キラルビルディングブロックスの酵素化学的創製と生物活性天然物の全合成への活用

Chemoenzymatic Synthesis of the Chiral Building Blocks and Their Application to the Total Synthesis of Biologically Active Natural Products

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化学専攻 化学合成法研究

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略語表

Ac	:	acetyl
AIBN	:	2,2'-azobisisobutyronitrile
9-BBN	:	9-borabicyclo[3.3.1]nonane
Bn	:	benzyl
Boc	:	*tert*-butoxycarbonyl
Bu	:	butyl
Bz	:	benzoyl
cod	:	1,5-cyclooctadiene
Cy	:	cyclohexyl
DBU	:	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	:	*N,N'*-dicyclohexylcarbodiimide
DDQ	:	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	:	diisobutylaluminum hydride
DIPEA	:	*N, N*-diisopropylethylamine
DMAP	:	4-*N,N*-dimethylaminopyridine
DMF	:	*N,N*-dimethylformamide
DMSO	:	dimethyl sulfoxide
DPPA	:	diphenylphosphoryl azide
EDCI	:	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	:	enantiomeric excess
EE	:	1-ethoxyethyl
equiv	:	equivalent
Et	:	ethyl
Hex	:	hexyl
HMPA	:	hexamethylphosphoric acid triamide
HOMO	:	highest occupied molecular orbital
HPLC	:	high performance liquid chromatography
IBX	:	*o*-iodoxybenzoic acid
KHMDS	:	potassium hexamethyldisilazide
KPB	:	potassium phosphate buffer pH
LDA	:	lithium diisopropylamide
LUMO	:	lowest unoccupied molecular orbital
Me	:	methyl
MOM	:	methoxymethyl

mp	:	melting point
MPM	:	*p*–methoxyphenylmethyl
Ms	:	methanesulfonyl
MS	:	mass spectrograph
MS	:	molecular sieves
NBS	:	*N*–bromosuccinimide
NCS	:	*N*–chlorosuccinimide
NIS	:	*N*–iodosuccinimide
NMO	:	*N*–methylmorpholine *N*–oxide
NOESY	:	nuclear Overhauser effect spectroscopy
N.R.	:	no reaction
PG	:	protecting group
Ph	:	phenyl
Piv	:	pivaloyl
PLE	:	pig liver esterase
PMB	:	*p*–methoxyphenylmethyl
PPTS	:	pyridinium *p*–toluenesulfonate
Pr	:	propyl
PTLC	:	preparative thin–layer chromatography
Py	:	pyridine
recryst.	:	recrystallization
rt	:	room temperature
S_N2	:	bimolecular nucleophilic substitution
TBAF	:	tetra–*n*–butylammonium fluoride
TBDPS	:	*tert*–butyldiphenylsilyl
TBHP	:	*tert*–butylhydroperoxide
TBS	:	*tert*–butyldimethylsilyl
temp	:	temperature
Tf	:	trifluoromethanesulfonyl
TFA	:	trifluoroacetic acid
THF	:	tetrahydrofuran
TLC	:	thin–layer chromatography
TMS	:	trimethylsilyl
tol	:	methylphenyl
TPAP	:	tetra–*n*–propylammonium perruthenate
TS	:	transition state

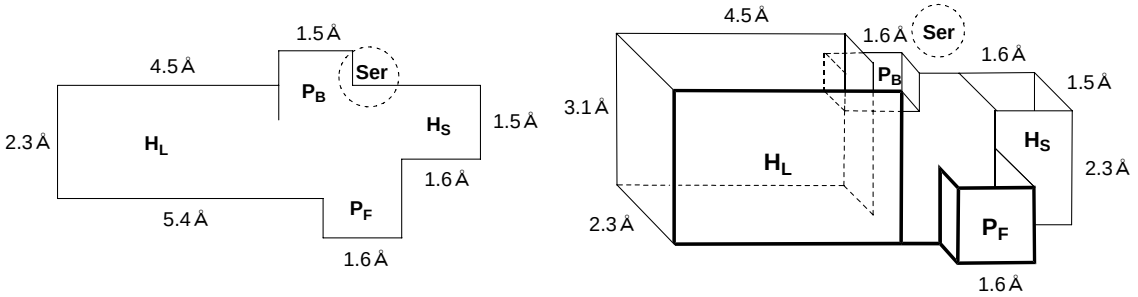
目次

第 1 章　序論

近年、 有機合成化学の進歩は著しく、多くの有用な不斉反応が開発されたことにより、光学純度の高い様々なキラルビルディングブロックが合成可能となり、天然物合成に用いられている。しかし、依然として適切な立体配置および官能基変換可能な置換基を有するキラルビルディングブロック、特に不斉 4 級炭素を有するものは合成難に直面することが多々あり、その創製は有機合成上重要な課題の一つである。一方、近年、化学物質による環境汚染が地球規模での問題となり、廃棄物の少ない効率的な環境調和型反応の開発が急務となっている。数ある有機反応の中で、酵素反応の多くは常温、常圧下、オープンエアーかつ含水条件で高エナンチオ選択的に進行するためエネルギー消費が少なく、また廃棄物が少ないことからも環境調和型の反応であり、さらにスケールアップも容易であることから、これまでに高い分子認識能を有する生体触媒が光学分割やキラルビルディングブロックの合成、および多くの不斉全合成研究に活用されてきた。その中でも低価格で入手可能であり、補因子を必要としない加水分解酵素 pig liver esterase(PLE)を用いたプロキラルなジエステルの不斉加水分解は、①PLE は X 線結晶構造解析がなされており、様々な基質での結果を経験的に考察することで活性部位の形状のモデル化が行われているため、あらかじめある程度選択性を予想することが可能であること(Figure 1-1)[1)]、②PLE は基質特異性が低いため、あらかじめ基質に種々の官能基を導入しておくことが可能であること、③これまでの純化学的な不斉合成例、つまりは不斉配位子や不斉素子を用いた合成では、しばしばその非天然型由来の鏡像異性体を入手することが困難であるが、本反応で得られるモノカルボン酸は区別できるカルボキシル基とエステル基を有しているため誘導体は両鏡像異性体として利用可能であること、④金属を用いた合成では、金属のリーチングにより生成物に金属が残留する可能性があるという問題点を含んでいるが、本反応は金属を用いないため、生成物に金属が残留することがない、といった利点を有しており、有機合成上非常に有用である。

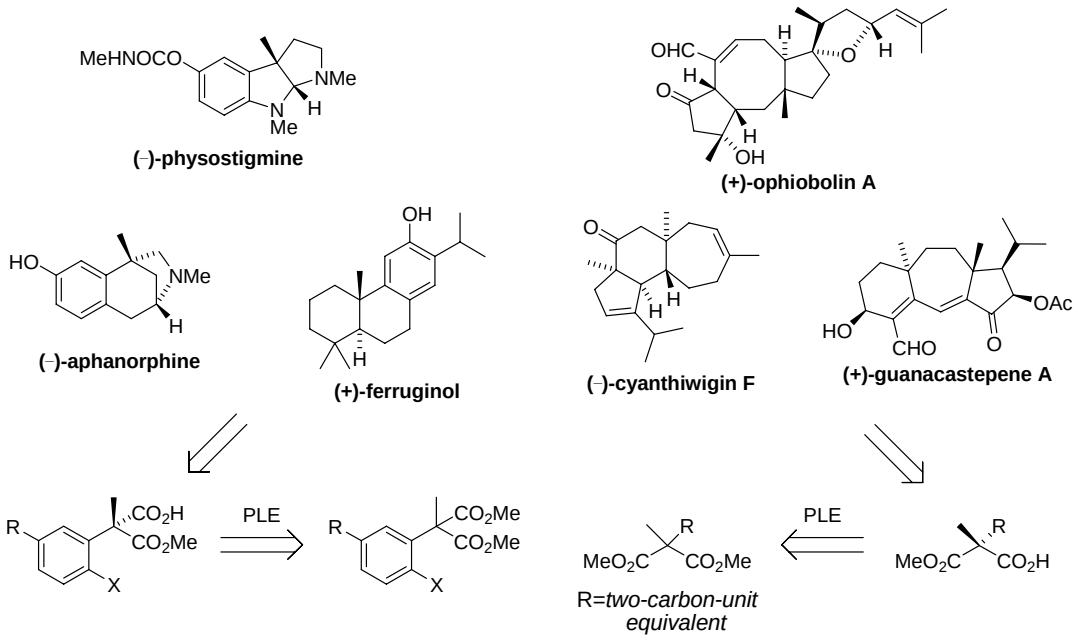
以上の観点から、2 種のプロキラルなマロネート、すなわち、①種々の官能基導入が可能となる置換基をオルト位に有するアリール基の置換するプロキラルなメチルマロネート、②官能基変換可能な 2 炭素等価体を側鎖に有するプロキラルなメチルマロネート、に対する PLE を用いた不斉加水分解を鍵とした、不斉 4 級炭素を有する新規キラルビルディングブロックの創製、およびそれらを活用する有用な生物活性天然物の不斉全合成を目的とし本研究を行った(Figure 1-2)。

Figure 1-1. Active-site model of PLE [1].



H_L は大きな(Large)疎水性(Hydrophobic)ポケット、H_S は小さな(Small)疎水性ポケット、また P_F は前面(Front)の極性(Polar)ポケット、P_B は背面(Back)の極性ポケット、点線で囲んだ Ser はセリン残基の位置を表しており、加水分解されるエステルはこの Ser 残基の位置に配置することが必要である。また、加水分解されない側のエステル基は P_F に結合すると考えられている。

Figure 1-2. New chiral building blocks and their proposed application to the synthesis of natural products.

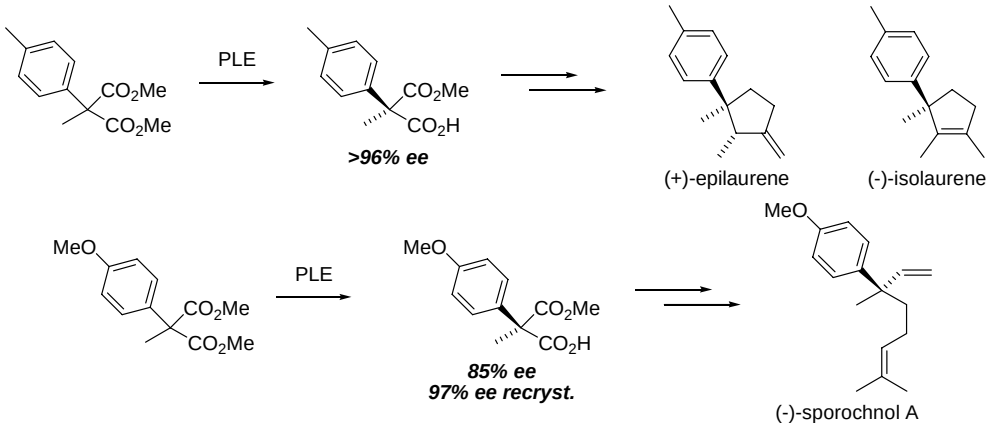


第２章　PLE を用いた不斉加水分解による不斉 4 級炭素の構築

第１節　dimethyl 2-aryl-2-methylmalonate の不斉加水分解

これまで、アリール基の置換したプロキラルなメチルマロネートに対する PLE を用いた不斉加水分解によるベンジル位不斉 4 級炭素の構築については、様々な基質において報告がなされており[2)]、その中でも Fadel らは得られたモノカルボン酸を数種天然物合成へと活用することで、その有用性を立証している(Scheme 2-1)[2b),2g)]。

Scheme 2-1. Synthesis of Natural Products via PLE-Mediated Hydrolysis

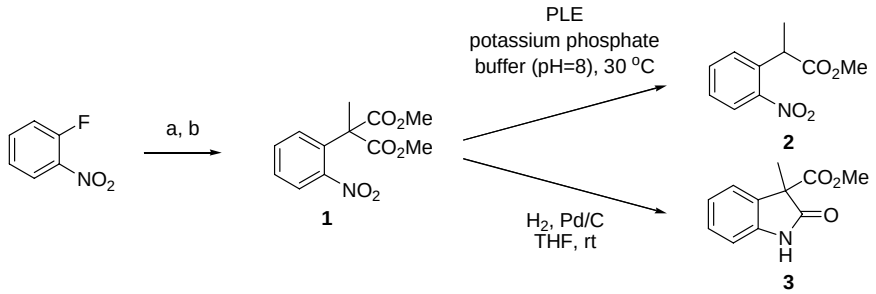


しかしながら、これまでに PLE を用いた不斉加水分解が報告されているアリール置換マロネートは、芳香環のメタあるいはパラ位に置換基を有するものがほとんどであり、オルト位に関してはメチル基を有する基質に限られていた[2f)]。そこで、各種アルカロイドの合成へと適用可能なオルト位にアミン、もしくはその等価体を有する基質、および種々の官能基導入が可能となるハロゲン原子をオルト位に有する基質を合成し、PLE を用いた不斉加水分解を行うことで、有用な新規キラルビルディングブロックを創製すべく検討を開始した。

まず、芳香環のオルト位に、容易にアミンへと変換可能であるニトロ基を有する基質を合成することとした。すなわち、市販の *o*-fluoro nitrobenzene に対し芳香族求核置換反応により dimethyl malonate を導入後[3)]、活性メチレン部位をメチル化することによりジエステル **1** を合成した(Scheme 2-2)。得られたジエステル **1** に対し PLE を作用させたところ、速やかに反応は進行するものの、所望のモノカルボン酸は全く得られず、脱炭酸が進行したエステル **2** が得られるのみであった。これはジエステルの加水分解により得られるカルボン酸のベンジル位に生じるアニオンが、芳香環上に置換する強い電子吸引性を有するニトロ基の共鳴効果により安定化されるためであると考えられる。そこで加水分解を行う前にニトロ基を還元することとし、Pd/C を用いて水素添加の条件

に付したところ、所望でないラクタム **3** が得られるのみであった。この結果は反応系中に補足剤として Ac_2O や Boc_2O を添加しても同様であった。

Scheme 2-2. Preparation of Diester **1** and Its Attempted Conversion

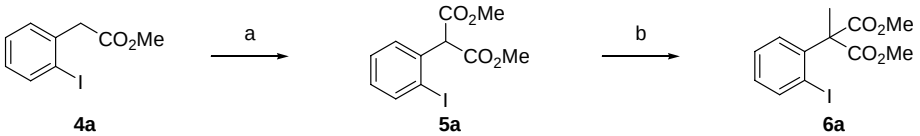


Reagents and conditions: (a) NaH, dimethyl malonate, THF, reflux, 12 h, 46%; (b) NaH, MeI, THF, rt, 2 h, 100%.

以上のように窒素原子を含む新規キラルビルディングブロックの合成は困難であることが予想されたので、続いて芳香環のオルト位にハロゲン原子を有する基質を合成することとした。本基質が合成できれば、後の段階で金属を用いたカップリング反応により窒素原子を導入することが可能であることから、直接合成することが困難であった芳香環のオルト位に窒素原子を有するキラルビルディングブロックも合成可能となり非常に有用であると言える。

オルト位にヨウ素原子が置換した基質 **6a** は、文献既知化合物 **4a** [4]に対し $(MeO)_2CO$ を反応させることでメチルエステルを導入後 [5]、活性メチレン部位をメチル化することにより合成した(Scheme 2-3)。また、同様の手法によりエチルエステル **6b** を合成した。

Scheme 2-3. Preparation of Diester **6a**

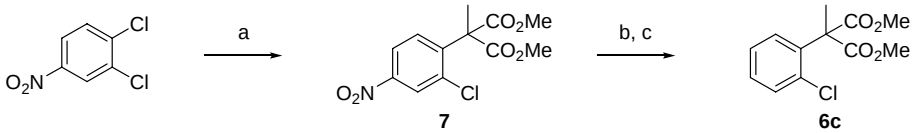


Reagents and conditions: (a) $(MeO)_2CO$, NaH, THF, 50 °C, 1.5 h, 94%; (b) MeI, NaH, THF, rt, 2 h, 80%.

オルト位に塩素原子が置換した基質 **6c** の合成は 3,4−dichloronitrobenzene に対し、芳香族求核置換反応により位置選択的に dimethyl 2−methylmalonate を導入することから開始した(Scheme 2-4) [6]。続くニトロ基の還元は Pd/C 存在下、MeOH 溶媒中で反応を行うとニトロ基の還元とともに、塩素原子が除去された化合物が得られるのみであった。しかし、溶媒として AcOEt を用いたところ、反応は化学選択的に進行し、ニト

ロ基のみが還元された所望のアニリン誘導体を得ることに成功した。最後に、アニリン誘導体を 50%H_3PO_2 水溶液中、$NaNO_2$ で処理することでジエステル **6c** へと変換した。

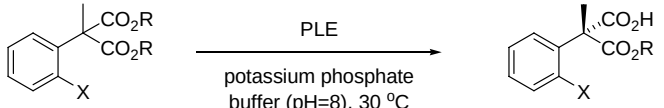
Scheme 2-4. Preparation of Diester **6c**



Reagents and conditions: (a) $CH_3CH(CO_2Me)_2$, NaH, DMF, 70 ºC, 12 h, 63%; (b) H_2, Pd/C, AcOEt, rt, 4 h, 100%; (c) $NaNO_2$, 50% H_3PO_2 aq, 0 ºC, 1 h, 93%.

