応した **62** が得られた。より低温で反応を行えば副生成物を抑制できると考えてラジカル開始剤として V-70[20b]を用いたところ若干ではあるが収率の改善が見られた。合成品と天然物のすべてのスペクトルデータは完全に一致した。

Scheme 3-5-1. Total Synthesis of (+)-Bucidarasin C

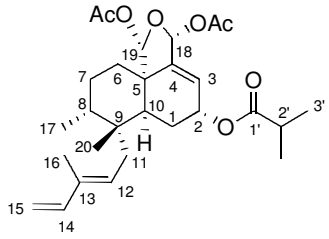


Scheme 3-5-2. Proposed Machanism of the Formation of Byproduct



我々は 3 環式 clerodane 型ジテルペン構造を有する天然物の初の不斉全合成を達成し、このことから側鎖の異なる数多く存在する天然物の全合成も可能であると考えており、その絶対立体配置の決定、また、創薬研究への発展にもつながると考えている。今後は第 2 章で合成した(-)-bucidarasin A や天然には存在しない 3 環式 clerodane 型ジテルペン構造を有する化合物を合成し構造活性相関を検討したいと考えている。

Table 3-5-1. Comparison of NMR Data for Natural and Synthetic (+)-Bucidarasin C



	Natural Compound		Synthetic Compound	
	^{1}H δ (multi, *J* [Hz])	^{13}C δ	^{1}H δ (multi, *J* [Hz])	^{13}C δ
1	1.90 (2H, m)	26.1	1.90 (2H, m)	26.1
2	5.40 (1H, br s)	66.3	5.42 (1H, br s)	66.3
3	5.89 (1H, dd, *J*=4.5, 1.6)	120.4	5.89 (1H, dd, *J*=4.6 1.5)	120.3
4		147.0		147.0
5		49.1		49.1
6	1.73 (2H, m)	29.1	1.74 (2H, m)	29.1
7	1.45 (1H, m), 1.50 (1H, m)	27.4	1.47 (2H, m)	27.4
8	1.63 (1H, m)	36.5	1.61 (1H, m)	36.5
9		37.4		37.4
10	2.23 (1H, br t *J*=8.4)	34.7	2.22 (1H, br t)	34.7
11	1.75 (1H, m), 2.23 (1H, dd, *J*=16.2, 8.1)	30.4	1.75 (1H, m), 2.23 (1H, dd, *J*=16.1, 8.2)	30.4
12	5.38 (1H, br d)	129.3	5.38 (1H, br d)	129.3
13		135.6		135.6
14	6.28 (1H, dd, *J*=17.1, 10.7)	141.3	6.28 (1H, dd, *J*=17.2, 10.8)	141.3
15	4.92 (1H, d, *J*=10.7), 5.08 (1H, d, *J*=17.1)	110.8	4.92 (1H, d, *J*=10.8), 5.08 (1H, d, J = 17.2)	110.8
16	1.66 (3H, s)	12.0	1.67 (3H, s)	12.0
17	0.88 (3H, d, *J*=7.0)	15.7	0.89 (3H, d, *J*=6.9)	15.6
18	6.73 (1H, t, *J*=1.5) *mistake*	94.5	6.67 (1H, dd, *J*=1.5, 1.5)	94.5
19	6.36 (1H, s)	98.8	6.36 (1H, s)	98.8
20	0.83 (3H, s)	25.7	0.83 (3H, s)	25.7
1'		176.5		176.4
2'	2.63 (1H, m)	34.1	2.63 (1H, qq, J = 6.9, 6.9)	34.1
3'	1.20 (3H, d, *J*=7.0)	18.7, 19.1	1.20 (3H, d, *J*=6.9)	18.7, 19.2
18-Acetyl Me	1.22 (3H, d, *J*=7.0)	21.4	1.22 (3H, d, *J*=6.9)	21.4
18-CO	1.94 (3H, s)	169.7	1.94 (3H, s)	169.7
19-Acetyl Me		21.2		21.2
19-CO	2.10 (3H, s)	170.3	2.10 (3H, s)	170.3

第 4 章　(-)-bruceantin の不斉全合成研究

第 1 節　序論

(-)-bruceantin は 1973 年に Kupchan らによりエチオピア産ニガキ科植物 *Brucea antidysenterica* またはガーナ産植物 *Brucea guineensis G* から単離、構造決定されたクアシノイドに分類されるトリテルペン[21]である。その構造的特徴として A から E までの環を持つ 5 環式骨格を持ち、2 つの全炭素四級不斉中心(C8、C10 位)を含む 10 連続不斉中心を有することが挙げられ、有機合成上非常に興味深い化合物である。その生物活性として抗腫瘍活性が挙げられるが、近年になって白血病細胞、リンパ腫細胞、骨髄腫細胞に対する強い活性(HL-60 IC_{50}=12.2 nM, RPMI 8226 IC_{50}=12.8 nM)が報告され[22]、有望な抗腫瘍性抗生物質として再度、注目されている(Figure 4-1-1)。数多い類縁体の中でも(-)-bruceantin は最も活性が強い。そしてアメリカの国立がん研究所において、抗がん剤として Phase Ⅱ での臨床試験まで実施された化合物である。現在まで 2 つの研究グループにより全合成が報告されているが[23]、どちらも工程数が長く、そのうち 1 例は不斉合成ではあるがリレー合成であるため、筆者は初の不斉全合成を目標とし、研究に着手した。

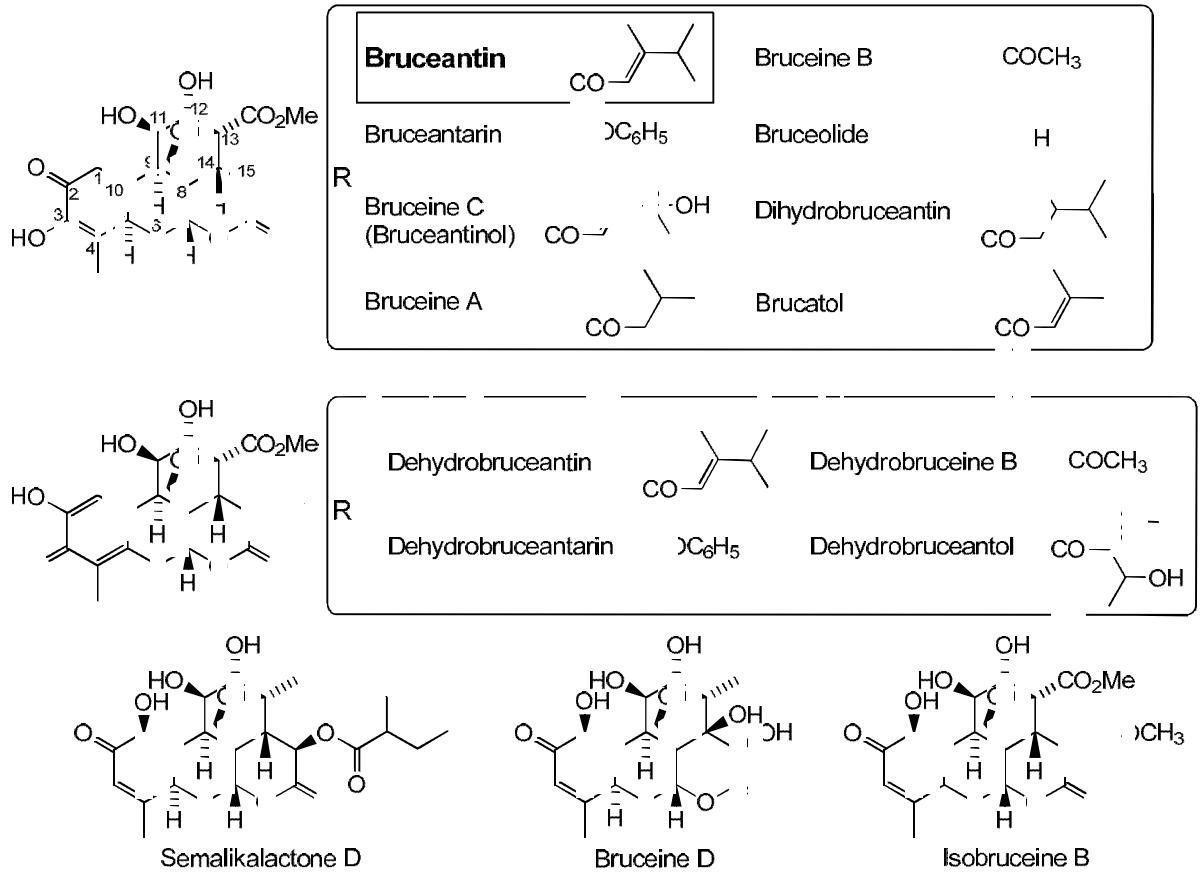
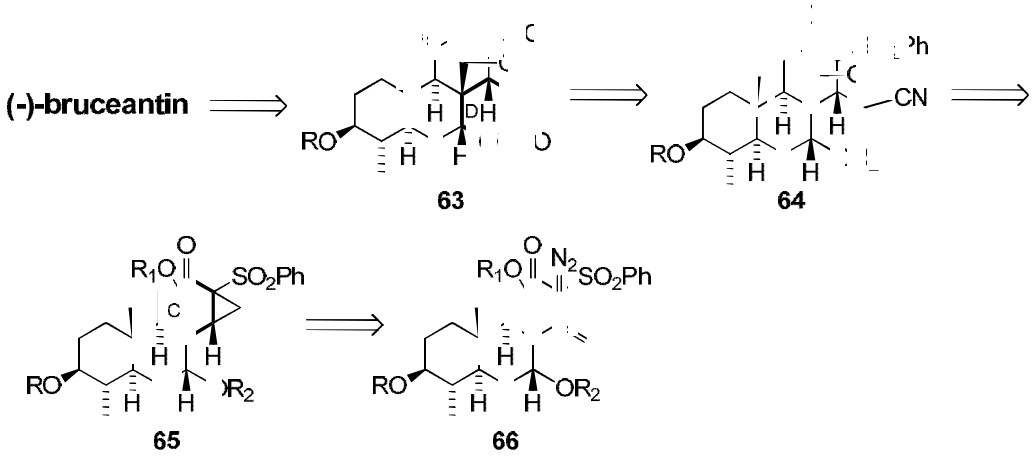


Figure 4-1-1. Quassinoid Triterpenes, Bruc[illegible]d its Congeners

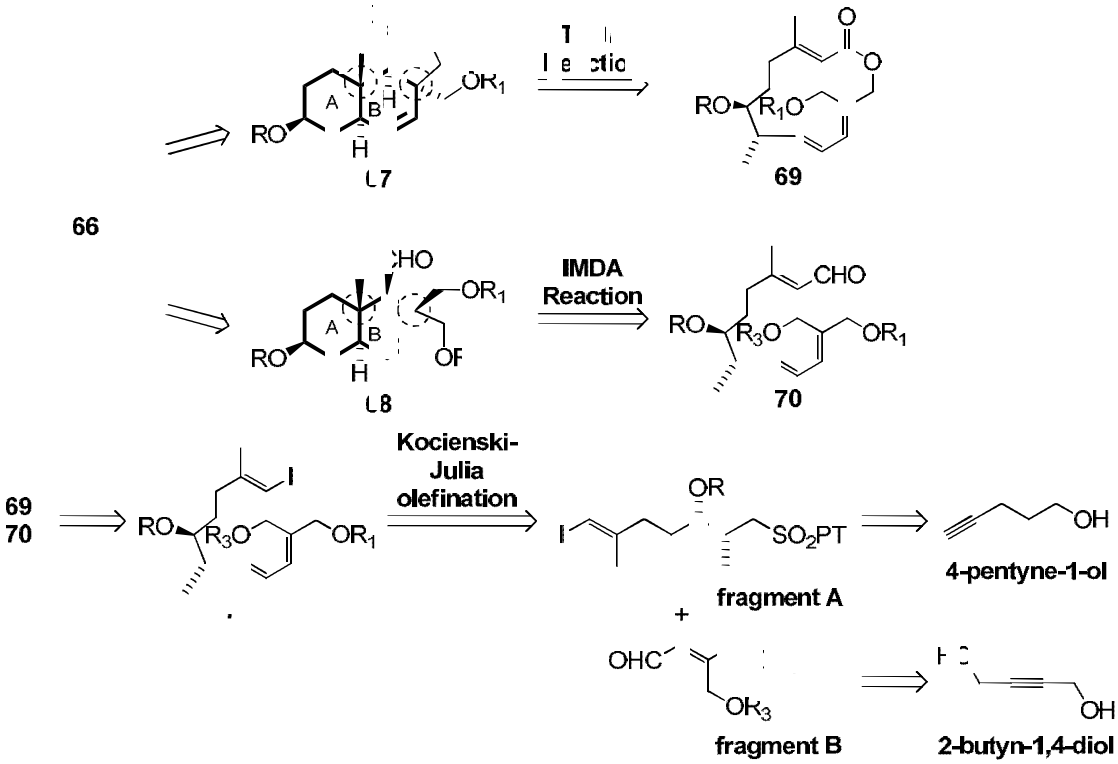
第 2 節　合成計画

(-)-bruceantin は分子内不斉シクロプロパン化反応[24]により C 環を構築し、続いて D 環は **64** からの分子内ラクトン化により構築できると考えた。また最後に **63** からの分子内 Michael 付加反応により E 環を構築し、側鎖の導入及び官能基変換を行うことにより(-)-bruceantin の全合成を達成する計画を立てた (Scheme 4-2-1)。

Scheme 4-2-1. Retrosynthetic Analysis toward Total Synthesis of (-)-Bruceantin



Scheme 4-2-2. Retrosynthetic Analysis of AB-ring Moiety



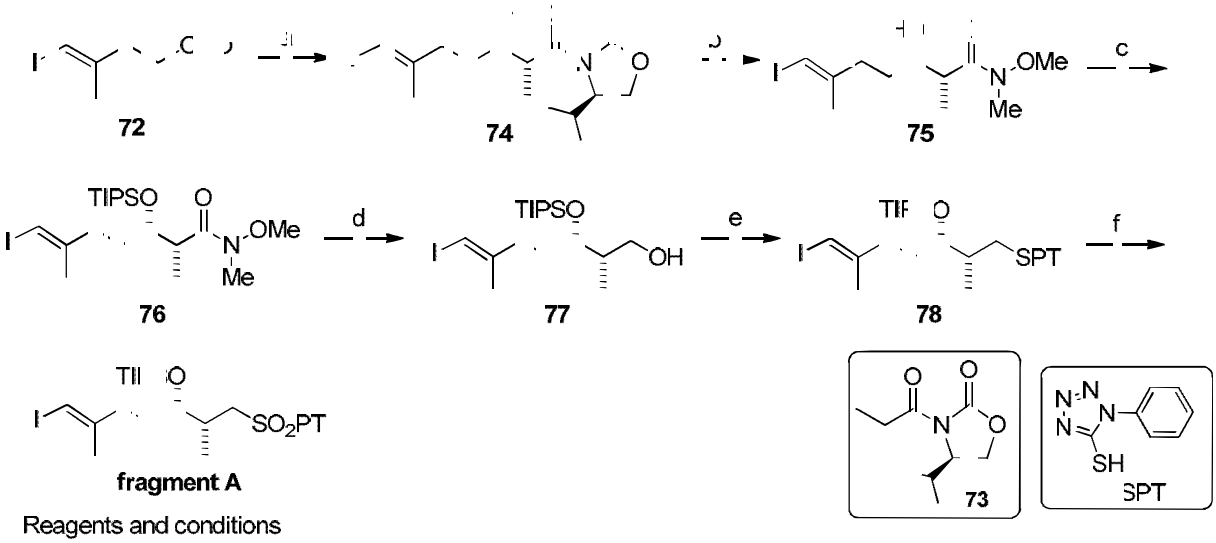
まずは(-)-bruceantin の AB 環の骨格に相当する *trans*-デカリン **67** および **68** を鍵中間体として設定し、その合成について検討することにした。ここでは 2 つの全炭素四級不斉中心(C8、C10 位)を如何に構築するかが課題となる。そこで TADA および IMDA 反応を用いて全炭素四級不斉中心を含む *trans*-デカリン骨格構築を

考えた。**67**および**68**のような立体配置を持つ*trans*-デカリン骨格を合成するには、ジエンの幾何配置が(*E*,*E*)であることと(*E*)-ジエノフィルを有している必要があり、*endo* 型の遷移状態を経ることによりジアステレオ選択的に望みの立体配置を得ることができると考えた。TADA および IMDA 反応の前駆体は **fragment A** と **fragment B** による Kocienski-Julia olefination[25)]により得られると考え、それらは容易に入手可能なアルコールからそれぞれ合成できるものとした (Scheme 4-2-2)。

第 3 節　3 置換アルケンを有する Diels-Alder 反応を用いた AB 環構築

fragment A の合成を Scheme 4-3-1 に示す。4-pentyne-1-ol から 2 工程で合成した文献既知化合物であるアルデヒド **72**[26]と (D)-valine 由来の不斉補助基 **73** を用いた Evans の不斉アルドール反応[27]により 1,2-*syn* のアルコール体 **74** を得た。**74** の不斉補助基を Weinreb アミド **75** へと変換後、水酸基を TIPS 基で保護し **76** とした。**76** を DIBAL 還元によりアルデヒドとし、精製することなしに $NaBH_4$ によりアルコール **77** へと還元した。そして光延条件下、**77** をスルフィド **78** とし Mo 触媒を用い酸化することにより **fragment A** を合成した(Scheme 4-3-1)。

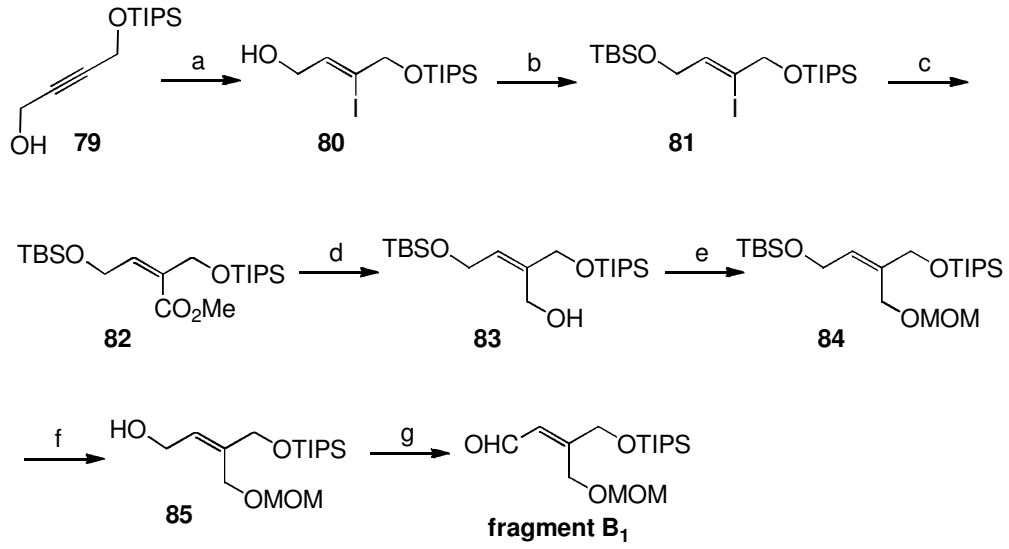
Scheme 4-3-1. Synthesis of Fragment A, the Substrate of the Kocienski-Julia Olefination



Reagents and conditions
(a) **73**, *n*-Bu_2BOTf, TEA, CH_2Cl_2, -78 °C to rt, 30 min, 85%; (b) Me_3AlCl, MeONHMe·HCl, CH_2Cl_2, 0 °C, rt, 1 h, 93%; (c) TIPSOTf, TEA, CH_2Cl_2, rt, 1 h, 90%; (d) DIBAL-H, THF, -78 °C, 2 h; then $NaBH_4$, MeOH, rt, 1 h, 93%; (e) HSPT, PPh_3, DEAD, THF, rt, 1 h, 95%; (f) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH/THF, rt, 1 d, 88%.

次に **fragment B_1** の合成を Scheme 4-3-2 に示す。2-butyn-1,4-diol から合成した文献既知化合物であるプロパルギルアルコール **79**[28]の水酸基を利用した Red-Al による位置選択的な還元を行い、ヨードアルケン **80** へと変換し水酸基を TBS 基で保護し **81** を得た。Pd を用いた一酸化炭素挿入反応により **81** をエステル **82** へと変換した。**82** を DIBAL-H によりアリルアルコール **83** へと還元し、水酸基を MOM 基により保護した。H_2SiF_6[29]を用い TBS 基の脱保護を行い、アリル位水酸基を活性 MnO_2 で酸化することにより **fragment B_1** を合成した。

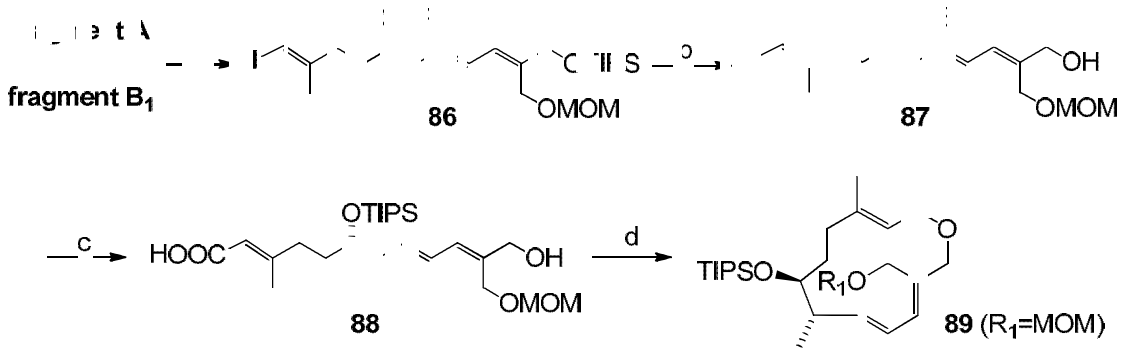
Scheme 4-3-2. Synthesis of Fragment B_1



Reagents and conditions
(a) Red-Al, Et_2O, 0 °C to rt, 10 min ;then I_2, -78 °C to 0 °C, 30 min, 88 %; (b) TBSCl, imidazole, CH_2Cl_2, rt, 30 min, 96%; (c) CO, $Pd(OAc)_2$, PPh_3, TEA, DMF/MeOH (3/2), 50 °C, 1 d, 68%; (d) DIBAL-H, CH_2Cl_2, -78 °C, 30 min, 100%; (e) MOMCl, DIPEA, NaI, CH_2Cl_2, 35 °C, 1 d, 96%; (f) H_2SiF_6, CH_3CN/*t*-BuOH (1/1), 0°C, 5 h, 93%; (g) MnO_2, CH_2Cl_2, rt, 1 h, 92%.

合成した **fragment A** と **fragment B_1** との Kocienski-Julia olefination により共役ジエン **86** を単一の生成物として得ることができた。H_2SiF_6 を用い選択的に TIPS 基の脱保護を行い、ジエノフィル部位をカルボン酸へと変換した。分子内マクロラクトン化は高希釈かつ低温下、光延条件で中程度の収率ではあるがマクロラクトン体 **89** を得ることに成功した (Scheme 4-3-3)。

Scheme 4-3-3. Synthesis of Macrolactone, the Substrate of the TADA Reaction

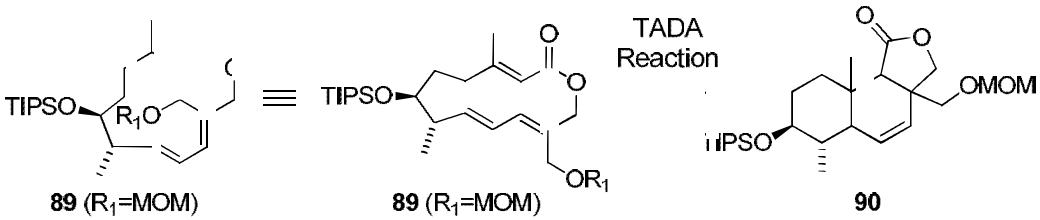


Reagents and conditions
(a) LDA, THF, -78 °C, 2 h, 63%; (b) H_2SiF_6, CH_3CN/*t*-BuOH (9/1), 0 °C, 5 h, 74%; (c) [illegible] PPh_3, 1*M*·KOH aq., 1,4-dioxane, 50 °C, 2 h, 85%; (d) DEAD, PPh_3, THF (0.002 M), -100 °C to -78 °C, 1 h, 49%.

ここで、得られた **89** を用い鍵反応である TADA 反応による AB 環の構築を試みた。熱による TADA 反応が全く進行しなかったため、Lewis 酸、超高圧実験[30]による反応の検討を行ったが、いずれの場合も環化体 **90** を経るには至らなかった (Table 4-3-1)。また、MOM 基を脱保護した基質及び TBS 基で保護した基質においても環化は進行しなかった。これは恐らく、ジエンが *s-cis* の立体配座をとること

ができず、*s-trans* に固定されているためと考えられる。その結果ジエノフィルとの軌道が重ならず反応が進行しなかったと考えられる。

Table 4-3-1. TADA Reaction

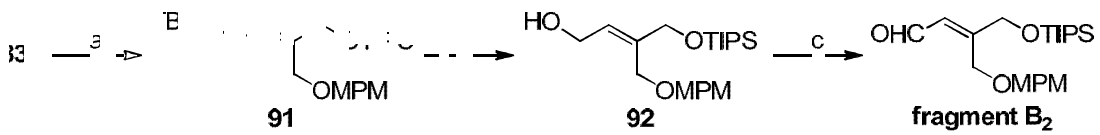


89 (R_1=MOM) *s-cis* ≡ **89** (R_1=MOM) *s-trans* → **90**

entry	reagent	solvent	temp (°C)	time (h)	results
1	BHT (sealed tube)	toluene	500	48	decomposition
2	Me_3Al (sealed tube)	toluene	300	48	decomposition
3	$LiClO_4$	toluene	110	24	decomposition
4	$SnCl_4$	CH_2Cl_2	-78 to 0	1	decomposition
5	$BF_3{\cdot}Et_2O$	toluene	50	0.5	decomposition
6	Me_2AlCl (sealed tube)	toluene	300	5	decomposition
7	[31] $TfNH_2$, Me_2AlCl	toluene	rt	24	decomposition
8	none (10000 atm)	CH_2Cl_2	40	2	N.R.
9	none (10000 atm)	toluene	60	2	N.R.

そこで *s-cis* の立体配座をとりやすくするために IMDA 反応による AB 環の合成を試みた。IMDA 反応での骨格構築は TADA 反応のルートと比較すると、マクロラクトン化と TADA 反応後のラクトン部位の開環の工程が短縮されるといった利点が挙げられる。しかし、IMDA 反応では TADA 反応と比べ、*endo*/*exo* 選択性またジアステレオ選択性が低くなるといった傾向になり得るが、ここで単一生成物が得られれば工程数の短縮につながる。そこで、効率的に合成を進めるために、ジエノフィル部位の LUMO のエネルギー準位を下げ反応を促進させることに加え、環形成後の官能基変換を行いやすくするためにジエノフィルの置換基をアルデヒドと決定した。この合成に必要な **fragment B_2** を新たに合成した。先程合成したアルコール体 **83** をイミデート法により MPM 基で保護し、続いて TBS 基を脱保護し、活性 MnO_2 で酸化して **fragment B_2** を合成した(Scheme 4-3-4)。

Scheme 4-3-4. Synthesis of Fragment B_2



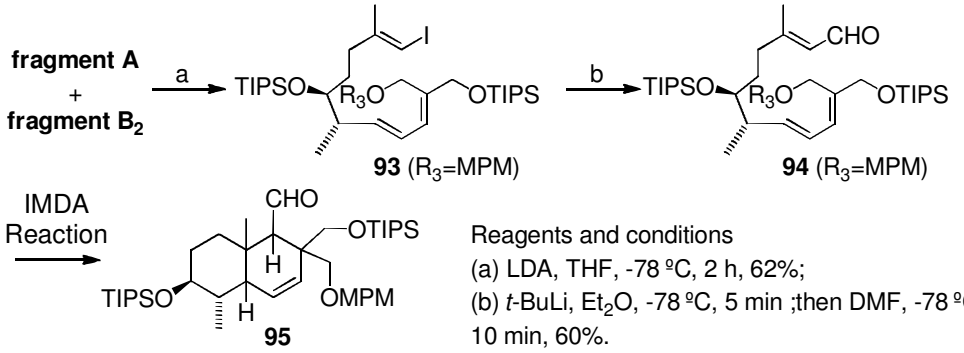
91 → **92** → **fragment B_2**

Reagents and conditions
(a) anisyl trichloroacetimi ate, PPTS, CH_2Cl_2, rt, 1 d, 76%) H_2SiF_6, CH_3CN/*t*-BuC (/1), (, 4 h, 74%; (c) MnO_2, CH_2Cl_2, rt, 30 min, 86%.

fragment A と **fragment B_1** との Kocienski-Julia olefination により共役ジエン **93** を単一の生成物として得ることができた。ジエノフィル部位をアルデヒドへと変換し、IMDA 反応を試みた。熱による反応は進行しなかったため、Lewis 酸によ

る検討を行った。Lewis 酸を用いると環化体 **95** は得られず、水素原子が 1,5-ヒドリドシフトした **95'**を主生成物として得る結果となってしまった(Table 4-3-2)。これは恐らく、共役ジエンの LUMO と MPM 基側のアリル位炭素の $\sigma_{C\text{-}H}$ 結合の HOMO との相互作用が、ジエノフィルの LUMO と共役ジエンの HOMO との相互作用よりも優先して起きていると考えられる。[1,5]-shift を抑えるためにジエンの 3 置換オレフィン部位を 2 置換へ変更すれば環化が進行すると考えた。

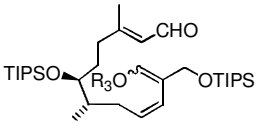
Scheme 4-3-5. Synthesis of **95**, the Substrate of the IMDA Reaction



Reagents and conditions
(a) LDA, THF, -78 ºC, 2 h, 62%;
(b) *t*-BuLi, Et_2O, -78 ºC, 5 min ;then DMF, -78 ºC, 10 min, 60%.