各種ジエステルが得られたので、PLE を用いた不斉加水分解によるベンジル位不斉 4 級炭素の構築について検討を行った(Table 2-1)。芳香環のオルト位にヨウ素原子を有するジエステル **6a** の不斉加水分解においては、ヨウ素の原子半径が大きいことから、前述した PLE の活性部位の形状モデルにおける大きな疎水性ポケット H_L に配置されず、その結果エナンチオ選択性が発現しないことが危惧されたが、一般的に用いられる条件で反応を行ったところ、問題なく反応は進行し、中程度の収率(58%)にて光学的にほぼ純粋な形でモノカルボン酸 **8a** が得られた(entry 1)。しかし、エチルエステル **6b** を用いると、そのエナンチオ選択性は 44% ee まで低下した(entry 2)。一方、オルト位に塩素原子を有するジエステル **6c** を用いたところ、高収率(92%)、かつ光学的にほぼ純粋な形でモノカルボン酸 **8c** を得ることに成功した(entry 3)。なお、光学純度はモノカルボン酸 **8a–c** を対応するアニリド誘導体へと変換後、HPLC により決定した(実験項参照)。また、絶対配置についてはこの段階では決定していなかったが、これまでのアリール置換マロネートの不斉加水分解の報告例から、以下に示すように *R* 体であると推測した。

Table 2-1. PLE-Mediated Hydrolysis of Diester **6a–c**



6a (R=Me, X=I)
6b (R=Et, X=I)
6c (R=Me, X=Cl)

8a (R=Me, X=I)
8b (R=Et, X=I)
8c (R=Me, X=Cl)

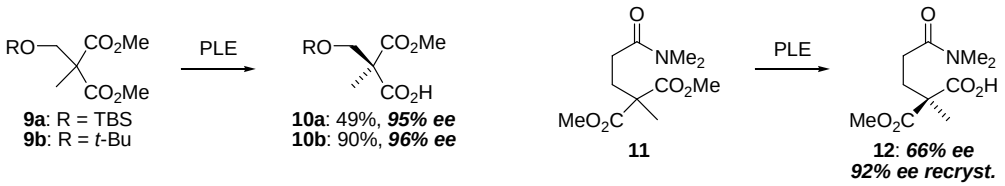
entry	substrate	time (d)	yield (%)	ee (%)
1	**6a**	2	58	99
2	**6b**	1	63	44
3	**6c**	3	92	99

以上のように、これまでに報告例のない、芳香環のオルト位に種々の官能基導入が可能となるハロゲン原子を有する新規キラルビルディングブロックを高エナンチオ選択的に合成することに成功した。本キラルビルディングブロックは区別できるカルボキシル基とエステル基を有しているため誘導体は両鏡像異性体として利用可能であるほか、スケールアップも容易であることから、ベンジル位不斉 4 級炭素を有する様々な天然物および誘導体合成、更には構造活性相関研究への活用が期待される。

第２節　dimethyl 2-alkyl-2-methylmalonate の不斉加水分解

プロキラルなジアルキルマロネートに対する PLE を用いた不斉加水分解により得られる不斉 4 級炭素を有するモノカルボン酸を天然物合成へと活用するためには、種々の官能基へと容易に、かつ多様な変換が可能であるような側鎖部位を導入しておく必要がある。しかしながら、これまでに報告されているジアルキルマロネートにおいて[7]、官能基変換可能であるのは、Keese らによって報告された 1 炭素ユニットを有するジエステル **9** [7c]および Trost らにより報告された 3 炭素ユニットを有するジエステル **11** [7g]に限られており、官能基変換が困難であった(Scheme 2-5)。

Scheme 2-5. PLE-Mediated Hydrolysis of **9** by Keese *et al.* and **11** by Trost *et al.*



9a: R = TBS
9b: R = *t*-Bu

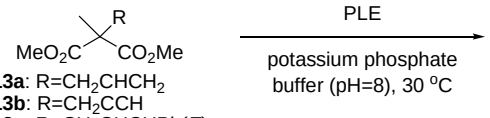
10a: 49%, ***95% ee***
10b: 90%, ***96% ee***

11

12: ***66% ee***
92% ee recryst.

そこで、本研究では、種々の官能基へと容易に、かつ多様な変換が可能である 2 炭素ユニットを側鎖部位に有するジアルキルマロネート **13a-d** の PLE を用いた不斉加水分解により、有用な新規キラルビルディングブロックを創製すべく検討を開始した。まず、一般的に用いられる条件であるリン酸カリウム緩衝液(pH=8、KPB 8)を溶媒として反応を行った(Table 2-2)。

Table 2-2. PLE-Mediated Hydrolysis of Diester **13a-d**



13a: R=CH_2CHCH_2
13b: R=CH_2CCH
13c: R=$CH_2CHCHPh$(*E*)
13d: R=CH_2CCPh

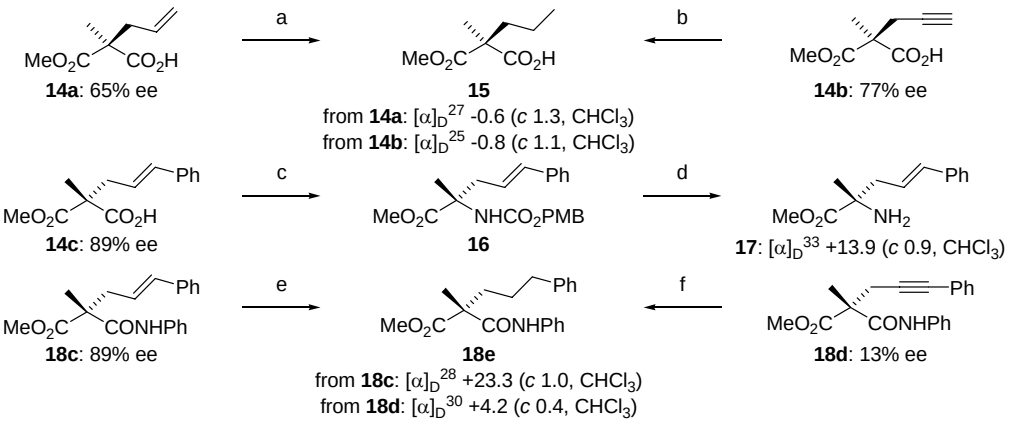
14a: R=CH_2CHCH_2
14b: R=CH_2CCH
14c: R=$CH_2CHCHPh$(*E*)
14d: R=CH_2CCPh

entry	substrate	time (h)	yield (%)	ee (%)
1	**13a**	18	100	37 (*S*)
2	**13b**	22	96	58 (*S*)
3	**13c**	9	100	89 (*R*)
4	**13c'** [a]	23	82	76 (*R*)
5	**13d**	7.5	56	13 (*R*)

[a] Ethyl ester was used.

その結果、側鎖にアリル基、プロパルギル基を有するジエステル **13a**、**13b** については、ほぼ定量的に対応するモノカルボン酸 **14a**、**14b** が得られるものの、その光学純度はそれぞれ 37% ee、58% ee と満足のいく結果は得られなかった(entry 1,2)。しかしながら、側鎖にシンナミル基を有するジエステル **13c** については、対応するモノカルボン酸 **14c** が定量的かつ良好なエナンチオ選択性(89% ee)にて得られてきた(entry 3)。また、エチルエステル **13c'**を用いた場合には、アリール置換の場合と同様、光学純度の低下(76% ee)が観測された(entry 4)。一方、アセチレン末端にフェニル基が置換した側鎖を有するジエステル **13d** については、収率、光学純度ともに低いものであった(entry 5)。なお、光学純度はモノカルボン酸 **14a–d** を対応するアニリド誘導体へと変換後、HPLC により決定した(実験項参照)。また、**14a–d** の絶対配置については文献既知化合物へと変換し、旋光度の符号を比較することによって明らかにした(Scheme 2-6)。モノカルボン酸 **14a**、**14b** は水素添加することにより **15** へと変換したところ、旋光度はマイナスの値を示したことから *S* 体であることが確認された [7b]。モノカルボン酸 **14c** については、one–pot でイソシアネートを経由してカルバメート **16** へと変換後、酸処理にてカルバメートを除去することでアミン **17** へと変換したところ、旋光度はプラスの値を示したことから *R* 体であることが確認された [8]。また、**14d** については、*R* 体であることが判明した **14c** より誘導したアニリド **18c** を水素添加することにより得られる **18e** と、モノカルボン酸 **14d** から誘導されるアニリド **18d** を水素添加することにより合成した **18e** の旋光度の符号を比較することにより *R* 体であることが確認された。

Scheme 2-6. Determination of Absolute Configuration of **14a–d**

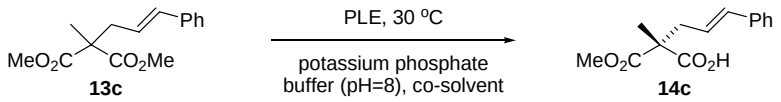


Reagents and conditions: (a) Pd/C, H_2, EtOH, rt, 12 h, 86%; (b) Pd/C, H_2, EtOH, rt, 12 h, 73%; (c) DPPA, Et_3N, $(CH_2Cl)_2$, reflux, 3 h; PMBOH, reflux, 24 h, 74%; (d) 10% TFA/CH_2Cl_2, rt, 10 min, 74%; (e) Pd/C, H_2, EtOH, rt, 12 h, 74%; (f) Pd/C, H_2, EtOH, rt, 12 h, 78%.

最も選択性良く得られた **13c** については、溶媒として KPB7、また反応温度を 0 ºC にする等、検討を行ったが、選択性の向上にはいたらなかった。さらに、本反応をマルチグラムスケールで行った際、2–3%エナンチオ選択性が低下する結果となった。この要因として、溶媒である KPB 8 の塩基性により PLE を介さずに加水分解が進行していること、また、反応進行とともに発生する MeOH により酵素の 3 次元構造が変化してしまうことなどが考えられたため、実験操作を高希釈条件下、KPB 8 と PLE の混合溶液中にジエステル **13c** をシリンジポンプを用いて滴下していく手法へと変換したところ、マルチグラムスケールにおいても光学純度は低下することなく、再現性良くモノカルボン酸 **14c** を得ることができた(実験項参照)。

PLE を用いた不斉加水分解反応によって得られる生成物の光学純度における共溶媒の影響について、これまでに多くの報告がなされている [9]。これは、水と混ざる、あるいは溶解度の大きな有機溶媒を添加すると、酵素の 3 次元構造中に取り込まれている水分子の一部が、添加された親水性溶媒と交換するために、水素結合生成の度合いや方向などがわずかに変化し、酵素の立体構造が変化するためであると推測されている。そこで、更なるエナンチオ選択性の向上を目指し、最も良い結果を与えたジエステル **13c** に対し、様々な共溶媒存在下、不斉加水分解反応を検討することとした(Table 2-3)。

Table 2-3. Co–Solvent Effect on PLE–Mediated Hydrolysis of Diester **13c**



entry	co-solvent [a]	time (h)	yield (%)	ee (%)
1	acetone	20	94	62
2	*t*–BuOH	8	95	66
3	DMF	21	90	78
4	MeCN	6	30	21
5	diglyme	9	75	83
6	DMSO	9	69	85
7	toluene	48	88	66

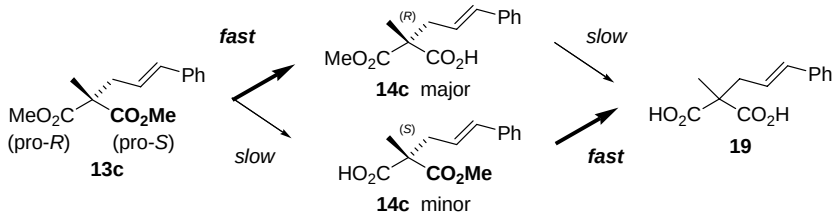
[a] 10% of co–solvent was used.

その結果、共溶媒として 10%の diglyme および DMSO を用いた不斉加水分解においてそれぞれ 83%、85% ee と、共溶媒を用いない場合と同程度のエナンチオ選択性にてモノカルボン酸 **14c** が得られるものの(entry 5,6)、ほとんどの共溶媒においてエナンチオ選択性は低下し、MeCN を用いると収率、エナンチオ選択性ともに大幅な低下が観測された(entry 1-4)。酵素反応の立体選択性に影響を与える共溶媒については、水と混ざる有機溶媒だけでなく、ほとんど水には溶けない溶媒を添加した 2 相系で反応を行った場合においても、エナンチオ選択性が変化する場合があることが報告されている。そこで、共溶媒として toluene を用いて反応を行ったが、この場合も選択性は低下する結果となった(entry 7)。

第３節　PLE を用いた速度論的光学分割

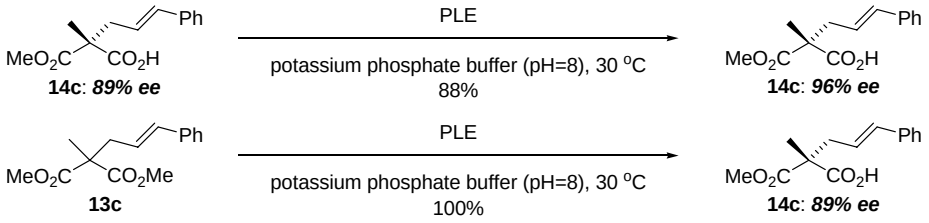
一般的に PLE を用いたプロキラルなジエステルの不斉加水分解は、対応するモノカルボン酸に変換された段階で反応は停止するため、高い収率で生成物であるモノカルボン酸が得られてくることが知られている [10]。しかし、仮に生成物であるモノカルボン酸 **14c** が再度 PLE による加水分解を受けるとすると、より加水分解を受けやすい pro-*S* 側のエステル、つまり *S* 体のモノカルボン酸のみが加水分解され、ジカルボン酸 **19** に変換されると考えられる。その結果、主生成物である *R* 体のモノカルボン酸の光学純度の向上が観測されるはずである(Scheme 2-7)。この手法は速度論的光学分割として有機合成において頻繁に用いられているが、これまで PLE を用いたこのようなモノカルボン酸の速度論的光学分割に関する報告はなされていない。そこで更なるエナンチオ選択性の向上を目指し、89% ee で合成することに成功したモノカルボン酸 **14c** に対し PLE を用いた速度論的光学分割について検討を行うこととした。

Scheme 2-7. Proposed Kinetic Resolution



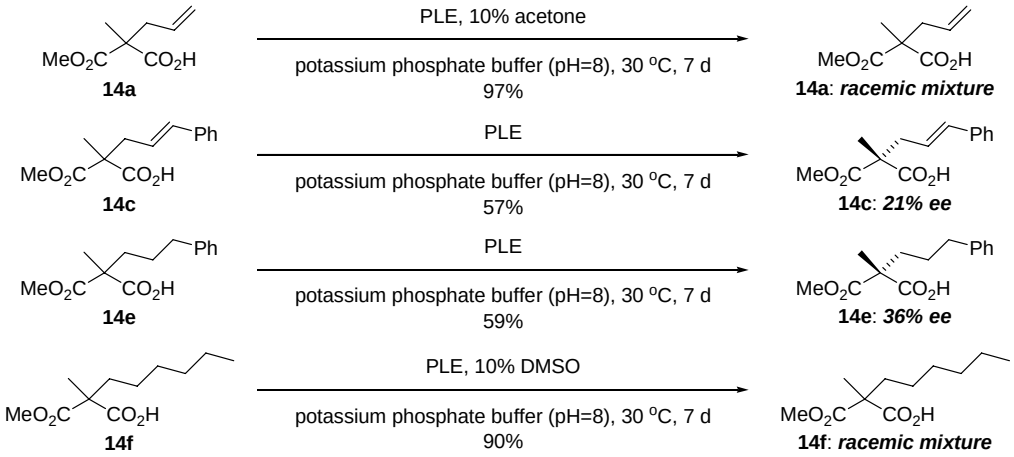
モノカルボン酸 **14c** に対し、前述と同様の条件を用いて再度 PLE で処理したところ、反応開始 2 日後、TLC 分析により **14c** が加水分解された生成物であるジカルボン酸 **19** の生成が観測され始めた。TLC 分析により反応が進行しなくなるのを確認した後、単離精製したところ、モノカルボン酸 **14c** が 88%の収率で回収された。対応するアニリド誘導体 **18c** へと変換後、HPLC により光学純度の測定を行ったところ、エナンチオ選択性は 89% ee から 96% ee まで向上していることが確認された(Scheme 2-8)。続いて、ジエステル **13c** に対しても PLE を用いて長時間反応させることで速度論的光学分割が進行し、エナンチオ選択性の向上が見られるのではないかと考え、同様の条件下、同時間をかけて反応を行ったが、驚くべきことに、ジカルボン酸の生成は確認されず、エナンチオ選択性の向上は観測されなかった。

Scheme 2-8. Treatment of **14c** and **13c** with PLE for a Week



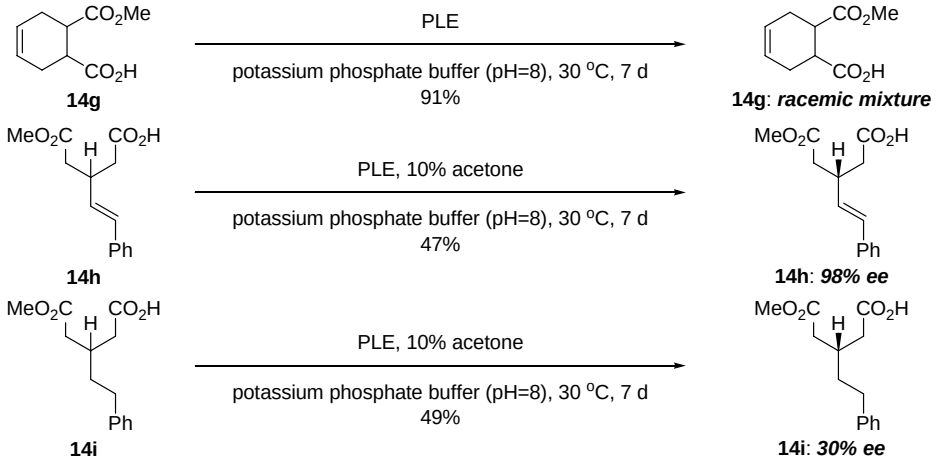
PLE を用いたこのようなモノカルボン酸の速度論的光学分割は、これまでに報告例がない。そこで、基質一般性を確かめることを目的とし、プロキラルなジエステルから誘導される様々なラセミ体のモノカルボン酸と PLE の反応を行うこととした。まず、側鎖の効果を調べるため、基質をマロネートに固定し、側鎖がアリル基である **14a**、シンナミル基である **14c** の他に、ヒドロシンナミル基である **14e**、ヘキシル基である **14f** を合成し、反応を行った(Scheme 2-9)。ここで、基質 **14f** における反応条件は、報告されている対応するプロキラルなジエステルの不斉加水分解と同様の条件を用いることとした [7b]。

Scheme 2-9. Kinetic Resolution of Racemic Malonates **14a**, **14c**, **14e**, and **14f** with PLE



その結果、側鎖が脂肪族のみからなるような基質 **14a**、**14f** の加水分解反応は進行せず、ラセミ体である原料が回収されるのみであった。一方、側鎖に芳香環を含む基質 **14c**、**14e** については加水分解反応が進行し、ジカルボン酸の生成を確認するとともに、回収したモノカルボン酸はそれぞれ21% ee、36% eeと速度論的光学分割が観測された。これらの結果により PLE を用いた速度論的光学分割には基質特異性があることが明らかとされた。そこで、マロネート以外のモノカルボン酸 **14g**、**14h**、**14i** を合成し、報告されている対応するプロキラルなジエステルの不斉加水分解反応と同様の条件を用いて反応を行うこととした(Scheme 2-10) [11),12)]。

Scheme 2-10. Kinetic Resolution of Racemic Substrates **14g**, **14h**, and **14i** with PLE



その結果、環状のモノカルボン酸 **14g** においては、加水分解は進行せず、ラセミ体が回収されるのみであった。一方、前述同様、側鎖部位に芳香環を含む基質 **14h**、**14i** については加水分解反応が進行し、ジカルボン酸の生成を確認するとともに、回収したモノカルボン酸はそれぞれ 98% ee、30% ee であったことから、速度論的光学分割が観測された。以上の結果から、PLE を用いた速度論的光学分割には側鎖部位の構造が重要な役割を果たしていることが示唆されるため、現在、芳香環以外の嵩高く、疎水性基である *t*-Bu 基や *c*-Hex 基等を側鎖に有する様々な基質に対する速度論的光学分割について検討を行っているところである。

以上のように、これまでに報告例のない側鎖部位に 2 炭素等価体、すなわちシンナミル基を有するジアルキルマロネートに対して PLE を用いた不斉加水分解を行うことで、良好なエナンチオ選択性にて対応するモノカルボン酸を得ることに成功し、それを再度 PLE で処理することで前例のない、PLE による速度論的光学分割が進行し、不斉全合成に適用可能なレベルにまで光学純度の高められた新規キラルビルディングブロックを創製することに成功した。また、今回見出した PLE を用いた速度論的光学分割は、基質特異性はあるものの、これまで高エナンチオ選択的に加水分解を行うことが困難であったジエステルに対して適用することで、効率的にキラルビルディングブロックを創製できる可能性を秘めており、有機合成上有用な手法となり得ると考えられる。

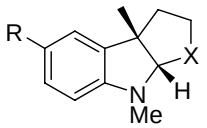
第３章　(−)-physostigmine の形式不斉全合成

第１節　研究背景

(−)-physostigmine (**1**) [13]は 1864 年に Jobst、Hesse らにより西アフリカ産豆科植物 *Physostigma veneosum* の種から主要成分として単離された 3 環式アルカロイドである(Figure 3-1) [14]。以来、下記に示した例のように、現在までに多くの類縁体が報告されている。(−)-physostigmine の絶対立体配置は 1969 年、Robinson らにより確立され、その後 X 線結晶構造解析によって確認されており [15]、その構造的特徴として特異な hexahydropyrrolo[2,3−*b*]indole 骨格上にベンジル位不斉 4 級炭素を含む 2 つの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。(−)-physostigmine は顕著なアセチルコリンエステラーゼおよびブチリルコリンエステラーゼ抑制活性を有しており、現在、緑内障や重症筋無力症の治療薬として用いられている [13),16)-18)]。また、(−)-physostigmine はアルツハイマー病治療薬の有望なリード化合物の 1 つとしても注目を集めており、国内外で活発に構造活性相関研究が行われている [13),16)-19)]。さらに興味深いことにアセチルコリンエステラーゼ抑制活性の発現は立体特異的であり、(−)-physostigmine はその(+)-enantiomer に比べ約 1000 倍もの活性を示すことが報告されていることから [20]、光学的に純粋な形で(−)-physostigmine およびその誘導体を供給することは非常に重要であると言える。このように構造と生物活性の両面から興味が持たれる(−)-physostigmine は、1935 年、Julian らによって初の全合成例が報告されて以来、これまでに多くの全合成例が報告されている [19]。

そこで、本研究では前述したベンジル位不斉 4 級炭素を有する新規キラルビルディングブロックを利用した独自の合成ルートにより(−)-physostigmine の不斉全合成を達成することで、本キラルビルディングブロックの絶対立体配置の確定、およびその有用性を立証するとともに、構造活性相関研究を展開することを目的とし研究に着手した。

Figure 3-1. Structure of (−)-physostigmine (**1**) and derivatives.

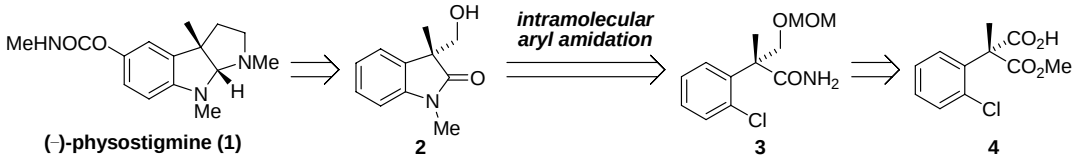


(-)-physostigmine (**1**)	: R=OCONHMe, X=NMe
(-)-phenseline	: R=OCONHPh, X=NMe
(-)-esermethole	: R=OMe, X=NMe
(-)-eserethole	: R=OEt, X=NMe
(-)-eseroline	: R=OH, X=NMe
(-)-deoxyeseroline	: R=H, X=NMe
(-)-N^8-norphysostigmine	: R=OCONHMe, X=NH
(-)-physovenine	: R=OCONHMe, X=O

第２節　逆合成解析

(−)-physostigmine の逆合成解析を以下に示す(Scheme 3-1)。(−)-physostigmine が有する hexahydropyrrolo[2,3-*b*]indole 骨格はラクタム **2** からの増炭、続く還元的アミノ化による構築が報告されているため、本研究では oxindole 骨格を有するラクタム **2** [19p),19q),19z)]を不斉合成することで(−)-physostigmine の形式不斉全合成を達成することとした。本合成において鍵となる oxindole 骨格は、第１級アミド **3** から Cu(I)を媒介とした分子内芳香族アミド化反応により合成できるものとした。一般的に、4 級炭素に隣接した官能基における反応はその立体障害のため進行し難く、加えて、Cu(I)を媒介とした芳香族アミド化反応において塩化アリールを用いた場合、反応が緩慢であることが知られている。しかしながら、本基質 **3** においては反応点が非常に近接していることから問題なく反応が進行するものと推測し、調製が容易であり、かつスケールアップにも適しているオルト位に塩素原子が置換した基質を用いることとした。第１級アミド **3** は、前述したオルト位にハロゲン原子を有するアリール基の置換したプロキラルなメチルマロネートの不斉加水分解により高エナンチオ選択的に得ることに成功した新規キラルビルディングブロック **4** から容易に合成できるものと考えた。

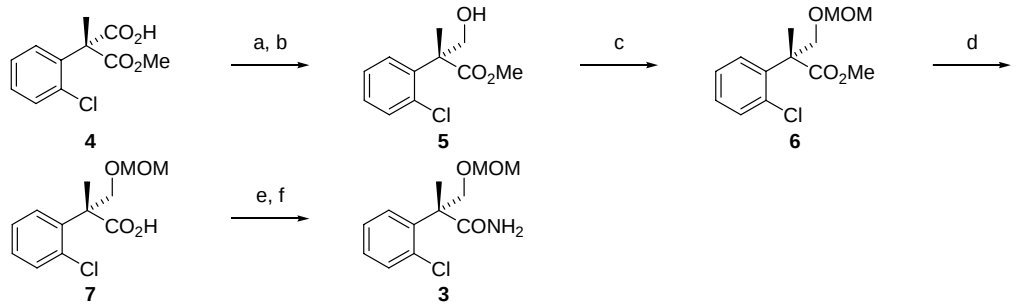
Scheme 3-1. Retrosynthetic Analysis of (−)-Physostigmine



第３節　(−)-physostigmine の形式不斉全合成

(−)-physostigmine の形式不斉全合成は、光学的にほぼ純粋なモノカルボン酸 **4** のカルボン酸部位をアルコールへと還元することから開始した(Scheme 3-2)。すなわち、モノカルボン酸 **4** のカルボン酸部位を酸塩化物へと変換後、砂合らの条件[21]に従い、溶媒として THF を用い、調製した酸塩化物と $NaBH_4$ の反応溶液中に、低温下、MeOH をシリンジポンプにより滴下することでアルコール **5** を得た。生じた水酸基を MOM エーテルとして保護した後、エステル部位を直接第 1 級アミドへと変換すべく種々検討を行ったが、エステル部位に隣接する 4 級炭素による立体障害の影響からか、いかなる条件においても反応は全く進行しなかった。エステル部位の第 1 級アミドへの直接の変換は困難であったため、段階的に変換することとし、まずエステル部位を塩基性条件下、加水分解することでカルボン酸 **7** を合成した。続いてカルボン酸部位を酸塩化物へと変換後、NH_3 と反応させることで環化前駆体である第 1 級アミド **3** を得た。

Scheme 3-2. Preparation of Primary Amide **3**

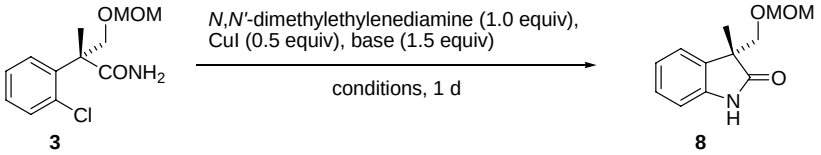


Reagents and conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, 0 ºC to rt, 2 h; (b) $NaBH_4$, MeOH, THF, −30 ºC, 3 h, 86% (2 steps); (c) MOMCl, DIPEA, NaI, CH_2Cl_2, reflux, 4 h, 91%; (d) 1M NaOH, MeOH, reflux, 12 h, 89%; (e) $(COCl)_2$, DMF, CH_2Cl_2, 0 ºC, 4 h; (f) NH_3, THF, 0 ºC, 30 min, 77% (2 steps).

アミド **3** が得られたので、Buchwald らが報告した条件[22]をもとに、鍵反応である分子内芳香族アミド化反応による oxindole 骨格の構築について検討を行った(Table 3-1)。まず、toluene 溶媒中、塩基として K_2CO_3 を用いて加熱還流下反応を行ったところ、所望のラクタム **8** が中程度の収率(66%)にて得られてきた(entry 1)。0.5 当量の CuI 存在下では原料の残存が観測されたため、量論量の CuI を用いて反応を行ったが収率の改善にはいたらなかった。また、塩基として K_3PO_4、Cs_2CO_3 を用いた際には、原料の残存とともに収率は低下する結果となった(entry 2,3)。ここで塩基を K_2CO_3 に固定し、続いて各種溶媒検討を行った。1,4-dioxane 中、加熱還流下反応を行ったところ、多量の原料の残存が確認され、収率は大幅に低下(24%)した(entry 4)。また、DMF 中、100

ºC ではこれまでと同様、原料は消失せず、収率は中程度(53%)に留まったものの、加熱還流させることにより原料は完全に消失し、良好な収率(76%)にて所望のラクタム **8** を得ることに成功した(entry 5,6)。

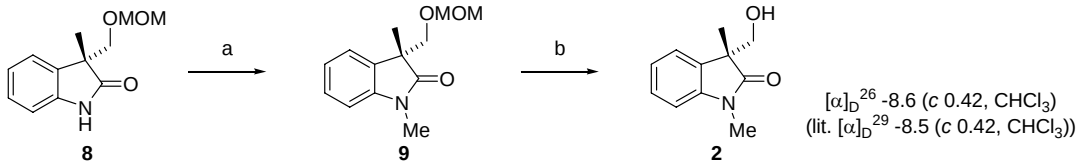
Table 3-1. Intramolecular Aryl Amidation of Primary Amide **3**



entry	solvent	base	temp	yield (%)
1	toluene	K_2CO_3	reflux	66
2	toluene	K_3PO_4	reflux	33
3	toluene	Cs_2CO_3	reflux	57
4	1,4−dioxane	K_2CO_3	reflux	24
5	DMF	K_2CO_3	100 ºC	53
6	DMF	K_2CO_3	reflux	76

得られたラクタム **8** は *N*−メチル化、続く酸性条件下 MOM 基を除去することでアルコール **2** へと変換した(Scheme 3-3)。合成したアルコール **2** は、文献既知のアルコール **2** と各種スペクトルデータ(^{1}H−NMR, ^{13}C−NMR, IR, MS and $[\alpha]_D$) [19z)]が完全な一致を示し、ここに(−)-physostigmine の形式不斉全合成を達成するとともに、新規キラルビルディングブロック **4** の絶対立体配置の確定、および有用性を立証することができた。

Scheme 3-3. Formal Total Synthesis of (−)-Physostigmine

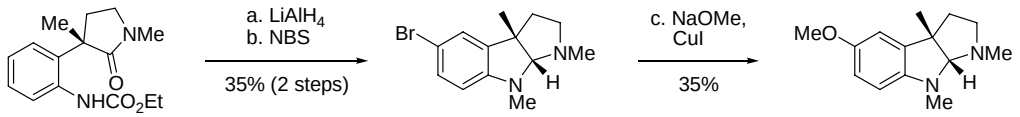


Reagents and conditions: (a) NaH, MeI, THF, 0 ºC, 2.5 h, 97%; (b) conc. HCl, MeOH, 50 ºC, 12 h, 81%.