Table 4-3-2. IMDA Reaction

entry	reagent	solvent	temp (°C)	time (h)	results
1	BHT (sealed tube)	toluene	500	10	N.R.
2	$SnCl_4$	CH_2Cl_2	-78	0.5	decomposition
3	$EtAlCl_2$	toluene	0 to rt	2	decomposition
4	Me_2AlCl	toluene	-20	24	**95'** 43%
5	Me_2AlCl	CH_2Cl_2	-10	24	decomposition
6	Me_3Al	toluene	-10	2	**95'** 46%
7	$ZnBr_2$	toluene	0 to rt	0.5	decomposition

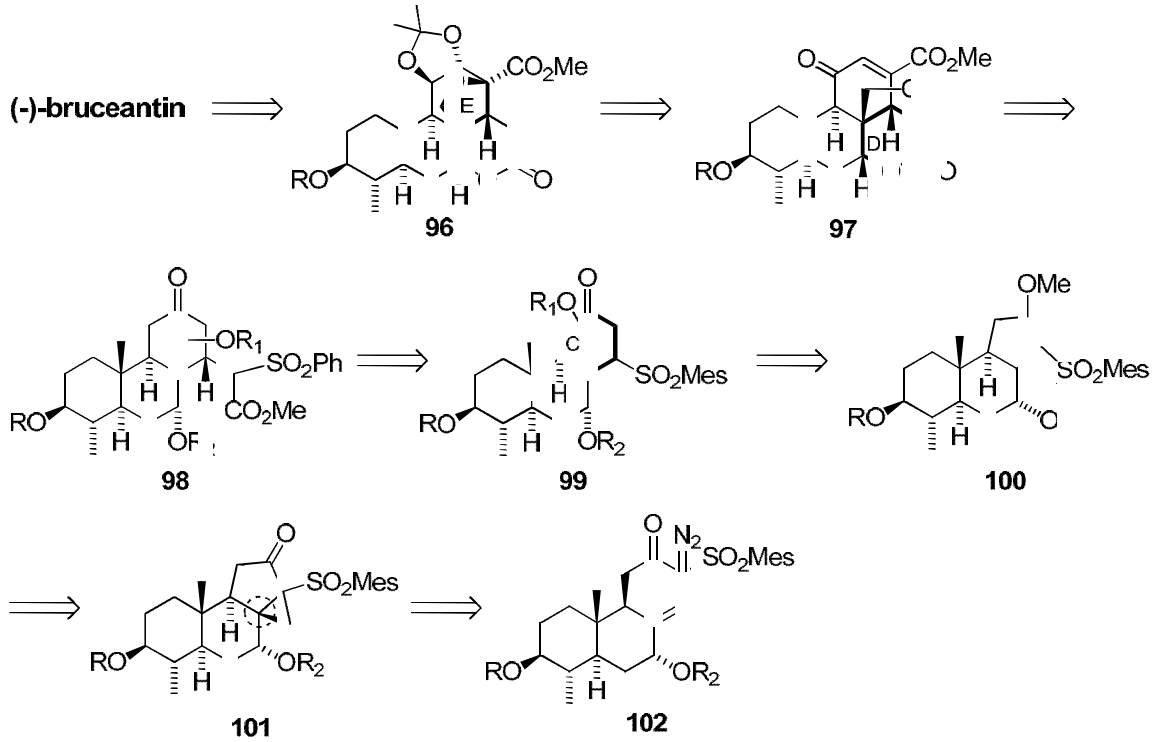


95' (R_3=MPM)

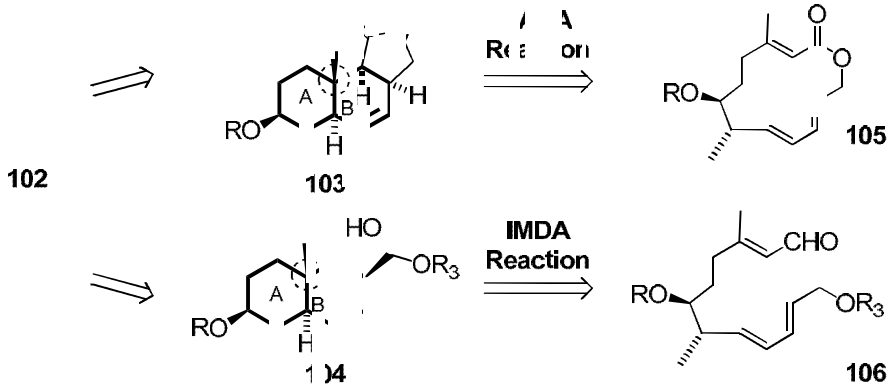
第 4 節　2 置換アルケンを有する Diels-Alder 反応を用いた AB 環構築

新たに Scheme4-4-1 に示すような逆合成解析を考えた。**96** は **97** からの分子内 Michael 付加反応により合成し、D 環は **98** からの分子内ラクトン化により構築できると考えた。続いて C 環は **100** からの環拡大反応により構築し、**101** は α-ジアゾ-β-ケトスルホン **102** からの分子内シクロプロパン化反応、続く開環反応により合成できるものとした。そして AB 環はジエンの 3 置換オレフィンを 2 置換オレフィンとした **105** からの TADA 反応、または **106** からの IMDA 反応により骨格構築ができるものと考えた。

Scheme 4-4-1. New Retrosynthetic Analysis of (-)-Bruceantin



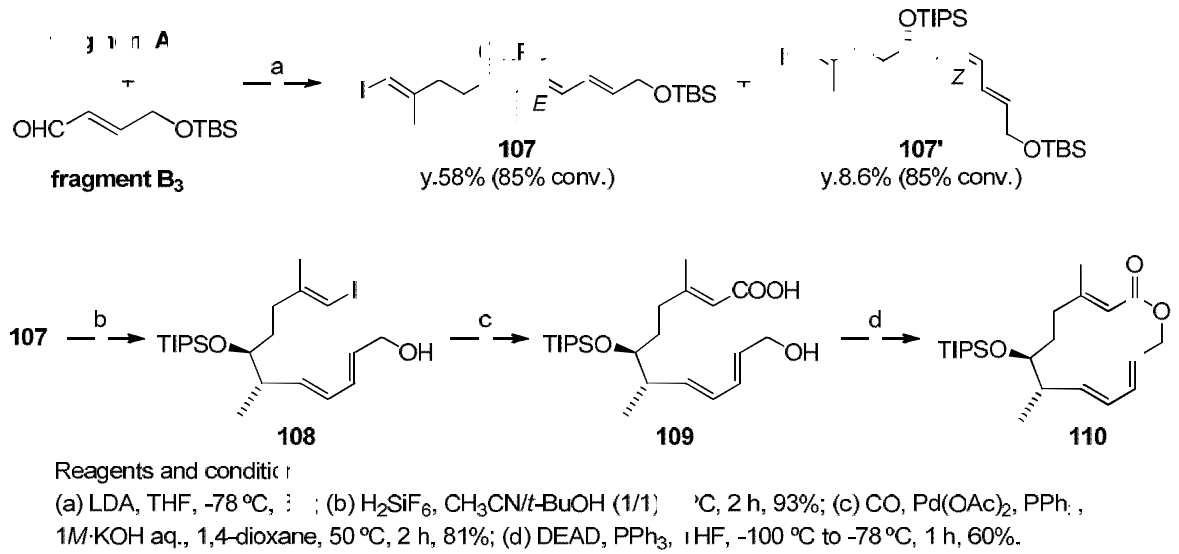
Scheme 4-4-2. New Retrosynthetic Analysis of Al -ri Moiety



fragment A と文献既知化合物 **fragment B**$_3$[32] との Kocienski-Julia olefination により共役ジエン **107** を(*E*/*Z*)=7/1 の混合物として得た。TBS 基の脱保護を行い、ジエノフィル部位をカルボン酸へと変換し、高希釈かつ低温下、光延条件でマクロラ

クトン体 **110** を合成した(Scheme 4-4-3)。

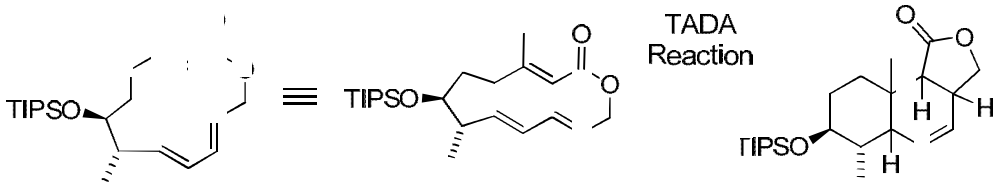
Scheme 4-4-3. Synthesis of Macrolactone, the Substrate of the TADA Reaction



Reagents and conditi
(a) LDA, THF, -78 °C, ; (b) H_2SiF_6, CH_3CN/*t*-BuOH (1/1) °C, 2 h, 93%; (c) CO, $Pd(OAc)_2$, PPh_3, 1*M*·KOH aq., 1,4-dioxane, 50 °C, 2 h, 81%; (d) DEAD, PPh_3, HF, -100 °C to -78 °C, 1 h, 60%.

ここで、得られた **110** から鍵反応である TADA 反応による AB 環の構築を試みた。熱、ルイス酸による反応の検討を行ったが、いずれの場合も環化体 **111** を得るには至らなかった(Table 4-4-1)。これらの結果は 3 置換オレフィンの時と同じ理由、すなわち、ジエンが *s-cis* の立体配座を取りにくいためと考えられる。そこで、次に IMDA 反応による AB 環の構築に移った。

Table 4-4-1. TADA Reaction



110 *s-cis* **110** *s-trans* **111**

entry	reagent	solvent	temp (°C)	time (h)	results
1	BHT (sealed tube)	1,2-$C_6H_4Cl_2$	400	24	N.R.
2	$LiClO_4$	toluene	110	24	N.R.
3	$SnCl_4$	CH_2Cl_2	-78 to 0	1	decomposition
4	Me_2AlCl	toluene	110	24	N.R.
5	$TfNH_2$, Me_2AlCl	toluene	0 to rt	1	N.R.
6	$ZnBr_2$	toluene	50	24	decomposition

共役ジエン **107** のジエノフィル部位のアルデヒドへの変換は、副生成物として得られる **113** を *n*-BuLi を用いることで痕跡量に抑えることができた。**112** の IMDA 反応は熱による反応は進行するものの、原料が消失する前に生成物が分解してしまった。そこで Lewis 酸の検討を行った。Lewis 酸性が強い試薬は反応直後に原料が分解してしまう傾向にあったので、Lewis 酸性のより低い Me_2AlCl を用いたところ反応は進行し、3/1 のジアステレオ比で環化体 **114** を得た(Table 4-4-2, entry 6)。

Scheme 4-4-4. Synthesis of **112**, the Substrate of the IMDA Reaction

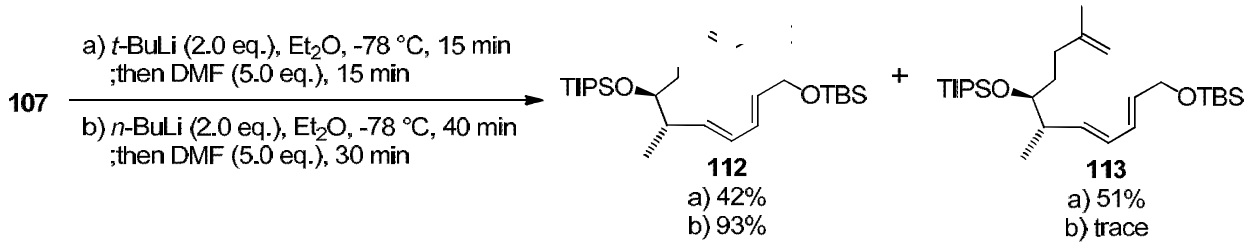
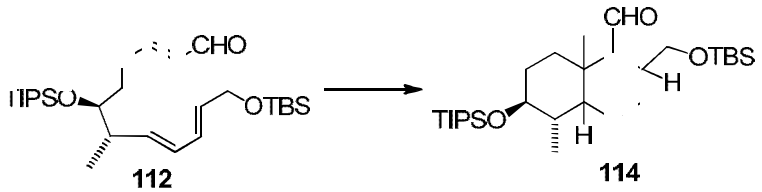


Table 4-4-2. IMDA Reaction of **112**

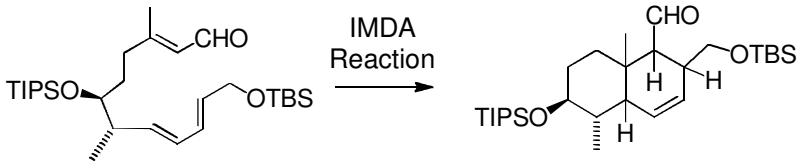


entry	reagent	solvent	temp (°C)	time (h)	results
1	BHT	1,2-$C_6H_4Cl_2$	reflux	24	decomposition
2	$SnCl_4$	CH_2Cl_2	-78	0.2	decomposition
3	$BF_3{\cdot}OEt_2$	CH_2Cl_2	-10	2	decomposition
4	$TiCl_4$	toluene	-50	0.5	decomposition
5	$EtAlCl_2$	toluene	0	24	multi spots
6	Me_2AlCl	toluene	rt	1	64% (dr = 3:1) [a]

a) Dr was determined by ^1H NMR.

Lewis 酸を Me_2AlCl に固定し溶媒および温度の検討を行なった(Table 4-4-3)。CH_2Cl_2 溶媒では基質が分解してしまったが Et_2O 溶媒では toluene 溶媒と同様に環化体が得られた。しかし、ジアステレオ比は 3/1 であった。溶媒を toluene に固定し、0℃で反応させたところ原料は残るがジアステレオ比は 33/1 と劇的に向上した。さらに最適化することで entry 6 に示すように-10℃で Me_2AlCl (0.4 equiv)を 3 回に分けて添加し 72 時間反応させることで単一の生成物として環化体を 74%収率で得ることに成功した。

Table 4-4-3. Optimization of the IMDA Reaction



112 **114**

entry	Me_2AlCl (equiv)	solvent	temp (°C)	time (h)	yield (%)
1	1.0	toluene	rt	3	64 (dr = 3/1) [c]
2	1.0	CH_2Cl_2	-10	3	decomposition
3	1.0	Et_2O	0	24	64 (dr = 3/1) [c]
4	1.0	toluene	0	24	63 (81% conv.) (*d.r.*= 33/1) [c]
5	[a] 1.2	toluene	-10	48	60 (dr = 1/0) [c]
6	[b] **1.2**	**toluene**	**-10**	**72**	**74 (dr = 1/0)** [c]

a) Me_2AlCl (0.6 equiv) was added at intervals of 24 h.
b) Me_2AlCl (0.4 equiv) was added at intervals of 24 h.
c) Dr was determined by ^1H NMR.

得られた環化体 **114** を NOESY 測定したところ Figure 4-4-1 に示す相関が得られた。ここでは構造決定出来る全ての相関は観測されなかったが C8 位 C9 位のプロトンは *cis* の関係にあることが示唆された。

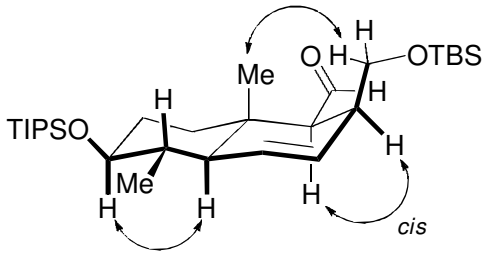
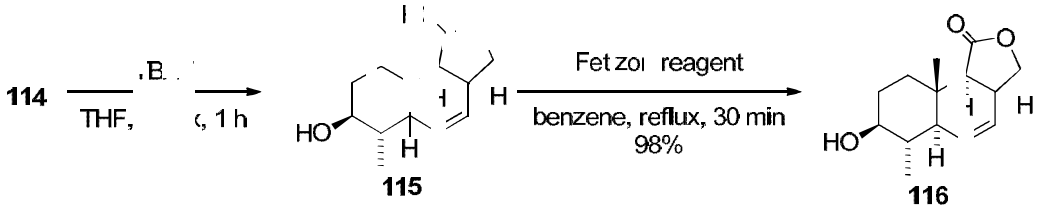


Figure 4-4-1. NOE Correlations in the NOESY Spectrum of **114**

環化体 **114** の構造を完全に決定するため、TBAF により脱シリル化し、ラクトール **115** を得て Fetizon 試薬 [33]を用いラクトール部位を選択的に酸化することによりラクトン **116** を合成した(Scheme 4-4-5)。**116** の NOESY 測定により絶対配置を推定した(Figure 4-4-2)。測定の結果、望みの立体配置を有する環化体であることが強く示唆された。反応機構としては、メチル基および OTIPS 基が pseudo equatorial に位置するコンフォーマーがエネルギー的に安定と考えられ、さらに二次的相互作用が働く *endo* 型の遷移状態を経由し反応が進行していると考えられる(Figure 4-4-3)。

Scheme 4-4-5. Synthesis of **116** for Structure Determination



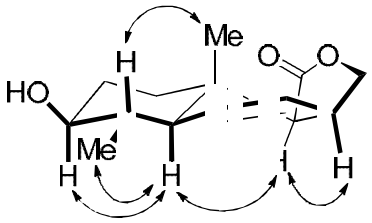
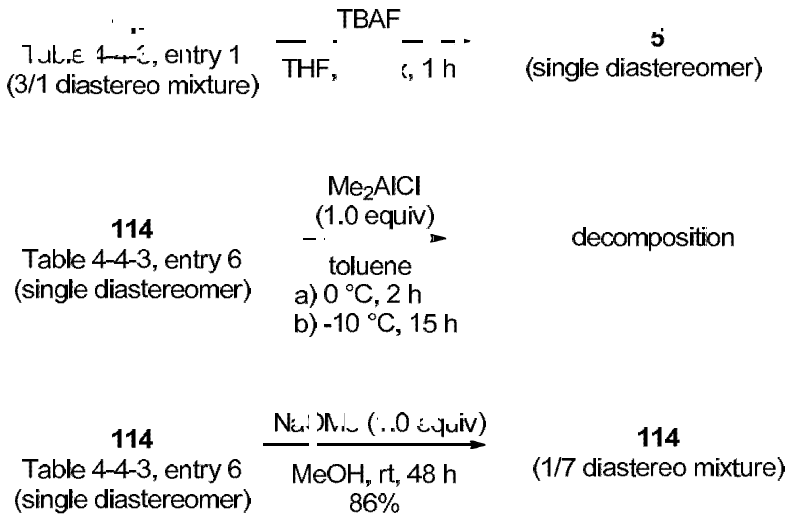


Figure 4-4-2. NOE Correlations in the NOESY Spectrum of **116**

IMDA 反応時の minor 生成物の構造決定を行なった。Table 4-4-3, entry 1 に示す条件で 3/1 のジアステレオ比で minor 体が得られているがカラムクロマトグラフィーによる分離は困難で単離できなかった。そこでシリル基を除去し分離できるか試みたところ、**115** が単一の生成物として得られた。このことは TBAF によりアルデヒドの α 位のエピメリ化が起きていると考えられ、IMDA 反応は Figure 4-4-3 に示す *exo* では進行していないことが示唆された。Table 4-4-3, entry 6 に示す条件で得られた単一の化合物を再度 Me_2AlCl で処理すると基質が分解した。そこで NaOMe で処理したところ ca.1/7 のジアステレオ比に変化したことから IMDA の minor 体は Figure 4-4-3 に示す **114'** であることが示唆された。

Scheme 4-4-6. Experiments for Structure Determination of the IMDA Reaction



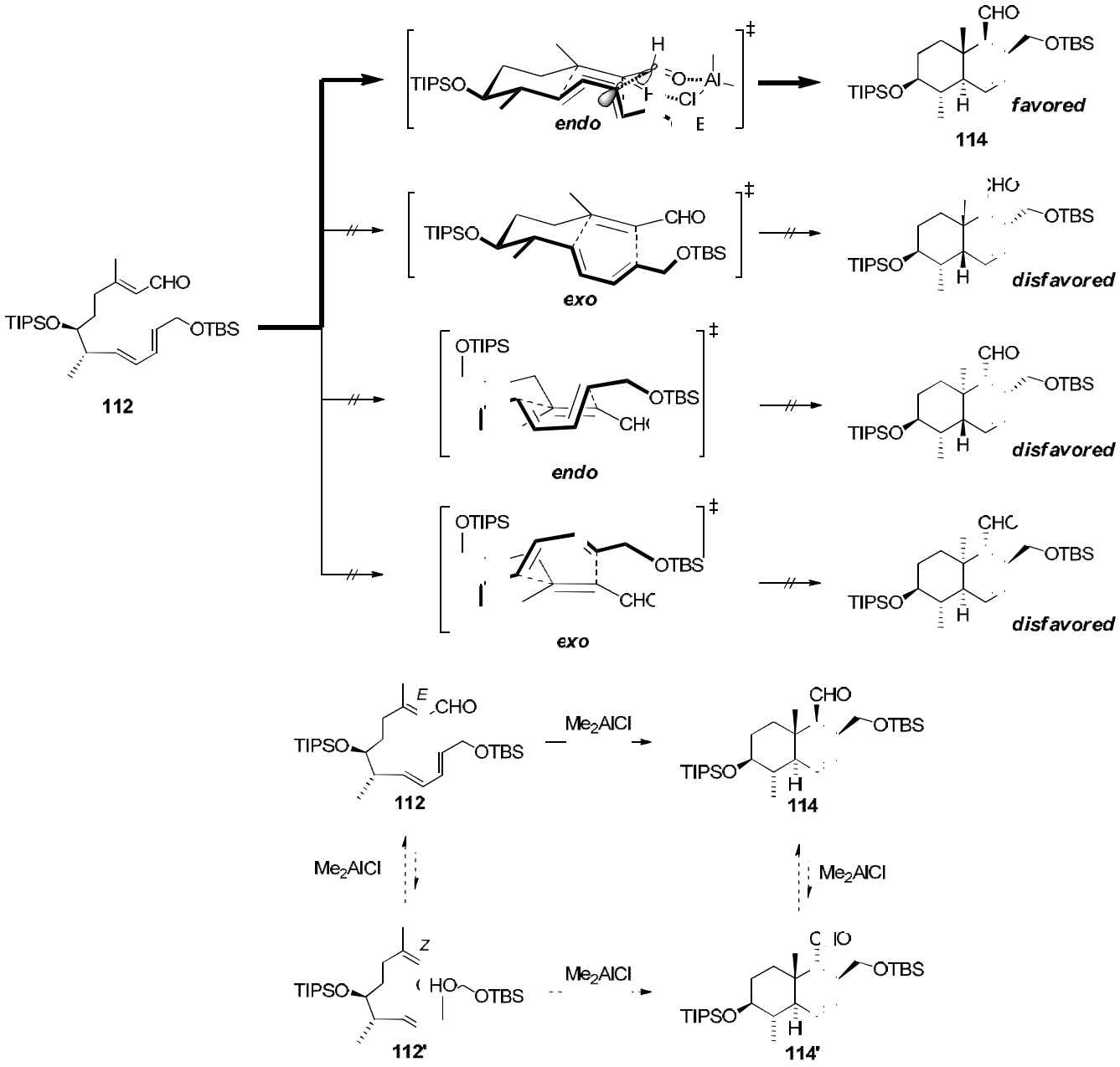
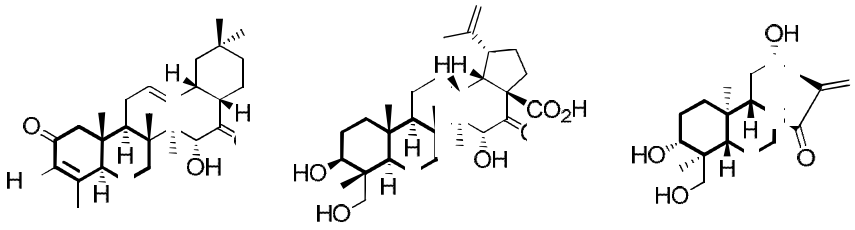


Figure 4-4-3. Proposed Mechanism of the IMDA Reaction

以上をまとめると **112** の IMDA 反応は Lewis 酸として Me_2AlCl を用いると室温では **114**/**114'**=ca.3/1 のジアステレオ比で環化体を与えた。おそらく Me_2AlCl の作用で **112** のジエノフィル部位が *Z* 体 **112'**に異性化し *endo* 選択的に IMDA 反応が進行したか、または生成物 **114** がエピメリ化し **114'**が得られてきていると推察される。一方、-10℃ではそれらの反応を抑制し **112** の *endo* 選択的な IMDA 反応が進行し単一の生成物として目的物 **114** を得ることが出来た。

IMDA 反応で C10 位にあたる全炭素四級不斉中心を含む *trans*-デカリン骨格を高立体選択的に収率良く構築でき、TADA 反応での合成よりも短工程で合成できたことになる。アルデヒドのα位が塩基性条件でエピメリ化しやすいことがわかったが、低温条件下では立体を保持して側鎖を変換できると考えている。

114 を合成できたことで bruceantin 以外にも Figure4-4-4 に示す生物活性を有する天然物合成も可能になったと考えている。



[34] ren angilone [35] hydroxybetulinulic acid [36] strobilinin L

Figure 4-4-4. t Remang nulic emioidin L

第 5 章　総括

本論文を以下のように総括する。

第 2 章　(-)-bucidarasin A の不斉全合成

当研究室において開発された baker's yeast を用いた 1,3-シクロヘキサンジオンの還元により得られるキラルビルディングブロック合成を活用しα-アルキリデンβ-ケトエステルを合成した。Lewis 酸として $SnCl_4$ を用いたビスシリルオキシペンタジエンとの BMDA 反応により *exo*/*endo* の比率は 9/1 であったものの、高収率かつ完全なジアステレオ面選択性で望みの立体配置を有する C5 位全炭素四級不斉中心を含む骨格構築に成功した。C9 位側鎖の(*E*)-3-メチル-2,4-ペンタジエニル基の構築については 2 つの難題を解決し成功に至った。1 つ目は立体障害の大きいネオペンチル位における反応を反応性の高いアルデヒドを利用しアルキンを付加、続くギ酸還元により増炭できた点である。2 つ目はプロパルギルアルコール体に対し MeMgCl/CuI を作用させメチル基が導入された(*E*)-アリルアルコール体を立体選択的に得たことである。そして C9 位側鎖である(*E*)-3-メチル-2,4-ペンタジエニル基の導入に成功した。ビスアセトキシ THF 環は、ジアルデヒド体から $AcONa/AcOH/Ac_2O/conc.H_2SO_4$ の条件で熱力学的支配により単一の異性体として得ることができた。これらの成功により(-)-bucidarasin A の不斉全合成を達成した。また、天然物の絶対立体配置を明らかにした。

第 3 章　(+)-bucidarasin A および C の不斉全合成

当研究室において開発された CBS 試薬を用いた 1,3-シクロヘキサンジオンの還元により得られるキラルビルディングブロックを合成し、(-)-bucidarasin A の合成中間体のエナンチオマーへと誘導できた。この合成中間体から(-)-bucidarasin A の全合成と同様の合成方法により(+)-bucidarasin A の初の不斉全合成を達成した。また、Barton-McCombie の手法により(+)-bucidarasin A の C6 位水酸基を選択的に除去することに成功し、(+)-bucidarasin C の初の不斉全合成も達成した。

第 4 章　(-)-bruceantin の不斉全合成研究

(-)-bruceantin の有する 2 つの全炭素四級不斉中心(C8、C10 位)を含む AB 環骨格に相当する *trans*-デヒドロデカリン骨格を 3 置換アルケン有する(*E*,*E*,*E*)トリエンからの TADA および IMDA 反応による構築を試みたが立体配座の関係により困難であった。そこでジエノフィルを 2 置換アルケンへと変更し、TADA および

IMDA 反応を行った。TADA 反応は全く反応が進行しなかったが、IMDA 反応では Lewis 酸として Me_2AlCl を用い、低温下反応を行ったところ所望の立体配置を有する環化体を高収率、高選択的に得ることに成功した。(-)-bruceantin の全炭素四級不斉中心(C10 位)を含む AB 環骨格の高立体選択的合成法を確立した。

第 6 章　実験項

第 1 節　General Information and Materials

General Information.

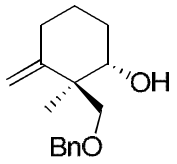
^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECS400 spectrometer, a BRUKER AVANCE 500 spectrometer and a BRUKER AVANCE 600 spectrometer. ^{1}H and ^{13}C chemical shifts are reported in ppm downfield from tetramethylsilane (TMS, δ scale) with the solvent resonances as internal standards. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; br, broad. IR spectra were recorded on a JASCO FT/IR-8300. Melting points (mp) are uncorrected, recorded on a Yamato capillary melting point apparatus. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a JASCO DIP-1000. Mass spectra and elemental analyses were provided at the Materials Characterization Central Laboratory, Waseda University. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and phosphomolybdic acid and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on self-made 0.3 mm E. Merck silica gel plates (60F-254).

Materials.

THF, Et_2O, diglyme and 1,4-dioxane were distilled from sodium/benzophenone ketyl, and methylene chloride (CH_2Cl_2), MeCN, benzene, hexane and heptane from calcium hydride. DMF and DMSO were distilled from CaH_2 under reduced pressure. Toluene and EtOH were distilled from sodium. MeOH was distilled from magnesium and I_2. All reagents were purchased from Aldrich, TCI, Merck, or Kanto Chemical Co. Ltd.

第 2 節　(-)-bucidarasin A の不斉全合成

(1*S*,2*R*)-2-[(benzyloxy)methyl]-2-methyl-3-methylidenecyclohexan-1-ol (8)

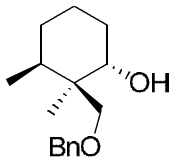


8

To a stirred solution of PPh_3CH_3Br (39.5 g, 111 mmol) in THF (352 mL) was added *n*-BuLi (1.65 M solution in hexane, 55.9 mL, 92.2 mmol) dropwise at 0 ºC, and the reaction mixture was stirred for 30 min. Then, to the reaction mixture was added a solution of **6** (9.16 g, 36.9 mmol) in THF (15.0 mL) via a cannula at -30 ºC. After the addition, the mixture was stirred at the same temperature for 16 h, and then was quenched by saturated aqueous NH_4Cl solution (222 mL). The aqueous layer was extracted with Et_2O (100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 4/1) to afford **8** (7.42 g, 82%) as a colorless oil and starting material **6** (920 mg, 10%).

R_f = 0.39 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.39-7.27 (5H, m), 4.75 (1H, s), 4.60 (1H, d, *J* = 11.9 Hz), 4.56, (1H, d, J = 11.9 Hz), 4.50 (1H, s), 3.73 (1H, d, *J* = 8.7 Hz), 3.69 (1H, ddd, *J* = 6.0, 4.6, 1.4 Hz), 3.65 (1H, d, *J* = 8.7 Hz), 3.61 (1H, d, *J* = 1.4 Hz), 2.22 (1H, ddd, *J* = 13.7, 13.7, 4.6 Hz), 2.06 (1H, ddd, *J* = 13.7, 3.2, 3.2 Hz), 1.85-1.70 (2H, m), 1.63-1.48 (1H, m), 1.37-1.23 (1H, m), 1.18 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 137.7, 128.5, 127.8, 127.5, 107.7, 79.2, 76.3, 73.8, 44.6, 32.6, 29.7, 24.2, 16.2; IR (neat) ν_{max} 3448, 2934, 2860, 1637, 1453, 1358, 1070, 888, 734, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{22}O_2Na$: 269.1512, found: 269.1511; $[\alpha]^{26}_D$ +10.6 (*c* 1.09, $CHCl_3$).

(1*S*,2*R*,3*S*)-2-[(benzyloxy)methyl]-2,3-dimethylcyclohexan-1-ol (9)



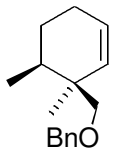
9

To a stirred solution of Crabtree's catalyst (45.6 mg, 0.0566 mmol) in $(CH_2Cl)_2$ (43.0 mL) was added a solution of **8** (2.79 g, 11.3 mmol) in $(CH_2Cl)_2$ (13.0 mL) via a cannula at room temperature. After the addition, the mixture was stirred at 80 ºC for

24 h, and then was quenched by saturated aqueous NH_4Cl solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (30 mL x 2). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 25/1) to afford **9** (2.69 g, 92%) as a colorless oil.

R_f = 0.63 (dichloromethane/methanol = 50/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.37-7.25 (5H, m), 4.55 (1H, d, *J* = 12.4 Hz), 4.49 (1H, d, *J* = 12.4 Hz), 3.89 (1H, dd, *J* = 8.2, 4.6 Hz), 3.65 (1H, d, *J* = 8.7 Hz), 3.31 (1H, d, *J* = 8.7 Hz), 2.89 (1H, br s), 1.77-1.61 (3H, m), 1.61-1.38 (3H, m), 1.27-1.17 (1H, m), 1.11 (3H, s), 0.86 (3H, d, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 128.4, 127.6, 127.4, 78.9, 73.6, 72.6, 40.9, 36.2, 29.7, 28.8, 19.2, 17.3, 14.8; IR (neat) ν_{max} 3435, 2932, 2862, 1453, 1360, 1065, 733, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{24}O_2Na$: 271.1669, found: 271.1668; $[\alpha]^{27}_D$ +5.4 (*c* 1.15, $CHCl_3$).

({[(1*S*,6*S*)-1,6-dimethylcyclohex-2-en-1-yl]methoxy}methyl)benzene (10)

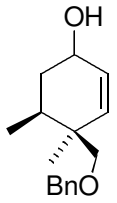


10

To a stirred solution of **9** (6.21 g, 25.0 mmol) in pyridine (46.5 mL) was added $POCl_3$ (5.67 mL, 62.5 mmol) at 0 ºC, the mixture was stirred at 80 ºC for 16 h. The reaction mixture was quenched by H_2O (50 mL), the aqueous layer was extracted with Et_2O (100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 100/1) to afford **10** (5.63 g, 98%) as a colorless oil.

R_f = 0.77 (hexane/ethyl acetate = 8/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.38-7.23 (5H, m), 5.68 (1H, ddd, *J* = 10.0, 3.6, 3.6 Hz), 5.42 (1H, ddd, *J* = 10.0, 2.3, 2.3 Hz), 4.49 (2H, s), 3.27 (2H, s), 2.08-1.91 (2H, m), 1.65-1.48 (3H, m), 1.05 (3H, s), 0.93 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 134.2, 128.2, 127.3, 127.2, 126.4, 76.1, 73.3, 38.5, 36.8, 27.2, 25.0, 24.3, 15.8; IR (neat) ν_{max} 2957, 2921, 2859, 1453, 1365, 1095, 733, 695 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{22}ONa$: 253.1563, found: 253.1563; $[\alpha]^{27}_D$ -33.7 (*c* 2.03, $CHCl_3$).

(4*S*,5*S*)-4-[(benzyloxy)methyl]-4,5-dimethylcyclohex-2-en-1-ol (11)

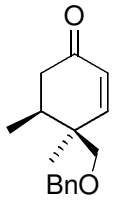


11

To a stirred solution of **10** (5.63 g, 24.4 mmol) in 1,4-dioxane/HCOOH (50/1, 290 mL) was added SeO_2 (3.53 mg, 31.8 mmol) at room temperature, the mixture was stirred at 80 ºC for 3 d. The reaction mixture was added H_2O (50 mL) and Et_2O (50 mL), filtered through a Celite pad, and the filtrate was evaporated. To a stirred solution of the residue in MeOH (50 mL) was added ca.30% NH_4OH (50 mL) at 0 ºC, the mixture was stirred at room temperature for 1 h. The mixture was extracted with Et_2O (100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford **11** (3.91 g, 65%) as a pale yellow oil.

R_f = 0.22 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ7.39-7.24 (5H, m), 5.82 (1H, ddd, *J* = 10.1, 4.6, 0.92 Hz), 5.63 (1H, dd, *J* = 10.1, 0.92 Hz), 4.46 (2H, s), 4.18 (1H, dd, *J* = 8.2, 4.6 Hz), 3.31 (1H, d, *J* = 9.2 Hz), 3.22 (1H, d, *J* = 9. 2 Hz), 1.91 (1H, ddd, *J* = 15.6, 11.0, 4.6 Hz), 1.86-1.76 (1H, m), 1.70-1.58 (1H, m), 1.07 (3H, s), 0.96 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.4, 128.2, 127.8, 127.3, 127.3, 75.0, 73.3, 64.4, 39.0, 36.8, 32.9, 24.4, 15.7; IR (neat) ν_{max} 3346, 2959, 2927, 2873, 1454, 1366, 1098, 1041, 734, 697 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{22}O_2Na$: 269.1512, found: 269.1513; $[\alpha]^{27}_D$ -67.7 (*c* 1.01, $CHCl_3$).

(4*S*,5*S*)-4-[(benzyloxy)methyl]-4,5-dimethylcyclohex-2-en-1-one (12)



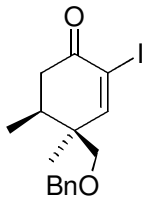
12

To a stirred solution of **11** (3.91 g, 15.9 mmol) in CH_2Cl_2 (53.0 mL) was added MS4Å (7.31 g, 0.46 g/mmol) and PDC (9.13 g, 23.8 mmol) successively at room temperature. The reaction mixture was stirred at the same temperature for 5 h, diluted with CH_2Cl_2 (30 mL), the mixture was filtered through a short pad of Florisil. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 8/1) to afford **12** (3.34 g, 86%) as a pale

yellow oil.

R_f = 0.37 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ7.40-7.22 (5H, m), 6.64 (1H, d, *J* = 10.0 Hz), 6.00 (1H, d, *J* = 10.0 Hz), 4.47 (2H, s), 3.54 (1H, d, *J* = 9.1 Hz), 3.32 (1H, d, *J* = 9.1 Hz), 2.58 (1H, dd, *J* = 17.2, 11.8 Hz), 2.36 (1H, dd, *J* = 17.2, 5.0 Hz), 2.15-2.00 (1H, m), 1.15 (3H, s), 1.01 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 156.5, 138.0, 128.5, 128.3, 127.6, 127.3, 74.1, 73.4, 42.9, 40.1, 37.3, 23.4, 15.6; IR (neat) ν_{max} 2963, 2875, 1673, 1454, 1372, 1095, 735, 697 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{20}O_2Na$: 267.1356, found: 267.1355; $[\alpha]^{28}_D$ -48.1 (*c* 1.10, $CHCl_3$).

(4*S*,5*S*)-4-[(benzyloxy)methyl]-2-iodo-4,5-dimethylcyclohex-2-en-1-one (13)

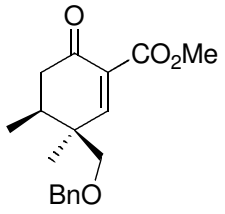


13

To a stirred solution of **12** (3.33 g, 13.6 mmol) in CCl_4/pyridine (1/1, 130 mL) was added DMAP (167 mg, 1.36 mmol) and I_2 (10.4 g, 40.9 mmol) successively at room temperature. The reaction mixture was stirred at 50 ºC for 24 h, quenched by saturated aqueous $NaHCO_3$ solution (50 mL) and saturated aqueous $Na_2S_2O_3$ solution (50 mL) successively, the aqueous layer was extracted with AcOEt (100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **13** (4.94 g, 98%) as a pale yellow oil.

R_f = 0.51 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ7.43 (1H, s), 7.38-7.23 (5H, m), 4.47 (2H, s), 3.54 (1H, d, *J* = 9.2 Hz), 3.29 (1H, d, *J* = 9.2 Hz), 2.80 (1H, dd, *J* = 16.9, 11.9 Hz), 2.59 (1H, dd, *J* = 16.9, 4.6 Hz), 2.19-2.07 (1H, m), 1.14 (3H, s), 1.00 (3H, d, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 164.7, 137.7, 128.4, 127.7, 127.5, 103.4, 73.5, 73.4, 45.0, 42.0, 37.4, 23.1, 15.4; IR (neat) ν_{max} 2964, 2873, 1683, 1594, 1453, 1097, 737, 698 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{19}O_2INa$: 393.0322, found: 393.0322; $[\alpha]^{28}_D$ -24.3 (*c* 1.54, $CHCl_3$).

methyl
(3*S*,4*S*)-3-[(benzyloxy)methyl]-3,4-dimethyl-6-oxocyclohex-1-ene-1-carboxylate
(4)

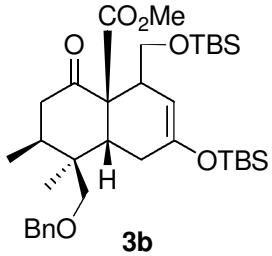


4

To a stirred solution of **13** (5.78 g, 15.6 mmol) in MeOH/THF (1/1, 180 mL) was added Et_3N (6.53 mL, 46.8 mmol) and $Pd(PPh_3)_4$ (541 mg, 0.468 mmol) successively at room temperature under an atmosphere of Ar. The reaction mixture was stirred at 55 ºC for 8 h under an atmosphere of CO, quenched by saturated aqueous NH_4Cl solution (100 mL). After evapotation of the volatile solvent, the residue was extracted with Et_2O (50 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 8/1) to afford **4** (4.62 g, 98%) as a pale yellow oil.

R_f = 0.40 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400MHz, $CDCl_3$) δ7.35 (1H, s), 7.34-7.24 (5H, m), 4.47 (2H, s), 3.81 (3H, s), 3.59 (1H, d, *J* = 9.2 Hz), 3.35 (1H, d, *J* = 9.2 Hz), 2.70 (1H, dd, *J* = 16.5, 11.4 Hz), 2.43 (1H, dd, *J* = 16.5, 4.6 Hz), 2.17-2.04 (1H, m), 1.19 (3H, s), 1.01 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3, 165.1, 161.7, 137.7, 131.5, 128.4, 127.7, 127.4, 73.6, 73.5, 52.2, 43.8, 40.8, 36.9, 22.9, 15.3; IR (neat) ν_{max} 2964, 2876, 1740, 1683, 1454, 1368, 1265, 1097, 738, 698 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{18}H_{22}O_4Na$: 325.1410, found: 325.1410; $[\alpha]^{28}_D$ -9.9 (*c* 0.74, $CHCl_3$).

methyl (1*S*,2*S*,4a*R*,8a*R*)-1-[(benzyloxy)methyl]-7-[(*tert*-butyldimethylsilyl)oxy]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-1,2-dimethyl-4-oxo-1,2,3,4,4a,5,8,8a-octahydronaphthalene-4a-carboxylate (3b)



3b

To a solution of **4** (3.61 g, 11.9 mmol) and **5b** (5.89 g, 17.9 mmol) in Et_2O (120 mL) at -60 ºC was added $SnCl_4$ (0.140 mL, 1.19 mmol) dropwise over 5 min maintaining the temperature at −55 to −60 ºC. The reaction mixture was stirred at -60 ºC for 17 h,

quenched by saturated aqueous $NaHCO_3$ solution (50 mL). The precipitate was filtered through a Celite pad, and the filtrate was extracted with Et_2O (100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. To a solution of crude residue in Et_2O (120 mL) at -60 ºC was added $SnCl_4$ (0.14 mL, 1.19 mmol) dropwise over 5 min maintaining the temperature at −55 to −60 ºC. The reaction mixture was stirred at -60 ºC for 17 h, quenched by saturated aqueous $NaHCO_3$ solution (50 mL). The precipitate was filtered through a Celite pad, and the filtrate was extracted with Et_2O (100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate/TEA = 20/1/2) to afford diastereo mixture **3b** (dr = 9/1) (7.16 g, 95%) as a pale yellow oil and starting material **4** (177 mg, 5%).

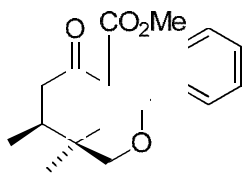
major product

R_f = 0.63 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ7.40-7.25 (5H, m), 4.97 (1H, d, *J* = 1.8 Hz), 4.53 (1H, d, *J* = 11.9 Hz), 4.39 (1H, d, *J* = 11.9 Hz), 4.00 (1H, dd, *J* = 9.6, 9.6 Hz), 3.61 (3H, s), 3.44 (1H, d, *J* = 9.6 Hz), 3.44-3.40 (1H, m), 3.40 (1H, d, *J* = 9.6 Hz), 3.08 (1H, dd, *J* = 11.0, 7.3 Hz), 2.86 (1H, dd, *J* = 15.1, 15.1 Hz), 2.78-2.70 (1H, m), 2.17 (2H, dt, *J* = 10.5, 4.6 Hz), 2.18-2.09 (1H, m), 1.92-1.80 (1H, m), 1.07 (3H, s), 0.94 (3H, d, *J* = 6.4 Hz), 0.90 (9H, s), 0.86 (9H, s), 0.13 (3H, s), 0.11 (3H, s), 0.019 (3H, s), -0.008 (3H, s)

minor product

R_f = 0.63 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ7.38-7.24 (5H, m), 4.97 (1H, br s), 4.52 (1H, d, *J* = 11.9 Hz), 4.44 (1H, d, *J* = 11.9 Hz), 3.90-3.79 (2H, m), 3.64 (3H, s), 3.35 (1H, d, *J* = 9.2 Hz), 3.26 (1H, d, *J* = 9.2 Hz), 3.17 (1H, dd, *J* = 7.3, 2.7 Hz), 2.92-2.84 (1H, m), 2.64-2.58 (2H, m), 2.24-2.11 (1H, m), 2.04-1.83 (2H, m), 1.11 (3H, s), 1.03 (3H, d, *J* = 6.9 Hz), 0.90 (9H, s), 0.87 (9H, s), 0.12 (3H, s), 0.10 (3H, s), 0.035 (3H, s), 0.011 (3H, s); HRMS (ESI) $[M+Na]^+$ calculated for $C_{35}H_{58}O_6NaSi_2$: 653.3664, found: 653.3661

(5*R*,6*S*)-methyl
5,6-dimethyl-8-oxo-2-phenyl-3-oxa-bicyclo[3.3.1]nonane-1-carboxylate (4')

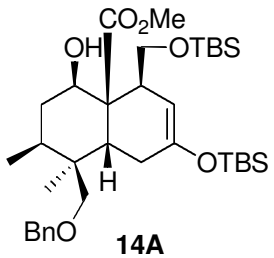


4'

To a solution of **4** (70.6 mg, 0.233 mmol) and **5a** (153 mg, 0.467 mmol) in toluene (1.5 mL) was added $ZnCl_2$ (47.7 mg, 0.350 mmol), and the mixture was stirred at 60 °C for 10 h. The reaction mixture was quenched with H_2O (5.0 mL), the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford **4'** (51.8 mg, 73%) as a pale yellow powder.

R_f = 0.34 (hexane/ethyl acetate = 4/1); mp 105.5-107.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.21 (5H, m), 4.82 (1H, s), 4.28 (1H, dd, *J* = 11.9, 2.7 Hz), 3.61 (3H, s), 3.49 (1H, dd, *J* = 11.9, 1.4 Hz), 2.89 (1H, dd, *J* = 16.9, 12.4 Hz), 2.70 (1H, dd, *J* = 16.9, 6.4 Hz), 2.43 (1H, dd, *J* = 13.3, 2.7 Hz), 2.15 (1H, d, *J* = 13.3 Hz), 2.06-1.94 (1H, m), 1.12 (3H, d, *J* = 6.9 Hz), 0.93 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8 (Cq), 170.5 (Cq), 137.9 (Cq), 128.2 (CH), 128.0 (CH), 127.8 (CH), 82.8 (CH), 73.6 (CH_2), 62.1 (Cq), 51.9 (CH_3), 49.4 (CH_2), 46.8 (CH_2), 40.1 (CH), 32.7 (Cq), 22.4 (CH_3), 16.1 (CH_3); IR (neat) ν_{max} 2959, 2865, 1049, 1703, 1253, 1134, 1073, 753, 700 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{18}H_{22}O_4Na$: 325.1410, found: 325.1410; $[\alpha]_D^{27}$ +1.9 (*c* 2.05, $CHCl_3$).

methyl (1*S*,2*S*,4*R*,4a*R*,5*S*,8a*R*)-1-[(benzyloxy)methyl]-7-[(*tert*-butyldimethylsilyl)oxy]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-4-hydroxy-1,2-dimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-4a-carboxylate (14A)

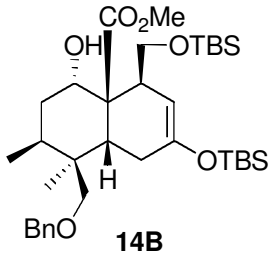


14A

To a solution of **3b** (9.31 g, 14.8 mmol) in CH_2Cl_2 (295 mL) at −78 °C was added DIBAL-H (1.02 M solution in hexane, 28.9 mL, 29.5 mmol) dropwise over 30 min. The reaction mixture was stirred at the same temperature for 30 min, and then was quenched with MeOH (2.0 mL) and saturated Rochelle's salt solution (200 mL). The mixture was stirred at room temperature for 4 h, the aqueous layer was extracted with CH_2Cl_2 (100 mL x 2). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford **14A** (6.22 g, 67%), **14B** (1.51 g, 16%), and **14C** (840 mg, 9%) as a colorless oil.

R_f = 0.37 (hexane/ethyl acetate = 15/1 x 2); ^{1}H NMR (400MHz, $CDCl_3$) δ7.37-7.24 (5H, m), 4.88 (1H, d, *J* = 1.8 Hz), 4.48 (1H, d, *J* = 12.4 Hz), 4.36 (1H, d, *J* = 12.4 Hz), 3.81-3.70 (2H, m), 3.60 (3H, s), 3.51 (1H, d, *J* = 11.0 Hz), 3.50 (1H, d, *J* = 11.0 Hz), 3.31 (1H, br d), 3.20 (1H, d, *J* = 9.6 Hz), 2.93-2.85 (1H, m), 2.80 (1H, dd, *J* = 11.0, 8.2 Hz), 2.08 (1H, qdd, *J* = 7.8, 1.8, 1.8 Hz), 2.01-1.70 (4H, m), 0.99 (3H, s), 0.92 (9H, s), 0.89-0.84 (12H, m), 0.15 (3H, s), 0.15 (3H, s), 0.019 (3H, s), 0.003 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 148.6, 138.7, 128.3, 127.4, 127.1, 102.0, 73.3, 72.8, 67.4, 64.8, 51.6, 47.3, 43.6, 43.5, 40.9, 38.5, 33.9, 29.4, 25.9, 25.7, 22.9, 18.2, 18.0, 16.1, -4.40, -5.31, -5.38; IR (neat) ν_{max} 3538, 2953, 2929, 2884, 2856, 1698, 1252, 1196, 1084, 836, 775, 735, 697 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{35}H_{60}O_6NaSi_2$: 655.3821, found: 655.3818; $[\alpha]^{28}_D$ -7.0 (*c* 2.02, $CHCl_3$).

methyl (1*S*,2*S*,4*S*,4a*R*,5*S*,8a*R*)-1-[(benzyloxy)methyl]-7-[(*tert*-butyldimethylsilyl)oxy]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-4-hydroxy-1,2-dimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-4a-carboxylate (14B)

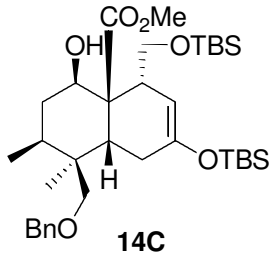


14B

R_f = 0.47 (hexane/ethyl acetate = 15/1 x 2); ^{1}H NMR (400MHz, $CDCl_3$) δ7.37-7.22 (5H, m), 4.67 (1H, s), 4.46 (1H, d, *J* = 12.3 Hz), 4.46 (1H, br s), 4.34 (1H, d, *J* = 12.3 Hz), 3.75 (1H, dd, *J* = 10.4, 1.8 Hz), 3.71-3.65 (1H, br), 3.61 (1H, dd, *J* = 10.4, 4.1 Hz), 3.52 (3H, s), 3.25-3.11 (2H, m), 2.93-2.79 (2H, m), 2.48 (1H, br t), 2.25-2.11 (1H, m), 2.01 (1H, dd, *J* = 15.4, 6.8 Hz), 1.84 (1H, br t), 1.63 (1H, ddd, *J* = 15.4, 3.2, 3.2 Hz), 1.05 (3H, s), 0.94-0.82 (21H, m), 0.15 (3H, s), 0.14 (3H, s), 0.094 (3H, s), 0.085 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 152.2, 138.9, 128.2, 127.2, 127.0, 101.7, 73.2, 72.9, 68.7, 62.9, 51.6, 50.6, 45.7, 41.0, 39.5, 35.4, 30.7, 28.5, 25.9, 25.7, 23.8, 18.2, 17.9, 16.1, -4.08, -4.37, -5.68, -5.78; IR (neat) ν_{max} 3504, 2953, 2928, 2883, 2857, 1715, 1252, 1178, 1091, 834, 778, 735, 698 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{35}H_{60}O_6NaSi_2$: 655.3821, found: 655.3818; $[\alpha]^{28}_D$ -0.8 (*c* 1.38, $CHCl_3$).

methyl (1*S*,2*S*,4*R*,4a*R*,5*R*,8a*R*)-1-[(benzyloxy)methyl]-7-[(*tert*-butyldimethylsilyl)oxy]-5-{[

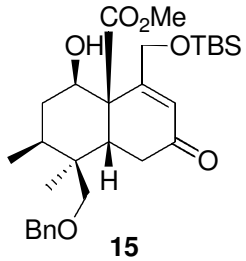
(*tert*-butyldimethylsilyl)oxy]methyl}-4-hydroxy-1,2-dimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene-4a-carboxylate (14C)



14C

R_f = 0.30 (hexane/ethyl acetate = 15/1 x 2); ^{1}H NMR (400MHz, $CDCl_3$) δ7.39-7.25 (5H, m), 4.80 (1H, d, *J* = 5.9 Hz), 4.48 (1H, d, *J* = 12.2 Hz), 4.37 (1H, d, *J* = 12.2 Hz), 4.10 (1H, d, *J* = 11.8 Hz), 3.64-3.47 (2H, m), 3.56 (3H, s), 3.38 (1H, dd, *J* = 10.9, 5.4 Hz), 3.21 (2H, s), 3.07 (1H, dd, *J* = 11.8, 5.4 Hz), 2.86 (1H, dd, *J* = 10.4, 8.6 Hz), 2.02 (1H, dd, *J* = 18.1, 8.2 Hz), 1.96-1.80 (2H, m), 1.75 (1H, ddd, *J* = 13.1, 4.1, 4.1 Hz), 1.71-1.59 (1H, m), 1.00 (3H, s), 0.91 (9H, s), 0.89 (3H, d, *J* = 6.8 Hz), 0.86 (9H, s), 0.14 (3H, s), 0.13 (3H, s), 0.0033 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 148.7, 138.7, 128.3, 127.4, 127.2, 101.9, 73.7, 73.3, 70.2, 65.4, 51.0, 50.6, 42.0, 41.3, 38.7, 37.8, 34.5, 28.8, 25.9, 25.7, 22.7, 18.3, 18.0, 16.5, -4.34, -4.38, -5.27, -5.41; IR (neat) ν_{max} 3504, 2952, 2929, 2883, 2857, 1701, 1254, 1197, 1091, 837, 778, 736, 697 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{35}H_{60}O_6NaSi_2$: 655.3821, found: 655.3818; $[\alpha]^{28}_D$ +14.2 (*c* 1.39, $CHCl_3$).

methyl (1*S*,2*S*,4*R*,4a*R*,8a*R*)-1-[(benzyloxy)methyl]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-4-hydroxy-1,2-dimethyl-7-oxo-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylate (15)



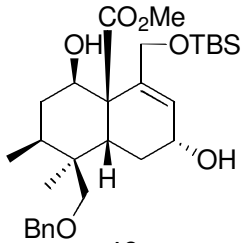
15

To a stirred solution of DDQ (49.0 mg, 0.216 mmol) in CH_3CN (1.0 mL) was added 2,6-lutidine (16.7 μL, 0.144 mmol) dropwise at 0 ºC, and the reaction mixture was stirred at the room temperature for 15 min. Then, to the reaction mixture was added a solution of **14A** (45.5 mg, 0.0719 mmol) in CH_3CN (1.0 mL) via a cannula at 0 ºC. After the addition, the reaction mixture was stirred at room temperature for 4 h, and then was added hexane/AcOEt (1/1, 2.0 mL), filtered through a Celite pad. The

filtrate was added saturated aqueous $NaHCO_3$ solution (5.0 mL), extracted with AcOEt (10 mL x 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **15** (31.7 mg, 85%) as a white solid.

R_f = 0.26 (hexane/ethyl acetate = 4/1); mp 158.8-161.0 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ7.38-7.24 (5H, m), 6.49 (1H, dd, *J* = 1.8, 1.8 Hz), 4.79 (1H, dd, *J* = 17.4, 1.8 Hz), 4.49 (1H, d, *J* = 11.9 Hz), 4.37 (1H, d, *J* = 11.9 Hz), 3.84 (1H, d, *J* = 17.4 Hz), 3.90-3.75 (1H, m), 3.59 (3H, s), 3.46 (1H, d, *J* = 9.6 Hz), 3.37 (1H, d, *J* = 11.0 Hz), 3.25 (1H, dd, *J* = 14.7, 5.0 Hz), 3.22 (1H, d, *J* = 9.6 Hz), 2.53 (1H, dd, *J* = 16.9, 5.0 Hz), 2.38 (1H, dd, *J* = 16.9, 14.7 Hz), 2.01-1.79 (3H, m), 1.03 (3H, s), 0.96-0.82 (12H, m), 0.047 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 176.0, 164.5, 138.2, 128.3, 127.5, 126.9, 123.6, 73.3, 73.1, 72.1, 63.6, 53.9, 52.1, 43.6, 40.6, 38.0, 35.2, 34.3, 25.8, 24.2, 18.3, 15.7, -5.46, -5.56; IR (neat) ν_{max} 3530, 2952, 2930, 2883, 2858, 1716, 1665, 1251, 1197, 1103, 835, 738, 700 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{29}H_{44}O_6NaSi$: 539.2799, found: 539.2800; $[\alpha]^{28}_D$ +18.1 (*c* 1.32, $CHCl_3$).

methyl (1*S*,2*S*,4*R*,4a*R*,7*R*,8a*R*)-1-[(benzyloxy)methyl]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-4,7-dihydroxy-1,2-dimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylate (16)



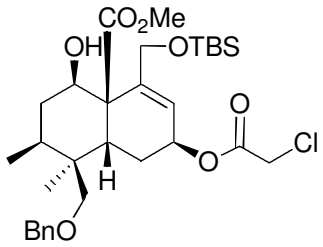
16

To a stirred solution of **15** (3.17 g, 6.13 mmol) in MeOH/CH_2Cl_2 (5/1, 156 mL) was added $CeCl_3 \cdot 7H_2O$ (4.57 g, 12.3 mmol) and $NaBH_4$ (1.16 g, 30.6 mmol) successively at -10 ºC. The reaction mixture was stirred at the same temperature for 15 min, quenched by saturated aqueous NH_4Cl solution (100 mL), the aqueous layer was extracted with Et_2O (100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 8/1) to afford **16** (4.94 g, 98%) as a white solid.

R_f = 0.35 (hexane/ethyl acetate = 2/1); mp 157.4-159.4 °C; ^{1}H NMR (400MHz,

$CDCl_3$) δ 7.42-7.20 (5H, m), 6.05 (1H, s), 4.61 (1H, d, *J* = 15.0 Hz), 4.49 (1H, d, *J* = 12.2 Hz), 4.45-4.37 (1H, br), 4.33 (1H, d, *J* = 12.2 Hz), 3.84 (1H, ddd, *J* = 11.8, 11.8, 5.4 Hz), 3.72 (1H, d, *J* = 15.0 Hz), 3.65 (1H, d, *J* = 11.8 Hz), 3.56 (3H, s), 3.46 (1H, d, *J* = 9.5 Hz), 3.21 (1H, d, *J* = 9.5 Hz), 2.73 (1H, dd, *J* = 14.0, 1.8 Hz), 2.14 (1H, dd, *J* = 14.0, 5.9 Hz), 1.94-1.68 (3H, m), 1.38 (1H, dd, *J* = 12.7, 10.4, 10.4 Hz), 1.07 (3H, s), 0.90 (9H, s), 0.86 (3H, d, *J* = 6.8 Hz), 0.048 (3H, s), 0.042 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 141.4, 138.5, 128.3, 127.4, 127.0, 126.8, 73.9, 73.3, 72.4, 68.4, 63.7, 53.3, 51.8, 43.6, 40.7, 38.7, 35.0, 29.9, 26.0, 25.2, 18.4, 15.9, -5.38, -5.41; IR (neat) ν_{max} 3481, 3377, 2952, 2928, 2881, 2855, 1732, 1706, 1250, 1079, 835, 737, 698 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{29}H_{46}O_6NaSi$: 541.2956, found: 541.2956; $[\alpha]^{28}_D$ +23.9 (*c* 0.76, $CHCl_3$).

methyl (1*S*,2*S*,4*R*,4a*R*,7*S*,8a*R*)-1-[(benzyloxy)methyl]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-7-[(2-chloroacetyl)oxy]-4-hydroxy-1,2-dimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylate (17)



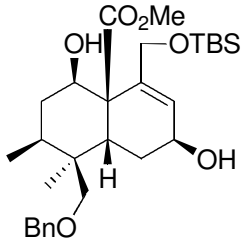
17

To a solution of **16** (3.05 g, 5.89 mmol), chloroacetic acid (2.22 g, 23.5 mmol) and Ph_3P (6.95 g, 26.5 mmol) in toluene (126 mL) was added DIAD (1.9 M solution in toluene, 10.8 mL, 20.6 mmol) dropwise at 0 ºC. The reaction mixture was stirred at the same temperature for 15 min, quenched by saturated aqueous $NaHCO_3$ solution (50 mL), the aqueous layer was extracted with hexane/AcOEt (1/1, 100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 25/1) to afford **17** (3.15 g, 90%) as a colorless oil.

R_f = 0.73 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.37-7.23 (5H, m), 6.18 (1H, d, *J* = 5.4 Hz), 5.44 (1H, br s), 4.70 (1H, d, *J* = 15.4 Hz), 4.49 (1H, d, *J* = 12.2 Hz), 4.38 (1H, d, *J* = 12.2 Hz), 4.09 (2H, s), 3.71 (1H, d, *J* = 15.4 Hz), 3.69 (1H, ddd, *J* = 11.3, 11.3, 4.5 Hz), 3.56 (3H, s), 3.54 (1H, d, *J* = 11.3 Hz), 3.46 (1H, d, *J* = 9.5 Hz), 3.25 (1H, d, *J* = 9.5 Hz), 2.93 (1H, dd, *J* = 14.0, 2.3 Hz), 1.98 (1H, d, *J* = 14.0 Hz), 1.93-1.67 (4H, m), 1.04 (3H, s), 0.93-0.84 (12H, m), 0.040 (3H, s), 0.030

(3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 167.0, 146.9, 138.6, 128.2, 127.3, 126.7, 117.8, 73.1, 72.9, 72.6, 68.3, 63.8, 53.2, 52.0, 41.2, 40.2, 39.2, 38.3, 34.8, 25.9, 25.3, 24.9, 18.4, 16.0, -5.43, -5.47; IR (neat) ν_{max} 3535, 2952, 2929, 2881, 2856, 1751, 1706, 1254, 1097, 835, 735, 697 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{31}H_{47}O_7ClNaSi$: 617.2672, found: 617.2670; $[\alpha]^{28}_D$ -1.7 (*c* 0.88, $CHCl_3$).

methyl (1*S*,2*S*,4*R*,4a*R*,7*S*,8a*R*)-1-[(benzyloxy)methyl]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-4,7-dihydroxy-1,2-dimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylate (18)

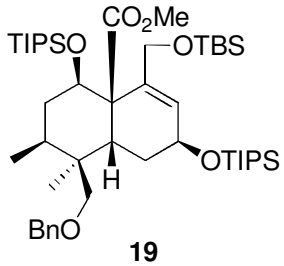


18

To a stirred solution of **17** (3.15 g, 5.29 mmol) in MeOH (134 mL) was added K_2CO_3 (1.46 g, 10.6 mmol) at 0 ºC, the reaction mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched by saturated aqueous NH_4Cl solution (100 mL), the aqueous layer was extracted with Et_2O (100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 9/1) to afford **18** (2.82 g, quant.) as a white solid.

R_f = 0.55 (hexane/ethyl acetate = 2/1); mp 106.5-107.5 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ7.38-7.23 (5H, m), 6.22 (1H, d, *J* = 5.0 Hz), 4.65 (1H, ddd, *J* = 15.1, 1.8, 1.8 Hz), 4.49 (1H, d, *J* = 12.4 Hz), 4.35 (1H, d, *J* = 12.4 Hz), 4.27 (1H, br s), 3.70 (1H, d, *J* = 15.1 Hz), 3.70-3.63 (1H, m), 3.61-3.52 (1H, m), 3.56 (3H, s), 3.45 (1H, d, *J* = 9.6 Hz), 3.25 (1H, d, *J* = 9.6 Hz), 2.85 (1H, dd, *J* = 14.2, 2.7 Hz), 1.94 (1H, d, *J* = 14.2 Hz), 1.85 (1H, dd, *J* = 13.7, 11.9 Hz), 1.80-1.54 (3H, m), 1.07 (3H, s), 0.90 (9H, s), 0.88 (3H, d, *J* = 6.9 Hz), 0.042 (3H, s), 0.038 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 143.4, 138.5, 128.2, 127.3, 126.9, 122.5, 73.2, 73.1, 72.7, 63.8, 63.3, 53.4, 51.8, 40.3, 38.6, 38.3, 34.9, 28.1, 25.9, 24.8, 18.3, 16.0, -5.43, -5.45; IR (neat) ν_{max} 3526, 3444, 2952, 2928, 2881, 2856, 1699, 1254, 1091, 998, 833, 737, 698 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{29}H_{46}O_6NaSi$: 541.2956, found: 541.2957; $[\alpha]^{28}_D$ +7.9 (*c* 1.12, $CHCl_3$).

methyl (1*S*,2*S*,4*R*,4a*R*,7*S*,8a*R*)-1-[(benzyloxy)methyl]-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-1,2-dimethyl-4,7-bis({[tris(propan-2-yl)silyl]oxy})-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylate (19)

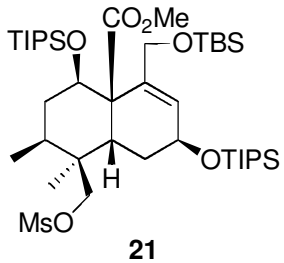


19

To a solution of **18** (2.79 g, 5.38 mmol) in CH_2Cl_2 (96 mL) was added 2,6-lutidine (3.13 mL, 26.9 mmol) and TIPSOTf (4.34 mL, 16.1 mmol) at 0 ºC, the reaction mixture was stirred at the same temperature for 12 h. The reaction mixture was quenched by H_2O (100 mL), the aqueous layer was extracted with CH_2Cl_2 (50 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 100/1) to afford **19** (4.04 g, 92% (2 steps)) as a colorless oil.

R_f = 0.73 (hexane/ethyl acetate = 8/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.37-7.18 (5H, m), 6.16 (1H, d, *J* = 5.0 Hz), 4.48 (1H, d, *J* = 15.0 Hz), 4.45 (1H, d, *J* = 12.2 Hz), 4.42-4.38 (1H, m), 4.38 (1H, d, *J* = 12.2 Hz), 4.10 (1H, dd, *J* = 12.2, 4.1 Hz), 3.67 (1H, d, *J* = 15.0 Hz), 3.59 (1H, d, *J* = 9.1 Hz), 3.42 (3H, s), 3.25 (1H, d, *J* = 9.1 Hz), 3.13 (1H, dd, *J* = 13.6, 2.3 Hz), 2.33 (1H, dd, *J* = 25.0, 13.6 Hz), 1.90 (1H, d, *J* = 13.6 Hz), 1.74-1.56 (3H, m), 1.18-0.98 (45H, m), 0.96-0.82 (12H, m), 0.00 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 142.4, 139.2, 128.0, 126.8, 126.4, 122.8, 74.5, 73.5, 72.8, 64.0, 63.4, 54.5, 50.8, 40.2, 39.2, 37.8, 35.8, 30.0, 25.8, 25.3, 18.3, 18.2, 18.2, 18.1, 18.1, 16.3, 13.6, 12.6, -5.52, -5.58; IR (neat) ν_{max} 2951, 2928, 2881, 2861, 1698, 1255, 1207, 1090, 999, 835, 735, 698 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{47}H_{86}O_6NaSi_3$: 853.5624, found: 853.5618; $[\alpha]^{28}_D$ -10.5 (*c* 2.20, $CHCl_3$).

(1*S*,2*S*,4*R*,4a*R*,7*S*,8a*R*)-methyl 5-((*tert*-butyldimethylsilyloxy)methyl)-1,2-dimethyl-1-((methylsulfonyloxy)methyl)-4,7-bis(triisopropylsilyloxy)-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylate (21)

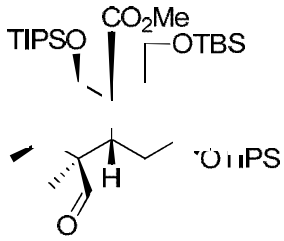


21

To a stirred solution of **20** (18.6 mg, 0.0251 mmol) in CH_2Cl_2 (1.0 mL) was added TEA (11.0 μL, 0.0753 mmol), MsCl (3.9 μL, 0.0502 mmol) at room temperature. The reaction mixture was stirred at room temperature for 15 min, quenched with saturated aqueous $NaHCO_3$ solution (5.0 mL), and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford **21** (15.2 mg, 74%) as a colorless oil.