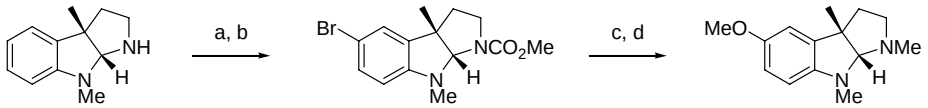
第４節　(−)-physostigmine の改良形式不斉全合成

(−)-physostigmine の形式不斉全合成を達成したものの、合成終盤における芳香環への酸素原子の導入は困難であり、低収率であったことが冨士らにより報告されている(Scheme 3-4)[19f]。また 2007 年、竹本らにより酸素原子の導入工程における収率の改善が報告されているが(Scheme 3-5)[19ae]、4 工程を要することから効率の面で問題を残している。そこであらかじめ芳香環上に酸素原子を導入しておくことができれば、より効率的に(−)-physostigmine を合成することが可能となるだけでなく、3 環式アルカロイド(−)-aphanorphine や拮抗性鎮痛剤(−)-eptazocine などのベンジル位不斉４級炭素を有する化合物、およびその誘導体合成にも利用できる汎用性の高いキラルビルディングブロックとして有機合成上意義深いと言える。そこで新規キラルビルディングブロック **11** を設計、合成し、天然物合成へ活用することとした(Scheme 3-6)。

Scheme 3-4. Introduction of an Oxygen Atom at the Benzene Ring by Fuji *et al.*

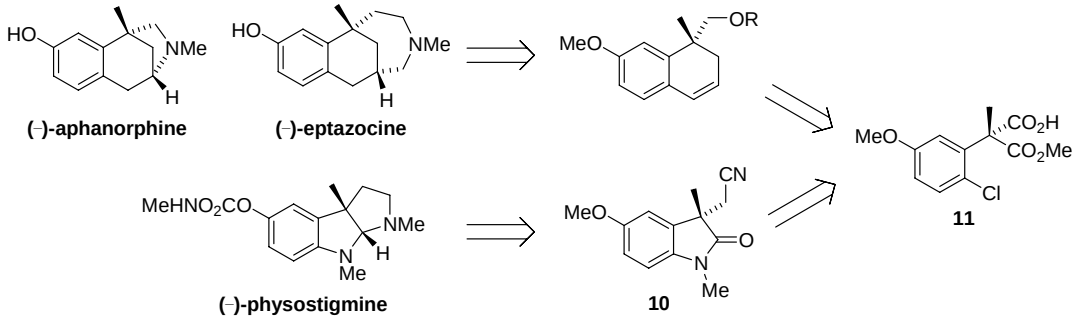


Scheme 3-5. Introduction of an Oxygen Atom at the Benzene Ring by Takemoto *et al.*



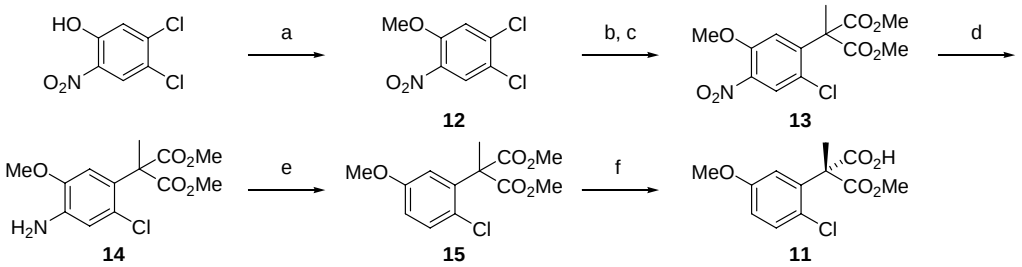
Reagents and conditions: (a) $ClCO_2Me$, Et_3N, DMAP, CH_2Cl_2, 0 ºC, 2 h, 78%; (b) NBS, DMF, 0 ºC, 2 h, 92%; (c) CuI, NaOMe, MeOH/DMF, 120 ºC, 2 h, 70%; (d) $LiAlH_4$, THF, reflux, 2 h, 96%.

Scheme 3-6. Design of New Chiral Building Block **11**



新規キラルビルディングブロック **11** の合成は、前述したキラルビルディングブロック **4** と同様の手法を用いて合成できるものと考え、文献既知化合物である 4,5-dichloro-2-nitrophenol [23]をメチル化することから開始した(Scheme 3-7)。得られた化合物 **12** に対し、dimethyl 2-methylmalonate を用いて芳香族求核置換反応を行ったが、反応は全く進行しなかった。これは芳香環上のメトキシ基の電子供与性により基質 **12** が不活性化されているためであると考えられる。そこで、段階的に合成を進めることとし、まず DMF 中 100 ºC で反応させることで位置選択的に dimethyl malonate を導入し、続く活性メチレン部位のメチル化により化合物 **13** を得た。その後、前述と同様に、ニトロ基の還元、脱アミノ化を行うことで化合物 **15** を合成した。得られた **15** に対し、モノカルボン酸 **4** の合成の際と同様の条件を用いて不斉加水分解を行ったところ、メトキシ基が導入されたジエステル **15** においても期待通り反応は進行し、高収率かつ高エナンチオ選択的にモノカルボン酸 **11** を得ることに成功した。なお、光学純度はモノカルボン酸 **11** を対応するアニリド誘導体へと変換後、HPLC により決定した(実験項参照)。

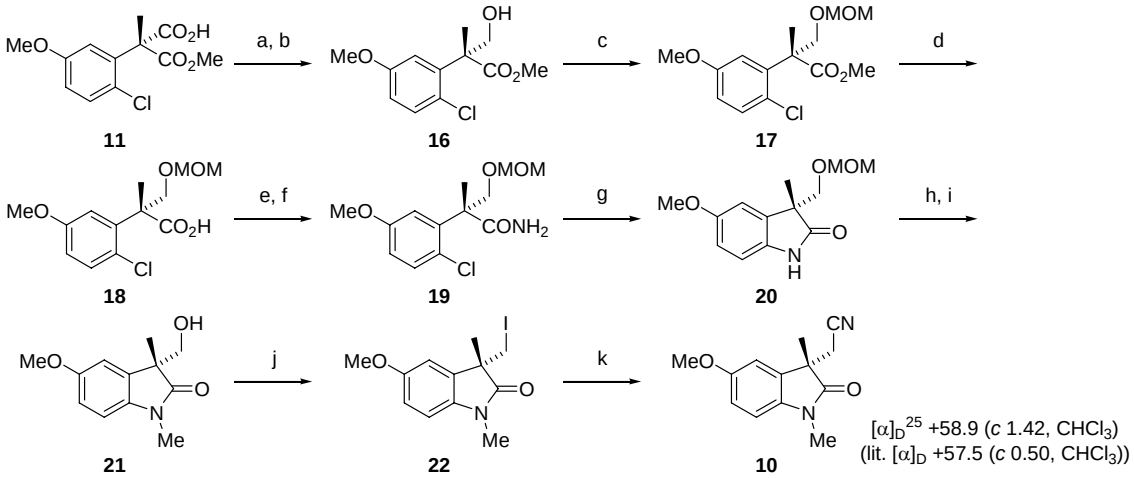
Scheme 3-7. Preparation of New Chiral Building Block **11**



Reagents and conditions: (a) K_2CO_3, MeI, acetone, rt, 12 h, 99%; (b) $CH_2(CO_2Me)_2$, NaH, DMF, 100 ºC, 8 h; (c) NaH, MeI, THF, 40 ºC, 12 h, 79% (2 steps); (d) Pd/C, H_2, AcOEt, rt, 4 h, 98%; (e) $NaNO_2$, 50% H_3PO_2 aq, 0 ºC, 2 h, 80%; (f) PLE, potassium phosphate buffer (pH=8), 30 ºC, 2 d, 86%, 99% ee.

得られた新規キラルビルディングブロック **11** の絶対立体配置は、キラルビルディングブロック **4** と同じ *R* 体であることが予想されたが、確証を得るためにも、Brossi らが報告した(-)-physostigmine の合成中間体であるニトリル **10** [19j]へと変換し、形式不斉全合成を達成することで決定することとした(Scheme 3-8)。すなわち第 3 節で述べたアルコール **2** の合成と同様の手法を用いてモノカルボン酸 **11** から 9 工程にてアルコール **21** へと変換後、生じた水酸基をヨウ素化、最後に DMSO 中、NaCN で処理することでニトリル **10** を合成した。合成したニトリル **10** は、文献既知のニトリル **10** と各種スペクトルデータ(^{1}H-NMR, ^{13}C-NMR, IR, MS and $[\alpha]_D$)が完全な一致を示し、新規キラルビルディングブロック **11** の絶対立体配置の確定、および(-)-physostigmine へのより効率的なルートの確立に成功した。

Scheme 3-8. Formal Total Synthesis of (−)-Physostigmine via the New Chiral Building Block



Reagents and conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt, 4 h; (b) $NaBH_4$, MeOH, THF, −30 °C, 3 h, 93% (2 steps); (c) MOMCl, DIPEA, NaI, CH_2Cl_2, reflux, 4 h, 93%; (d) 1M NaOH, MeOH, reflux, 12 h, 97%; (e) $(COCl)_2$, DMF, CH_2Cl_2, 0 °C to rt, 4 h; (f) NH_3, THF, 0 °C, 30 min; (g) K_2CO_3, CuI, *N*,*N*′-dimethylethylenediamine, DMF, reflux, 12 h, 96% (3 steps); (h) NaH, MeI, THF, 0 °C, 3 h; (i) conc. HCl, MeOH, 50 °C,12 h, 73% (2 steps); (j) PPh_3, imidazole, I_2, toluene, reflux, 12 h, 66%; (k) NaCN, DMSO, 80 °C, 12 h, 86%.

第 4 章　抗腫瘍細胞性セスタテルペノイド(+)-ophiobolin A の不斉全合成研究

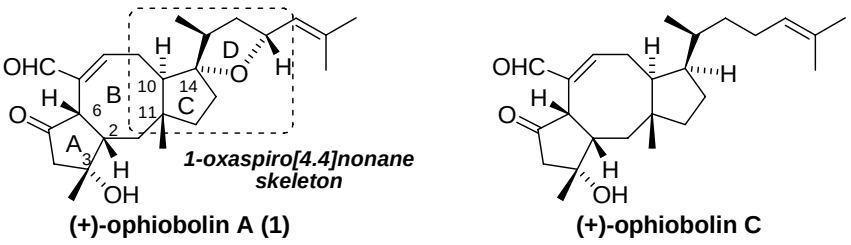
第 1 節　研究背景

(+)-ophiobolin A (**1**)は 1958 年、植物病原菌 *Ophiobolus miyabeanus* の培養液から単離[24a]された天然で初めて見出されたセスタテルペノイドであり、1965 年、その誘導体における X 線結晶構造解析により絶対配置の決定が行われた(Figure 4-1)[24b]。以来、現在までに多くの同族体・類縁体が報告されている[25]。

(+)-ophiobolin A の構造的特徴として C14 位オキサスピロ環を含む 5–8–5 員環が縮環した特異な 4 環式骨格、3 つの不斉 4 置換炭素を含む 8 つの不斉炭素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、白癬菌、トリコモナスなどに対する抗菌性、イネに対して毒性を示すほか、近年、L1210 白血病細胞に対するアポトーシス活性[25n]、様々なガン細胞に対する強い細胞毒性(A–549, HT–29, and Mel–20 with IC_{50} = 25 nM; P–335 with IC_{50} = 62.5 nM)[25m]を示すことが報告されている。また、C6–*epi* 同族体に強い細胞毒性を示すものが多いことが明らかとされているため[25h),25p)]、作用機序の解明、構造活性相関研究に興味が持たれているのみならず、医薬品のリード化合物としても注目を集めている。更に、(+)-ophiobolin A 類縁体の合成研究に関しては多くの報告がなされているものの[26]、ophiobolin 類に関して全合成は、岸らによる(+)-ophiobolin C の 1 例に限られており[27]、その他の研究グループによる類縁体の合成研究を含めても 1–oxaspiro[4.4]nonane 骨格を含む ophiobolin 類および類縁体の全合成は未だ報告例がない。

このように、特異な構造および有用な生物活性の両面から興味が持たれる(+)-ophiobolin A を標的化合物として設定し、第 2 章で述べた側鎖にシンナミル基を有する新規キラルビルディングブロックを C11 位不斉 4 級炭素源として活用した収束的かつ効率的な世界初の不斉全合成とそれに基づく構造活性相関研究を目的とし、合成研究を行った。

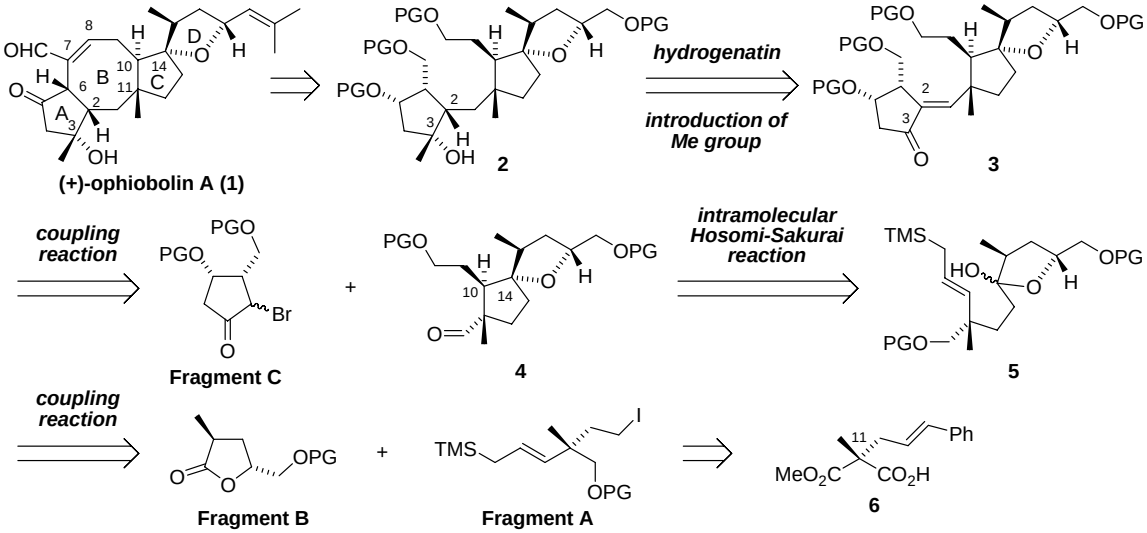
Figure 4-1. Structure of (+)-ophiobolin A (**1**) and (+)-ophiobolin C.



第２節　逆合成解析

(+)-ophiobolin A (**1**)の全合成を達成する上で解決すべき課題として以下の点が挙げられる。すなわち、①4 つの連続した不斉中心、2 つの不斉 4 置換炭素を含む計 5 つの不斉中心を有する CD 環部位の効率的かつ立体選択的構築、②AB 環縮環部位に存在する C2 位不斉中心の導入、③エントロピー的な要因や渡環相互作用のため一般的に構築困難とされる 8 員環の構築、の 3 点である。以上の点を考慮し、次のような逆合成解析を行った(Scheme 4-1)。

Scheme 4-1. Retrosynthetic Analysis of (+)-Ophiobolin A



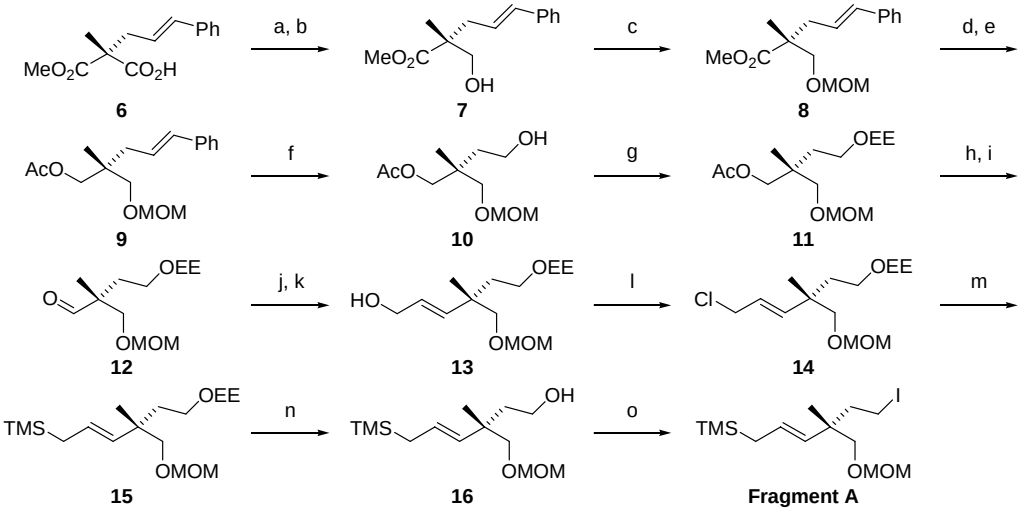
すなわち、鍵となる 8 員環構築は C7–C8 位間で行うこととし、第 5 節で述べるような様々な八員環構築法を検討できるよう、種々の官能基へと変換可能な側鎖を有する **2** を鍵中間体として設定した。鍵中間体 **2** の C2 位および C3 位不斉中心は、基質の立体的な環境を利用したジアステレオ選択的水素添加、続く Me 基の導入により構築できるものとし、エノン体 **3** は A 環フラグメントである **Fragment C** と CD 環フラグメント **4** とのカップリング反応により合成できるものと考えた。本合成における課題となる CD 環フラグメント **4** の合成については、その骨格および C10、C14 位の 2 つの不斉中心を一挙に構築することを考え、アリルトリメチルシランおよびヘミケタールを同一分子内に有する **5** からの分子内 Hosomi–Sakurai 反応 [28]により合成できるものとした。また、環化前駆体 **5** は **Fragment A** と **Fragment B** とのカップリング反応により合成できるものとし、**Fragment A** については、前述した側鎖にシンナミル基を有する新規キラルビルディングブロック **6** を C11 位不斉 4 級炭素源として活用することで合成できるものと考えた。

第３節　1-oxaspiro[4.4]nonane 骨格の構築

Fragment A の合成：

第 2 章 第 2 節で述べた通り、官能基変換可能な 2 炭素等価体、すなわち側鎖にシンナミル基を有するモノカルボン酸を高エナンチオ選択的に合成することに成功したので、本キラルビルディングブロックを(+)-ophiobolin A の C11 位不斉 4 級炭素源として **Fragment A** の合成を開始した(Scheme 4-2)。

Scheme 4-2. Synthesis of **Fragment A**



Reagents and conditions: (a) $(COCl)_2$, DMF, CH_2Cl_2, 0 ºC to rt, 2 h; (b) $NaBH_4$, MeOH, THF, −30 ºC to rt, 3 h, 86% (2 steps); (c) MOMCl, DIPEA, NaI, CH_2Cl_2, reflux, 7 h, 99%; (d) $LiAlH_4$, Et_2O, rt, 5 min; (e) Ac_2O, Py, DMAP, CH_2Cl_2, rt, 2 h, 100% (2 steps); (f) O_3, MeOH, −78 ºC, 2 h; $NaBH_4$, −78 ºC to 0 ºC, 1 h, 94%; (g) ethyl vinyl ether, PPTS, CH_2Cl_2, rt, 30 min, 96%; (h) K_2CO_3, MeOH, rt, 3 h, 100%; (i) SO_3·Py, DMSO, Et_3N, 0 ºC, 30 min, 98%; (j) *t*-BuOK, $(EtO)_2P(O)CH_2CO_2Et$, THF, −78 ºC to rt, 2 h, 100%; (k) DIBAL-H, CH_2Cl_2, −78 ºC, 30 min, 99%; (l) MsCl, 2,6-lutidine, LiCl, DMF, 0 ºC, 2 h, 98%; (m) $Me_3SiSiMe_3$, MeLi, Et_2O/HMPA (4:1), −60 ºC, 30 min, 88%; (n) PPTS, EtOH, rt, 1.5 d, 100%; (o) PPh_3, imidazole, I_2, benzene, rt, 3 h, 94%.

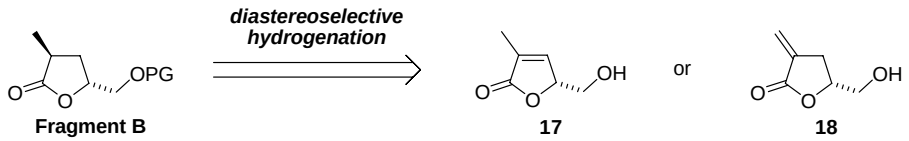
当初、モノカルボン酸 **6** におけるカルボン酸部位のアルコールへの還元は、酸塩化物へと変換後、diglyme 溶媒中 $NaBH_4$ を用いて行っていたが、本手法を用いた場合、実験操作が煩雑なだけでなく再現性も得られなかった。そこで、硤合らの条件 [21]に従い、溶媒として THF を用い、酸塩化物と $NaBH_4$ の反応溶液中に、低温下、MeOH をシリンジポンプにより滴下することで再現性良く高収率にてアルコール **7** へと変換することに成功

した。生じた水酸基を MOM エーテルとして保護、エステル部位を $LiAlH_4$ により還元、生じた水酸基を Ac 基で保護した後、オゾンにより二重結合を酸化的に開裂し、one–pot で $NaBH_4$ にて処理することでアルコール **10** を合成した。アルコール **10** の水酸基を EE エーテルとして保護した後、Ac 基の除去、生じた水酸基を Parrikh–Doering 酸化の条件に付すことによりアルデヒド **12** を得た。得られたアルデヒド **12** に対し、Horner–Wadsworth–Emmons 反応を行うことで α,β–不飽和エステルへと変換後、エステル部位を DIBAL 還元することでアリルアルコール **13** を合成した。生じたアリルアルコールを MsCl および LiCl で処理することによりクロロ体 **14** へと変換後 [29]、Still の手法 [30] を用い、$Me_3SiSiMe_3$ と MeLi から系中で TMSLi を調製し、クロロ体 **14** と反応させることで望みのアリルシラン **15** を高収率にて合成した。続いて EE 基を除去しアルコール **16** へと変換後、CH_2Cl_2 溶媒中、ヨウ素化を行ったところ予期せぬことに、MOM 基で保護された水酸基と、反応途中に生成するアルコキシホスホニウム塩中間体との間で S_N2 反応が進行し、テトラヒドロフラン誘導体が副生成物として得られてきた。しかし、無極性溶媒であるベンゼン溶媒中で反応を行うことで副反応は抑制され、出発原料であるモノカルボン酸 **6** から 15 工程 60%、1 工程平均 97%という高収率にて **Fragment A** を合成することに成功した。

<u>**Fragment B** の合成</u>：

Fragment B の合成は、*endo* もしくは *exo* オレフィンを有するラクトンから水酸基との配位を利用したジアステレオ選択的水素添加により行うことを計画した(Scheme 4-3)。

Scheme 4-3. Synthetic Approach via Diastereoselective Hydrogenation

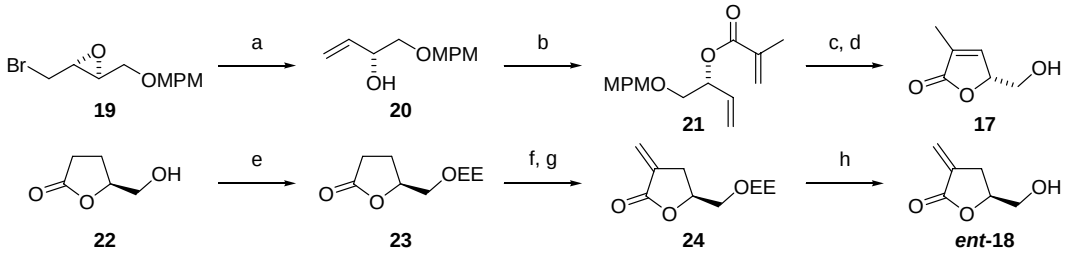


市販の 2–butyne–1,4–diol から容易に変換可能なブロモ体 **19** [31]に対し、*n*–BuLi を作用させることでハロゲン–リチウム交換、続くエポキシドの開環を行いアルコール **20** を得た(Scheme 4-4)。得られたアルコール **20** に対し、DCC を用いた methacryl 酸との脱水縮合、続く第二世代 Grubbs 触媒 [32]を用いた閉環メタセシス、最後に DDQ により MPM 基を除去することで *endo* オレフィンを有するラクトン **17** を合成した。

また、*exo* オレフィンを有するラクトン **18** の合成は以下のように行った。すなわち、グルタミン酸（不斉が逆ではあるが、予備実験として安価で入手可能な天然型を用いた。）から容易に誘導可能なラクトン **22** [33]の水酸基を EE 基で保護、続いて $PivOCH_2I$、

LDA を用いてカルボニル基の α 位にヒドロキシメチルユニットを導入後、DBU で処理することで *exo* オレフィンへと変換した。最後に PPTS により EE 基を除去することで *exo* オレフィンを有するラクトン ***ent*-18** を得た。

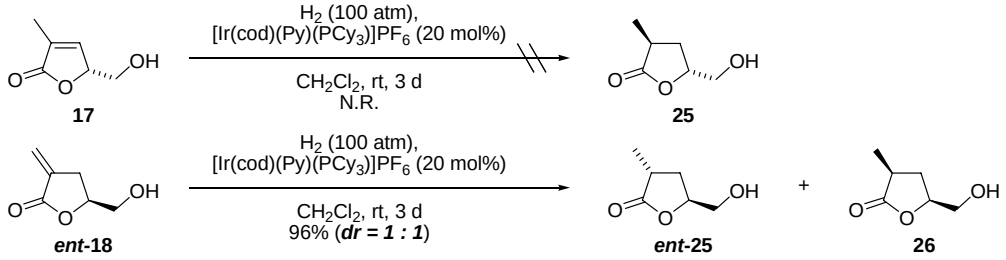
Scheme 4-4. Preparation of Lactones **17** and ***ent*-18**



Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, 30 min, 91%; (b) methacrylic acid, DCC, DMAP, CH_2Cl_2, reflux, 12 h, 87%; (c) Grubbs cat. 2nd, CH_2Cl_2, reflux, 18 h, 80%; (d) DDQ, CH_2Cl_2/*t*-BuOH/KPB 7 (8:1:1), rt, 1 h, 70%; (e) ethyl vinyl ether, PPTS, CH_2Cl_2, rt, 1 h, 82%; (f) $PivOCH_2I$, LDA, THF, −78 °C, 1 h; (g) DBU, CH_2Cl_2, rt, 24 h, 65% (2 steps); (h) PPTS, MeOH, rt, 7.5 h, 78%.

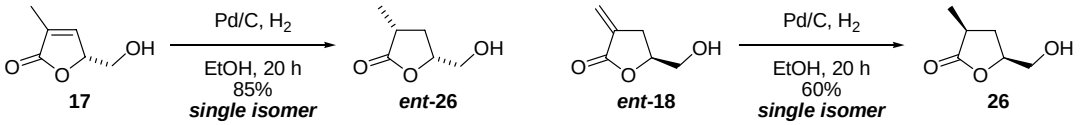
得られたラクトン **17**、***ent*-18** に対し、それぞれ Crabtree 触媒[34]([Ir(cod)(Py)(PCy_3)]PF_6 を用いて水素添加を行った(Scheme 4-5)。しかしながら、*endo* オレフィンを有するラクトン **17** においては加圧条件下においても反応は全く進行せず、*exo* オレフィンを有するラクトン ***ent*-18** については加圧条件においてのみ反応は進行するものの、1,3-*cis* 体および *trans* 体が 1:1 で得られるのみであった。

Scheme 4-5. Attempted Diastereoselective Hydrogenation of Lactones **17** and ***ent*-18**



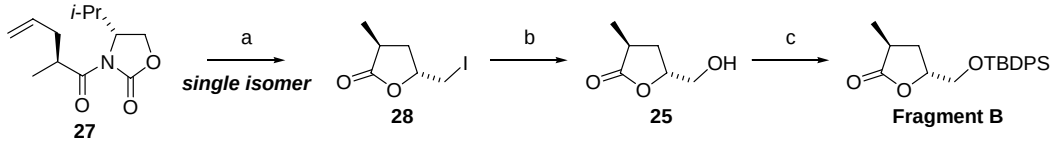
また、ラクトン **17**、***ent*-18** に対し、それぞれ Pd/C 触媒存在下、水素添加を行ったところ、反応は予想通り立体的に空いている面から選択的に進行し、単一の異性体として生成物 ***ent*-26** および **26** が得られることが分かった(Scheme 4-6)。

Scheme 4-6. Pd/C Catalyzed Hydrogenation of Lactones **17** and ***ent*-18**



以上の結果から、水酸基の配位を利用したジアステレオ選択的水素添加による **Fragment B** の合成は困難であることが分かったので、新たに以下に示す手法により合成を行った(Scheme 4-7)。D-valine 由来の oxazolidinone からジアステレオ選択的アリル化反応[35]により得られる **27** を用い、Williams の条件下[36]、系中で調製した NIS を用いたヨードラクトン化反応を行ったところ、単一の異性体としてヨードラクトン **28** を得ることに成功した。得られたヨードラクトン **28** を CF_3CO_2Na と反応させることでトリフルオロアセテートへと変換後、Et_2NH で処理することによりトリフルオロアセチル基を除去し、アルコール **25** を得た。最後に生じた水酸基を TBDPS 基で保護することで **Fragment B** の合成を完了した[37]。

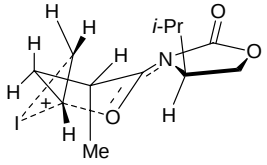
Scheme 4-7. Preparation of **Fragment B**



Reagents and conditions: (a) NCS, NaI, $NaHCO_3$, AcOEt/H_2O (2:1), rt, 1 d, 92%; (b) CF_3CO_2Na, DMF, 90 °C, 2 d; Et_2NH, rt, 12 h, 63%; (c) TBDPSCl, imidazole, CH_2Cl_2, rt, 3 h, 97%.

ヨードラクトン化におけるジアステレオ選択性の発現については、以下のように説明できる(Figure 4-2)[38]。まず、oxazolidinone のカルボニル基と側鎖のカルボニル基が双極子反発を避けるように位置した 5 員環の遷移状態をとる。このとき、Me 基とヨードメチル部分がともに擬 equatorial に位置するコンフォメーションが最も有利であると考えられるが、その場合、生じたイミニウムイオンの C(sp^2)-N 結合部分と Me 基との間で $A^{1,3}$ ひずみが生じてしまう。そこで、Me 基は擬 axial を占め、それによりヨードメチル部分は 1,3-diaxial 相互作用を避けるように擬 equatorial に位置する。このような遷移状態を経由して反応が進行するため、1,3-*trans* のヨードラクトンがジアステレオ選択的に得られてくるものと考えられる。

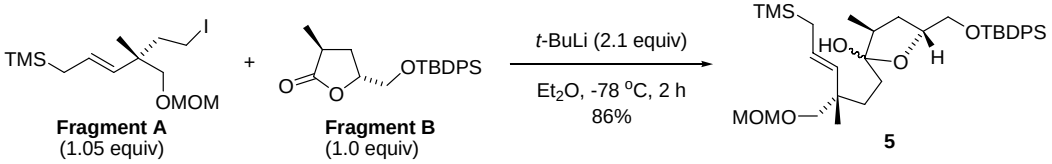
Figure 4-2. Transition state of the iodolactonization.



1-oxaspiro[4.4]nonane 骨格の構築：

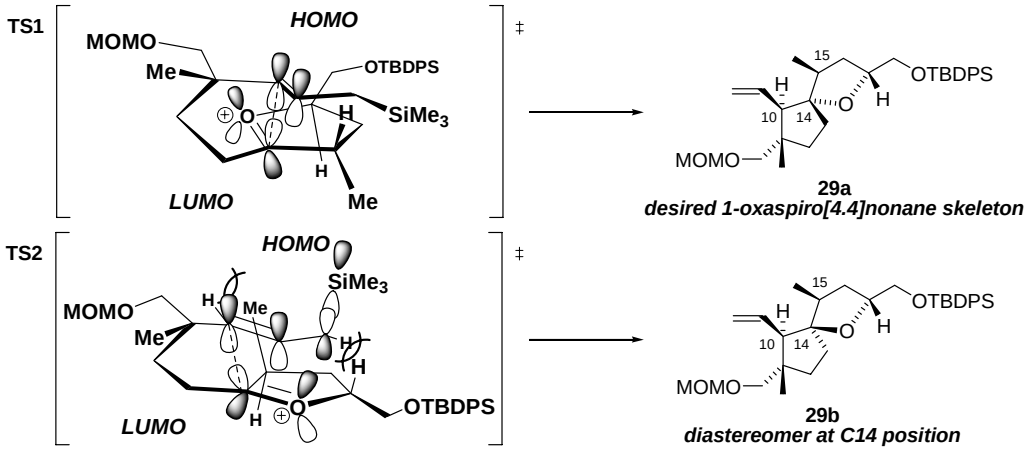
Fragment A および **Fragment B** の合成に成功したので両者のカップリング反応を行った(Scheme 4-8)。すなわち、**Fragment A** を *t*-BuLi を用いたハロゲン-リチウム交換により有機リチウム試薬へと変換後、**Fragment B** と反応させることでジアステレオマーの混合物として高収率にて環化前駆体 **5** を得た。

Scheme 4-8. Coupling Reaction of **Fragment A** with **Fragment B**



前述したように、アリルトリメチルシランおよびヘミケタールを同一分子内に有する環化前駆体 **5** の分子内 Hosomi-Sakurai 反応により 1-oxaspiro[4.4]nonane 骨格および C10、C14 位の 2 つの不斉中心を一挙に立体選択的に構築することができれば、不斉全合成を達成する上で効率的であるだけでなく、ophiobolin 類の数種が共通して有する CD 環骨格の初の合成例となるため有機合成上非常に意義深いものと考えられる。Hosomi-Sakurai 反応が進行するためにはアリルシランの HOMO の軌道と反応途中に生成するオキソニウムイオンの LUMO の軌道の重なりが必要となることを考慮し、環化前駆体 **5** のアリルシランおよびテトラヒドロフラン環のジアステレオ選択的反応による 4 つの遷移状態を考えると(Figure 4-3)、所望の環化体を与える TS1 においては立体障害の影響は全くないものの、TS4 においては顕著な立体障害が存在し、TS2、TS3 においても立体障害が存在することから、結果として所望の環化体が優先して得られてくるものと推測し、様々な Lewis 酸を用いて本環化反応の検討を開始した(Table 4-1)。

Figure 4-3. Transition state of the intramolecular Hosomi-Sakurai reaction.