R_f = 0.60 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.18-6.16 (1H, d, *J* = 5.1 Hz), 4.50-4.45 (1H, dt, *J* = 14.9, 1.7 Hz), 4.27 (1H, br), 4.13 (2H, s), 4.13-4.08 (1H, m), 3.69 (3H, s), 3.69-3.65 (1H, m), 2.98 (3H, s), 2.98-2.94 (1H, m), 2.25-2.16 (1H, m), 1.86-1.83 (1H, br d, *J* = 13.4 Hz), 1.79-0.95, (3H, m), 1.06-1.05 (45H, m), 0.92-0.91 (3H, d, *J* = 7.1 Hz), 0.88 (9H, s), 0.003 (3H, s), -0.005 (3H, s)

methyl (1*S*,2*S*,4*R*,4a*R*,7*S*,8a*R*)-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-1-formyl-1,2-dimethyl-4,7-bis({[tris(propan-2-yl)silyl]oxy})-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylate (22)



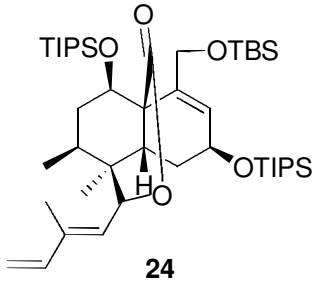
22

To a stirred solution of **19** (3.86 g, 4.64 mmol) in AcOEt (231 mL) was added Al_2O_3 (7.31 g, 0.46 g/mmol) and $Pd(OH)_2/C$ (10% Pd, 7.31 g, 0.46 g/mmol) at 0 ºC under an atmosphere of Ar. The reaction mixture was stirred at 0 ºC for 30 min under an atmosphere of H_2, the reaction mixture was filtered through a Celite pad, and the filtrate was concentrated. The crude alcohol, which due to its instability, required use without purification. To a solution of crude alcohol in CH_2Cl_2 (106 mL) was added pyridine (1.88 mL, 23.2 mmol) and Dess-Martin periodinane (2.95 g, 6.96

mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h, quenched by saturated aqueous $NaHCO_3$ solution (50 mL) and saturated aqueous $Na_2S_2O_3$ solution (50 mL) successively, the aqueous layer was extracted with CH_2Cl_2 (100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford **22** (3.27 g, 96% (2 steps)) as a colorless oil.

R_f = 0.83 (hexane/ethyl acetate = 8/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.50 (1H, s), 6.15 (1H, d, *J* = 4.6 Hz), 4.46 (1H, d, *J* = 16.0 Hz), 4.42 (1H, br s), 4.08 (1H, dd, *J* = 12.4, 4.6 Hz), 3.70 (1H, d, *J* = 16.0 Hz), 3.54 (3H, s), 3.03 (1H, dd, *J* = 13.3, 2.7 Hz), 2.60 (1H, dd, *J* = 25.6, 13.3 Hz), 1.83 (1H, d, *J* = 13.3 Hz), 1.77-1.61 (3H, m), 1.13-1.02 (45H, m), 1.00 (3H, s), 0.88 (9H, s), -0.001 (3H, s), -0.010 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 173.5, 141.8, 123.1, 74.2, 63.5, 63.4, 54.9, 51.2, 49.9, 40.7, 37.8, 33.5, 28.6, 25.8, 20.8, 18.2, 18.1, 18.1, 18.0, 15.7, 13.6, 12.5, -5.56, -5.58; IR (neat) ν_{max} 2942, 2865, 1726, 1717, 1462, 1255, 1209, 1100, 881, 836, 737, 680 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{40}H_{78}O_6NaSi_3$: 761.4998, found: 761.4994; $[\alpha]^{28}_D$ -16.6 (*c* 1.08, $CHCl_3$).

(1*R*,4*S*,6*R*,7*S*,11*R*,13*S*)-2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-7,13-dimethyl-8-[(1*E*)-2-methylbuta-1,3-dien-1-yl]-4,11-bis({[tris(propan-2-yl)silyl]oxy})-9-oxatricyclo[5.3.3.0^{1,6}]tridec-2-en-10-one (24)



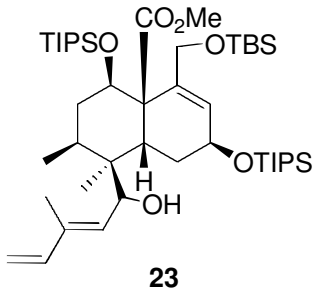
24

To a stirred solution of (*E*)-1-iodo-2-methylbuta-1,3-diene (89.2 mg, 0.460 mmol) in Et_2O (1.0 mL) was added *t*-BuLi (1.65 M solution in pentane, 209 μL, 0.345 mmol) dropwise at -78 °C, and the reaction mixture was stirred for 15 min. Then, to the reaction mixture was added a solution of **22** (34.0 mg, 0.0460 mmol) in Et_2O (1.0 mL) via a cannula at -78 °C. After the addition, the reaction mixture was stirred at the same temperature for 30 min, quenched with saturated aqueous NH_4Cl solution (5.0 mL). The aqueous layer was extracted with Et_2O (5.0 mL × 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was diluted with MeOH (1.0 mL), added K_2CO_3

(12.7 mg, 0.0920 mmol) and sttired at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (5.0 mL). The aqueous layer was extracted with Et_2O (5.0 mL × 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford **24** (28.2 mg, 80%) and **23** (2.6 mg, 7.0%) as a colorless oil.

R_f = 0.67 (hexane/ethyl acetate = 10/1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.31 (1H, dd, *J* = 17.6, 11.0 Hz), 6.23 (1H, d, *J* = 4.4 Hz), 5.59 (1H, d, *J* = 10.5 Hz), 5.27 (1H, d, *J* = 10.5 Hz), 5.23 (1H, d, *J* = 17.6 Hz), 5.09 (1H, d, *J* = 11.0 Hz), 4.81 (1H, d, *J* = 15.9 Hz), 4.66 (1H, d, *J* = 15.9 Hz), 4.38 (1H, br), 4.25 (1H, dd, *J* = 11.0, 4.4 Hz), 2.74 (1H, dd, *J* = 12.9, 3.2 Hz), 1.92-1.75 (3H, m), 1.82 (3H, s), 1.74-1.62 (2H, m), 1.13-0.95 (45H, m), 0.91 (9H, m), 0.73 (3H, s), 0.05 (6H, s).

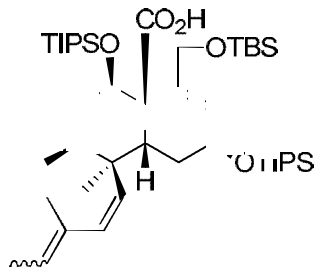
(1*S*,2*S*,4*R*,4a*R*,7*S*,8a*R*)-methyl 5-((*tert*-butyldimethylsilyloxy)methyl)-1-((*R*,*E*)-1-hydroxy-3-methylpenta-2,4-dienyl)-1,2-dimethyl-4,7-bis(triisopropylsilyloxy)-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylate (23)



23

R_f = 0.50 (hexane/ethyl acetate = 10/1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.38 (1H, dd, *J* = 17.2, 10.9 Hz), 6.18 (1H, d, *J* = 4.5 Hz), 5.74 (1H, d, *J* = 9.1 Hz), 5.18 (1H, d, *J* = 17.2 Hz), 5.03 (1H, d, *J* = 10.9 Hz), 4.53 (1H, dt, *J* = 15.0, 1.4 Hz), 4.44-4.39 (1H, m), 4.13 (1H, dd, *J* = 11.8, 4.1 Hz), 3.73 (3H, s), 3.15 (1H, dd, *J* = 13.1, 2.3 Hz), 2.14-2.11 (1H, m), 1.94-1.91 (1H, m), 1.77-1.55 (3H, m), 1.07-1.06 (42H, m), 0.98 (3H, s), 0.89 (9H, s), 0.82 (3H, d, *J* = 7.25 Hz), 0.02 (3H, s), 0.01 (3H, s)

(1*R*,2*S*,4*R*,4a*R*,7*S*,8a*R*)-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-1,2-dimethyl-1-[(1*Z*)-3-methylpenta-1,3-dien-1-yl]-4,7-bis({[tris(propan-2-yl)silyl]oxy})-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylic acid (25)

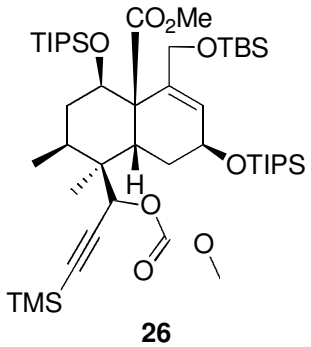


25'

To a stirred solution of **24** (1.50 mg, 0.00193 mmol), HCO_2NH_4 (1.22 mg, 0.0193 mmol), and dppe (0.617 mg, 0.0015 mmol) in 1,4-dioxane (0.5 mL) was added $Pd_2(dba)_3$ (0.354 mg, 0.000387 mmol) at room temperature. The reaction mixture was stirred at 70 °C for 3 h, diluted with Et_2O (5.0 mL), and the reaction mixture was filtered through a Celite pad. The filtrate was washed with H_2O (5.0 mL), brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **25** (0.9 mg, 60%) as a pale yellow oil.

R_f = 0.49 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.2 (1H, br), 6.21-6.13 (1H, m), 6.05 (1H, d, *J* = 15.9 Hz), 5.82 (1H, d, *J* = 15.9 Hz), 5.47 (1H, q, *J* = 6.6 Hz), 4.41-4.17 (2H, m), 3.96 (1H, d, *J* = 15.4 Hz), 2.77 (1H, dd, *J* = 13.7, 2.9 Hz), 2.09-1.92 (2H, m), 1.81-1.43 (3H, m), 1.77 (3H, s), 1.70 (3H, d, *J* = 6.6 Hz), 1.17-0.97 (45H, m), 0.86 (9H, s), 0.80 (3H, d, *J* = 6.6 Hz), -0.02 (6H, s).

methyl (1*S*,2*S*,4*R*,4a*R*,7*S*,8a*R*)-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-1-{1-[(methoxycarbonyl)oxy]-3-(trimethylsilyl)prop-2-yn-1-yl}-1,2-dimethyl-4,7-bis({[tris(propan-2-yl)silyl]oxy})-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylate (26)



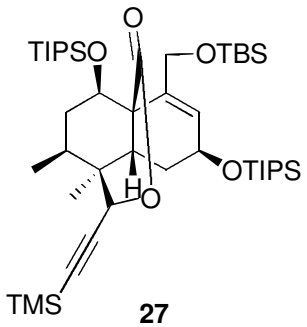
26

To a stirred solution of TMS acetylene (1.55 gmL, 11.2 mmol) in THF (44.6 mL) was added *n*-BuLi (1.58 M solution in hexane, 6.39 mL, 10.1 mmol) dropwise at -78 °C, and the reaction mixture was stirred for 20 min. Then, to the reaction mixture was added a solution of **22** (1.66 g, 2.44 mmol) in THF (58.0 mL) via a cannula

maintaining the temperature at −65 to −78 °C. After the addition, the mixture was stirred at −65 °C for 1.5 h, and then was added methyl chloroformate as the anion trapping reagent. The reaction mixture was stirred at −10 °C for 12 h, quenched by saturated aqueous NH_4Cl solution (100 mL). The aqueous layer was extracted with Et_2O (100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 100/1) to afford **26** (1.35 g, 69%) as a white amorphous.

R_f = 0.59 (hexane/ethyl acetate = 8/1); ^{1}H NMR (400MHz, $CDCl_3$) δ6.12 (1H, s), 5.12 (1H, br s), 4.45 (1H, ddd, *J* = 14.2, 1.8, 1.8 Hz), 4.40 (1H, br d), 4.24-4.02 (1H, br), 3.78 (3H, s), 3.81-3.53 (1H, m), 3.62 (3H, s), 3.18 (1H, dd, *J* = 11.4, 2.7 Hz), 2.35-2.13 (1H, m), 1.89 (1H, br d), 1.81-1.58 (3H, m), 1.36-0.95 (48H, m), 0.88 (9H, s), 0.14 (9H, s), 0.004 (3H, s), -0.001 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0, 154.4, 142.1, 123.1, 102.7, 94.3, 74.1, 70.9, 63.9, 63.3, 55.1, 54.7, 51.7, 43.4, 38.9, 37.9, 36.6, 30.8, 29.7, 25.8, 22.1, 18.2, 18.2, 18.1, 18.1, 13.6, 12.5, -0.49, -5.49; IR (neat) ν_{max} 2943, 2865, 1756, 1737, 1463, 1440, 1250, 1087, 838, 680 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{47}H_{90}O_8NaSi_4$: 917.5605, found: 917.5597; $[\alpha]^{28}_D$ -23.9 (*c* 1.18, $CHCl_3$).

(1*R*,4*S*,6*R*,7*S*,11*R*,13*S*)-2-{[(*tert*-butyldimethylsilyl)oxy]methyl}-7,13-dimethyl-11-[(tri-*tert*-butylsilyl)oxy]-8-[2-(trimethylsilyl)ethynyl]-4-{[tris(propan-2-yl)silyl]oxy}-9-oxatricyclo[5.3.3.0^{1,6}]tridec-2-en-10-one (27)

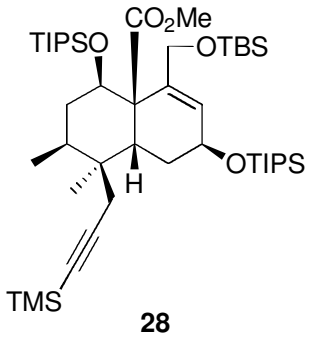


27

R_f = 0.93 (benzene/ethyl acetate = 50/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (1H, d, *J* = 4.1 Hz), 5.08 (1H, s), 4.77 (1H, d, *J* = 15.9 Hz), 4.68 (1H, d, *J* = 15.9 Hz), 4.37 (1H, br), 4.22 (1H, dd, *J* = 11.0, 4.6 Hz), 2.89 (1H, dd, *J* = 13.4, 3.2 Hz), 1.93-1.78 (3H, m), 1.77-1.69 (1H, m), 1.63-1.47 (1H, m), 1.13-0.94 (45H, m), 0.93-0.84 (12H, s), 0.13 (9H, s), 0.07 (3H, s), 0.05 (3H, s).

methyl (1*S*,2*S*,4*R*,4a*R*,7*S*,8a*R*)-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-1,2-dimethyl-1-[3-

(trimethylsilyl)prop-2-yn-1-yl]-4,7-bis({[tris(propan-2-yl)silyl]oxy})-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylate (28)

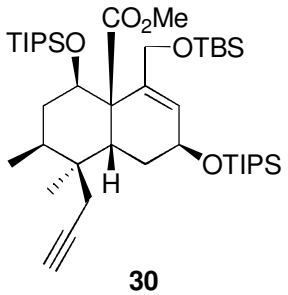


28

To a stirred solution of **26** (2.62 g, 2.92 mmol), HCO_2NH_4 (1.84 g, 29.2 mmol), and $Pd(OAc)_2$ (65.6 mg, 0.292 mmol) in THF (59.0 mL) was added *n*-Bu_3P (146 μL, 0.585 mmol) at room temperature. The reaction mixture was stirred at 60 ºC for 24 h, diluted with Et_2O (20 mL), the reaction mixture was filtered through a Celite pad. The filtrate was washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 200/1) to afford **28** (2.38 g, 99%) as a colorless oil.

R_f = 0.86 (hexane/ethyl acetate = 10/1); ^{1}H NMR (500MHz, $CDCl_3$) δ6.14 (1H, d, *J* = 4.5 Hz), 4.48 (1H, d, *J* = 14.7 Hz), 4.38 (1H, br s), 4.03 (1H, dd, *J* = 11.9, 4.0 Hz), 3.68 (1H, d, *J* = 14.7 Hz), 3.64 (3H, s), 3.00 (1H, dd, *J* = 13.6, 2.8 Hz), 2.40 (1H, d, *J* = 17.6 Hz), 2.20 (1H, dd, *J* = 25.5, 13.6 Hz), 2.13 (1H, d, *J* = 17.6 Hz), 1.88 (1H, d, *J* = 13.6 Hz), 1.76-1.63 (2H, m), 1.57 (1H, ddd, *J* = 13.0, 3.4, 3.4 Hz), 1.16-0.97 (45H, m), 0.89 (9H, s), 0.83 (3H, d, *J* = 6.8 Hz), 0.11 (9H, s), 0.011 (3H, s), 0.002 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 142.1, 122.6, 105.3, 86.3, 74.6, 63.9, 63.4, 54.0, 51.1, 40.5, 38.9, 37.3, 36.1, 30.1, 26.3, 25.8, 24.7, 18.3, 18.2, 18.2, 18.1, 15.9, 13.6, 12.5, 0.12, -5.54, -5.58; IR (neat) ν_{max} 2943, 2865, 2173, 1733, 1463, 1248, 1215, 1102, 1013, 838, 739, 681 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{45}H_{88}O_5NaSi_4$: 843.5601, found: 843.5592; $[\alpha]^{26}_D$ -26.1 (*c* 2.31, $CHCl_3$).

methyl
(1*S*,2*S*,4*R*,4a*R*,7*S*,8a*R*)-5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-1,2-dimethyl-1-(prop-2-yn-1-yl)-4,7-bis({[tris(propan-2-yl)silyl]oxy})-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylate (30)

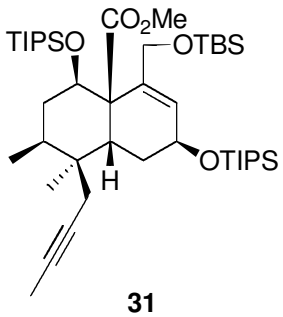


30

To a stirred solution of **28** (1.45 g, 1.77 mmol) in MeOH/THF (2.5/1, 52.0 mL) was added K_2CO_3 (978 mg, 7.08 mmol) at room temperature, the reaction mixture was stirred at 50 ºC for 24 h. The reaction mixture was poured into saturated aqueous NH_4Cl solution (100 mL), the aqueous layer was extracted with Et_2O (100 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 100/1) to afford **30** (1.31 g, 99%) as a white solid.

R_f = 0.56 (hexane/ethyl acetate = 20/1); mp 66.8-68.6 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ6.17 (1H, d, *J* = 4.5 Hz), 4.48 (1H, d, *J* = 14.7 Hz), 4.40 (1H, br s), 4.05 (1H, dd, *J* = 11.9, 4.5 Hz), 3.68 (1H, d, *J* = 14.7 Hz), 3.63 (3H, s), 3.17 (1H, dd, *J* = 13.6, 2.3 Hz), 2.37 (1H, d, *J* = 17.6 Hz), 2.23 (1H, dd, *J* = 25.5, 13.6 Hz), 2.02 (1H, dd, *J* = 17.6, 2.3 Hz), 1.91-1.83 (1H, m), 1.86 (1H, br t), 1.76-1.53 (3H, m), 1.12-1.01 (45H, m), 0.89 (9H, s), 0.84 (3H, d, *J* = 6.8 Hz), 0.006 (3H, s), 0.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 142.2, 122.8, 82.3, 74.3, 70.2, 63.9, 63.4, 54.2, 51.1, 40.1, 38.8, 37.2, 36.3, 30.1, 26.6, 25.8, 23.6, 18.2, 18.2, 18.2, 18.0, 15.8, 13.6, 12.6, -5.54, -5.60; IR (neat) ν_{max} 3312, 2941, 2864, 1734, 1463, 1248, 1213, 1101, 836, 680 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{42}H_{80}O_5NaSi_3$: 771.5206, found: 771.5198; $[\alpha]^{27}_D$ -22.5 (*c* 3.48, $CHCl_3$).

(1*S*,2*S*,4*R*,4a*R*,7*S*,8a*R*)-methyl 1-(but-2-ynyl)-5-((*tert*-butyldimethylsilyloxy)methyl)-1,2-dimethyl-4,7-bis(triisopropylsilyloxy)-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylate (31)

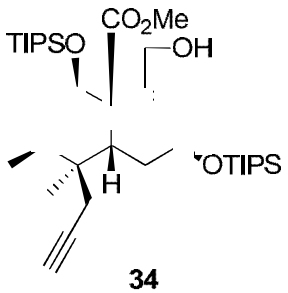


31

To a solution of **30** (10.6 mg, 0.0141 mmol) in THF (1.0 mL) was added LHMDS (1.09 M solution in THF, 19.5 μL, 0.0212 mmol) at –78 °C. The reaction mixture was stirred at 0°C for 30 min, added MeI (2.6 μL, 0.0424 mmol) at –78 °C. After the addition, the reaction mixture was stirred at room temperature for 11 h, quenched with saturated aqueous NH_4Cl solution (5.0 mL). The aqueous layer was extracted with Et_2O (5.0 mL × 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford **31** (11.1 mg, quant.) as a colorless oil.

R_f = 0.56 (hexane/ethyl acetate = 20/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (1H, d, *J* = 4.6 Hz), 4.48 (1H, dd, *J* = 14.6, 2.0 Hz), 4.39 (1H, br s), 4.04 (1H, dd, *J* = 12.0, 4.6 Hz), 3.68 (1H, dd, *J* = 14.6, 1.5 Hz), 3.63 (3H, s), 3.13 (1H, dd, *J* = 13.7, 2.7 Hz), 2.33 (1H, d, *J* = 16.8 Hz), 2.24 (1H, q, *J* = 12.9 Hz), 1.98-1.80 (2H, m), 1.72 (1H, t, *J* = 2.4 Hz), 1.75-1.47 (3H, m), 1.18-0.95 (45H, m), 0.89 (9H, s), 0.82 (3H, d, *J* = 6.8 Hz), 0.009 (3H, s), 0.003 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 142.4, 122.7, 74.5, 64.1, 63.4, 54.2, 50.8, 40.0, 39.0, 37.3, 36.2, 30.1, 26.8, 25.8, 23.7, 18.3, 18.2, 18.2, 18.1, 15.7, 13.6, 12.6, 3.43, -5.52, -5.60.

methyl (1*S*,2*S*,4*R*,4a*R*,7*S*,8a*R*)-5-(hydroxymethyl)-1,2-dimethyl-1-(prop-2-yn-1-yl)-4,7-bis({[tris(propan-2-yl)silyl]oxy})-1,2,3,4,4a,7,8,8a-octahydronaphthalene-4a-carboxylate (34)

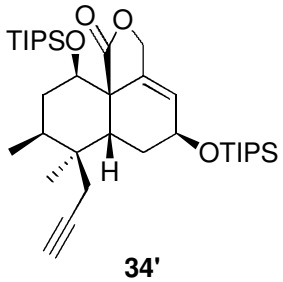


34

To a stirred solution of **30** (76.0 mg, 0.101 mmol) in EtOH/CH_2Cl_2 (15/1, 3.20 mL) was added PPTS (10.2 mg, 0.0406 mmol) at room temperature, the reaction mixture was stirred at the same temperature for 3 d. The reaction mixture was quenched by saturated aqueous $NaHCO_3$ solution (5.0 mL), the aqueous layer was extracted with Et_2O (5.0 mL x 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 30/1) to afford **34** (55.9 mg, 87%) and **34'** (2.0 mg, 3.3%) as a white solid.

R_f = 0.21 (hexane/ethyl acetate = 10/1); mp 92.2-101.2 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ6.04 (1H, d, *J* = 5.0 Hz), 4.38 (1H, br s), 4.19 (1H, dd, *J* = 14.2, 8.2 Hz), 4.07 (1H, dd, *J* = 11.9, 4.6 Hz), 4.00 (1H, dd, *J* = 14.2, 4.6 Hz), 3.68 (3H, s), 3.15 (1H, dd, *J* = 13.7, 2.7 Hz), 2.48 (1H, dd, *J* = 17.4, 2.7 Hz), 2.38 (1H, dd, *J* = 25.2, 13.7 Hz), 2.13 (1H, dd, *J* = 8.2, 4.6 Hz), 2.02 (1H, dd, *J* = 17.4, 2.7 Hz), 1.93-1.84 (1H, m), 1.87 (1H, dd, *J* = 2.7, 2.7 Hz), 1.79-1.54 (3H, m), 1.17-0.96 (45H, m), 0.86 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.9, 144.1, 125.9, 82.0, 75.0, 70.5, 65.0, 63.8, 54.3, 51.4, 40.1, 38.8, 37.0, 36.3, 29.9, 26.6, 23.7, 18.2, 18.1, 18.0, 18.0, 15.7, 13.6, 12.5; IR (neat) ν_{max} 3468, 3312, 2941, 2865, 1733, 1463, 1247, 1213, 1082, 881, 810, 679 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{36}H_{66}O_5NaSi_2$: 657.4341, found: 657.4336; $[\alpha]^{27}_D$ -33.6 (*c* 1.54, $CHCl_3$).

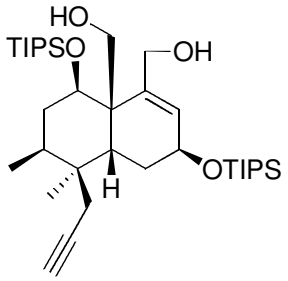
(5*S*,6a*R*,7*S*,8*S*,10*R*,10a*R*)-7,8-dimethyl-7-(prop-2-yn-1-yl)-5,10-bis({[tris(propan-2-yl)silyl]oxy})-1H,3H,5H,6H,6aH,7H,8H,9H,10H-naphtho[4,4a-c]furan-1-one (34')



34'

R_f = 0.56 (hexane/ethyl acetate = 10/1); mp 89.7-91.0 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ5.79 (1H, d, *J* = 1.8 Hz), 4.85 (1H, ddd, *J* = 10.5, 2.3, 2.3 Hz), 4.57 (1H, d, *J* = 10.5 Hz), 4.40 (1H, br s), 4.18 (1H, dd, *J* = 11.9, 4.1 Hz), 3.94 (1H, dd, *J* = 16.5, 2.3 Hz), 2.63 (1H, dd, *J* = 13.3, 3.2 Hz), 2.06 (1H, dd, *J* = 16.5, 2.3 Hz), 2.01 (1H, dd, *J* = 24.7, 13.3 Hz), 1.94 (1H, br d), 1.89 (1H, dd, *J* = 2.3, 2.3 Hz), 1.79 (1H, ddd, *J* = 24.7, 13.3, 4.6 Hz), 1.78-1.67 (1H, m), 1.52 (1H, ddd, *J* = 13.3, 3.7, 3.7 Hz), 1.15-0.96 (45H, m), 0.90 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 140.1, 124.2, 83.7, 75.4, 70.9, 70.8, 63.9, 53.7, 37.8, 36.9, 36.7, 36.0, 32.0, 27.1, 25.7, 18.1, 18.0, 15.7, 13.3, 12.3; IR (neat) ν_{max} 3311, 2942, 2865, 1774, 1463, 1378, 1192, 1058, 882, 809, 680 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{35}H_{62}O_4NaSi_2$: 625.4079, found: 625.4075; $[\alpha]^{26}_D$ -61.8 (*c* 1.24, $CHCl_3$).

[(1*S*,2*S*,4*R*,4a*S*,7*S*,8a*R*)-5-(hydroxymethyl)-1,2-dimethyl-1-(prop-2-yn-1-yl)-4,7-bis({[tris(propan-2-yl)silyl]oxy})-1,2,3,4,4a,7,8,8a-octahydronaphthalen-4a-yl]methanol (35)

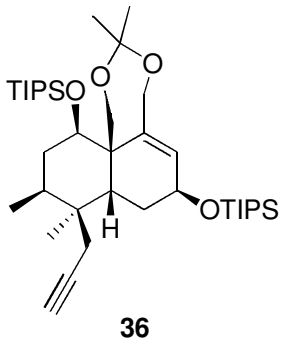


35

To a stirred solution of **34** (71.2 mg, 0.112 mmol) in THF (3.3 mL) was added $LiBH_4$ (3.0 M solution in THF, 112 μL, 0.336 mmol) at room temperature, the reaction mixture was stirred at 50 ºC for 24 h. The reaction mixture was quenched by saturated aqueous NH_4Cl solution (10 mL), the aqueous layer was extracted with Et_2O (5.0 mL x 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **35** (61.8 mg, 91%) as a white solid.

R_f = 0.45 (hexane/ethyl acetate = 4/1); mp 86.8-88.1 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ6.14 (1H, d, *J* = 5.0 Hz), 4.58 (1H, d, *J* = 11.8 Hz), 4.38-4.23 (2H, m), 4.14 (1H, dd, *J* = 11.8, 5.0 Hz), 4.04 (1H, d, *J* = 13.6 Hz), 3.96 (1H, dd, *J* = 11.8 5.0 Hz), 3.11-2.97 (1H, m), 2.81 (1H, dd, *J* = 17.9 1.8 Hz), 2.74 (1H, dd, *J* = 13.1, 2.3 Hz), 2.26 (1H, dd, *J* = 17.9, 2.7 Hz), 2.19 (1H, dd, *J* = 2.7, 2.7 Hz), 1.92 (1H, d, *J* = 13.1 Hz), 1.81-1.63 (2H, m), 1.59 (1H, ddd, *J* = 13.1, 4.1, 4.1 Hz), 1.45 (1H, dd, *J* = 25.4, 13.1 Hz), 1.13 (3H, s), 1.10-0.95 (42H, m), 0.85 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 132.5, 83.1, 75.3, 73.1, 65.3, 64.1, 62.2, 50.2, 38.8, 38.0, 35.7, 35.4, 30.7, 28.5, 27.6, 18.3, 18.2, 18.1, 18.1, 15.5, 13.4, 12.4; IR (neat) ν_{max} 3315, 2939, 2864, 1463, 1255, 1060, 997, 881, 803, 680 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{35}H_{66}O_4NaSi_2$: 629.4392, found: 629.4388; $[\alpha]^{25}_D$ -52.9 (*c* 0.80, $CHCl_3$).

{[(7*S*,8a*R*,9*S*,10*S*,12*R*,12a*S*)-3,3,9,10-tetramethyl-9-(prop-2-yn-1-yl)-7-{[tris(propan-2-yl)silyl]oxy}-1H,3H,5H,7H,8H,8aH,9H,10H,11H,12H-naphtho[4,4a-e][1,3]dioxepin-12-yl]oxy}tris(propan-2-yl)silane (36)

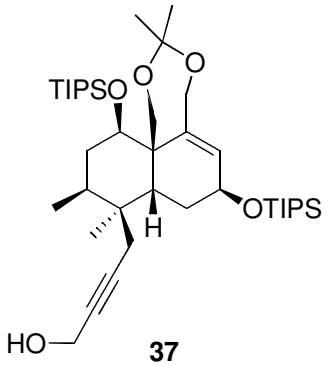


36

To a stirred solution of **35** (376 mg, 0.620 mmol) in 2,2-dimethoxypropane (10.7 mL) was added PPTS (15.6 mg, 0.0620 mmol) at room temperature, the reaction mixture was stirred at the same temperature for 3 d. The reaction mixture was poured into saturated aqueous $NaHCO_3$ solution (20 mL), the aqueous layer was extracted with Et_2O (10 mL x 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 60/1) to afford **36** (396 mg, 99%) as a colorless oil.

R_f = 0.68 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ5.76 (1H, d, *J* = 4.6 Hz), 4.82 (1H, d, *J* = 12.4 Hz), 4.54 (1H, d, *J* = 12.4 Hz), 4.27 (1H, br s), 4.16 (1H, dd, *J* = 7.3, 7.3 Hz), 3.80 (2H, d, *J* = 12.4 Hz), 2.65-2.48 (2H, m), 2.18 (1H, dd, *J* = 17.4, 2.3 Hz), 2.06 (1H, dd, *J* = 2.3, 2.3 Hz), 1.85 (1H, d, *J* = 13.7 Hz), 1.76-1.51 (4H, m), 1.32 (3H, s), 1.28 (3H, s), 1.15-0.98 (45H, m), 0.84 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 128.8, 101.2, 81.9, 75.4, 72.4, 69.5, 64.5, 63.0, 49.1, 39.2, 38.7, 37.9, 36.5, 31.3, 28.4, 28.2, 25.7, 24.4, 18.4, 18.2, 18.1, 15.6, 13.6, 12.4; IR (neat) ν_{max} 3314, 2940, 2865, 1460, 1370, 1220, 1053, 880, 810, 676 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{38}H_{70}O_4NaSi_2$: 669.4705, found: 669.4701; $[\alpha]^{24}_D$ -46.8 (*c* 1.27, $CHCl_3$).

4-[(7*S*,8a*R*,9*S*,10*S*,12*R*,12a*S*)-3,3,9,10-tetramethyl-7,12-bis({[tris(propan-2-yl)silyl]oxy})-1H,3H,5H,7H,8H,8aH,9H,10H,11H,12H-naphtho[4,4a-e][1,3]dioxepin-9-yl]but-2-yn-1-ol (37)

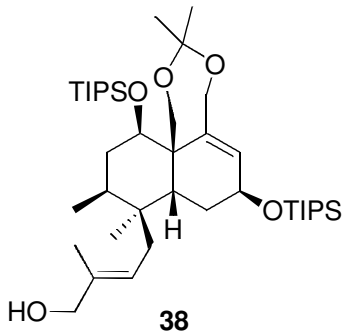


37

To a solution of **36** (29.0 mg, 0.0448 mmol) in THF (1.5 mL) was added *n*-BuLi (1.60 M solution in hexane, 56.0 μL, 0.0900 mmol) at –78 ºC. After 30 min, the mixture was added $(CH_2O)n$ (13.5 mg, 0.448 mmol) at –78 ºC. After the addition, the reaction mixture was stirred at the same temperature for 1 h and at room temperature for 30 min, and then was quenched by saturated aqueous NH_4Cl solution (5.0 mL). The mixture was stirred for 1 h vigorously, the aqueous layer was extracted with Et_2O (10 mL x 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 40/1) to afford **37** (27.9 mg, 92%) as a white amorphous.

R_f = 0.33 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ5.78 (1H, d, *J* = 5.0 Hz), 4.80 (1H, d, *J* = 11.9 Hz), 4.71 (1H, d, *J* = 11.9 Hz), 4.24 (1H, br s), 4.21-3.99 (4H, m), 3.84 (1H, d, *J* = 11.9 Hz), 2.83 (1H, d, *J* = 12.4 Hz), 2.71 (1H, d, *J* = 17.9 Hz), 2.44 (1H, br s), 2.11 (1H, d, *J* = 17.9 Hz), 1.84 (1H, d, *J* = 13.3 Hz), 1.74-1.63 (1H, m), 1.63-1.51 (2H, m), 1.49-1.34 (1H, m), 1.37 (3H, s), 1.25 (3H, s), 1.18-0.98 (45H, m), 0.82 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 127.0, 101.9, 85.4, 84.2, 74.4, 71.5, 64.4, 59.4, 51.3, 50.8, 38.9, 38.2, 37.8, 35.7, 30.4, 29.1, 28.3, 26.6, 24.2, 18.2, 18.1, 18.1, 15.3, 13.8, 12.3; IR (neat) ν_{max} 3437, 2940, 2865, 1462, 1381, 1223, 1058, 881, 809, 678 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{39}H_{72}O_5NaSi_2$: 699.4810, found: 699.4805; $[\alpha]^{26}_D$ -39.8 (*c* 1.82, $CHCl_3$).

(2*E*)-4-[(7*S*,8a*R*,9*S*,10*S*,12*R*,12a*S*)-3,3,9,10-tetramethyl-7,12-bis({[tris(propan-2-yl)silyl]oxy})-1H,3H,5H,7H,8H,8aH,9H,10H,11H,12H-naphtho[4,4a-e][1,3]dioxepin-9-yl]-2-methylbut-2-en-1-ol (38)



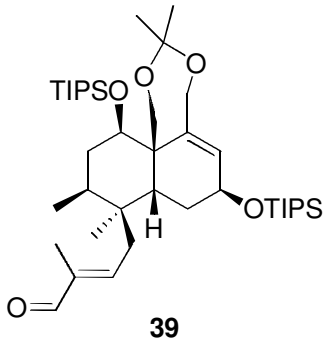
38

To a stirred solution of **37** (65.0 mg, 0.0960 mmol) in benzene (1.5 mL) was added MeMgCl (3.0 M solution in THF, 320 μL, 0.960 mmol) and CuI (18.3 mg, 0.0960 mmol) successively at 0 ºC. The reaction mixture was stirred at 70 ºC for 1 h, quenched by saturated aqueous aqueous NH_4Cl solution (5.0 mL), the aqueous layer was extracted with Et_2O (5.0 mL x 2). The combined organic layer was washed with

brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 30/1) to afford **38** (66.6 mg, 100%) as a colorless oil.

R_f = 0.56 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.75 (1H, d, *J* = 5.0 Hz), 5.52 (1H, d, *J* = 8.2 Hz), 4.75 (1H, d, *J* = 11.9 Hz), 4.57 (1H, d, *J* = 11.9 Hz), 4.22 (1H, br s), 4.11 (1H, dd, *J* = 10.5, 5.5 Hz), 4.03 (1H, d, *J* = 12.8 Hz), 3.98-3.85 (2H, m), 3.47 (1H, d, *J* = 11.9 Hz), 2.95-2.57 (1H, m), 2.51 (1H, dd, *J* = 16.0, 9.6 Hz), 2.43 (1H, d, *J* = 13.3 Hz), 1.90 (1H, d, *J* = 16.0 Hz), 1.83 (1H, d, *J* = 13.3 Hz), 1.69 (3H, s), 1.73-1.41 (4H, m), 1.30 (3H, s), 1.21 (3H, s), 1.14-0.98 (45H, m), 0.88 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 136.5, 127.6, 124.0, 101.5, 74.4, 71.2, 69.9, 64.6, 58.5, 51.1, 38.8, 38.1, 37.0, 36.5, 34.5, 30.5, 29.4, 25.9, 24.7, 18.2, 18.1, 18.1, 15.6, 14.5, 13.7, 12.3; IR (neat) ν_{max} 3463, 2941, 2864, 1655, 1463, 1380, 1222, 1057, 881, 810, 738, 678 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{40}H_{76}O_5NaSi_2$: 715.5123, found: 715.5118; $[\alpha]^{24}_D$ -31.6 (*c* 1.90, $CHCl_3$).

(2*E*)-4-[(7*S*,8a*R*,9*S*,10*S*,12*R*,12a*S*)-3,3,9,10-tetramethyl-7,12-bis({[tris(propan-2-yl)silyl]oxy})-1H,3H,5H,7H,8H,8aH,9H,10H,11H,12H-naphtho[4,4a-e][1,3]dioxepin-9-yl]-2-methylbut-2-enal (39)



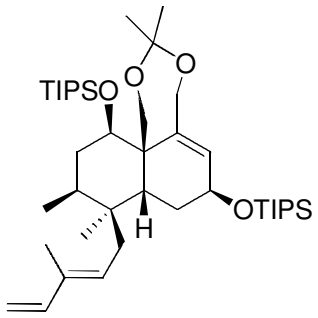
39

To a solution of **38** (299 mg, 0.431 mmol) in CH_2Cl_2 (8.6 mL) was added pyridine (174 μL, 2.15 mmol) and Dess-Martin periodinane (275 mg, 0.646 mmol) successively at 0 ºC. The reaction mixture was stirred at room temperature for 1 h, quenched by saturated aqueous $NaHCO_3$ solution (10 mL) and saturated aqueous $Na_2S_2O_3$ solution (10 mL) successively, the aqueous layer was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford **39** (286 mg, 96%) as a colorless oil.

R_f = 0.68 (hexane/ethyl acetate = 5/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.38 (1H, s), 6.82 (1H, br t), 5.80 (1H, d, *J* = 4.6 Hz), 4.74 (1H, d, *J* = 12.8 Hz), 4.64 (1H, d, *J* = 12.8

Hz), 4.25 (1H, br, s), 4.16 (1H, dd, *J* = 10.1, 6.0 Hz), 3.91 (1H, d, *J* = 11.9 Hz), 3.67 (1H, d, *J* = 11.9 Hz), 2.80 (1H, dd, *J* = 16.0, 6.9 Hz), 2.39 (1H, br s), 2.33 (1H, dd, *J* = 16.0, 6.9 Hz), 1.83 (1H, d, *J* = 13.3 Hz), 1.76 (3H, s), 1.78-1.48 (4H, m), 1.26 (3H, s), 1.24 (3H, s), 1.15-0.97 (45H, m), 0.94 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 195.6, 152.1, 145.2, 140.7, 129.6, 101.1, 74.6, 70.0, 64.4, 60.2, 50.7, 40.1, 38.1, 37.2, 36.4, 30.9, 29.1, 25.9, 24.9, 18.3, 18.1, 18.1, 18.1, 15.8, 13.5, 12.4, 9.64; IR (neat) ν_{max} 2940, 2865, 1689, 1643, 1462, 1377, 1221, 1058, 881, 810, 677 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{40}H_{74}O_5NaSi_2$: 713.4967, found: 713.4962; $[\alpha]^{24}_D$ -40.6 (*c* 2.24, $CHCl_3$).

{[(7*S*,8a*R*,9*S*,10*S*,12*R*,12a*S*)-3,3,9,10-tetramethyl-9-[(2*E*)-3-methylpenta-2,4-dien-1-yl]-7-{[tris(propan-2-yl)silyl]oxy}-1H,3H,5H,7H,8H,8aH,9H,10H,11H,12H-naphtho[4,4a-e][1,3]dioxepin-12-yl]oxy}tris(propan-2-yl)silane (40)



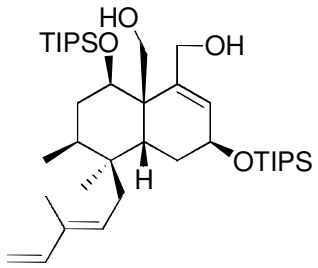
40

To a stirred solution of PPh_3CH_3Br (426 mg, 1.19 mmol) in THF (7.4 mL) was added *n*-BuLi (1.60 M solution in hexane, 621 μL, 0.994 mmol) dropwise at 0 ºC, and the reaction mixture was stirred for 30 min. Then, to the reaction mixture was added a solution of **39** (275 mg, 0.397 mmol) in THF (3.7 mL) via a cannula at 0 ºC. After the addition, the reaction mixture was stirred at the same temperature for 15 min, and then was quenched by saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with Et_2O (10 mL x 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 80/1) to afford **40** (263 mg, 96%) as a colorless oil.

R_f = 0.81 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ6.39 (1H, dd, *J* = 17.4, 11.0 Hz), 5.76 (1H, d, *J* = 4.1 Hz), 5.71 (1H, br t), 5.04 (1H, d, *J* = 17.4 Hz), 4.89 (1H, d, *J* = 11.0 Hz), 4.78 (1H, d, *J* = 12.4 Hz), 4.57 (1H, d, *J* = 12.4 Hz), 4.25 (1H, br s), 4.14 (1H, dd, *J* = 11.0, 4.1 Hz), 3.83 (1H, d, *J* = 12.4 Hz), 3.67 (1H, d, *J* = 12.4 Hz), 2.54 (1H, dd, *J* = 16.0, 6.9 Hz), 2.32 (1H, br s), 2.13 (1H, dd, *J* = 16.0, 6.9 Hz), 1.85-1.49 (5H, m), 1.74 (3H, s), 1.28 (3H, s), 1.26 (3H, s), 1.16-1.00 (42H, m), 0.97 (3H, s), 0.91 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4,

142.1, 135.2, 129.7, 129.2, 109.8, 101.0, 75.2, 69.8, 64.6, 61.9, 50.0, 39.6, 38.0, 37.5, 35.1, 31.0, 28.8, 25.2, 18.4, 18.2, 18.1, 15.8, 13.6, 12.4, 12.2; IR (neat) ν_{max} 2941, 2865, 1606, 1463, 1368, 1221, 1059, 882, 811, 678 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{41}H_{76}O_4NaSi_2$: 711.5174, found: 711.5168; $[\alpha]^{25}_D$ -42.0 (*c* 0.81, $CHCl_3$).

[(1*S*,2*S*,4*R*,4a*S*,7*S*,8a*R*)-5-(hydroxymethyl)-1,2-dimethyl-1-[(2*E*)-3-methylpenta-2,4-dien-1-yl]-4,7-bis({[tris(propan-2-yl)silyl]oxy})-1,2,3,4,4a,7,8,8a-octahydronaphthalen-4a-yl]methanol (41)



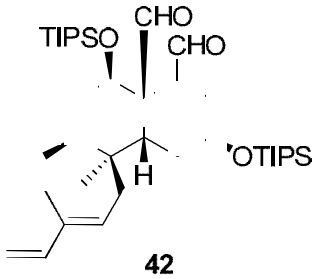
41

To a stirred solution of **40** (149 mg, 0.217 mmol) in CH_2Cl_2/MeOH (4/1, 41.3 mL) was added TFA (3.32 μL, 0.0433 mmol) at -10 ºC, the mixture was stirred at the same temperature for 18 h. The reaction mixture was quenched by saturated aqueous $NaHCO_3$ solution (10 mL), the aqueous layer was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 30/1) to afford **41** (115 mg, 82%) as a colorless oil.

R_f = 0.50 (hexane/ethyl acetate = 4/1); ^1H NMR (400MHz, $CDCl_3$) δ6.35 (1H, dd, *J* = 17.4, 11.0 Hz), 6.09 (1H, d, *J* = 5.0 Hz), 5.76 (1H, br t), 5.10 (1H, d, *J* = 17.4 Hz), 4.94 (1H, d, *J* = 11.0 Hz), 4.56 (1H, d, *J* = 11.9 Hz), 4.33-4.27 (1H, m), 4.23 (1H, dd, *J* = 11.9, 3.2 Hz), 4.14 (1H, dd, *J* = 10.1, 5.0 Hz), 3.95 (2H, d, *J* = 12.4 Hz), 2.75 (1H, dd, *J* = 16.0, 8.2 Hz), 2.45 (1H, dd, *J* = 13.3, 2.3 Hz), 2.24-2.00 (2H, m), 1.90 (1H, d, *J* = 13.3 Hz), 1.80 (3H, s), 1.76-1.50 (4H, m), 1.15-0.96 (45H, m), 0.91 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 141.0, 136.3, 132.7, 129.6, 111.3, 75.6, 65.5, 64.2, 61.5, 50.3, 38.9, 37.9, 36.9, 34.9, 34.8, 30.7, 28.8, 18.3, 18.2, 18.1, 18.1, 15.8, 13.4, 12.4, 12.1; IR (neat) ν_{max} 3291, 2865, 1605, 1463, 1382, 1059, 994, 881, 804, 736, 678 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{38}H_{72}O_4NaSi_2$: 671.4861, found: 671.4858; $[\alpha]^{23}_D$ -43.8 (*c* 1.42, $CHCl_3$).

(3*S*,4a*R*,5*S*,6*S*,8*R*,8a*R*)-5,6-dimethyl-5-[(2*E*)-3-methylpenta-2,4-dien-1-yl]-3,8-bis(

{[tris(propan-2-yl)silyl]oxy})-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1,8a-dicarbaldehyde (42)

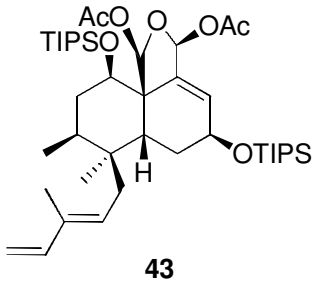


42

To a solution of $(COCl)_2$ (169 μL, 1.94 mmol) and DMSO (236 μL, 3.33 mmol) in CH_2Cl_2 (9.5 mL) was added a solution of **41** (180 mg, 0.277 mmol) in CH_2Cl_2 (9.5 mL) via a cannula at –78 °C. After 30 min, to the reaction mixture was added TEA (619 μL, 4.44 mmol) and the reaction mixture was stirred at the same temperature for 1 h and at room temperature for 1 h. The mixture was quenched by saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 100/1) to afford **42** (170 mg, 95%) as a white solid.

R_f = 0.54 (hexane/ethyl acetate = 10/1); mp 55.2-56.5 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ10.5 (1H, s), 9.34 (1H, s), 6.87 (1H, d, *J* = 5.0 Hz), 6.34 (1H, dd, *J* = 17.4, 11.0 Hz), 5.35 (1H, br t), 5.03 (1H, d, *J* = 17.4 Hz), 4.88 (1H, d, *J* = 11.0 Hz), 4.58-4.48 (1H, m), 4.12 (1H, dd, *J* = 11.9, 5.0 Hz), 2.66 (1H, dd, *J* = 13.3, 2.3 Hz), 2.20 (1H, dd, *J* = 16.0, 8.7 Hz), 1.98 (1H, dd, *J* = 25.6, 13.3 Hz), 1.88 (1H, d, *J* = 13.3 Hz), 1.85-1.61 (4H, m), 1.69 (3H, s), 1.16-0.97 (42H, m), 0.95 (3H, d, *J* = 6.9 Hz), 0.84 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 191.8, 145.9, 145.3, 141.9, 136.0, 127.5, 110.2, 74.0, 63.5, 56.0, 39.1, 38.7, 37.7, 36.2, 31.3, 29.5, 25.4, 18.1, 18.0, 18.0, 15.8, 13.2, 12.3, 12.2; IR (neat) ν_{max} 2941, 2865, 1713, 1702, 1635, 1463, 1383, 1061, 881, 801, 735, 678 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{38}H_{68}O_4NaSi_2$: 667.4548, found: 667.4545; $[\alpha]^{23}_D$ -46.3 (*c* 1.08, $CHCl_3$).

(1*R*,3*S*,5*S*,6a*R*,7*S*,8*S*,10*R*,10a*R*)-3-(acetyloxy)-7,8-dimethyl-7-[(2*E*)-3-methylpenta-2,4-dien-1-yl]-5,10-bis({[tris(propan-2-yl)silyl]oxy})-1H,3H,5H,6H,6aH,7H,8H,9H,10H-naphtho[4,4a-c]furan-1-yl acetate (43)

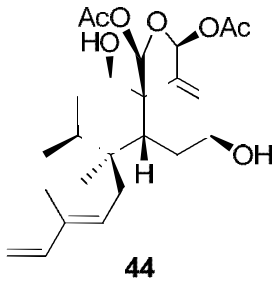


43

To a solution of **42** (47.8 mg, 0.0741 mmol) in AcOH/Ac_2O (3/2, 3.25 mL) was added NaOAc (30.4 mg, 0.370 mmol) and H_2SO_4 (1% solution in AcOH, 2.08 mL, 0.222 mmol) successively at 0 ºC. The reaction mixture was stirred at room temperature for 2 d, poured into saturated aqueous $NaHCO_3$ solution (200 mL), the aqueous layer was extracted with Et_2O (50 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 60/1) to afford **43** (41.9 mg, 76%) as a colorless oil.

R_f = 0.33 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ6.71 (1H, s), 6.48 (1H, s), 6.24 (1H, dd, *J* = 17.2, 10.9 Hz), 5.94 (1H, d, *J* = 4.1 Hz), 5.43 (1H, br d), 5.05 (1H, d, *J* = 17.2 Hz), 4.89 (1H, d, *J* = 10.9 Hz), 4.49 (1H, br s), 4.16-4.05 (1H, m), 2.62 (1H, dd, *J* = 13.6, 2.7 Hz), 2.18 (1H, dd, *J* = 16.8, 8.2 Hz), 2.04 (3H, s), 1.93-1.82 (1H, m), 1.86 (3H, s), 1.79-1.58 (5H, m), 1.64 (3H, s), 1.18-0.99 (42H, m), 0.90 (3H, d, *J* = 5.4 Hz), 0.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.9, 142.2, 141.4, 135.0, 130.0, 126.1, 110.5, 97.9, 96.3, 73.7, 64.4, 54.4, 37.5, 37.3, 37.0, 36.1, 30.6, 30.2, 25.2, 21.6, 21.1, 18.1, 18.1, 18.1, 18.0, 15.8, 13.3, 12.5, 11.8; IR (neat) ν_{max} 2941, 2865, 1752, 1605, 1464, 1370, 1224, 1063, 883, 817, 677, cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{42}H_{74}O_7NaSi_2$: 769.4865, found: 769.4858; $[\alpha]^{22}_D$ -21.2 (*c* 0.58, $CHCl_3$).

(1*R*,3*S*,5*S*,6a*R*,7*S*,8*S*,10*R*,10a*R*)-3-(acetyloxy)-5,10-dihydroxy-7,8-dimethyl-7-[(2*E*)-3-methylpenta-2,4-dien-1-yl]-1H,3H,5H,6H,6aH,7H,8H,9H,10H-naphtho[4,4a-c]furan-1-yl acetate (44)



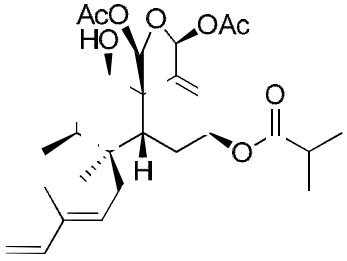
44

To a solution of **43** (111 mg, 0.149 mmol) in THF (3.0 mL) was added TBAF (1.0 M solution in THF, 446 μL, 0.446 mmol) at 0 ºC, the reaction mixture was stirred at

room temperature for 1.5 h. The reaction mixture was quenched by saturated aqueous NH_4Cl solution (10 mL), the aqueous layer was extracted with Et_2O (10 mL x 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 3/1) to afford **44** (57.6 mg, 89%) as a white solid.

R_f = 0.13 (hexane/ethyl acetate = 1/1); mp 96.6-99.0 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.73 (1H, br t), 6.52 (1H, s), 6.31 (1H, dd, *J* = 17.4, 10.5 Hz), 6.05 (1H, dd, *J* = 4.1, 1.4 Hz), 5.44 (1H, dd, *J* = 7.8, 2.3 Hz), 5.09 (1H, d, *J* = 17.4 Hz), 4.93 (1H, d, *J* = 10.5 Hz), 4.43 (1H, br s), 3.77 (1H, br s), 2.33 (1H, dd, *J* = 11.9, 5.5 Hz), 2.25 (1H, dd, *J* = 16.0, 7.8 Hz), 2.11 (3H, s), 1.95 (3H, s), 1.98-1.86 (2H, m), 1.86-1.68 (2H, m), 1.66 (3H, s), 1.63-1.53 (2H, m), 0.93 (3H, d, *J* = 6.9 Hz), 0.86 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.6, 143.4, 141.2, 135.6, 129.2, 125.1, 110.9, 97.1, 95.7, 73.0, 64.0, 53.5, 37.6, 37.3, 36.7, 35.8, 30.4, 29.4, 25.0, 21.7, 21.3, 15.6, 11.9; IR (neat) ν_{max} 3381, 2966, 2938, 1747, 1732, 1637, 1373, 1225, 1002, 890, 677 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{24}H_{34}O_7Na$: 457.2197, found: 457.2197; $[\alpha]^{24}_D$ -4.3 (*c* 2.12, $CHCl_3$).

(1*R*,3*S*,5*S*,6a*R*,7*S*,8*S*,10*R*,10a*R*)-1,3-bis(acetyloxy)-10-hydroxy-7,8-dimethyl-7-[(2*E*)-3-methylpenta-2,4-dien-1-yl]-1H,3H,5H,6H,6aH,7H,8H,9H,10H-naphtho[4,4a-c]furan-5-yl 2-methylpropanoate (45: (-)-bucidarasin A))



(-)-bucidarasin A

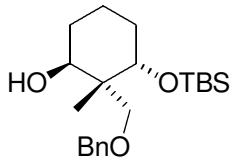
To a solution of **44** (23.4 mg, 0.0539 mmol) in CH_2Cl_2 (1.5 mL) was added TEA (75.1 μL, 0.539 mmol) and isobutyryl chloride (16.9 μL, 0.162 mmol) successively at 0 ºC, the reaction mixture was stirred at 35 ºC for 30 min. The reaction mixture was quenched by saturated aqueous NH_4Cl solution (5.0 mL) and ca.25% NH_4OH solution (5.0 mL) successively, the aqueous layer was extracted with CH_2Cl_2 (10 mL x 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 3/1) to afford **(-)-bucidarasin A** (26.0 mg, 96%) as a colorless oil.

R_f = 0.43 (hexane/ethyl acetate = 1/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.73 (1H, dd, *J* =

1.4, 1.4 Hz), 6.51 (1H, s), 6.27 (1H, dd, *J* = 17.4, 10.5 Hz), 5.99 (1H, dd, *J* = 4.6, 1.4 Hz), 5.47-5.41 (1H, m), 5.41-5.33 (1H, m), 5.10 (1H, d, *J* = 17.4 Hz), 4.93 (1H, d, *J* = 10.5 Hz), 3.80 (1H, ddd, *J* = 12.4, 9.6, 3.7 Hz), 2.64 (1H, qq, *J* = 6.9, 6.9 Hz), 2.36 (1H, dd, *J* = 11.4, 5.5 Hz), 2.24 (1H, dd, *J* = 16.5, 7.8 Hz), 2.10 (3H, s), 1.94 (3H, s), 1.92-1.83 (2H, m), 1.82-1.54 (4H, m), 1.66 (3H, s), 1.22 (3H, d, *J* = 6.9 Hz), 1.20 (3H, d, *J* = 6.9 Hz), 0.93 (3H, d, *J* = 6.9 Hz), 0.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 170.2, 169.4, 145.2, 141.2, 135.7, 129.0, 121.8, 111.1, 96.9, 95.6, 72.8, 66.0, 53.5, 37.5, 37.3, 36.8, 36.7, 34.0, 30.3, 26.7, 25.0, 21.6, 21.2, 19.2, 18.7, 15.6, 12.0; IR (neat) νmax 3469, 2969, 2933, 2878, 1749, 1728, 1605, 1371, 1225, 889, 735 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{28}H_{40}O_8Na$: 527.2615, found: 527.2616; $[\alpha]^{25}_D$ -33.6 (*c* 0.25, MeOH).

第 3 節　(+)-bucidarasin A および C の不斉全合成

(1*S*,2*R*,3*S*)-2-(benzyloxymethyl)-3-(*tert*-butyldimethylsilyloxy)-2-methylcyclohexanol (49)

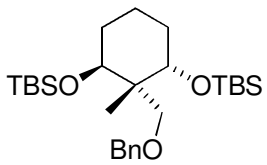


49

To a solution of (1S,3S)-2-[(benzyloxy)methyl]-2-methylcyclohexane-1,3-diol (93.7 mg, 0.374 mmol) and 2,6-lutidine (87.2 μL, 0.749 mmol) in CH_2Cl_2 (15 mL) was added a solution of TBSOTf (0.129 mL, 0.561 mmol) in CH_2Cl_2 (15 mL) at -60 °C via a syringe pump over 5 h, the reaction mixture was stirred at the same temperature for 2 h. The reaction mixture was quenched with H_2O (20 mL), the aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **49** (98.4 mg, 72%) and **50** (24.7 mg, 13%) as a colorless oil and starting material (14.0 mg, 15%)

R_f = 0.51 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (5H, m), 4.55 (1H, d, *J* = 11.9 Hz), 4.50, (1H, d, J = 11.9 Hz), 4.01 (1H, dd, *J* = 11.0, 4.1 Hz), 3.88 (1H, d, *J* = 8.7 Hz), 3.57 (1H, s), 3.36 (1H, s), 3.25 (1H, d, *J* = 8.7 Hz), 1.78-1.56 (3H, m), 1.52-1.32 (3H, m), 0.99 (3H, s), 0.83 (9H, s), -0.014 (3H, s), -0.049 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8 (Cq), 128.4 (CH), 127.6 (CH), 127.6 (CH), 79.7 (CH_2), 74.4 (CH), 73.7 (CH_2), 72.8 (CH), 43.4 (Cq), 29.3 (CH_2), 28.3 (CH_2), 25.7 (CH_3), 18.0 (Cq), 18.0 (CH_2), 14.1 (CH_3), -4.46 (CH_3), -5.31 (CH_3); IR (neat) ν_{max} 3448, 2928, 2856, 1471, 1360, 1252, 1074, 1026, 859, 773, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{21}H_{36}O_3NaSi$: 387.2326, found: 387.2325; $[\alpha]_D^{25}$ +14 (*c* 0.6, $CHCl_3$).

1-((((2*S*,6*S*)-2,6-bis(*tert*-butyldimethylsilyloxy)-1-methylcyclohexyl)methoxy)methyl)benzene (50)

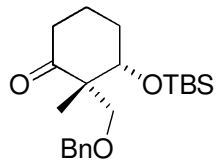


50

R_f = 0.91 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (5H,

m), 4.57 (1H, d, *J* = 11.9 Hz), 4.35, (1H, d, J = 11.9 Hz), 3.94 (1H, dd, *J* = 5.5, 1.8 Hz), 3.82 (1H, dd, *J* = 8.7, 4.1 Hz) , 3.51 (1H, d, *J* = 8.2 Hz) , 3.38 (1H, d, *J* = 8.2 Hz), 1.73-1.34 (6H, m), 0.99 (3H, s), 0.89 (9H, s), 0.83 (9H, s), 0.027 (3H, s), 0.017 (3H, s), 0.0079 (3H, s), -0.022 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2 (Cq), 128.1 (CH), 127.4 (CH), 127.1 (CH), 73.8 (CH), 73.2 (CH), 72.2 (CH_2), 71.2 (CH_2), 44.9 (Cq), 29.9 (CH_2), 28.7 (CH_2), 26.0 (CH_3), 25.9 (CH_3), 18.6 (CH_2), 18.1 (Cq), 18.0 (Cq), 16.1 (CH_3), -4.02 (CH_3), -4.31 (CH_3), -5.08 (CH_3), -5.25 (CH_3); IR (neat) ν_{max} 2928, 2856, 1471, 1360, 1251, 1078, 1070, 831, 772, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{27}H_{50}O_3NaSi_2$: 501.3191, found: 501.3192; $[\alpha]_D^{26}$ +18 (*c* 1.0, $CHCl_3$).

(2*S*,3*S*)-2-(benzyloxymethyl)-3-(*tert*-butyldimethylsilyloxy)-2-methylcyclohexanone (51)

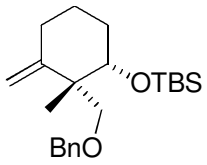


51

To a solution of **49** (189 mg, 0.518 mmol) in CH_2Cl_2 (13 mL) was added Dess-Martin periodinane (331 mg, 0.778 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h, quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and saturated aqueous $Na_2S_2O_3$ solution (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **51** (177 mg, 94%) as a colorless oil.

R_f = 0.56 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (5H, m), 4.55 (1H, d, *J* = 12.4 Hz), 4.41 (1H, d, *J* = 12.4 Hz), 4.00 (1H, dd, *J* = 6.0, 2.7 Hz), 3.68 (1H, d, *J* = 9.2 Hz), 3.63 (1H, d, *J* = 9.2 Hz), 2.47 (1H, ddd, *J* = 14.7, 9.6, 6.0 Hz), 2.36-2.24 (1H, m), 2.13-1.89 (2H, m), 1.86-1.75 (1H, m) , 1.74-1.62 (1H, m), 1.24 (3H, s), 0.86 (9H, s), 0.033 (3H, s), 0.024 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5 (Cq), 138.6 (Cq), 128.2 (CH), 127.4 (CH), 127.3 (CH), 75.5 (CH), 73.2 (CH_2) , 71.7 (CH_2), 55.1 (Cq), 37.8 (CH_2), 28.7 (CH_2), 25.8 (CH_3), 20.4 (CH_2), 19.4 (CH_3), 18.0 (Cq), -4.43 (CH_3), -5.27 (CH_3); IR (neat) ν_{max} 2928, 2855, 1707, 1462, 1360, 1249, 1078, 830, 774, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{21}H_{34}O_3NaSi$: 385.2169, found: 385.2170; $[\alpha]_D^{25}$ +0.56 (*c* 0.71, $CHCl_3$).

((1*S*,2*S*)-2-(benzyloxymethyl)-2-methyl-3-methylenecyclohexyloxy)(*tert*-butyl)dimethylsilane (52)

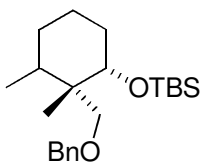


52

To a stirred suspension of PPh_3CH_3Br (482 mg, 1.35 mmol) in THF (6.0 mL) was added KHMDS (0.50 M solution in toluene, 2.25 mL, 1.12 mmol) dropwise at 0 °C, and the reaction mixture was stirred for 30 min. Then, to the reaction mixture was added a solution of **51** (163 mg, 0.450 mmol) in THF (6.0 mL) via a cannula at 0 °C. After the addition, the reaction mixture was stirred at 60 °C for 1.5 h, and then was quenched with saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 100/1) to afford **52** (157 mg, 97%) as a colorless oil.

R_f = 0.77 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (5H, m), 4.85 (1H, d, *J* = 1.8 Hz), 4.71 (1H, d, *J* = 1.8 Hz), 4.53 (1H, d, *J* = 12.4 Hz), 4.48 (1H, d, *J* = 12.4 Hz), 3.68 (1H, d, *J* = 9.2 Hz), 3.49 (1H, d, *J* = 9.2 Hz), 3.47 (1H, dd, *J* = 8.7, 3.7 Hz), 2.24-2.09 (2H, m), 1.81-1.648 (2H, m), 1.63-1.49 (1H, m), 1.40-1.24 (1H, m), 1.19 (3H, s), 0.85 (9H, s) 0.00 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6 (Cq), 139.0 (Cq), 128.2 (CH), 127.4 (CH), 127.2 (CH), 109.3 (CH_2), 76.7 (CH), 73.2 (CH_2), 72.5 (CH_2), 46.7 (Cq), 32.5 (CH_2), 30.6 (CH_2), 25.8 (CH_3), 24.0 (CH_2), 20.8 (CH_3), 18.0 (Cq), -4.14 (CH_3), -5.08 (CH_3); IR (neat) ν_{max} 2930, 2855, 1638, 1461, 1360, 1250, 1080, 830, 772, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{22}H_{36}O2NaSi$: 383.2377, found: 383.2376; $[\alpha]_D^{25}$ +31 (*c* 0.69, $CHCl_3$).