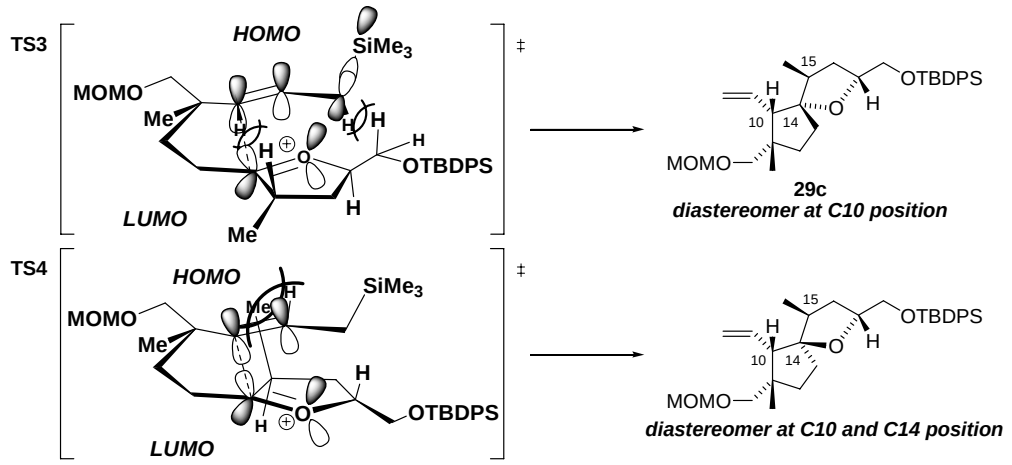
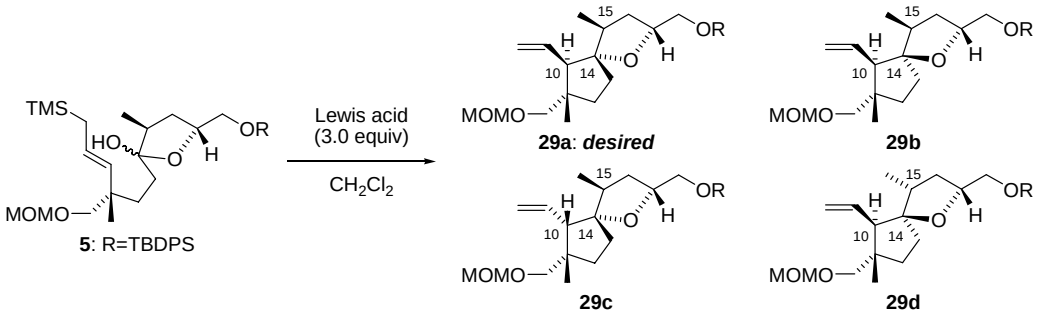


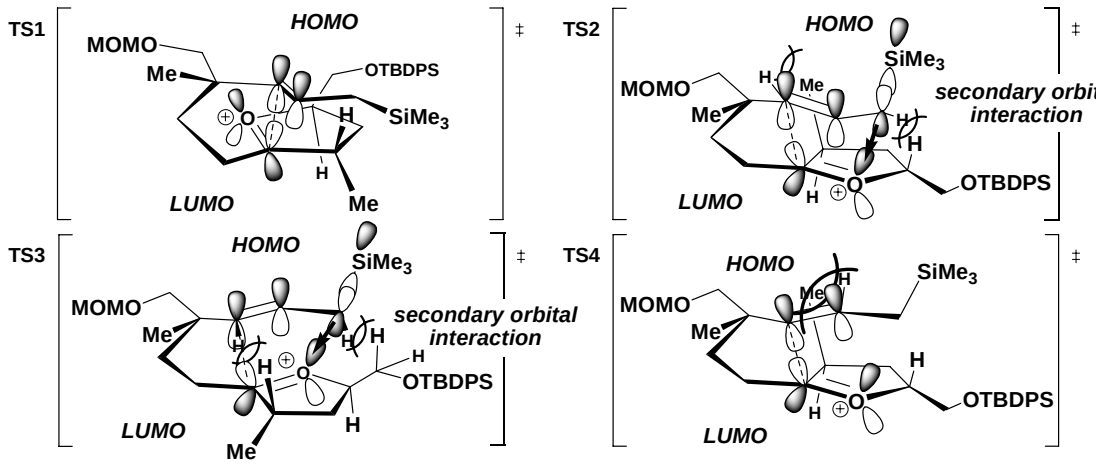
Table 4-1. Intramolecular Hosomi–Sakurai Reaction



				yield (%)			
entry	Lewis acid	temp (°C)	time (h)	**29a**	**29b**	**29c**	**29d**
1	$TiCl_4$	−78	2	decomposition			
2	$Ti(O\textit{i}\text{-}Pr)_4$	−78, −50, −20, rt	2, 5, 12, 2	N.R.			
3	$TiCl_3(O\textit{i}\text{-}Pr)$	−78	4	29	31	40	0
4	$TiCl_2(O\textit{i}\text{-}Pr)_2$	−78, −50	4, 1.5	18	0	19	57
5	$TiCl(O\textit{i}\text{-}Pr)_3$	−78, −50, −20	2, 2, 12	0	0	0	84
6	$BF_3{\cdot}OEt_2$	−78	4	45	25	27	0
7	$ZnCl_2$	−78, −50	2, 8	25	22	27	0
8	$EtAlCl_2$	−78	6	20	40	40	0
9	Et_2AlCl	−78, −50, −20	5, 8, 12	25	36	36	0
10	$SnCl_4$	−78	2	25	24	49	0

まず、Hosomi–Sakurai 反応において一般的に用いられる $TiCl_4$ を用いて反応を行ったところ、Lewis 酸性の強さから基質が分解するのみであった(entry 1)。また、$Ti(O\textit{i}\text{–}Pr)_4$ を用いた際には、逆に Lewis 酸性が弱すぎるため原料を回収するのみであった(entry 2)。そこで、順次 Lewis 酸性を弱めていくこととし、$TiCl_3(O\textit{i}\text{–}Pr)$を用いたところ、所望の環化体 **29a** は得られるものの低収率(29%)であり、更に、所望でない異性体 **29b**、**29c** がそれぞれ 31%、40%で得られてきた(entry 3)(なお、環化体の構造決定については後に詳細を説明する。)。続いて $TiCl_2(O\textit{i}\text{–}Pr)_2$ を Lewis 酸として用いたところ、収率の低下(18%)とともに、驚くべきことに C15 位が *epi* 化した **29d** が主生成物として得られ、さらに Lewis 酸性の弱い $TiCl(O\textit{i}\text{–}Pr)_3$ を用いたところ、高収率(84%)かつ単一の異性体として **29d** が得られてきた(entry 4,5)。また、$BF_3{\cdot}OEt_2$ を用いて反応を行ったところ、中程度の収率(45%)ではあるが、これまでで最も良い収率にて所望の環化体を得ることに成功した(entry 6)。更なる収率向上を目指し、様々な Lewis 酸($ZnCl_2$、$EtAlCl_2$、Et_2AlCl、$SnCl_4$)を用いて検討を行ったが、生成比に変化はあるものの収率の向上にはいたらなかった(entry 7-10)。以上の実験結果より、所望の環化体 **29a** のみならず、**29b**、**29c** も同程度副生することから本環化反応においては前述した遷移状態において、立体障害のみならず、C–Si 結合性軌道とオキソニウムイオンの反結合性軌道との二次的相互作用[39]が強く作用していることが示唆された(Figure 4-4)。

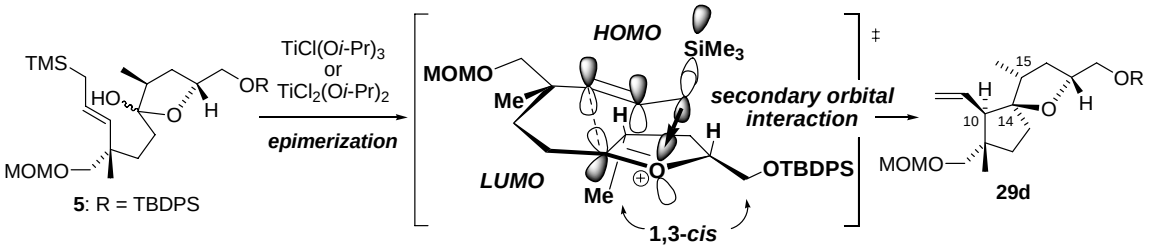
Figure 4-4. Secondary orbital interaction in the cyclization reaction.



また、C15 位が *epi* 化した環化体 **29d** が得られたメカニズムについては以下のように結論付けた。環化前駆体 **5** の段階では *epi* 化は起こっておらず、また、オキサスピロ環形成後は *epi* 化が起こり得ない。更に、Lewis 酸として $TiCl_2(O\textit{i}\text{–}Pr)_2$ および $TiCl(O\textit{i}\text{–}Pr)_3$ を用いた場合にのみ C15 位の *epi* 化が観測されることから、反応途中にオキソニウムイオンあるいはヒドロキシケトンが生成した際、チタンのカウンターアニオンであるイソプロポキシドの塩基性により C15 位での脱プロトン化が起こっているた

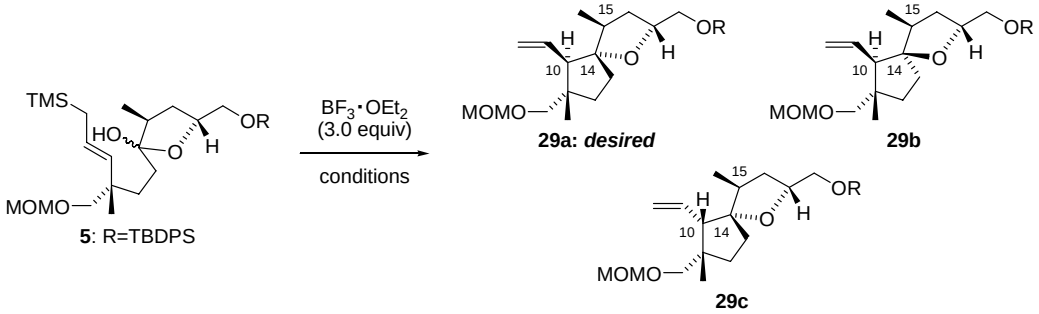
めであると考えられる。C15 位での *epi* 化が起こると **29d** を与える遷移状態はラクトン由来の 2 つの置換基が 1,3-*cis* の関係となっているため、一方の面の立体障害が小さく、また、軌道の二次的相互作用によりエネルギー的に著しく有利になることが予想され、そのために環化体 **29d** が単一の異性体として得られたものと推測した(Figure 4-5)。

Figure 4-5. Proposed transition state of the intramolecular Hosomi–Sakurai reaction proviving **29d**.



更なる選択性の向上を目指し、最も収率良く環化体を与えた $BF_3{\cdot}OEt_2$ を最適 Lewis 酸と決定し、続いて各種溶媒の検討を行った(Table 4-2)。

Table 4-2. Solvent Effect on the Intramolecular Hosomi–Sakurai Reaction

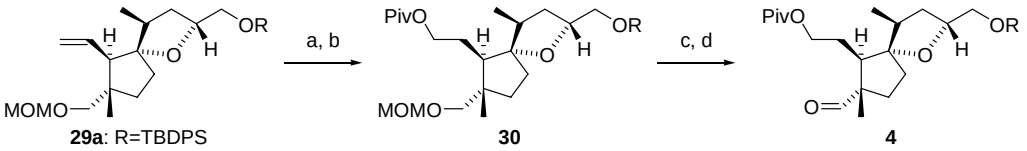


				yield (%)		
entry	solvent	temp (°C)	time (h)	**29a**	**29b**	**29c**
1	CH_2Cl_2	−78	4	45	25	27
2	MeCN	−40	12		decomposition	
3	*n*-heptane	−60	12	9	22	46
4	toluene	−60	12	63	7	20
5	Et_2O	−60	12	56	30	trace
6	Et_2O/toluene (4:1)	−60	12	56	28	4
7	Et_2O/toluene (1:4)	−60	12	51	30	10
8	Et_2O/toluene (1:1)	−60	12	68	17	trace

その結果、無極性溶媒である *n*-heptane 中で反応を行ったところ、大幅な収率の低下(9%)が観測され、極性溶媒として MeCN を用いた際には、基質が分解するのみであった(entry 2,3)。しかしながら、toluene および Et_2O を用いることで所望の環化体 **29a** の収率向上(63%, 56%)とともに、それぞれ異性体 **29b**、**29c** の副生が抑制されるという知見が得られた(entry 4,5)。異性体 **29b**、**29c** の副生が抑制された理由としては、前述した遷移状態において toluene の π 電子および Et_2O の酸素原子の lone pair とオキソニウムイオンの反結合性軌道との相互作用により軌道の二次的相互作用が緩和されたためであると現在のところ推測している。続いて、両溶媒の相乗効果を期待し、Et_2O、toluene を混合溶媒として反応に用いることとした(entry 6-8)。その結果、Et_2O/toluene (1:1)で反応を行った際、良好な収率(68%)、および選択性(4:1)にて所望の立体配置を有する環化体 **29a** を与えることを見出し、これにより全合成における問題点①を解決することに成功した。

所望の環化体 **29a** はヒドロホウ素化後、塩基性条件下 H_2O_2 で処理することで対応するアルコールへと変換し、生じた水酸基を Piv 基で保護、続く $BF_3{\cdot}OEt_2$、Me_2S を用いた MOM 基の脱保護、Dess–Martin 酸化により CD 環フラグメントとなるアルデヒド **4** へと変換した(Scheme 4-9)。

Scheme 4-9. Preparation of CD–Ring Fragment **4**



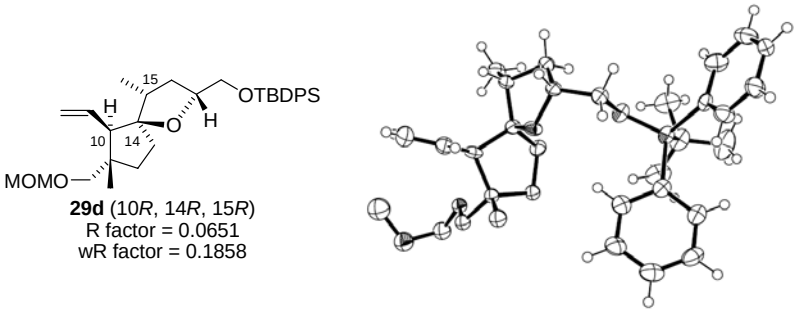
29a: R=TBDPS　　**30**　　**4**

Reagents and conditions: (a) 9–BBN, THF, rt, 3 h; 3M NaOH, 30% H_2O_2 aq, rt, 3 h, 100%; (b) PivCl, Py, DMAP, CH_2Cl_2, rt, 12 h, 100%; (c) $BF_3{\cdot}OEt_2$, Me_2S, CH_2Cl_2, −30 °C, 3 h, 92%; (d) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h, 94%.

<u>環化体 **29a–d** の構造決定</u>：

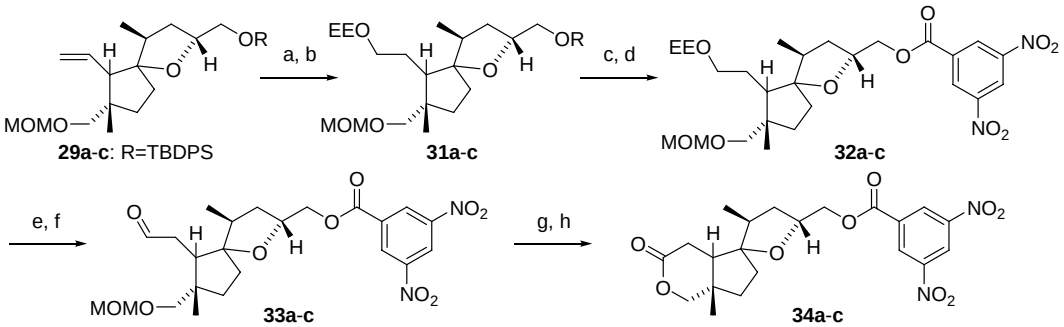
本環化反応における生成物 **29a–d** の構造決定は以下のように行った。単一の異性体として得られた **29d** は他の異性体 **29a–c** とは異なり、高い結晶性を有していたため X 線結晶構造解析を行うことにより、その立体配置を決定した(Figure 4-6)。その結果、C10 位については望みの立体配置を有していたが、C14 位は望みの立体配置とは異なり、さらに興味深いことに C15 位が *epi* 化を起こしていることが確認された。

Figure 4-6. X-ray crystallographic structure of **29d**.