((1*S*,2*S*)-2-(benzyloxymethyl)-2,3-dimethylcyclohexyloxy)(*tert*-butyl)dimethylsilane (53)



53

To a stirred solution of **52** (151 mg, 0.418 mmol) in benzene (8.4 mL) was added Wilkinson reagent (19.4 mg, 5 mol%). The reaction mixture was stirred at 60 °C for 2

h under an atmosphere of hydrogen, the reaction mixture was diluted with hexane/ethyl acetate (5/1, 10 mL), filtered through a Celite pad, and the filtrate was concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate = 100/1) to afford **53** (150 mg, 99%) as a colorless oil.

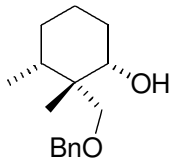
major product

R_f = 0.76 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.22 (5H, m), 4.46 (2H, s), 3.63 (1H, d, *J* = 9.2 Hz), 3.39 (1H, d, *J* = 9.2 Hz), 3.35 (1H, dd, *J* = 9.6, 5.0 Hz), 1.75-1.17 (7H, m), 1.03 (3H, d, *J* = 6.9 Hz), 0.97 (3H, s), 0.88 (9H, s), 0.024 (6H, s).

minor product

R_f = 0.76 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.22 (5H, m), 4.54 (1H, d, *J* = 12.4 Hz), 4.36 (1H, d, *J* = 12.4 Hz), 3.84 (1H, br s), 3.48 (1H, d, *J* = 8.2 Hz), 3.25 (1H, d, *J* = 8.2 Hz), 1.87-1.76 (1H, m), 1.75-1.17 (6H, m), 0.90 (9H, s), 0.88 (3H, s), 0.74 (3H, d, *J* = 6.9 Hz), 0.0045 (6H, s); HRMS (ESI) $[M+Na]^+$ calculated for $C_{22}H_{38}O_2NaSi$: 385.2533, found: 385.2533

(1*S*,2*S*,3*R*)-2-(benzyloxymethyl)-2,3-dimethylcyclohexanol (54)



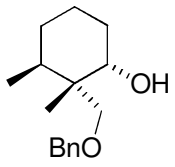
54

To a solution of **53** (135 mg, 0.372 mmol) in THF (3.7 mL) was added TBAF (1.0 M solution in THF, 745 μL, 0.745 mmol), and the reaction mixture was stirred at 75 °C for 24 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL), and the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford **54** (69.4 mg, 75%) and **54'** (12.8 mg, 14%) as a colorless oil.

R_f = 0.41 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (5H, m), 4.49 (2H, s), 3.95 (1H, d, *J* = 9.2 Hz), 3.99-3.70 (1H, br), 3.55 (1H, d, *J* = 9.2 Hz), 3.24 (1H, dd, *J* = 11.9, 4.1 Hz), 1.90-1.80 (1H, m), 1.76-1.66 (1H, m), 1.65-1.43 (1H, m), 1.42-1.27 (3H, m), 1.26 (3H, s), 1.23-1.05 (1H, m), 0.83 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7 (Cq), 128.4 (CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 79.7 (CH), 74.0 (CH_2), 72.6 (CH_2), 41.3 (Cq), 40.7 (CH), 31.8 (CH_2), 30.3 (CH_2), 24.4 (CH_2), 21.7 (CH_3), 15.8 (CH_3); IR (neat) ν_{max} 3450, 2927, 2858,

1453, 1074, 1015, 733, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{24}O_2Na$: 271.1669, found: 271.1667; $[\alpha]_D^{25}$ +3.7 (*c* 0.60, $CHCl_3$).

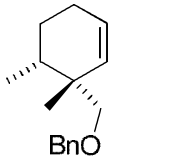
(1*S*,2*S*,3*S*)-2-(benzyloxymethyl)-2,3-dimethylcyclohexanol (54')



54'

R_f = 0.46 (hexane/ethyl acetate = 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (5H, m), 4.57 (1H, d, *J* = 11.9 Hz), 4.47 (1H, d, *J* = 11.9 Hz), 3.72 (1H, t, *J* = 2.7 Hz), 3.57 (1H, d, *J* = 11.9 Hz), 3.32 (1H, d, *J* = 11.9 Hz), 2.21-2.08 (1H, m), 1.83-1.68 (1H, m), 1.67-1.52 (2H, m), 1.48-1.36 (2H, m), 1.29-1.14 (1H, m), 0.76 (3H, d, *J* = 6.9 Hz), 0.70 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6 (Cq), 128.5 (CH), 127.8 (CH), 127.7 (CH), 78.1 (CH_2), 76.1 (CH), 73.6 (CH_2), 40.7 (Cq), 29.8 (CH_2), 28.9 (CH), 28.8 (CH_2), 20.0 (CH_2), 15.4 (CH_3), 15.2 (CH_3); IR (neat) ν_{max} 3483, 2932, 2856, 1454, 1071, 1014, 734, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{24}O_2Na$: 271.1669, found: 271.1667; $[\alpha]_D^{25}$ +1.0 (*c* 0.53, $CHCl_3$).

1-((((1*R*,6*R*)-1,6-dimethylcyclohex-2-enyl)methoxy)methyl)benzene (10')



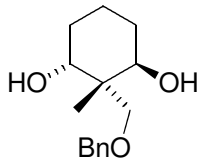
10'

To a stirred solution of **54** (65.0 mg, 0.262 mmol) in pyridine (2.5 mL) was added $POCl_3$ (71.2 μL, 0.785 mmol) at 0 °C, and the mixture was stirred at 80 °C for 2 h. The reaction mixture was quenched with H_2O (5.0 mL), the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 100/1) to afford **10'** (56.1 mg, 93%) as a colorless oil.

R_f = 0.77 (hexane/ethyl acetate = 8/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.24 (5H, m), 5.70 (1H, ddd, *J* = 10.1, 3.7, 3.7 Hz), 5.44 (1H, ddd, *J* = 10.1, 2.3, 2.3 Hz), 4.50 (2H, s), 3.28 (2H, s), 2.09-1.94 (2H, m), 1.65-1.53 (3H, m), 1.07 (3H, s), 0.94 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0 (Cq), 134.2 (CH), 128.2 (CH), 127.3 (CH), 127.2 (CH), 126.4 (CH), 76.0 (CH_2), 73.3 (CH_2), 38.5 (Cq), 36.8 (CH),

27.2 (CH_2), 25.0 (CH_3), 24.3 (CH_2), 15.8 (CH_3); IR (neat) ν_{max} 2957, 2921, 2859, 1453, 1365, 1095, 732, 695 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{22}ONa$: 253.1563, found: 253.1563; $[\alpha]_D^{26}$ +33 (*c* 2.0, $CHCl_3$).

(1*R*,3*R*)-2-(benzyloxymethyl)-2-methylcyclohexane-1,3-diol (48)

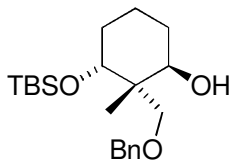


48

A solution of 2-Benzyloxymethyl-2-methylcyclohexane-1,3-dione (10.0 g, 40.6 mmol) in CH_2Cl_2 (750 mL) was added to a mixture of (*S*)-Me-CBS (1.0 M solution in toluene, 6.09 mL, 6.09 mmol) and 90% BH_3-SMe_2 (10.3 mL, 97.4 mmol) in CH_2Cl_2 (1850 mL) at 30 °C via a syringe pump over 6 h. The reaction was quenched with MeOH (20 mL) and 2*N* HCl (120 mL) was added to the reaction mixture, and stirred for 10 h at room temperature. After dilution with CH_2Cl_2 (100 mL), the organic layer was separated, washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford **48** (9.55 g, 94%, >99% ee) as a white solid

R_f = 0.17 (hexane/ethyl acetate = 2/1); mp 77.2-78.3 ° C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.27 (5H, m), 4.60 (1H, d, *J* = 11.9 Hz), 4.53 (1H, d, *J* = 11.9 Hz), 4.15 (1H, dd, *J* = 11.0, 4.6 Hz), 3.80 (1H, t, *J* = 3.2 Hz), 3.68 (1H, d, *J* = 9.2 Hz), 3.56 (1H, d, *J* = 9.2 Hz), 3.35 (1H, br s), 1.89 (1H, br), 1.90-1.70 (3H, m), 1.69-1.41 (4H, m), 0.85 (3H, s); ^{13}C NMR (125 MHz, CDCl3) *δ* 137.5 (Cq), 128.5 (CH), 127.9 (CH), 127.6 (CH), 77.3 (CH_2), 75.8 (CH), 73.6 (CH_2), 69.0 (CH), 43.0 (Cq), 29.8zR (neat) ν_{max} 3399, 2943, 2863, 1454, 1364, 1070, 1047, 998, 741, 694 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{15}H_{22}O_3Na$: 273.1461, found: 273.1461; $[\alpha]_D^{23}$ -18 (*c* 1.0, $CHCl_3$).

(1*R*,2*S*,3*R*)-2-(benzyloxymethyl)-3-(*tert*-butyldimethylsilyloxy)-2-methylcyclohexanol (55)

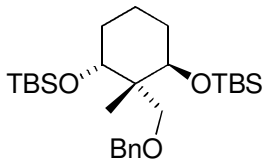


55

To a solution of **48** (16.1 g, 64.3 mmol) and 2,6-lutidine (15.0 mL, 129 mmol) in

CH_2Cl_2 (700 mL) was added a solution of TBSOTf (16.2 mL, 70.7 mmol) in CH_2Cl_2 (20 mL) at -60 °C via a syringe pump over 7 h, the reaction mixture was stirred at the same temperature for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (100 mL), the aqueous layer was extracted with CH_2Cl_2 (150 mL × 2). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **55** (14.2 g, 61%) and **56** (6.23 g, 20%) as a colorless oil and starting material (2.54 g, 16%).
R_f = 0.51 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (5H, m), 4.55 (1H, d, *J* = 11.8 Hz), 4.50, (1H, d, *J* = 11.8 Hz), 4.01 (1H, dd, *J* = 11.3, 4.5 Hz), 3.88 (1H, d, *J* = 8.6 Hz), 3.57 (1H, s), 3.36 (1H, s), 3.25 (1H, d, *J* = 8.6 Hz), 1.77-1.68 (1H, m), 1.68-1.56 (2H, m), 1.52-1.31 (3H, m), 0.99 (3H, s), 0.84 (9H, s), -0.013 (3H, s), -0.048 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8 (Cq), 128.4 (CH), 127.7 (CH), 127.6 (CH), 79.9 (CH_2), 74.5 (CH), 73.8 (CH_2), 72.9 (CH), 43.4 (Cq), 29.3 (CH_2), 28.4 (CH_2), 25.8 (CH_3), 18.0 (Cq), 18.0 (CH_2), 14.2 (CH_3), -4.41 (CH_3), -5.27 (CH_3); IR (neat) ν_{max} 3436, 2930, 2856, 1471, 1360, 1252, 1075, 1026, 859, 773, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{21}H_{36}O_3NaSi$: 387.2326, found: 387.2327; $[\alpha]_D^{23}$ -13 (*c* 0.58, $CHCl_3$).

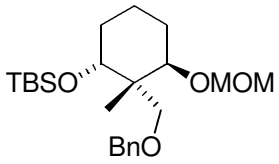
1-((((2*R*,6*R*)-2,6-bis(*tert*-butyldimethylsilyloxy)-1-methylcyclohexyl)methoxy)methyl)benzene (56)



56

R_f = 0.91 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.22 (5H, m), 4.56 (1H, d, *J* = 11.9 Hz), 4.34, (1H, d, J = 11.9 Hz), 3.93 (1H, dd, *J* = 6.0, 1.8 Hz), 3.80 (1H, dd, *J* = 8.7, 3.7 Hz) , 3.50 (1H, d, *J* = 8.2 Hz) , 3.37 (1H, d, *J* = 8.2 Hz), 1.66-1.37 (6H, m), 0.97 (3H, s), 0.88 (9H, s), 0.82 (9H, s), 0.018 (3H, s), 0.0079 (3H, s), -0.0013 (3H, s), -0.032 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1 (Cq), 128.1 (CH), 127.4 (CH), 127.1 (CH), 73.7 (CH), 73.1 (CH), 72.2 (CH_2), 71.2 (CH_2), 44.9 (Cq), 29.9 (CH_2), 28.7 (CH_2), 25.9 (CH_3), 25.8 (CH_3), 18.6 (CH_2), 18.1 (Cq), 18.0 (Cq), 16.0 (CH_3), -4.02 (CH_3), -4.32 (CH_3), -5.10 (CH_3), -5.27 (CH_3); IR (neat) ν_{max} 2928, 2856, 1471, 1360, 1251, 1079, 831, 772, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{27}H_{50}O_3NaSi_2$: 501.3191, found: 501.3192; $[\alpha]_D^{23}$ -18 (*c* 0.98, $CHCl_3$).

((1*R*,2*S*,3*R*)-2-(benzyloxymethyl)-3-(methoxymethoxy)-2-methylcyclohexyloxy)(*tert*-butyl)dimethylsilane (57)

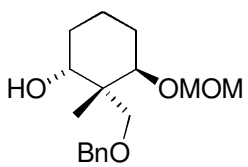


57

To a solution of **55** (15.4 g, 42.2 mmol) in CH_2Cl_2 (420 mL) was added DIPEA (29.4 mL, 169 mmol), MOMCl (6.42 mL, 84.5 mmol) and NaI (6.33 g, 42.2 mmol) successively at room temperature. The reaction mixture was stirred at 35 °C for 2 d, quenched with H_2O (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (100 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 40/1) to afford **57** (17.1 g, 99%) as a colorless oil.

R_f = 0.63 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.23 (5H, m), 4.64 (1H, d, *J* = 6.9 Hz), 4.55 (1H, d, *J* = 11.9 Hz), 4.53 (1H, d, *J* = 6.9 Hz), 4.38 (1H, d, *J* = 11.9 Hz), 3.92 (1H, dd, *J* = 5.5, 2.3 Hz), 3.69 (1H, dd, *J* = 8.7, 4.1 Hz), 3.59 (1H, d, *J* = 8.2 Hz), 3.44 (1H, d, *J* = 8.2 Hz), 3.31 (3H, s), 1.80-1.69 (1H, m), 1.69-1.39 (5H, m), 1.05 (3H, s), 0.88 (9H, s), 0.021 (3H, s), 0.0090 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1 (Cq), 128.1 (CH), 127.3 (CH), 127.2 (CH), 96.0 (CH_2), 77.5 (CH_2), 73.7 (CH), 73.1 (CH_2), 72.4 (CH), 55.4 (CH_3), 44.3 (Cq), 28.6 (CH_2), 26.6 (CH_2), 25.9 (CH_3), 18.5 (CH_2), 18.1 (Cq), 16.3 (CH_3), -4.41 (CH_3), -5.16 (CH_3); IR (neat) ν_{max} 2929, 2856, 1471, 1360, 1250, 1080, 1030, 833, 774, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{23}H_{40}O_4NaSi$: 431.2588, found: 431.2586; $[\alpha]_D^{22}$ -17 (*c* 0.96, $CHCl_3$).

(1*R*,2*R*,3*R*)-2-(benzyloxymethyl)-3-(methoxymethoxy)-2-methylcyclohexanol (58)



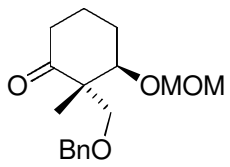
58

To a solution of **57** (17.1 g, 41.8 mmol) in THF (250 mL) was added TBAF (1.0 M solution in THF, 62.8 mL, 62.8 mmol), and the reaction mixture was stirred at 60 °C for 24 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution

(50 mL), and the aqueous layer was extracted with Et_2O (100 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **58** (11.4 g, 93%) as a colorless oil.

R_f = 0.29 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (5H, m), 4.63 (1H, d, *J* = 11.9 Hz), 4.61 (1H, d, *J* = 11.9 Hz), 4.53 (2H, s), 4.11 (1H, br s), 4.03 (1H, dd, *J* = 10.5, 4.6 Hz), 3.84 (1H, t, *J* = 2.7 Hz) , 3.75 (1H, d, *J* = 9.2 Hz), 3.36 (1H, d, *J* = 9.2 Hz), 3.34 (3H, s), 1.92-1.68 (2H, m), 1.66-1.43 (4H, m), 0.84 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3 (Cq), 128.5 (CH), 127.9 (CH), 127.7 (CH), 96.1 (CH_2), 76.6 (CH_2), 76.5 (CH), 74.5 (CH), 73.6 (CH_2), 55.3 (CH), 42.8 (Cq), 28.2 (CH_2), 27.3 (CH_2), 18.8 (CH_2), 15.3 (CH_3); IR (neat) ν_{max} 3472, 2939, 1453, 1362, 1213, 1143, 1032, 915, 735, 697 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{17}H_{26}O_4Na$: 317.1723, found: 317.1729; $[\alpha]_D^{22}$ +0.38 (*c* 1.6, $CHCl_3$).

(2*S*,3*R*)-2-(benzyloxymethyl)-3-(methoxymethoxy)-2-methylcyclohexanone (59)



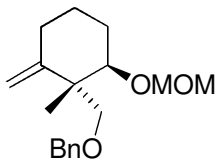
59

To a solution of oxalyl chloride (5.07 mL, 58.15 mmol) and DMSO (5.50 mL, 77.4 mmol) in CH_2Cl_2 (192 mL) was added a solution of **58** (11.4 g, 38.7 mmol) in CH_2Cl_2 (30 mL) via a cannula at -78 °C. After 15 min, to the reaction mixture was added TEA (18.9 mL, 136 mmol) and the reaction mixture was stirred at the same temperature for 1 h, and at room temperature for 1 h. The mixture was quenched with saturated aqueous NH_4Cl solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (100 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 6/1) to afford **59** (11.3 g, 100%) as a colorless oil.

R_f = 0.36 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.24 (5H, m), 4.63 (1H, d, *J* = 13.3 Hz), 4.61 (1H, d, *J* = 13.3 Hz), 4.55 (1H, d, *J* = 11.9 Hz), 4.47 (1H, d, *J* = 11.9 Hz), 4.05 (1H, dd, *J* = 9.2, 3.7 Hz), 3.71 (1H, d, *J* = 8.7 Hz), 3.37 (1H, d, *J* = 8.7 Hz), 3.35 (3H, s), 2.45-2.27 (2H, m), 2.11-2.01 (1H, m), 1.98-1.78 (2H, m), 1.70-1.60 (1H, m), 1.06 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8 (Cq), 138.3 (Cq), 128.2 (CH), 127.6 (CH), 127.5 (CH), 96.2 (CH_2), 77.5 (CH),

73.3 (CH_2), 71.4 (CH_2), 55.6 (CH), 55.5 (Cq), 37.9 (CH_2), 26.4 (CH_2), 19.7 (CH_2), 15.8 (CH_3); IR (neat) ν_{max} 2942, 2874, 1709, 1453, 1369, 1093, 1028, 916, 736, 698 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{17}H_{24}O_4Na$: 315.1567, found: 313.51569; $[\alpha]_D^{23}$ -15 (*c* 2.0, $CHCl_3$).

1-((((1*S*,2*R*)-2-(methoxymethoxy)-1-methyl-6-methylenecyclohexyl)methoxy)methyl)benzene (60)

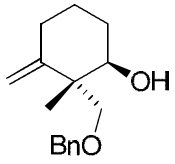


60

To a stirred suspension of PPh_3CH_3Br (38.7 g, 108 mmol) in THF (127 mL) was added KHMDS (0.5 M solution in toluene, 193 mL, 96.6 mmol) dropwise at 0 °C, and the reaction mixture was stirred at room temperature for 30 min. Then, to the reaction mixture was added a solution of **59** (11.3 g, 38.6 mmol) in THF (30 mL) via a cannula at 0 °C. After the addition, the mixture was stirred at room temperature for 1 h, and then was quenched with saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with Et_2O (100 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **60** (10.9 g, 97%) as a colorless oil.

R_f = 0.64 (hexane/ethyl acetate = 4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38-7.24 (5H, m), 4.86 (1H, d, *J* = 1.4 Hz), 4.82 (1H, d, *J* = 1.4 Hz), 4.64 (1H, d, *J* = 10.4 Hz), 4.62 (1H, d, *J* = 10.4 Hz), 4.54 (1H, d, *J* = 11.8 Hz), 4.48 (1H, d, *J* = 11.8 Hz), 3.72 (1H, dd, *J* = 8.2, 4.1 Hz), 3.52 (1H, d, *J* = 9.1 Hz), 3.39 (1H, d, *J* = 9.1 Hz), 3.35 (3H, s), 2.27-2.09 (2H, m), 1.88-1.78 (1H, m), 1.77-1.65 (2H, m), 1.48-1.35 (1H, m), 1.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4 (Cq), 138.4 (Cq), 128.3 (CH), 127.7 (CH), 127.5 (CH), 109.5 (CH_2), 96.3 (CH_2), 78.5 (CH), 73.8 (CH_2), 73.3 (CH_2), 55.5 (CH), 46.2 (Cq), 32.4 (CH_2), 27.3 (CH_3), 23.2 (CH_2), 18.2 (CH_3); IR (neat) ν_{max} 2935, 2860, 1640, 1454, 1144, 1099, 1035, 892, 734, 697 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{18}H_{26}O_3Na$: 313.1774, found: 313.1774; $[\alpha]_D^{22}$ +2.2 (*c* 1.2, $CHCl_3$).

(1*R*,2*S*)-2-(benzyloxymethyl)-2-methyl-3-methylenecyclohexanol (8')

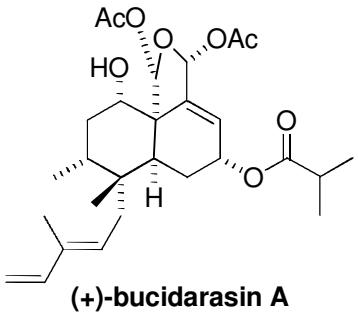


8'

To a solution of **60** (10.8 g, 37.2 mmol) in MeOH (186 mL) was added 5*N* HCl (18.6 mL), and the reaction mixture was stirred at 50 °C for 12 h. The reaction mixture was added H_2O (200 mL), and the aqueous layer was extracted with Et_2O (100 mL × 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 15/1) to afford **8'** (8.58 g, 94%) as a colorless oil.

R_f = 0.39 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (5H, m), 4.74 (1H, s), 4.60 (1H, d, *J* = 12.4 Hz), 4.56 (1H, d, J = 12.4 Hz), 4.49 (1H, s), 3.73 (1H, d, *J* = 8.7 Hz), 3.68 (1H, ddd, *J* = 10.5, 4.1, 1.4 Hz), 3.65 (1H, d, *J* = 8.7 Hz), 3.61 (1H, d, *J* = 1.4 Hz), 2.22 (1H, ddd, *J* = 13.7, 13.7, 4.6 Hz), 2.06 (1H, ddd, *J* = 13.7, 3.2, 3.2 Hz), 1.85-1.70 (2H, m), 1.63-1.49 (1H, m), 1.37-1.22 (1H, m), 1.18 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7 (Cq), 137.7 (Cq), 128.5 (CH), 127.8 (CH), 127.5 (CH), 107.7 (CH_2), 79.2 (CH_2), 76.3 (CH), 73.8 (CH_2), 44.6 (Cq), 32.5 (CH_2), 29.7 (CH_2), 24.2 (CH_2), 16.1 (CH_3); IR (neat) ν_{max} 3438, 2935, 2859, 1637, 1453, 1358, 1071, 895, 734, 696 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{16}H_{22}O_2Na$: 269.1512, found: 269.1512; $[\alpha]_D^{27}$ -13 (*c* 1.1, $CHCl_3$).

(1*S*,3*R*,5*R*,6a*S*,7*R*,8*R*,10*S*,10a*S*)-1,3-bis(acetyloxy)-10-hydroxy-7,8-dimethyl-7-[(2*E*)-3-methylpenta-2,4-dien-1-yl]-1H,3H,5H,6H,6aH,7H,8H,9H,10H-naphtho[4,4a-c]furan-5-yl 2-methylpropanoate ((+)-bucidarasin A)



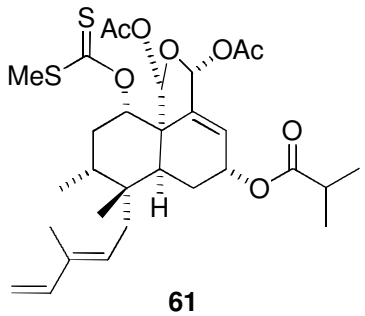
(+)-bucidarasin A

To a solution of (1S,3R,5R,6aS,7R,8R,10S,10aS)-3-(acetyloxy)-5,10-dihydroxy-7,8-dimethyl-7-[(2E)-3-methylpenta-2,4-dien-1-yl]-1H,3H,5H,6H,6aH,7H,8H,9H,10H-naphtho[4,4a-c]furan-1-yl acetate (15.0 mg, 0.0345 mmol) in CH_2Cl_2 (1.5 mL) was added triethylamine (48.1 μL, 0.345 mmol) and isobutyryl chloride (10.9 μL, 0.104 mmol)

successively at 0 °C, and the reaction mixture was stirred at 35 °C for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (5.0 mL) and ca.25% NH_4OH solution (5.0 mL) successively, and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 3/1) to afford **(+)-bucidarasin A** (17.0 mg, 98%) as a white amorphous.

R_f = 0.43 (hexane/ethyl acetate = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (1H, dd, *J* = 1.4, 1.4 Hz), 6.51 (1H, s), 6.27 (1H, dd, *J* = 17.4, 10.5 Hz), 5.99 (1H, dd, *J* = 4.1, 1.4 Hz), 5.47-5.41 (1H, m), 5.41-5.32 (1H, m), 5.09 (1H, d, *J* = 17.4 Hz), 4.93 (1H, d, *J* = 10.5 Hz), 3.80 (1H, ddd, *J* = 12.4, 9.6, 3.7 Hz), 2.64 (1H, qq, *J* = 6.9, 6.9 Hz), 2.36 (1H, dd, *J* = 11.4, 5.5 Hz), 2.24 (1H, dd, *J* = 16.5, 7.8 Hz), 2.10 (3H, s), 1.94 (3H, s), 1.92-1.83 (2H, m), 1.82-1.54 (4H, m), 1.66 (3H, s), 1.22 (3H, d, *J* = 6.9 Hz), 1.20 (3H, d, *J* = 6.9 Hz), 0.93 (3H, d, *J* = 6.9 Hz), 0.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (Cq), 170.1 (Cq), 169.4 (Cq), 145.3 (Cq), 141.2 (CH), 135.7 (Cq), 129.0 (CH), 121.8 (CH), 111.0 (CH_2), 97.0 (CH), 95.6 (CH), 72.8 (CH), 66.1 (CH), 53.5 (Cq), 37.6 (CH_2), 37.3 (Cq), 36.8 (CH), 36.7 (CH), 34.0 (CH), 30.3 (CH_2), 26.7 (CH_2), 25.0 (CH_3), 21.6 (CH_3), 21.2 (CH_3), 19.1 (CH_3), 18.7 (CH_3), 15.6 (CH_3), 11.9 (CH_3); IR (neat) νmax 3469, 2969, 2933, 2878, 1749, 1728, 1605, 1371, 1225, 889, 735 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{28}H_{40}O_8Na$: 527.2615, found: 527.2616; $[\alpha]_D^{25}$ +34 (*c* 0.85, MeOH).

(1*S*,3*R*,5*R*,6a*S*,7*R*,8*R*,10*S*,10a*S*)-1,3-bis(acetyloxy)-7,8-dimethyl-7-[(2*E*)-3-methylpenta-2,4-dien-1-yl]-10-methylsulfanylmethanethioyloxy-1H,3H,5H,6H,6aH,7H,8H,9H,10H-naphtho[4,4a-c]furan-5-yl 2-methylpropanoate (61)



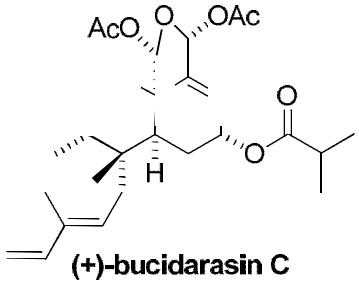
61

To a stirred solution of **(+)-bucidarasin A** (14.0 mg, 0.0277 mmol) in THF (2.0 mL) was added CS_2 (10.1 μL, 0.166 mmol) and NaH (60%, 3.3 mg, 0.0832 mmol) successively at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 15 min, and then was added MeI (13.8 μL, 0.222 mmol). The reaction mixture was stirred at room temperature for 14 h, quenched with quenched with

saturated aqueous NH_4Cl solution (5.0 mL), and the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **61** (13.2 mg, 80%) as a colorless oil.

R_f = 0.63 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, s), 6.53 (1H, dd, *J* = 1.7, 1.7 Hz), 6.29 (1H, dd, *J* = 17.0, 10.8 Hz), 6.00 (1H, br d), 5.96 (1H, dd, *J* = 11.9, 4.0 Hz), 5.49-5.43 (1H, m), 5.41-5.36 (1H, m), 5.11 (1H, d, *J* = 17.0 Hz), 4.95 (1H, d, *J* = 10.8 Hz), 2.64 (1H, qq, *J* = 6.8, 6.8 Hz), 2.58 (3H, s), 2.47 (1H, dd, *J* = 13.0, 3.4 Hz), 2.28 (1H, dd, *J* = 17.0, 8.5 Hz), 2.08 (3H, s), 2.11-1.99 (1H, m), 1.96 (3H, s), 1.98-1.87 (3H, m), 1.81-1.64 (2H, m), 1.68 (3H, s), 1.23 (3H, d, *J* = 6.8 Hz), 1.21 (3H, d, *J* = 6.8 Hz), 0.95 (3H, d, *J* = 6.8 Hz), 0.85 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.1 (Cq), 176.3 (Cq), 170.0 (Cq), 169.4 (Cq), 143.6 (Cq), 141.1 (CH), 135.9 (Cq), 128.7 (CH), 123.4 (CH), 111.2 (CH_2), 97.1 (CH), 95.1 (CH), 82.2 (CH), 65.8 (CH), 52.2 (Cq), 37.7 (CH), 37.6 (Cq), 36.2 (CH), 34.0 (CH), 32.3 (CH_2), 30.3 (CH_2), 26.7 (CH_2), 25.0 (CH_3), 21.7 (CH_3), 21.2 (CH_3), 19.1 (CH_3), 18.7 (CH_3), 18.5 (CH_3), 15.4 (CH_3), 12.0 (CH_3); IR (neat) νmax 2970, 2934, 1755, 1732, 1601, 1471, 1323, 1222, 1055, 836, 737 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{30}H_{42}O_8NaS_2$: 617.2213, found: 617.2212; $[\alpha]_D^{24}$ +54 (*c* 0.53, $CHCl_3$).

(1*S*,3*R*,5*R*,6a*S*,7*R*,8*R*,10a*S*)-1,3-bis(acetyloxy)-7,8-dimethyl-7-[(2*E*)-3-methylpenta-2,4-dien-1-yl]-1H,3H,5H,6H,6aH,7H,8H,9H,10H-naphtho[4,4a-c]furan-5-yl 2-methylpropanoate ((+)-bucidarasinC)



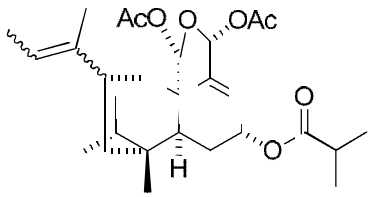
(+)-bucidarasin C

To a solution of **61** (10.0 mg, 0.0168 mmol) in toluene (1.0 mL) was added catalytic amount of V-70 and *n*-Bu_3SnH (44.1 μL, 0.168 mmol) successively at 0 °C. After removed air, the reaction mixture was stirred at 40 °C for 1 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 30/1) to afford **(+)-bucidarasin C** (4.0 mg, 49%) and **62** (3.1 mg, 38%, mixture of diastereomers (dr = 10/7)) as a colorless oil.

R_f = 0.31 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (1H, dd, *J* = 1.5, 1.5 Hz), 6.36 (1H, s), 6.28 (1H, dd, *J* = 17.2, 10.8 Hz), 5.89 (1H, dd, *J* = 4.6,

1.5 Hz), 5.42 (1H, br s), 5.38 (1H, br d), 5.08 (1H, d, *J* = 17.2 Hz), 4.92 (1H, d, *J* = 10.8 Hz), 2.63 (1H, qq, *J* = 6.9, 6.9 Hz), 2.23 (1H, dd, *J* = 16.1, 8.2 Hz), 2.22 (1H, br t), 2.10 (3H, s), 1.94 (3H, s), 1.92-1.87 (2H, m), 1.79-1.69 (2H, m), 1.67 (3H, s), 1.64-1.58 (1H, m), 1.53-1.41 (2H, m), 1.22 (3H, d, *J* = 6.9 Hz), 1.20 (3H, d, *J* = 6.9 Hz), 0.89 (3H, d, *J* = 6.9 Hz), 0.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (Cq), 170.3 (Cq), 169.7 (Cq), 147.0 (Cq), 141.3 (CH), 135.6 (Cq), 129.3 (CH), 120.3 (CH), 110.8 (CH_2), 98.8 (CH), 94.5 (CH), 66.3 (CH), 49.1 (Cq), 37.4 (Cq), 36.5 (CH), 34.7 (CH), 34.1 (CH), 30.4 (CH_2), 29.1 (CH_2), 27.4 (CH_2), 26.1 (CH_2), 25.7 (CH_3), 21.4 (CH_3), 21.2 (CH_3), 19.2 (CH_3), 18.7 (CH_3), 15.6 (CH_3), 12.0 (CH_3); IR (neat) νmax 2940, 1750, 1731, 1458, 1374, 1230, 1152, 1066, 935, 669 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{28}H_{40}O_7Na$: 511.2666, found: 511.2679; $[\alpha]_D^{25}$ +17 (*c* 0.20, MeOH).