他の異性体 **29a–c** は結晶化しなかったため、結晶性誘導体へと変換し、X 線結晶構造解析により構造決定を行うこととした(Scheme 4-10)。環化体 **29** をヒドロホウ素化後、塩基性条件下 H_2O_2 で処理することでアルコールへと変換し、生じた水酸基を EE エーテルとして保護することで **31** を得た。続いて、TBAF を用いた TBDPS 基の除去、生じた水酸基を 3,5-ジニトロベンゾエートとして保護することで **32** へと変換後、EE 基の除去、生じた水酸基を Dess-Martin 酸化することでアルデヒド **33** を合成した。最後に酸性条件下 MOM 基を除去することでラクトールへと変換後、Fetizon 試薬[40]を用いて酸化することで δ-ラクトン **34** を合成した。

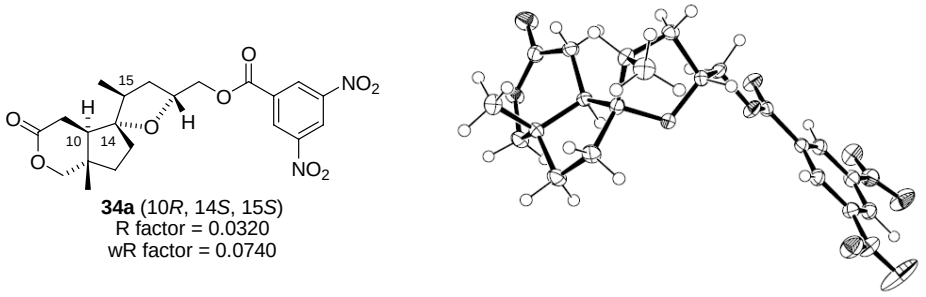
Scheme 4-10. Synthesis of δ-Lactones **34a–c**



Reagents and conditions: (a) 9-BBN, THF, **29a**: rt, 3 h, **29b**: 50 ºC, 6 h, **29c**: rt, 7.5 h; 3M NaOH, 30% H_2O_2 aq, rt, 3 h, from **29a**: 100%, **29b**: 85%, **29c**: 100%; (b) ethyl vinyl ether, PPTS, CH_2Cl_2, rt, 30 min, from **29a'**: 93%, **29b'**: 100%, **29c'**: 93%; (c) TBAF, THF, rt, 4 h, from **31a**: 100%, **31b**: 98%, **31c**: 97%; (d) 3,5-$(NO_2)_2$BzCl, Et_3N, DMAP, CH_2Cl_2, rt, 3 h, from **31a'**: 100%, **31b'**: 100%, **31c'**: 100%; (e) PPTS, EtOH, rt, 1.5 d, from **32a**: 88%, **32b**: 64%, **32c**: 74%; (f) Dess-Martin periodinane, CH_2Cl_2, rt, 2 h, from **32a'**: 99%, **32b'**: 100%, **32c'**: 95%; (g) THF/2N HCl (2:1), reflux, 8 h; (h) Fetizon reagent, benzene, reflux, 10 h, from **33a**: 66%, **33b**: 57%, **33c**: 53% (2 steps).

δ-ラクトン **34a** は結晶化したため、X 線結晶構造解析を行うことにより、その立体配置を決定した(Figure 4-7)。その結果、C10、C14 位はともに望みの立体配置を有しており、C15 位の *epi* 化も起こっていないことが確認された。よって **29a** は所望の立体配置を有する環化体であることが分かった。

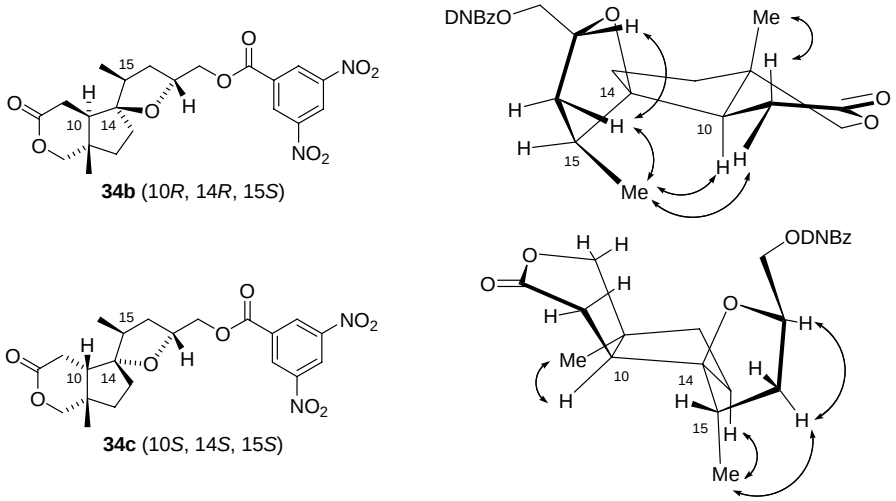
Figure 4-7. X-ray crystallographic structure of δ-lactone **34a**.



34a (10*R*, 14*S*, 15*S*)
R factor = 0.0320
wR factor = 0.0740

異性体である δ-ラクトン **34b**、**34c** は結晶化したものの、良好な単結晶が得られなかったため、NOESY 測定により立体配置を決定することとした(Figure 4-8)。その結果、**34b** においては、C15 位での *epi* 化は起こっておらず、C10 位とともに望みの立体配置を有しているが、C14 位は望みの立体配置とは異なる異性体であり、また、**34c** についても C15 位での *epi* 化は起こっておらず、C14 位とともに望みの立体配置を有しているが、C10 位は望みの立体配置とは異なり 5-6 員環が *cis* に縮環している δ-ラクトンであることが強く示唆された。

Figure 4-8. NOESY experiment on δ-lactones **34b** and **34c**.



34b (10*R*, 14*R*, 15*S*)

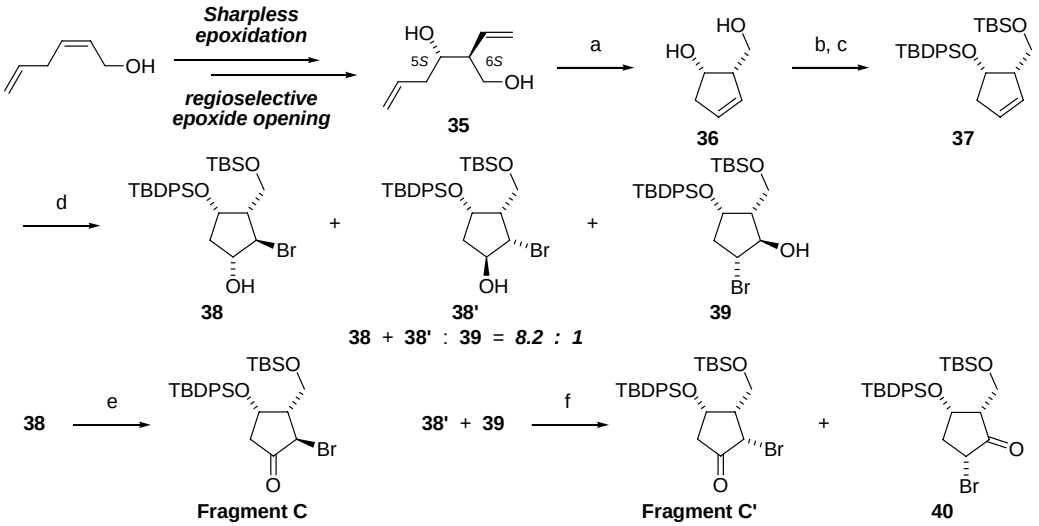
34c (10*S*, 14*S*, 15*S*)

第４節　C2 位および C3 位不斉中心の構築

Fragment C（A 環フラグメント）の合成：

Fragment C（A 環フラグメント）は以下の点を考慮し設計・合成した(Scheme 4-11)。すなわち、①**Fragment C** を位置選択的に CD 環部位とカップリングさせるため、結合を生成する側のカルボニル基 α 位に臭素原子を導入すること、②**Fragment C** を合成する際のブロモヒドリン化反応、および CD 環部位とカップリング後の水素添加をそれぞれ位置および立体選択的に行うために 5*S*、6*S* の 2 つの不斉中心を導入すること、の 2 点である。実際、シス体のアリルアルコールから Sharpless 不斉エポキシ化、続く位置選択的なエポキシドの開環により所望の不斉中心(5*S*、6*S*)を導入後[41]、第二世代 Grubbs 触媒を用いた閉環メタセシスによりシクロペンテン誘導体 **36** を得た。1 級および 2 級水酸基をそれぞれ TBS、TBDPS 基で保護した後、NBS で処理したところ、予期した通り高い位置選択性にて所望のブロモヒドリン **38** および **38'**を得ることに成功した。最後に、**38** を Dess–Martin 酸化することで **Fragment C** を、またカラムクロマトグラフィーにて分離不可能であった **38'**と位置異性体 **39** は混合物のまま Dess–Martin 酸化することで分離可能となり、**Fragment C'**を効率よく合成することに成功した。

Scheme 4-11. Synthesis of **Fragment C** and **Fragment C'**

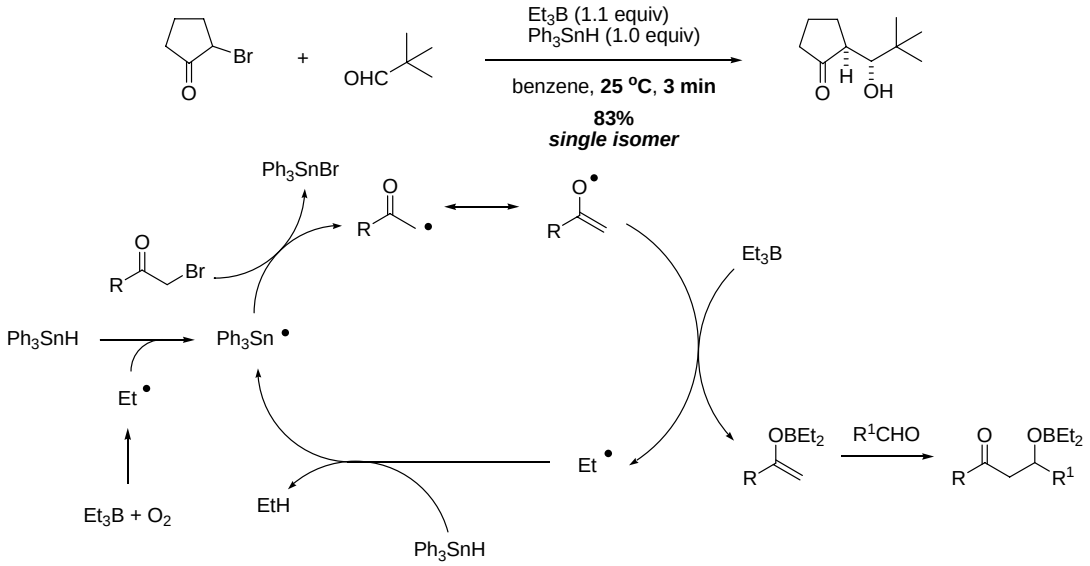


Reagents and conditions: (a) Grubbs cat. 2nd, CH_2Cl_2, rt, 12 h, 92%; (b) TBSCl, imidazole, CH_2Cl_2, 0 ºC, 4.5 h, 87%; (c) TBDPSCl, imidazole, DMAP, CH_2Cl_2/DMF (10:1), rt, 3 h, 98%; (d) NBS, acetone/H_2O (3:1), rt, 2 d, **38**: 58%, **38'+39**: 25%; (e) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h, 98%; (f) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h, **Fragment C'**: 61%, **40**: 34%.

C2 位および C3 位不斉中心の構築：

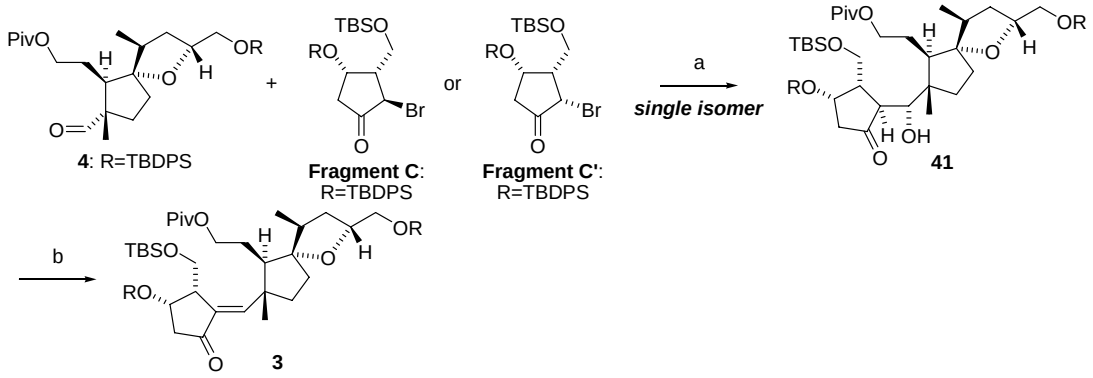
CD 環フラグメント **4** および A 環フラグメントである **Fragment C** の合成に成功したので、内本らが報告した手法 [42]に着目し、両フラグメントのカップリング反応を行うこととした。内本らは、benzene 中、Ph_3SnH および Et_3B 存在下、様々な α-ハロケトンとカルボニル化合物との間で Reformatsky タイプのカップリング反応が進行することを報告している。特筆すべきは、反応条件が温和であり、かつ非常に反応性に富んでいる点である(Scheme 4-12)。

Scheme 4-12. Et_3B-Mediated Reformatsky Type Reaction by Utimoto *et al.*



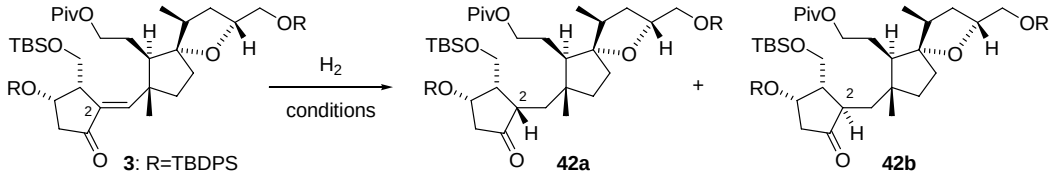
実際、本反応を CD 環フラグメント **4** および **Fragment C**、または **Fragment C'**に対し適用したところ、期待通り **Fragment C**、**C'**両ジアステレオマーとも同様に反応は進行し、高収率かつ単一の異性体としてカップリング成績体 **41** を得ることに成功した(Scheme 4-13)。続く脱水反応は、加熱条件下、**41** を MsCl、imidazole で処理したところ、retro-aldol 反応が同時に進行し、所望のエノン体 **3** は低収率(28%)で得られるのみであった。また、$SOCl_2$ を用いたところ基質が分解するのみであり、Tf_2O、Ac_2O、Martin sulfran [43]を用いた際には全く反応は進行しなかった。しかしながら、Burgess 試薬 [44]を用いることで所望のエノン体 **3** が高収率(92%)で得られることが分かった。次いで、合成における第二の問題点である C2 位不斉中心の構築を行うべく、得られたエノン体 **3** に対する水素添加の検討を行った(Table 4-3)。前述したように、エノン体 **3** に対する水素添加は適切な立体配置を備えた A 環上の 2 つの置換基による遮蔽効果により、ジアステレオ選択的に進行し、所望の立体配置を有する生成物が優先して得られてくるものと予想した。

Scheme 4-13. Preparation of Enone **3**



Reagents and conditions: (a) **Fragment C** or **C'** (2.0 equiv), Ph_3SnH, Et_3B, benzene, rt, 1 h, from **Fragment C**: 90%, **C'**: 83%; (b) Burgess reagent, benzene, rt, 12 h, 92%.