(1*R*,2*S*,3*S*,5*R*,8*R*,10*S*,11*R*,12*R*)-3,5-Bis(acetyloxy)-14-(but-2-en-2-yl)-11,12-dimethyl-4-oxatetracyclo[9.2.2.0^{2,6}.0^{2,10}]pentadec-6-en-8-yl 2-methylpropanoate (62)



62

major product

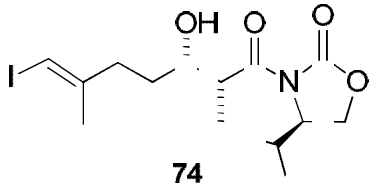
R_f = 0.40 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (1H, dd, *J* = 1.8, 1.8 Hz), 6.33 (1H, br s), 6.02 (1H, br s), 5.65-5.56 (1H, m), 5.32-5.24 (1H, m), 2.66-2.57 (1H, m), 2.51-2.40 (1H, m), 2.28-2.20 (1H, m), 2.19 (3H, s), 2.20-2.16 (1H, m), 2.10 (3H, s), 1.81-1.58 (7H, m), 1.61 (3H, s), 1.58-1.49 (1H, m), 1.38-1.24 (1H, m), 1.21 (3H, d, *J* = 6.9 Hz), 1.21 (3H, d, *J* = 6.9 Hz), 0.86 (3H, s), 0.78 (3H, d, *J* = 6.0 Hz).

minor product

R_f = 0.40 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (1H, s), 6.66 (1H, dd, *J* = 1.8, 1.8 Hz), 6.01 (1H, br s), 5.47-5.34 (2H, m), 2.63-2.54 (1H, m), 2.39-2.29 (1H, m), 2.21-2.15 (1H, m), 2.14 (3H, s), 2.05 (3H, s), 1.88-1.81 (1H, m), 1.81-1.58 (2H, m), 1.70 (3H, s), 1.65 (3H, br d) 1.50-1.41 (1H, m), 1.38-1.24 (1H, m), 1.20 (6H, d, *J* = 6.9 Hz), 0.97 (3H, d, *J* = 6.9 Hz), 0.97 (3H, s); HRMS (ESI) $[M+Na]^+$ calculated for $C_{28}H_{40}O_7Na$: 511.2666, found: 511.2679.

第 4 節　(-)-bruceantin の不斉全合成研究

(*R*)-3-((2*R*,3*S*,*E*)-3-hydroxy-7-iodo-2,6-dimethylhept-6-enoyl)-4-isopropyloxazolidin-2-one (74)

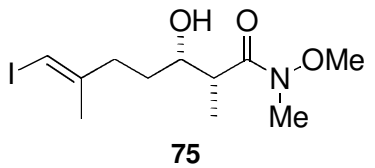


74

To a solution of **73** (3.37 g, 18.2 mmol) and TEA (3.17 mL, 22.8 mmol) in CH_2Cl_2 (99 mL) was added *n*-Bu_2BOTf (1.0 M solution in CH_2Cl_2, 16.7 mL, 16.7 mmol) at -78 °C, and the reaction mixture was stirred at the same temperature for 1 h. Then, to the reaction mixture was added **72** (3.40 g, 15.2 mmol) in CH_2Cl_2 (13 mL) via a cannula at -78 °C. After the addition, the reaction mixture was stirred at the same temperature for 30 min and at room temperature for 30 min, and then was quenched with KPB8 (33.0 mL), MeOH (33.0 ml) and 30% H_2O_2 aq. (16.0 ml) at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (50 mL × 2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **74** (5.28 g, 85%) as a colorless oil.

R_f = 0.16 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.94 (1H, s), 4.47 (1H, ddd, *J*=7.8, 3.6, 3.6 Hz), 4.30 (1H, dd, *J*=8.7, 8.7 Hz), 4.23 (1H, dd, *J*=8.7, 3.2 Hz), 3.88 (1H, ddd, *J*=6.0, 3.2, 3.2 Hz), 3.75 (1H, qd, *J*=6.9, 2.3 Hz), 3.01 (1H, br s), 2.48-2.22 (3H, m), 1.84 (3H, s), 1.74-1.61 (1H, m), 1.59-1.44 (1H, m), 1.25 (3H, d, *J*=6.9 Hz), 0.90 (6H, dd, *J*=16.5, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 153.4, 147.3, 75.1, 70.1, 63.3, 58.1, 42.1, 35.8, 31.6, 28.3, 23.8, 17.8, 14.6, 10.8; IR (neat) ν_{max} 3504, 2963, 2876, 1772, 1686, 1383, 1200, 988, 735 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{15}H_{24}O_4NINa$: 432.0642, found: 432.0642; $[\alpha]_D^{26}$ -33 (*c* 1.4, $CHCl_3$).

(2*R*,3*S*,*E*)-3-hydroxy-7-iodo-N-methoxy-N,2,6-trimethylhept-6-enamide (75)



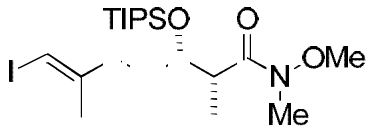
75

To a solution of MeNHMe·HCl (2.94 g, 30.1 mmol) in THF (120 mL) was added $AlMe_3$ (1.09 M solution in hexane, 27.6 mL, 30.1 mmol) at 0 °C, and the reaction mixture was stirred for 1 h at room temperature. Then, to the reaction mixture was

added **74** (4.93 g, 12.0 mmol) in THF (15 mL) via a cannula at 0 °C. After the addition, the reaction mixture was stirred at room temperature for 1 h, and then was quenched with KPB8 (10 mL) at 0 °C. The aqueous layer was extracted with Et_2O (50 mL × 2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford **75** (3.82 g, 93%) as a white powder.

R_f = 0.34 (hexane/ethyl acetate = 1/1); mp 46.4-47.4 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ 5.93 (1H, s), 3.87-3.78 (1H, m), 3.70 (3H, s), 3.20 (3H, s), 2.85 (1H, br s), 2.49-2.36 (1H, m), 2.34-2.21 (1H, m), 1.85 (3H, s), 1.76-1.62 (1H, m), 1.52-1.38 (1H, m), 1.17 (3H, d, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 147.4, 74.9, 70.6, 61.4, 38.8, 35.8, 31.9, 31.7, 23.7, 10.3; IR (neat) ν_{max} 3432, 2938, 1632, 1420, 1386, 1266, 991, 773 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{11}H_{20}O_3NINa$: 364.0380, found: 364.0382; $[\alpha]_D^{27}$ -8.6 (*c* 0.99, $CHCl_3$).

(2*R*,3*S*,*E*)-7-iodo-N-methoxy-N,2,6-trimethyl-3-(triisopropylsilyloxy)hept-6-enamide (76)

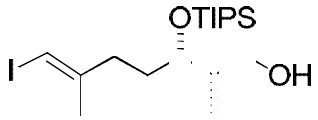


76

To a solution of **75** (3.82 g, 11.2 mmol) in CH_2Cl_2 (111 mL) was added TEA (2.34 mL, 16.8 mmol) and TIPSOTf (3.31 mL, 16.1 mmol) at 0 °C, the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (50 mL), the aqueous layer was extracted with CH_2Cl_2 (50 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **76** (5.00 g, 90%) as a colorless oil.

R_f = 0.45 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.86 (1H, s), 4.15 (1H, ddd, *J*=8.7, 5.0, 5.0 Hz), 3.69 (3H, s), 3.17 (3H, s), 2.99 (1H, br s), 2.38-2.16 (2H, m), 1.80 (3H, s), 1.75-1.55 (2H, m), 1.21 (3H, d, *J*=6.9 Hz), 1.11-1.03 (21H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 147.9, 74.5, 73.3, 61.4, 40.3, 34.0, 33.9, 32.1, 23.9, 18.2, 18.1, 14.3, 12.9; IR (neat) ν_{max} 2941, 2865, 1659, 1460, 1380, 1270, 1106, 994, 882, 676 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{20}H_{40}O_3NINaSi$: 520.1714, found: 520.1713; $[\alpha]_D^{27}$ +7.2 (*c* 1.1, $CHCl_3$).

(2*S*,3*S*,*E*)-7-iodo-2,6-dimethyl-3-(triisopropylsilyloxy)hept-6-en-1-ol (77)

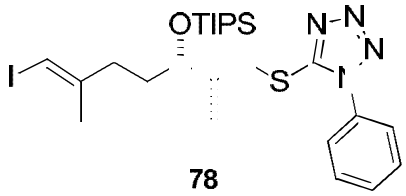


77

To a solution of **76** (4.99 g, 10.0 mmol) in THF (100 mL) at −78 °C was added DIBAL-H (1.02 M solution in hexane, 12.8 mL, 13.0 mmol) dropwise over 10 min. The reaction mixture was stirred at the same temperature for 2 h, and then was quenched with MeOH (2.0 mL) and saturated Rochelle's salt solution (50 mL). The mixture was stirred at room temperature for 30 min, and the aqueous layer was extracted with Et_2O (100 mL × 2). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. $NaBH_4$ (379 mg, 10.0 mmol) was added to the residue in MeOH (29 ml), and stirred at the same temperature for 1 h. The reaction mixture was quenched by saturated aqueous NH_4Cl solution (20 mL), and the aqueous layer was extracted with Et_2O (50 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **77** (4.09 g, 93%) as a colorless oil.

R_f = 0.41 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.91 (1H, s), 3.93 (1H, ddd, *J*=6.4, 6.4, 2.7 Hz), 3.73 (1H, ddd, *J*=11.0, 7.8, 4.1 Hz), 3.57 (1H, ddd, *J*=11.0, 5.5, 5.5 Hz), 2.35-2.24 (2H, m), 2.17 (1H, m), 2.04-1.91 (1H, m), 1.85 (3H, s), 1.76-1.58 (2H, m), 1.17-1.02 (21H, m), 0.86 (3H, d, *J*=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 75.2, 74.9, 65.8, 39.6, 36.3, 31.5, 24.0, 18.2, 18.2, 12.9, 11.6; IR (neat) ν_{max} 3399, 2942, 2865, 1460, 1378, 1264, 1044, 881, 739, 669 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{18}H_{37}O_2INaSi$: 463.1500, found: 463.1500; $[\alpha]_D^{27}$ +4.9 (*c* 1.5, $CHCl_3$).

5-((2*R*,3*S*,*E*)-7-iodo-2,6-dimethyl-3-(triisopropylsilyloxy)hept-6-enylthio)-1-phenyl-1H-tetrazole (78)



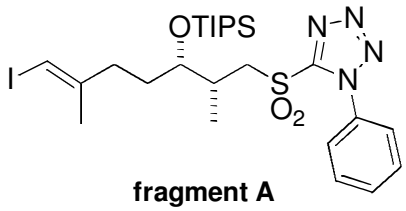
78

To a solution of **77** (4.07 g, 9.24 mmol), 1-phenyl-1H-tetrazole-5-thiol (2.47 g, 13.9 mmol), and Ph_3P (3.64 g, 13.9 mmol) in THF (92 mL) was added DEAD (diethyl

azodicarboxylate) (2.2 M solution in toluene, 6.30 mL, 13.9 mmol) dropwise at room temperature. The reaction mixture was stirred at the room temperature for 1 h, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **78** (5.27 g, 95%) as a colorless oil.

R_f = 0.60 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.66-7.48 (5H, m), 5.88 (1H, s), 3.94 (2H, ddd, *J*=6.4, 6.4, 2.3 Hz), 3.54 (1H, dd, *J*=12.8, 6.4 Hz), 3.30 (1H, dd, *J*=12.8, 7.8 Hz), 2.28-2.06 (3H, m), 1.82 (3H, d, *J*=0.98 Hz), 1.67 (2H, dd, *J*=15.1, 8.2 Hz), 1.09-1.03 (21H, m), 1.02 (3H, d, *J*=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 147.1, 133.7, 130.0, 129.7, 123.8, 75.2, 73.8, 37.1, 37.1, 35.7, 32.0, 23.9, 18.2, 18.2, 13.0, 13.0; IR (neat) ν_{max} 2941, 2864, 1499, 1382, 1087, 1013, 881, 758, 679 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{25}H_{41}ON_4INaSSi$: 623.1707, found: 623.1706; $[\alpha]_D^{23}$ +13 (*c* 3.7, $CHCl_3$).

5-((2*R*,3*S*,*E*)-7-iodo-2,6-dimethyl-3-(triisopropylsilyloxy)hept-6-enylsulfonyl)-1-phenyl-1H-tetrazole (fragment A)

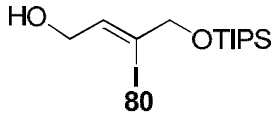


fragment A

To a solution of **78** (5.11 g, 8.51 mmol) in EtOH/THF (2/1, 64 mL) was added $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (1.05 g, 0.851 mmol) and 30% H_2O_2 aq. (19.3 ml, 170 mmol) successively at room temperature. The reaction mixture was stirred at room temperature for 24 h, quenched by saturated aqueous $Na_2S_2O_3$ solution (100 mL), and the aqueous layer was extracted with AcOEt (100 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **fragment A** (4.74 g, 88%) as a colorless oil.

R_f = 0.60 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.73-7.67 (2H, m), 7.66-7.56 (3H, m), 5.92 (1H, s), 4.08 (1H, dd, *J*=14.2, 3.7 Hz), 3.97 (1H, ddd, *J*=6.4, 6.4, 2.7 Hz), 3.63 (1H, dd, *J*=14.2, 8.7 Hz), 2.61-2.46 (1H, m), 2.32-2.20 (1H, m), 2.20-2.07 (1H, m), 1.84 (3H, s), 1.74-1.50 (2H, m), 1.13 (3H, d, *J*=6.9 Hz), 1.11-1.00 (21H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 146.9, 133.0, 131.4, 129.6, 125.0, 75.4, 74.7, 58.9, 35.9, 33.0, 31.6, 23.9, 18.2, 18.1, 13.9, 12.9; IR (neat) ν_{max} 2943, 2866, 1461, 1339, 1152, 1098, 881, 736 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{25}H_{41}O_3N_4INaSSi$: 655.1606, found: 655.1603; $[\alpha]_D^{23}$ +2.9 (*c* 1.5, $CHCl_3$).

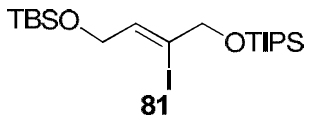
(*Z*)-3-iodo-4-(triisopropylsilyloxy)but-2-en-1-ol (80)



To a stirred solution of 4-Triisopropylsilanyloxy-but-2-yn-1-ol (1.23 g, 5.07 mmol) in Et_2O (25 mL) was added Red-Al (3.6 M solution in toluene, 2.11 mL, 7.61 mmol) at 0 ºC. The reaction mixture was stirred at room temperature for 10 min, quenched by AcOEt (0.992 mL, 10.1 mmol) at 0 ºC and stirred for 30 min. I_2 (1.93 g, 7.61 mmol) in THF (12.7 mL) was added to the solution at -78 ºC, and stirred at 0 ºC for 30 min, quenched by saturated aqueous $NaHCO_3$ solution (10 mL) and saturated aqueous $Na_2S_2O_3$ solution (10 mL) successively, the aqueous layer was extracted with Et_2O (20 mL x 2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **80** (1.65g, 88%) as a colorless oil.

R_f = 0.51 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.36 (1H, ddt, *J*=5.9, 5.9, 1.7 Hz), 4.34 (1H, ddd, *J*=1.7, 1.7, 1.7 Hz), 4.29 (1H, dddd, *J*=5.9, 5.9, 1.5, 1.5 Hz), 1.50 (1H, t, *J*=5.9 Hz), 1.10-1.05 (21H, m).

(*Z*)-4-(*tert*-butyldimethylsilyloxy)-2-iodo-1-(triisopropylsilyloxy)but-2-ene (81)

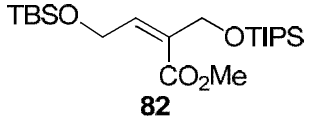


To a stirred solution of **80** (1.65 g, 4.45 mmol) in CH_2Cl_2 (45 mL) was added imidazole (0.424 g, 6.23 mmol) and TBSCl (0.805 g, 5.34 mmol) successively at room temperature, the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was quenched by H_2O (50 mL), the aqueous layer was extracted with CH_2Cl_2 (30 mL x 2). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford **81** (2.07 g, 96%) as a colorless oil.

R_f = 0.80 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.26 (1H, dd, *J*=4.4, 4.4 Hz), 4.31 (2H, s), 4.30-4.27 (2H, m), 1.17-1.03 (21H, m), 0.90 (9H, s), 0.08 (6H, s).

(*Z*)-methyl

4-(*tert*-butyldimethylsilyloxy)-2-((triisopropylsilyloxy)methyl)but-2-enoate (82)

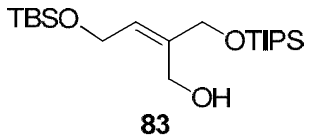


82

To a stirred solution of **81** (3.20 g, 6.60 mmol) in MeOH/DMF (2/3, 60 mL) was added TEA (2.02 mL, 14.5 mmol), PPh_3 (346 mg, 1.32 mmol) and $Pd(OAc)_2$ (148 mg, 0.660 mmol) successively at room temperature. The reaction mixture was stirred at 50 °C for 24 h under an atmosphere of CO, and quenched with saturated aqueous NH_4Cl solution (50 mL). After evapotation of MeOH, the residue was extracted with Et_2O (50 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 8/1) to afford **82** (1.87 g, 68%) as a pale yellow oil.

R_f = 0.67 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.56-6.51 (1H, m), 4.70 (2H, ddd, *J*=4.6, 2.4, 2.4 Hz), 4.39 (2H, dd, *J*=4.4, 2.2 Hz), 3.73 (3H, s), 1.10-1.03 (21H, m), 0.90 (9H, s), 0.07 (6H, s).

(*E*)-4-(*tert*-butyldimethylsilyloxy)-2-((triisopropylsilyloxy)methyl)but-2-en-1-ol (83)

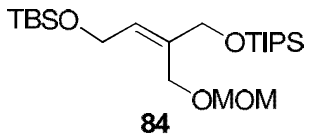


83

To a stirred solution of **82** (2.26 g, 5.42 mmol) in CH_2Cl_2 (54 mL) at −78 °C was added DIBAL-H (0.94 M solution in hexane, 12.7 mL, 11.9 mmol) dropwise over 30 min. The reaction mixture was stirred at the same temperature for 30 min, and then was quenched with MeOH (2.0 mL) and saturated Rochelle's salt solution (100 mL). The mixture was stirred at room temperature for 1 h, and the aqueous layer was extracted with CH_2Cl_2 (50 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **83** (2.10 g, 100%) as a colorless oil.

R_f = 0.23 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.70 (1H, ddd, *J*=6.1, 6.1, 0.49 Hz), 4.31 (2H, dt, *J*=6.1, 0.49 Hz), 4.29 (2H, d, *J*=6.1 Hz), 4.19 (2H, d, *J*=5.9 Hz), 2.75 (1H, t, *J*=6.1 Hz), 1.09-1.04 (21H, m), 0.90 (9H, s), 0.08 (6H, s).

(*E*)-4-(*tert*-butyldimethylsilyloxy)-2-((methoxymethoxy)methyl)-1-(triisopropylsilyloxy)but-2-ene (84)

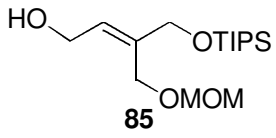


84

To a stirred solution of **83** (2.11 g, 5.44 mmol) in CH_2Cl_2 (50 mL) was added DIPEA (1.61 mL, 9.24 mmol), MOMCl (0.619 mL, 8.15 mmol) and NaI (0.0815 g, 0.544 mmol) successively at room temperature. The reaction mixture was stirred at 35 °C for 1 d, quenched with saturated aqueous $NaHCO_3$ solution (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **84** (2.26 g, 96%) as a colorless oil.

R_f = 0.43 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 5.85 (1H, t, *J*=6.3 Hz), 4.59 (2H, s), 4.32 (2H, d, *J*=6.3 Hz), 4.25 (2H, s), 4.08 (2H, s), 3.36 (3H, s), 1.12-1.02 (21H, m), 0.89 (9H, s), 0.07 (6H, s).

(*E*)-3-((methoxymethoxy)methyl)-4-(triisopropylsilyloxy)but-2-en-1-ol (85)

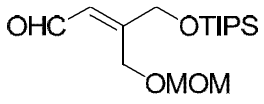


85

To a stirred solution of **84** (2.26 g, 5.22 mmol) in CH_3CN/*t*-BuOH(1/1, 50 mL) was added 20% H_2SiF_6 aq. (0.924 mL, 1.57 mmol) at 0 °C, and stirred at the same temperature for 5 h, quenched with saturated aqueous $NaHCO_3$ solution (10 mL), and the aqueous layer was extracted with Et_2O (20 mL × 2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 4/1) to afford **85** (1.55 g, 93%) as a colorless oil.

R_f = 0.17 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.04 (1H, t, *J*=6.8 Hz), 4.62 (2H, s), 4.26 (2H, s), 4.24 (2H, dd, *J*=6.8, 6.1 Hz), 4.15 (2H, s), 3.38 (3H, s), 1.96 (1H, t, *J*=6.1 Hz), 1.09-1.04 (21H, m).

(*E*)-3-((methoxymethoxy)methyl)-4-(triisopropylsilyloxy)but-2-enal (fragment B_1)



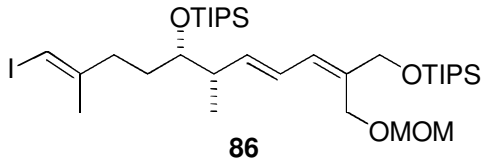
fragment B_1

To a stirred solution of **85** (303 mg, 0.951 mmol) in CH_2Cl_2 (9.5 mL) was added MnO_2 (303 mg) at room temperature, and stirred at the same temperature for 1 h,

diluted with CH_2Cl_2 (10 mL), and the reaction mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **fragment B_1** (278 mg, 92%) as a colorless oil.

R_f = 0.43 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 10.1 (1H, d, *J*=7.6 Hz), 6.37 (1H, d, *J*=7.6 Hz), 4.65 (2H, s), 4.50 (2H, s), 4.46 (2H, d, *J*=2.0 Hz), 3.38 (3H, s), 1.09-1.04 (21H, m).

(1*E*,5*S*,6*S*,7*E*,9*E*)-1-iodo-10-((methoxymethoxy)methyl)-2,6-dimethyl-5,11-bis(triisopropylsilyloxy)undeca-1,7,9-triene (86)

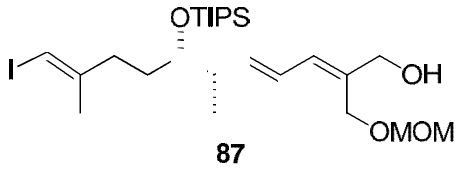


86

To a stirred solution of DIPA (365 μL, 2.60 mmol) in THF (17 mL) was added *n*-BuLi (1.58 M solution in hexane, 1.55 mL, 2.44 mmol) at -78 °C, and the reaction mixture was stirred at the same temperature for 15 min. Then, to the reaction mixture was added **fragment A** (1.03 g, 1.63 mmol) in THF (8.4 mL) via a cannula at -78 °C. After the addition, the reaction mixture was stirred at the same temperature for 30 min, and then was added **fragment B_1** (0.567 g, 1.79 mmol) in THF (8.4 mL) via a cannula at -78 °C. After the addition, the reaction mixture was stirred at the same temperature for 2 h, quenched with saturated aqueous NH_4Cl solution (20 mL), and the aqueous layer was extracted with Et_2O (20 mL × 2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford **86** (0.648 g, 63%) as a colorless oil.

R_f = 0.47 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.39 (1H, d, *J*=11.2 Hz), 6.33 (1H, dd, *J*=14.4, 11.2 Hz), 5.87 (1H, d, *J*=0.98 Hz), 5.85 (1H, dd, *J*=14.4, 7.3 Hz), 4.61 (2H, s), 4.30 (2H, s), 4.19 (2H, s), 3.75 (1H, ddd, *J*=5.4, 5.4, 5.4 Hz), 3.38 (3H, s), 2.43 (1H, ddq, *J*=7.3, 6.8, 5.4 Hz), 2.24 (2H, ddd, *J*=24.2, 20.3, 4.4 Hz), 1.81 (3H, d, *J*=0.98 Hz), 1.53-1.51 (2H, m), 1.09-1.04 (42H, m), 1.02 (6H, d, *J*=6.8 Hz).

(2*Z*,4*E*,6*S*,7*S*,10*E*)-11-iodo-2-((methoxymethoxy)methyl)-6,10-dimethyl-7-(triisopropylsilyloxy)undeca-2,4,10-trien-1-ol (87)

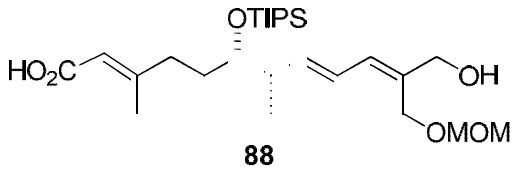


87

To a stirred solution of **86** (110 mg, 0.152 mmol) in CH_3CN/*t*-BuOH(1/1, 1.4 mL) was added 20% H_2SiF_6 aq. (9.0 μL, 0.0152 mmol) at 0 °C, and stirred at the same temperature for 5 h, quenched with saturated aqueous $NaHCO_3$ solution (5.0 mL), and the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **87** (63.6 mg, 74%) as a colorless oil.

R_f = 0.49 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.31 (1H, dd, *J*=14.9, 11.0 Hz), 6.21 (1H, d, *J*=11.0 Hz), 5.92 (1H, dd, *J*=14.9, 7.1 Hz), 5.87 (1H, d, *J*=0.98 Hz), 4.66 (2H, s), 4.31 (2H, s), 4.20 (2H, d, *J*=6.1 Hz), 3.75 (1H, ddd, *J*=5.4, 5.4, 5.4 Hz), 3.40 (3H, s), 2.47 (1H, ddq, *J*=7.1, 6.8, 5.4 Hz), 2.28 (2H, ddd, *J*=24.2, 14.6, 6.1 Hz), 2.22 (1H, ddd, *J*=24.2, 13.4, 5.4 Hz), 2.02 (1H, t, *J*=6.1 Hz), 1.60-1.53 (2H, m), 1.11-1.04 (21H, m), 1.02 (3H, d, *J*=6.8 Hz).

(2*E*,6*S*,7*S*,8*E*,10*Z*)-11-(hydroxymethyl)-12-(methoxymethoxy)-3,7-dimethyl-6-(triisopropylsilyloxy)dodeca-2,8,10-trienoic acid (88)



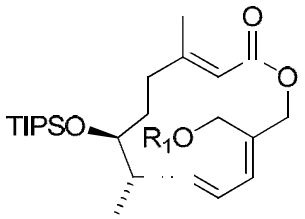
88

To a stirred solution of **87** (660 mg, 1.16 mmol) in 1,4-dioxane (11 mL) was added 1M-KOH (1.16 mL, 1.16 mmol), PPh_3 (30.6 mg, 0.116 mmol) and $Pd(OAc)_2$ (13.1 mg, 0.0582 mmol) successively at room temperature. The reaction mixture was stirred at 50 °C for 2 h under an atmosphere of CO, and quenched with saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with Et_2O (10 mL × 2), the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 2/1) to afford **88** (483 mg, 85%) as a pale yellow oil.

R_f = 0.43 (hexane/ethyl acetate = 1/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.33 (1H, dd, *J*=15.1, 11.0 Hz), 6.21 (1H, d, *J*=11.0 Hz), 5.91 (1H, dd, *J*=15.1, 7.1 Hz), 5.67 (1H, d, *J*=0.98 Hz), 4.66 (2H, s), 4.31 (2H, s), 4.20 (2H, s), 3.78 (1H, ddd, *J*=5.4, 5.4, 5.4 Hz), 3.40 (3H, s), 2.48 (1H, ddq, *J*=7.1, 7.1, 5.4 Hz), 2.27 (2H, ddd, *J*=11.0, 11.0,

5.6 Hz), 2.21-2.11 (1H, m), 2.15 (3H, d, *J*=0.98 Hz), 1.59 (2H, dddd, *J*=29.8, 18.8, 11.0, 5.4 Hz), 1.09-1.06 (21H, m), 1.04 (3H, d, *J*=7.1 Hz).

(3*E*,7*S*,8*S*,9*E*,11*E*)-12-[(methoxymethoxy)methyl]-4,8-dimethyl-7-{[tris(propan-2-yl)silyl]oxy}-1-oxacyclotrideca-3,9,11-trien-2-one

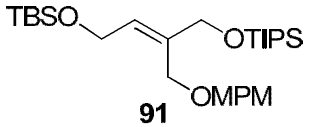


89 (R_1=MOM)

To a stirred solution of **88** (331 mg, 0.683 mmol) and Ph_3P (538 mg, 2.05 mmol) in toluene (340 mL) was added DEAD (2.2 M solution in toluene, 929 μL, 2.05 mmol) dropwise at -100 °C. The reaction mixture was stirred at -100°C to -78 °C for 1 h, quenched by saturated aqueous $NaHCO_3$ solution (50 mL), and the aqueous layer was extracted with Et_2O (50 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **89** (156 mg, 49%) as a colorless oil.

R_f = 0.37 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.38 (1H, d, *J*=11.0 Hz), 6.33 (1H, dd, *J*=13.9, 11.0 Hz), 5.98 (1H, dd, *J*=13.9, 5.9 Hz), 5.62 (1H, d, *J*=0.98 Hz), 4.71-4.59 (4H, m), 4.29 (1H, d, *J*=11.5 Hz), 4.21 (1H, d, *J*=11.5 Hz), 3.74 (1H, ddd, *J*=7.8, 3.2, 3.2 Hz), 3.38 (3H, s), 2.56 (1H, ddq, *J*=7.8, 6.8, 5.9 Hz), 2.37 (2H, ddd, *J*=15.9, 13.2, 4.4 Hz), 2.14-2.03 (1H, m), 1.56-1.48 (2H, m), 1.11-1.06 (21H, m), 1.04 (3H, d, *J*=6.8 Hz).

(*E*)-1-((4-(*tert*-butyldimethylsilyloxy)-2-((triisopropylsilyloxy)methyl)but-2-enyloxy)methyl)-4-methoxybenzene (91)



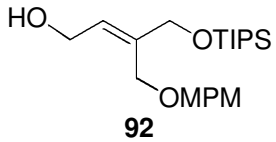
91

To a stirred solution of **83** (1.48 g, 3.81 mmol) in CH_2Cl_2 (38 mL) was added anisyl trichloroacetimidate (5.38 g, 19.0 mmol) and PPTS (1.44 g, 5.71 mmol) successively at room temperature. The reaction mixture was stirred at the same temperature for 1 d, quenched with saturated aqueous $NaHCO_3$ solution (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **91** (1.48 g, 76%) as a colorless oil.

R_f = 0.38 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.24 (2H, d, *J*=8.5 Hz), 6.87 (2H, d, *J*=8.5 Hz), 5.85 (1H, t, *J*=6.1 Hz), 4.38 (2H, s), 4.27 (2H, d, *J*=6.1 Hz), 4.25 (2H, s), 4.01 (2H, s), 3.80 (3H, s), 1.09-1.03 (21H, m), 0.88 (9H, s), 0.05 (6H, s).

(*E*)-3-((4-methoxybenzyloxy)methyl)-4-(triisopropylsilyloxy)but-2-en-1-ol (92)

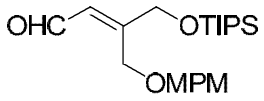


92

To a stirred solution of **91** (1.71 g, 3.36 mmol) in CH_3CN/*t*-BuOH(1/1, 35 mL) was added 20% H_2SiF_6 aq. (0.595 mL, 1.01 mmol) at 0 °C, and stirred at the same temperature for 4 h, quenched with saturated aqueous $NaHCO_3$ solution (10 mL), and the aqueous layer was extracted with Et_2O (20 mL × 2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 4/1) to afford **92** (0.978 g, 74%) as a colorless oil.

R_f = 0.19 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.25-7.22 (2H, m), 6.88 (2H, d, *J*=8.8 Hz), 5.98 (1H, t, *J*=6.8 Hz), 4.43 (2H, s), 4.24 (2H, s), 4.20 (2H, d, *J*=6.8 Hz), 4.04 (2H, s), 3.80 (3H, s), 1.82 (1H, OH), 1.09-1.02 (21H, m).

(*E*)-3-((4-methoxybenzyloxy)methyl)-4-(triisopropylsilyloxy)but-2-enal (fragment B_2)

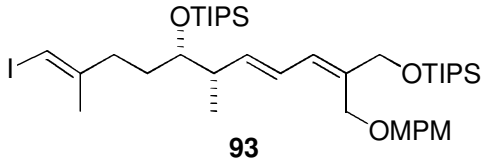


fragment B_2

To a stirred solution of **92** (611 mg, 1.55 mmol) in CH_2Cl_2 (15 mL) was added MnO_2 (6.11 g) at room temperature, and stirred at the same temperature for 30 min, diluted with CH_2Cl_2 (15 mL), and the reaction mixture was filtered through a Celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **fragment B_2** (524 mg, 86%) as a colorless oil.

R_f = 0.47 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 10.1 (1H, d, *J*=7.6 Hz), 7.24 (2H, d, *J*=8.5 Hz), 6.89 (2H, d, *J*=8.5 Hz), 6.35 (1H, d, *J*=7.6 Hz), 4.48 (2H, s), 4.44 (2H, s), 4.40 (2H, s), 3.81 (3H, s), 1.09-1.02 (21H, m).

1-(((2*E*,4*E*,6*S*,7*S*,10*E*)-11-iodo-6,10-dimethyl-7-(triisopropylsilyloxy)-2-((triisopropylsilyloxy)methyl)undeca-2,4,10-trienyloxy)methyl)-4-methoxybenzene (93)

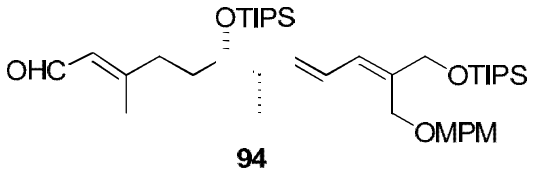


93

To a stirred solution of DIPA (393 μL, 2.81 mmol) in THF (18 mL) was added *n*-BuLi (1.58 M solution in hexane, 1.67 mL, 2.63 mmol) at -78 °C, and the reaction mixture was stirred at the same temperature for 15 min. Then, to the reaction mixture was added **fragment A** (1.11 g, 1.75 mmol) in THF (9.0 mL) via a cannula at -78 °C. After the addition, the reaction mixture was stirred at thesame temperature for 30 min, and then was added **fragment B_2** (0.758 g, 1.93 mmol) in THF (9.0 mL) via a cannula at -78 °C. After the addition, the reaction mixture was stirred at the same temperature for 2 h, quenched with saturated aqueous NH_4Cl solution (20 mL), and the aqueous layer was extracted with Et_2O (20 mL × 2). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford **93** (0.769 g, 62%) as a colorless oil.

R_f = 0.61 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.87 (2H, d, *J*=8.5 Hz), 6.31 (1H, dd, *J*=13.9, 11.2 Hz), 6.26 (1H, d, *J*=11.2 Hz), 5.86 (1H, d, *J*=0.98 Hz), 5.83 (1H, dd, *J*=13.9, 7.1 Hz), 4.40 (2H, s), 4.31 (2H, s), 4.12 (2H, s), 3.80 (3H, s), 3.74 (1H, ddd, *J*=5.4, 5.4, 5.4 Hz), 2.39 (2H, ddq, *J*=7.1, 6.8, 5.4 Hz), 2.23 (2H, dddd, *J*=23.2, 13.7, 13.7, 5.9 Hz), 1.81 (3H, d, *J*=0.98 Hz), 1.61-1.51 (2H, m), 1.10-1.04 (42H, m), 1.00 (3H, d, *J*=6.8 Hz).

(2*E*,6*S*,7*S*,8*E*,10*E*)-11-((4-methoxybenzyloxy)methyl)-3,7-dimethyl-6,12-bis(triisopropylsilyloxy)dodeca-2,8,10-trienal (94)



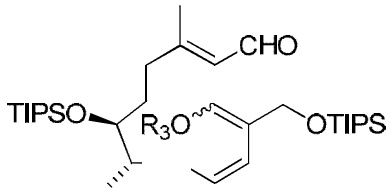
94

To a stirred solution of **93** (688 mg, 0.862 mmol) in Et_2O (9.0 mL) was added *t*-BuLi (1.46 M solution in hexane, 1.18 mL, 1.72 mmol) at –78 °C. After 5 min, to the mixture was added DMF (331 μL, 4.31 mmol) at –78 °C. After the addition, the reaction mixture was stirred at the same temperature for 10 min, quenched with saturated aqueous NH_4Cl solution (10 mL), and the aqueous layer was extracted with

Et_2O (20 mL × 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford **94** (364 mg, 60%) as a colorless oil.

R_f = 0.31 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.97 (1H, d, *J*=8.1 Hz), 7.25-7.22 (2H, m), 6.87 (2H, d, *J*=8.5 Hz), 6.32 (1H, dd, *J*=14.4, 11.0 Hz), 6.27 (1H, d, *J*=11.0 Hz), 5.86 (1H, dd, *J*=8.1, 0.98 Hz), 5.83 (1H, dd, *J*=14,4, 9.0 Hz), 4.40 (2H, s), 4.30 (2H, s), 4.12 (2H, s), 3.80 (3H, s), 2.48-2.39 (1H, m), 2.25 (1H, ddq, *J*=9.0, 6.8, 6.8 Hz), 2.25 (2H, dddd, *J*=29.5, 13.7, 13.7, 4.9 Hz), 2.13 (3H, d, *J*=0.98 Hz), 1.66-1.58 (2H, m), 1.12-1.05 (42H, m), 1.02 (3H, d, *J*=6.8 Hz).

(2*E*,6*S*,7*S*,9*Z*)-12-[(4-methoxyphenyl)methoxy]-3,7-dimethyl-6-{[tris(propan-2-yl)silyl]oxy}-11-({[tris(propan-2-yl)silyl]oxy}methyl)dodeca-2,9,11-trienal (95')

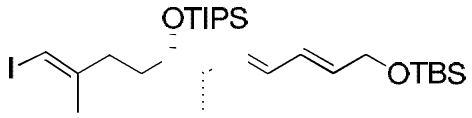


95' (R_3=MPM)

To a stirred solution of **94** (8.2 mg, 0.0117 mmol) in toluene (1.0 mL) was added Me_2Al (1.01 M solution in hexane, 57.9 μL, 0.0585 mmol) at -10 °C. The reaction mixture was stirred at the same temperature for 2 h, quenched with saturated aqueous $NaHCO_3$ solution (5.0 mL), and the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to afford **95'** (3.8 mg, 46%) as a colorless oil.

R_f = 0.24 (hexane/ethyl acetate = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.97 (1H, d, *J*=8.1 Hz), 7.30-7.25 (2H, m), 6.88 (2H, d, *J*=8.5 Hz), 6.27 (1H, dd, *J*=13.9, 11.0 Hz), 6.22 (1H, d, *J*=11.0 Hz), 5.95 (1H, ddd, *J*=6.8, 6.8, 6.8 Hz), 5.85 (1H, d, *J*=8.1 Hz), 4.45 (2H, s), 4.22 (2H, s), 3.81 (3H, s), 3.69-3.63 (1H, m), 2.53-2.42 (1H, m), 2.29 (1H, ddd, *J*=11.5, 11.5, 5.6 Hz), 2.19 (1H, ddd, *J*=16.4, 11.5, 5.6 Hz), 1.70-1.49 (2H, m), 2.14 (3H, s), 1.12-1.04 (42H, m), 1.02 (3H, d, *J*=6.8 Hz).

(1*E*,5*S*,6*S*,7*E*,9*E*)-11-(*tert*-butyldimethylsilyloxy)-1-iodo-2,6-dimethyl-5-(triisopropylsilyloxy)undeca-1,7,9-triene (107)

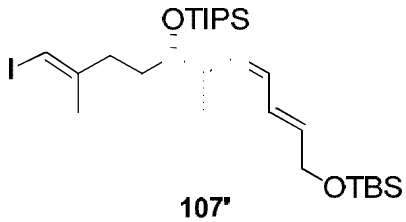


107

To a solution of DIPA (1.03 ml, 7.37 mmol) in THF (49 mL) was added ^{n}BuLi (1.63 M solution in hexane, 4.22 mL, 6.88 mmol) at -78 °C, and the reaction mixture was stirred at the same temperature for 15 min. Then, to the reaction mixture was added **fragment A** (3.11 g, 4.92 mmol) in THF (9.8 mL) via a cannula at -78 °C. After the addition, the reaction mixture was stirred at the same temperature for 30 min, and then was added **fragment B_3** (1.18 g, 5.90 mmol) in THF (9.8 mL) via a cannula at -78 °C. After the addition, the reaction mixture was stirred at the same temperature for 3 h, quenched with saturated aqueous NH_4Cl solution (50 mL), and the aqueous layer was extracted with Et_2O (100 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/CH_2Cl_2 = 20/1) to afford **107** (1.47 g, 58%) and **107'** (218 mg, 8.6%) as a colorless oil and starting material **fragment A** (472 mg, 15%).

R_f = 0.61 (hexane/CH_2Cl_2 = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.19 (1H, dd, *J*=15.1, 10.5 Hz), 6.02 (1H, dd, *J*=15.6, 10.5 Hz), 5.86 (1H, s), 5.75 (1H, dd, *J*=15.6, 6.9 Hz), 5.66 (1H, ddd, *J*=15.1, 5.0, 5.0 Hz), 4.20 (2H, d, *J*=5.0 Hz), 3.73 (1H, dd, *J*=10.1, 5.0 Hz), 2.47-2.34 (1H, m), 2.34-2.13 (2H, m), 1.81 (3H, s), 1.62-1.47 (2H, m), 1.12-1.02 (21H, m), 1.00 (3H, d, *J*=6.9 Hz), 0.91 (9H, s), 0.07 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 136.5, 130.5, 130.4, 129.1, 76.0, 74.5, 63.6, 41.6, 35.5, 32.4, 26.0, 24.0, 18.4, 18.2, 15.1, 12.9, -5.18; IR (neat) νmax 2943, 2864, 1462, 1378, 1263, 1098, 836, 738, 675 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{28}H_{55}O_2INaSi_2$: 629.2677, found: 629.2676; $[\alpha]_D^{22}$ -4.7 (*c* 1.4, $CHCl_3$).

(1*E*,5*S*,6*S*,7*Z*,9*E*)-11-(*tert*-butyldimethylsilyloxy)-1-iodo-2,6-dimethyl-5-(triisopropylsilyloxy)undeca-1,7,9-triene (107')

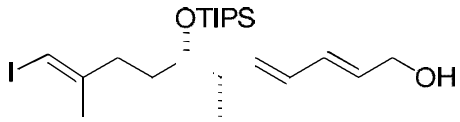


107'

R_f = 0.65 (hexane/CH_2Cl_2 = 4/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.49 (1H, dd, *J*=14.7, 11.4 Hz), 5.96 (1H, dd, *J*=11.4, 11.4 Hz), 5.85 (1H, s), 5.75 (1H, ddd, *J*=14.7, 4.6, 4.6 Hz), 5.35 (1H, dd, *J*=11.4, 11.4 Hz), 4.24 (2H, d, *J*=4.6 Hz), 3.72 (1H, dd, *J*=10.5,

5.5 Hz), 2.79-2.66 (1H, m), 2.34-2.10 (2H, m), 1.80 (3H, s), 1.69-1.59 (2H, m), 1.14-1.03 (21H, m), 1.00 (3H, d, *J*=6.4 Hz), 0.92 (9H, s), 0.08 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 134.7, 133.0, 127.1, 124.9, 75.7, 74.5, 63.5, 36.8, 34.5, 33.5, 25.9, 23.9, 18.4, 18.3, 16.2, 13.0, -5.21; IR (neat) νmax 2928, 2864, 1462, 1377, 1252, 1103, 835, 776, 673 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{28}H_{55}O_3INaSi_2$: 645.2627, found: 645.2624; $[\alpha]_D^{23}$ +27 (*c* 1.7, $CHCl_3$).

(2*E*,4*E*,6*S*,7*S*,10*E*)-11-iodo-6,10-dimethyl-7-(triisopropylsilyloxy)undeca-2,4,10-trien-1-ol (108)

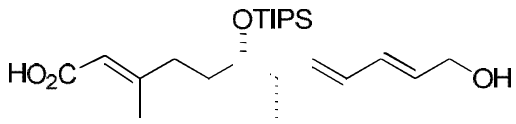


108

To a stirred solution of **107** (431 mg, 0.710 mmol) in CH_3CN/*t*-BuOH(1/1, 14 mL) was added 20% H_2SiF_6 aq. (0.126 mL, 2.13 mmol) at 0 °C, and stirred at the same temperature for 2 h, quenched with saturated aqueous $NaHCO_3$ solution (10 mL), and the aqueous layer was extracted with Et_2O (20 mL × 2). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 4/1) to afford **108** (0.327 g, 93%) as a colorless oil.

R_f = 0.10 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.24 (1H, dd, *J*=15.1, 10.5 Hz), 6.04 (1H, dd, *J*=15.4, 10.5 Hz), 5.86 (1H, s), 5.83 (1H, dd, *J*=15.1, 8.5 Hz), 5.76 (1H, dt, *J*=15.4, 5.9 Hz), 4.20 (2H, dd, *J*=5.9, 5.9 Hz), 3.74 (1H, ddd, *J*=5.1, 5.1, 5.1 Hz), 3.74 (1H, ddq, *J*=8.5, 6.8, 5.1 Hz), 2.28 (1H, ddd, *J*=24.2, 13.9, 5.1 Hz), 2.21 (1H, ddd, *J*=24.2, 13.9, 5.1 Hz), 1.82 (3H, s), 1.74-1.59 (2H, m), 1.28 (1H, t, *J*=5.9 Hz), 1.09-1.04 (21H, m), 1.01 (3H, d, *J*=6.8 Hz).

(2*E*,6*S*,7*S*,8*E*,10*E*)-12-hydroxy-3,7-dimethyl-6-(triisopropylsilyloxy)dodeca-2,8,10-trienoic acid (109)



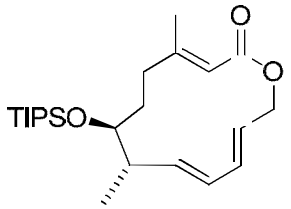
109

To a stirred solution of **108** (315 mg, 0.640 mmol) in 1,4-dioxane (7.0 mL) was added 1M-KOH (0.640 mL, 0.640 mmol), PPh_3 (33.5 mg, 0.128 mmol) and $Pd(OAc)_2$ (14.4 mg, 0.0640 mmol) successively at room temperature. The reaction mixture was stirred at 50 °C for 2 h under an atmosphere of CO, and quenched with saturated aqueous

NH_4Cl solution (5.0 mL). The aqueous layer was extracted with Et_2O (10 mL × 2), the combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 2/1) to afford **109** (213 mg, 81%) as a pale yellow oil.

R_f = 0.43 (hexane/ethyl acetate = 1/1); ^1H NMR (400MHz, $CDCl_3$) δ 6.24 (1H, dd, *J*=15.1, 10.5 Hz), 6.06 (1H, dd, *J*=15.1, 10.5 Hz), 5.82 (1H, dd, *J*=15.1, 7.1 Hz), 5.76 (1H, dt, *J*=15.1, 5.9 Hz), 5.68 (1H, s), 4.18 (2H, d, *J*=5.9 Hz), 3.77 (1H, ddd, *J*=5.1, 5.1, 5.1 Hz), 2.45 (1H, ddq, *J*=7.1, 7.1, 5.1 Hz), 2.28 (1H, ddd, *J*=11.2, 11.2, 5.6 Hz), 2.22-2.09 (1H, m), 2.15 (3H, s), 1.77-1.44 (3H, m), 1.12-1.05 (21H, m), 1.03 (3H, d, *J*=7.1 Hz).

(3*E*,7*S*,8*S*,9*E*,11*E*)-4,8-dimethyl-7-{[tris(propan-2-yl)silyl]oxy}-1-oxacyclotrideca-3,9,11-trien-2-one (110)

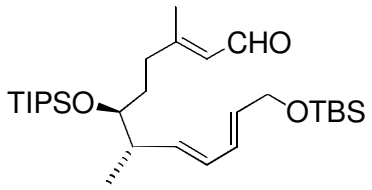


110

To a stirred solution of **109** (132 mg, 0.321 mmol) and Ph_3P (253 mg, 0.964 mmol) in toluene (160 mL) was added DEAD (2.2 M solution in toluene, 438 μL, 0.964 mmol) dropwise at -100 °C. The reaction mixture was stirred at -100°C to -78 °C for 1 h, quenched by saturated aqueous $NaHCO_3$ solution (30 mL), and the aqueous layer was extracted with Et_2O (30 mL × 2). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 50/1) to afford **110** (126 mg, 60%) as a colorless oil.

R_f = 0.69 (hexane/ethyl acetate = 4/1); ^1H NMR (400MHz, $CDCl_3$) δ 6.31 (1H, dd, *J*=15.1, 10.3 Hz), 6.04 (1H, dd, *J*=15.4, 10.3 Hz), 5.89 (1H, dd, *J*=15.1, 5.6 Hz), 5.73 (1H, ddd, *J*=15.4, 7.1, 7.1 Hz), 5.60 (1H, s), 4.63 (1H, dd, *J*=12.0, 6.3 Hz), 4.52 (1H, dd, *J*=12.0, 7.8 Hz), 3.78-3.69 (1H, m), 2.58-2.46 (1H, m), 2.41-2.25 (2H, m), 2.16 (3H, s), 2.13-1.95 (2H, m), 1.11-1.05 (21H, m), 1.01 (3H, d, *J*=6.8 Hz).

(2*E*,6*S*,7*S*,8*E*,10*E*)-12-(*tert*-butyldimethylsilyloxy)-3,7-dimethyl-6-(triisopropylsilyloxy)dodeca-2,8,10-trienal (112)

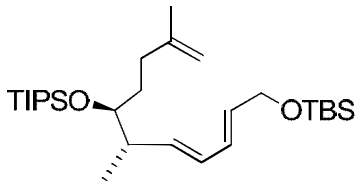


112

To a solution of **107** (741 mg, 1.22 mmol) in Et_2O (12 mL) was added *n*-BuLi (1.63 M solution in hexane, 1.50 mL, 2.44 mmol) at –78 °C. After 40 min, to the mixture was added DMF (470 μL, 6.11 mmol) at –78 °C. After the addition, the reaction mixture was stirred at the same temperature for 30 min, quenched with saturated aqueous NH_4Cl solution (50 mL), and the aqueous layer was extracted with Et_2O (50 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1) to afford **112** (575 mg, 93%) and trace amount of **113** as a colorless oil.

R_f = 0.23 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.98 (1H, d, *J*=7.8 Hz), 6.19 (1H, dd, *J*=15.1, 10.5 Hz), 6.04 (1H, dd, *J*=15.1, 10.5 Hz), 5.86 (1H, d, *J*=8.2 Hz), 5.74 (1H, dd, *J*=15.1, 5.0 Hz), 5.67 (1H, dt, *J*=15.1, 5.0 Hz), 4.20 (2H, d, *J*=5.0 Hz), 3.78 (1H, dd, *J*=10.1, 5.0 Hz), 2.49-2.37 (1H, m), 2.36-2.15 (2H, m), 2.15 (3H, s), 1.70-1.50 (2H, m), 1.16-1.03 (21H, m), 1.02 (3H, d, *J*=6.9 Hz), 0.91 (9H, s), 0.07 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 164.4, 136.0, 130.8, 130.2, 129.3, 127.1, 75.9, 63.6, 41.7, 36.3, 31.7, 25.9, 18.4, 18.2, 17.7, 15.4, 12.9, -5.20; IR (neat) νmax 2928, 2864, 1676, 1462, 1253, 1097, 989, 834, 775, 676 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{29}H_{56}O_3NaSi_2$: 531.3660, found: 531.3665; $[\alpha]_D^{23}$ -6.5 (*c* 2.6, $CHCl_3$).

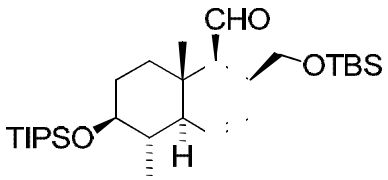
(5*S*,6*S*,7*E*,9*E*)-11-(*tert*-butyldimethylsilyloxy)-2,6-dimethyl-5-(triisopropylsilyloxy)undeca-1,7,9-triene (113)



113

R_f = 0.88 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 6.19 (1H, dd, *J*=15.1, 10.5 Hz), 6.03 (1H, dd, *J*=15.6, 10.5 Hz), 5.78 (1H, dd, *J*=15.6, 7.3 Hz), 5.65 (1H, ddd, *J*=15.1, 5.5, 5.5 Hz), 4.67 (2H, d, *J*=10.5 Hz), 4.20 (2H, d, *J*=5.0 Hz), 3.79-3.72 (1H, m), 2.46-2.34 (1H, m), 2.12-1.94 (2H, m), 1.71 (3H, s), 1.62-1.51 (2H, m), 1.11-1.04 (21H, m), 1.00 (3H, d, *J*=6.9 Hz), 0.91 (9H, s), 0.07 (6H, s).

(1*S*,2*S*,4a*S*,5*S*,6*S*,8a*S*)-2-((*tert*-butyldimethylsilyloxy)methyl)-5,8a-dimethyl-6-(triisopropylsilyloxy)-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde (114)

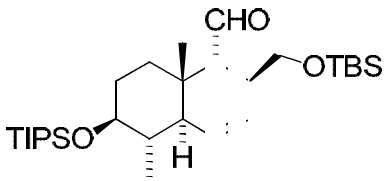


114

To a solution of **112** (200 mg, 0.393 mmol) in toluene (20 mL) was added Me_2AlCl (1.00 M solution in hexane, 146 μL, 0.157 mmol) at -10 °C, the reaction mixture was stirred at -10~-5 °C for 24 h. The reaction mixture was added Me_2AlCl (1.00 M solution in hexane, 146 μL, 0.157 mmol) at -10 °C, and stirred at -10~-5 °C for 24 h. The reaction mixture was added Me_2AlCl (1.00 M solution in hexane, 146 μL, 0.157 mmol) at -10 °C, and stirred at -10~-5 °C for 24 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 mL), and saturated Rochelle's salt solution (20 mL), the aqueous layer was extracted with Et_2O (50 mL × 2). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 100/1) to afford **114** (149 mg, 74%) as a colorless oil.

R_f = 0.61 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.84 (1H, d, *J*=4.6 Hz), 5.79 (1H, d, *J*=10.1 Hz), 5.65 (1H, d, *J*=10.1 Hz), 3.87 (1H, dd, *J*=10.1, 10.1 Hz), 3.65 (1H, dd, *J*=10.1, 5.5 Hz), 3.35-3.20 (1H, m), 2.83-2.70 (1H, m), 2.30 (1H, dd, *J*=7.8, 4.6 Hz), 1.87-1.77 (1H, m), 1.76-1.61 (2H, m), 1.53-1.40 (2H, m), 1.15 (3H, s), 1.19-0.98 (25H, m), 0.87 (9H, s), 0.03 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 129.0, 126.9, 77.6, 63.8, 60.4, 49.9, 41.2, 37.8, 35.5, 34.2, 30.7, 25.8, 18.3, 18.2, 18.1, 15.4, 14.8, 12.9, -5.60, -5.62; IR (neat) νmax 2929, 2864, 1716, 1630, 1463, 1253, 1091, 835, 775, 676 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{29}H_{56}O_3NaSi_2$: 531.3660, found: 531.3662; $[\alpha]_D^{23}$ +11 (*c* 1.5, $CHCl_3$).

(1*R*,2*S*,4a*S*,5*S*,6*S*,8a*S*)-2-((*tert*-butyldimethylsilyloxy)methyl)-5,8a-dimethyl-6-(triisopropylsilyloxy)-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde (114')



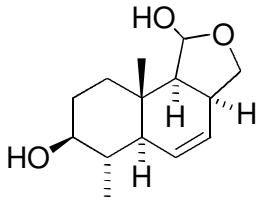
114'

To a solution of **114** (5.00 mg, 0.00982 mmol) in MeOH (1 mL) was added NaOMe (0.53 mg, 0.00982 mmol) at room temperature for 48 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL), the aqueous layer was extracted with Et_2O (5 mL × 2). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 100/1) to afford **114'** as a mixture of starting material (dr = 7/1) (4.3 mg, 86%) as a colorless oil.

major product

R_f = 0.61 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.78 (1H, d, *J*=4.1 Hz), 5.82 (1H, ddd, *J*=10.1, 2.3, 2.3 Hz), 5.74 (1H, ddd, *J*=10.1, 2.7, 2.7 Hz), 3.65 (1H, dd, *J*=9.6, 6.9 Hz), 3.53 (1H, dd, *J*=9.6, 8.2 Hz), 3.26 (1H, ddd, *J*=10.5, 10.5, 5.0 Hz), 2.60-2.49 (1H, m), 2.35 (1H, dd, *J*=4.1, 0.9 Hz), 1.88-1.78 (1H, m), 1.78-1.68 (2H, m), 1.62 (1H, ddd, *J*=13.3, 3.2, 3.2 Hz), 1.52-1.37 (2H, m), 1.08 (3H, d, *J*=6.4 Hz), 1.13-0.98 (21H, m), 0.94 (3H, s), 0.88 (9H, s), 0.04 (3H, s), 0.04 (3H, s); HRMS (ESI) $[M+Na]^+$ calculated for $C_{29}H_{56}O_3NaSi_2$: 531.3660, found: 531.3662.

(1*R*,3a*S*,5a*S*,6*S*,7*S*,9a*S*,9b*R*)-6,9a-dimethyl-1,3,3a,5a,6,7,8,9,9a,9b-decahydronapht ho[2,1-c]furan-1,7-diol (115)



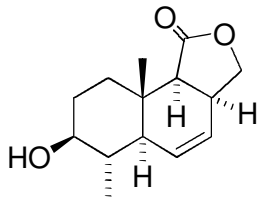
115

To a solution of **114** (190 mg, 0.373 mmol) in THF (3.7 mL) was added TBAF (1.0 M solution in THF, 933 μL, 0.933 mmol) at room temperature, and the reaction mixture was stirred at 60 °C for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL), and the aqueous layer was extracted with AcOEt (10 mL × 2). The combined organic layer was washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 1/1) to afford **115** (83.1 mg, 93%) as a white solid.

R_f = 0.27 (hexane/ethyl acetate = 1/2); mp 140.0-141.2 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ 5.70 (2H, s), 5.47 (1H, d, *J*=1.8 Hz), 4.32 (1H, dd, *J*=10.1, 8.2 Hz), 3.60 (1H, dd, *J*=8.2, 8.2 Hz), 3.26-3.04 (2H, m), 2.45 (1H, br s), 2.03 (1H, d, *J*=8.7 Hz), 1.91-1.76 (2H, m), 1.68-1.48 (2H, m), 1.47-1.36 (1H, m), 1.31 (1H, ddd, *J*=13.3, 13.3, 4.7 Hz), 1.10 (3H, d, *J*=6.4 Hz), 0.77 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.9,

126.8, 100.3, 76.5, 73.2, 57.2, 47.6, 37.5, 36.6, 36.2, 33.1, 30.2, 15.3, 13.8; IR (neat) νmax 3290, 2917, 2881, 1434, 1242, 1056, 895 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{14}H_{22}O_3Na$: 261.1461, found: 261.1462; $[\alpha]_D^{22}$ -44 (*c* 1.3, $CHCl_3$).

(3a*S*,5a*S*,6*S*,7*S*,9a*S*,9b*R*)-7-hydroxy-6,9a-dimethyl-3,3a,5a,6,7,8,9,9a-octahydronaphtho[2,1-c]furan-1(9bH)-one (116)



116

To a stirred solution of **115** (76.0 mg, 0.319 mmol) in benzene (3.0 mL) was added Fetizon reagent (478 mg, 0.60 g/mmol) at room temperature. After the reaction mixture was stirred at 80 °C for 30 min, the reaction mixture was filtered through a Celite pad, and the filtrate was concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate = 2/1) to afford **116** (73.6 mg, 98%) as a white solid.

R_f = 0.55 (hexane/ethyl acetate = 1/2); mp 136.3-137.0 °C; ^1H NMR (400MHz, $CDCl_3$) δ 5.84 (1H, ddd, *J*=10.1, 2.3, 2.3 Hz), 5.65 (1H, ddd, *J*=10.1, 2.7, 2.7 Hz), 4.49 (1H, dd, *J*=10.1, 10.1 Hz), 3.88 (1H, dd, *J*=10.1, 8.7 Hz), 3.28-3.12 (2H, m), 2.42 (1H, d, *J*=10.1 Hz), 2.33 (1H, ddd, *J*=13.7, 3.7, 3.7 Hz), 1.88 (1H, ddd, *J*=12.4, 8.2, 3.7 Hz), 1.70-1.49 (2H, m), 1.48-1.30 (2H, m), 1.12 (3H, d, *J*=6.4 Hz), 0.90 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 129.4, 123.7, 76.2, 71.4, 50.0, 47.4, 37.7, 35.5, 34.9, 34.7, 29.9, 15.3, 14.3; IR (neat) νmax 3256, 2932, 2882, 1743, 1452, 1380, 1167, 997, 743 cm^{-1}; HRMS (ESI) $[M+Na]^+$ calculated for $C_{14}H_{20}O_3Na$: 259.1305, found: 259.1305; $[\alpha]_D^{22}$ -69 (*c* 1.7, $CHCl_3$).

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研究業績

種類別	題名、　発表・発行掲載誌名、　発表・発行年月、　連名者（申請者含む）
論文	“First Total Synthesis of Antimitotic Compound, (+)-Phomopsidin” Suzuki, T.; Usui, K.; Miyake, Y.; Namikoshi, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 553–556. “Alternative synthetic approach for (+)-phomopsidin via the highly stereoselective TADA reaction” Hayashi, N.; Suzuki, T.; Usui, K.; Nakada, M. *Tetrahedron* **2009**, *65*, 888–895. “Asymmetric total synthesis of MK8383: The iron-mediated coupling reaction is the only effective method for the construction of the (*Z*)-trisubstituted side-chain alkene” Hayashi, N.; Suzuki, T.; Usui, K.; Nakada, M. *Tetrahedron Lett.* **2009**, *50*, 232–235. ○“Total Synthesis of (-)-Bucidarasin A Starting from an Original Chiral Building Block” Usui, K.; Kanbe, M; Nakada, M. *Org. Lett.* **2014**, *16*, 4734–4737. ○“Enantioselective Total Synthesis of (+)-Bucidarasins A and C” Usui, K.; Nakada, M. *Heterocycles* **2015**, *91*, 332–350. ○“A highly stereoselective intramolecular Diels-Alder reaction for construction of the AB ring moiety of bruceantin” Usui, K.; Suzuki, T.; Nakada, M. *Tetrahedron Lett.* **2015**, *56*, in press. DOI:10.1016/j.tetlet.2015.01.139.
講演	「抗腫瘍性抗生物質 phomopsidin の全合成研究」 鈴木　孝洋、三宅　祥元、臼井　研二、浪越　通夫、中田　雅久 第 45 回天然有機化合物討論会、京都、2003 年 10 月. 「(+)-ホモプシジンの全合成」 鈴木　孝洋、臼井　研二、三宅　祥元、浪越　通夫、中田　雅久 日本化学会第 83 春季年会、神戸、2004 年 3 月. 「(+)-Phomopsidin の全合成」 鈴木　孝洋、臼井　研二、三宅　祥元、浪越　通夫、中田　雅久 第 85 回有機合成シンポジウム、東京、2004 年 6 月.

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講演	“First Total Synthesis of Antimitotic Compound, (+)-Phomopsidin” Suzuki, T.; Usui, K.; Miyake, Y.; Namikoshi, M.; Nakada, M. 15th International Conference on Organic Synthesis, Aichi, Japan, Aug, 2004. “First Total Synthesis of Antimitotic Compound, (+)-Phomopsidin” Suzuki, T.; Usui, K.; Miyake, Y.; Namikoshi, M.; Nakada, M. 229th ACS National Meeting, San Diego, CA, United States, March, 2005. 「(-)-ブルセアンチンの全合成研究」 臼井　研二、鈴木　孝洋、中田　雅久 日本化学会第 86 春季年会、神奈川、2006 年 3 月. 「(+)-ホモプシジンの不斉全合成研究」 林　伸行、臼井　研二、鈴木　孝洋、中田　雅久 日本化学会第 86 春季年会、神奈川、2006 年 3 月. “FURTHER SYNTHETIC STUDIES ON (+)-PHOMOPSIDIN” Hayashi, N.; Usui, K.; Suzuki, T.; Nakada, M. ICOB-5 & ISCNP-25 IUPAC International Conference on Biodiversity and Natural Products, Kyoto, Japan, July, 2006. 「(+)-Phomopsidin の改良合成研究」 林　伸行、臼井　研二、鈴木　孝洋、中田　雅久 第 4 回 21COE「実践的ナノ化学」国際シンポジウム、早稲田大学、東京、2006 年 12 月. 「(+)-Phomopsidin の改良不斉全合成」 林　伸行、臼井　研二、鈴木　孝洋、中田　雅久 第 91 回有機合成シンポジウム、東京、2007 年 11 月. 「Clerodane 型ジテルペン Bucidarasin A および C の初の不斉全合成と絶対配置決定」 臼井　研二、神戸　美咲、中田　雅久 第 56 回天然有機化合物討論会、高知、2014 年 10 月.