Table 4-3. Construction of the C2 Stereogenic Carbon Center

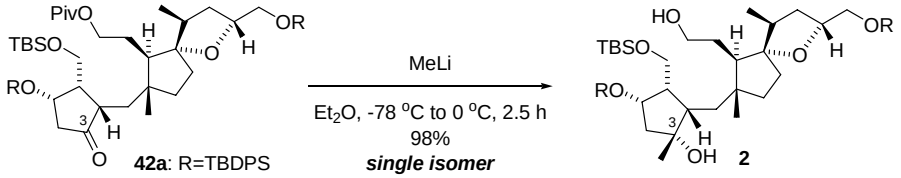


					yield (%)	
entry	catalyst	solvent	temp (^oC)	time (h)	**42a**	**42b**
1	Pd/C	EtOH	50	12	62	25
2	$Pd(OH)_2/C$	EtOH	50	12	56	32
3	PtO_2	EtOH	50	3	decomposition	
4	PtO_2	AcOEt	50	3	40	40
5	Raney Ni	EtOH	rt	5	74	14
6	Raney Ni	EtOH/THF (1:1)	rt	9	87	9
7	Raney Ni	THF	rt	12	N.R.	
8	Raney Ni	AcOEt	rt	12	N.R.	
9	Raney Ni	MeOH/THF (1:1)	rt	3	82	2

まず､水素添加において一般的に用いられる Pd/C および Pearlman 触媒($Pd(OH)_2/C$)を用いたところ、所望の生成物 **42a** が優先して得られるものの、その選択性はそれぞれ 2.5:1、1.8:1 であり満足のいく結果は得られなかった(entry 1,2)。次に Adams 触媒(PtO_2)を用いて反応を行った。その結果、EtOH 溶媒中では基質が分解するのみであり、AcOEt 中で反応を行った際には選択性の低下(1:1)が観測された(entry 3,4)。続いて EtOH 中、Raney Ni を触媒として用いたところ、立体選択性の大幅な向上(5.3:1)が観

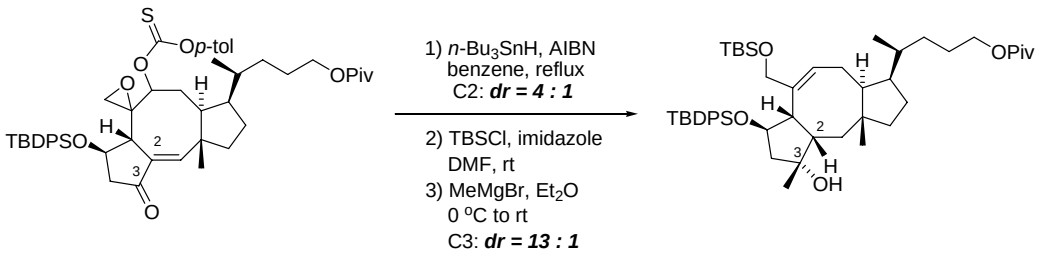
測され、さらに幸運なことに、スケールアップした際、基質の溶解性の問題から THF を添加して反応させたところ、その立体選択性は 9.8:1 まで向上した(entry 5,6)。この結果を踏まえ、非プロトン性溶媒のみで反応を行うこととし THF、AcOEt を溶媒として用いたが、いずれの場合も反応は全く進行しなかった(entry 7,8)。このことから本反応においてはプロトン性溶媒の存在は必須であることが明らかとなった。最後に、プロトン性溶媒を EtOH から MeOH へと変えることにより、更なる立体選択性の向上(35:1)が観測され、ほぼ単一の異性体として所望の立体配置を有する化合物 **42a** が得られることを見出し、これにより全合成における問題点②を解決することに成功した(entry 9)。また、本反応により得られる **42a**、**42b** に対し、それぞれを水素添加の条件に付しても C2 位の異性化は観測されないことを確認している。続くケトンに対する MeLi の付加反応も水素添加と同様に立体的に空いている面から進行し、単一の異性体として付加体 **2** を与え、ここに(+)-ophiobolin A が有するすべての不斉中心を効率的に構築することに成功した(Scheme 4-14)。

Scheme 4-14. Construction of the C3 Stereogenic Carbon Center



また、本合成における C2 位および C3 位の立体選択性は、岸らによって達成された ophiobolin 類における唯一の全合成例である(+)-ophiobolin C [27]の問題点であった C2 位(4:1)、C3 位(13:1)の立体選択性を大幅に上回るものであり、合成上非常に意義深いものであると言える(Scheme 4-15)。

Scheme 4-15. Construction of the C2, C3 Stereogenic Carbon Centers by Kishi *et al.*



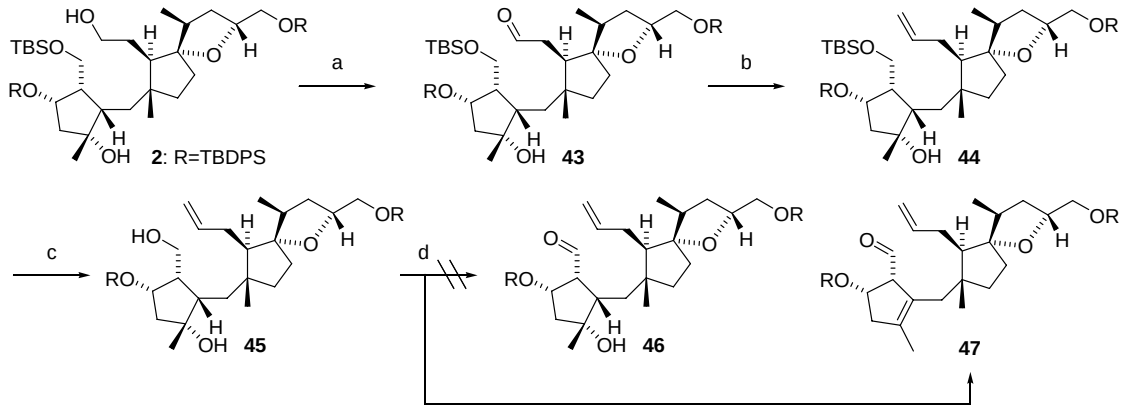
第５節　８員環構築の検討

閉環メタセシスによる８員環構築の検討：

有機金属触媒を用いる炭素−炭素結合形成反応は、現在の有機合成化学において不可欠であり多くの手法が開発されているが、その中でも容易に入手可能であり、高い官能基許容性、取扱容易性を有する Grubbs 触媒を用いた閉環メタセシス反応[32]は、一般的に構築困難とされる中員環、大員環の構築においても有効であることから、天然物の全合成戦略に革新をもたらし、実際、多くの天然物合成に活用されてきた。

本反応が(+)-ophiobolin A の B 環部位に相当する８員環構築に適用可能であれば、合成終盤において煩雑な官能基変換を行う必要がなくなることから、全合成を行う上で非常に効率的であると言える。そこで、本反応を用いた８員環構築を検討すべく、合成することに成功した鍵中間体 **2** からの官能基変換を開始した(Scheme 4-16)。

Scheme 4-16. Attempted Preparation of Aldehyde **46**

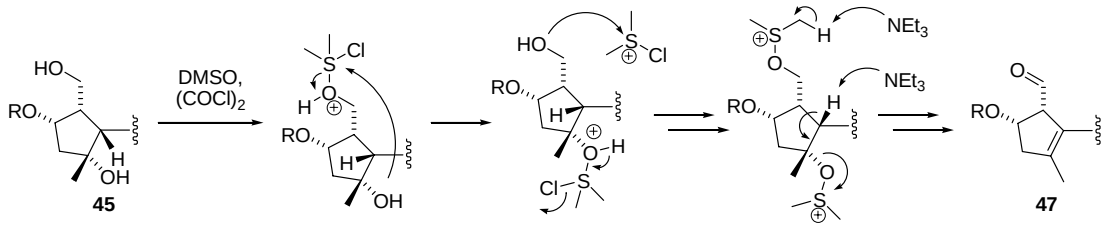


Reagents and conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 ºC, 30 min; Et_3N, rt, 30 min, 100%; (b) $Ph_3P^+MeBr^-$, *t*–BuOK, THF, 0 ºC, 30 min, 100%; (c) PPTS, EtOH, rt, 7 h, 100%; (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 ºC, 30 min; Et_3N, rt, 30 min, 98%.

鍵中間体 **2** の１級水酸基を Swern 酸化することでアルデヒド **43** へと変換後、Wittig 反応によりオレフィンを導入し、PPTS で処理することでジオール **45** を得た。ジオール **45** に対し、Swern 酸化を行ったところ、予期せぬことに所望のアルデヒド **46** は得られず、３級アルコールの脱水を伴った **47** が高収率にて得られてきた。本反応機構は以下のように推測した(Scheme 4-17)。ジオール **45** と同様に無保護の３級水酸基が存在するジオール **2** に対する Swern 酸化では３級水酸基の脱水は観測されないことから、$(COCl)_2$ と DMSO から系中で生じるクロロスルホニウム塩と１級水酸基との反応で生成する中間体に対し、立体的に近接している３級アルコールからの分子内攻撃が進行す

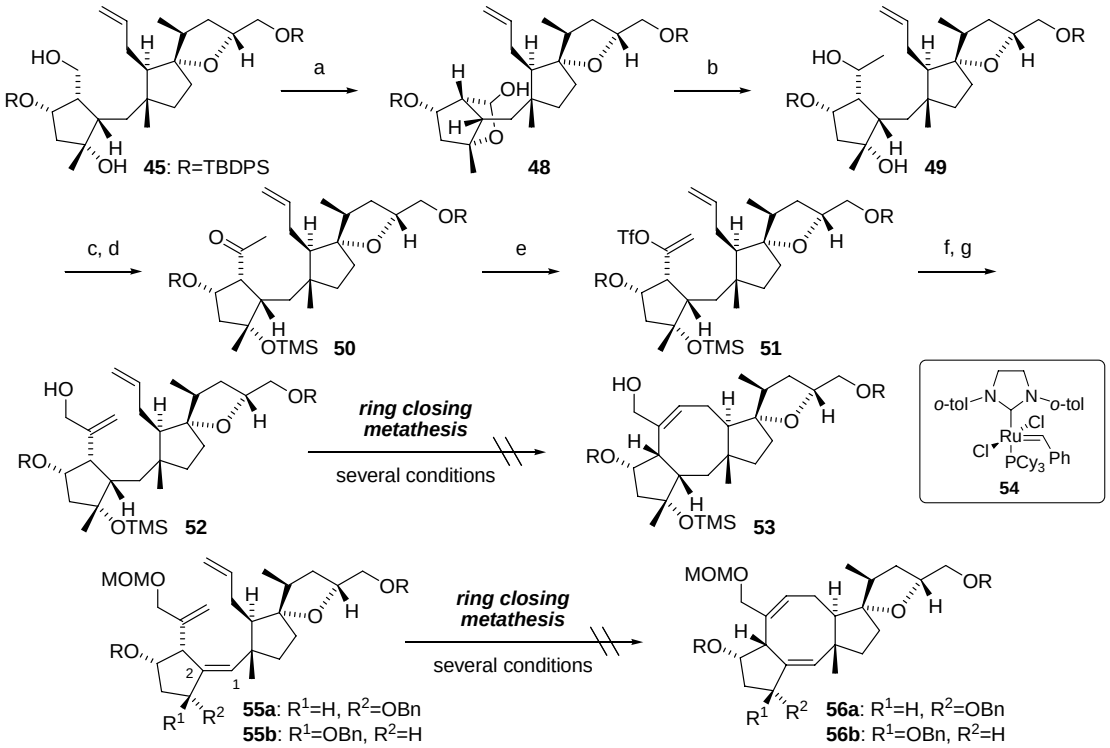
ることによりアルコキシスルホニウム塩が生じ、続く Et_3N による β-脱離が進行したものと考えられる。

Scheme 4-17. Proposed Mechanism of Dehydration of Diol **45**



この問題を解決すべく、種々酸化反応を検討したところ、IBX を用いたとき高収率にてアルデヒド **46** の等価体であるラクトール **48** を得ることに成功した(Scheme 4-18)。

Scheme 4-18. Attempted Construction of the Eight-Membered Ring via Ring Closing Metathesis



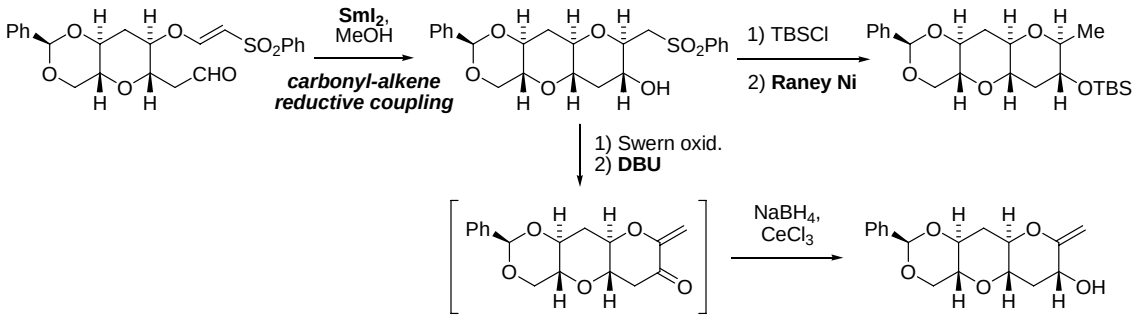
Reagents and conditions: (a) IBX, DMSO, rt, 2 h; (b) MeLi, Et_2O, 0 ºC, 3 h; (c) Dess-Martin periodinane, CH_2Cl_2, rt, 1 h, 100% (3 steps); (d) TMSCl, imidazole, DMF, rt, 12 h, 100%; (e) Comins' reagent, KHMDS, THF, −78 ºC, 1.5 h, 82%; (f) $Pd(PPh_3)_4$, Et_3N, CO (1 atm), MeOH, 50 ºC, 2 h, 88%; (g) DIBAL-H, hexane, −78 ºC, 1 h, 99%.

得られたラクトール **48** に対しメチル基の付加、生じた 2 級水酸基を Dess–Martin 酸化することでメチルケトンへと変換後、3 級水酸基を TMS エーテルとして保護することで **50** を得た。メチルケトン **50** を Comins 試薬 [45]と反応させることでエノールトリフラート **51** へと変換後、続く Pd 触媒を用いた一酸化炭素の挿入、DIBAL 還元により環化前駆体 **52** を合成した。環化前駆体 **52** に対し、第二世代 Grubbs 触媒、および第二世代 Hoveyda–Grubbs 触媒を用い、toluene および$(CH_2Cl)_2$ 中、加熱条件下反応を行ったが、所望の 8 員環環化成績体 **53** は全く得られず、原料の回収とともに側鎖のアリル部位がスチレン誘導体へと変換された生成物が得られるのみであった。また、立体的に混み合ったオレフィンに対して有効であることが報告されている **54** [32),46)]を触媒として用いた場合も同様の結果であった。さらに、渡環相互作用を緩和することを目的とし、C1–C2 位間がオレフィンである環化前駆体 **55a**、**55b** をそれぞれ合成し種々検討を行ったが、これらの基質を用いた際も同様の結果を与えるのみであった。

SmI_2およびアシルラジカルを用いた環化反応による 8 員環構築の検討：

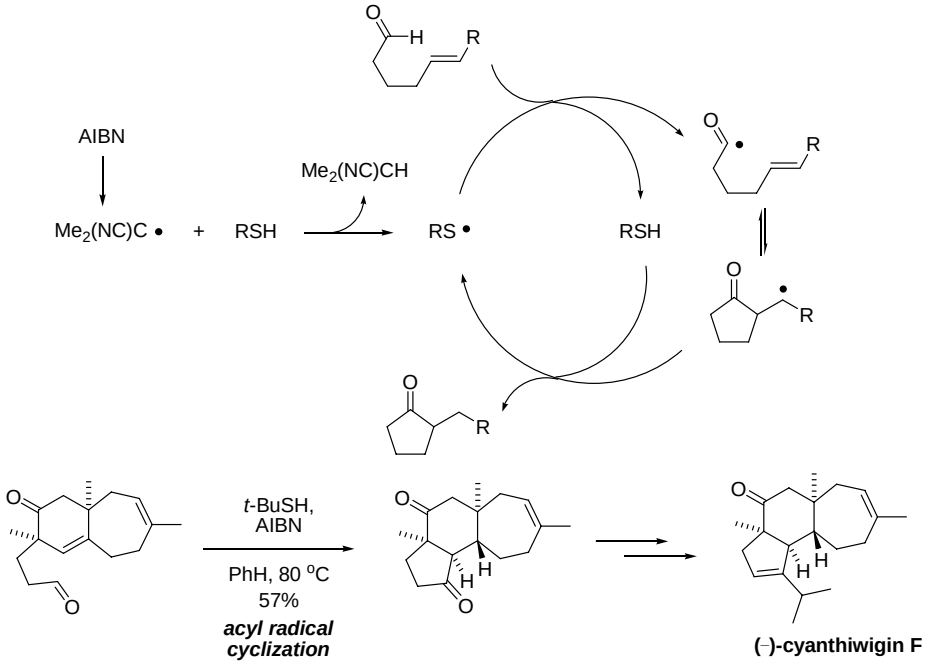
1977 年、Kagan らにより SmI_2 が有機合成の反応剤として研究され始めて以来 [47]、これまでに SmI_2 を用いた Barbier 型反応、Reformatsky および aldol タイプの反応、radical–alkyne/alkene 環化反応、carbonyl–alkene/alkyne 還元的カップリング反応、pinacol タイプのカップリング反応など多くの有用な炭素–炭素結合形成反応が開発され、天然物合成に活用されてきた [48]。carbonyl–alkene/alkyne 還元的カップリング反応は、分子間、分子内反応ともに適用可能であり、特に分子内反応においては温和な条件下、高立体選択的に、様々なサイズの環状アルコールの合成が報告されている。さらに、用いる基質は donor としてアルデヒド、ケトンともに適用可能であり、acceptor としてはアルケンおよびアルキンの活性化の有無に関わらず適用可能であることから非常に有用な反応である。その中でも中田忠らによって報告された [49]、アルケニルスルホンを acceptor とした環化反応により得られる環化成績体は(+)-ophiobolin A の全合成において必要な 1 炭素ユニットを側鎖に有する環状アルコールであることから、本反応を(+)-ophiobolin A の B 環構築に適用することとした(Scheme4-19)。

Scheme 4-19. Carbonyl–Alkene Reductive Coupling and Further Transformations



また 2004 年、富岡らにより thiol を触媒とした alkenal のアシルラジカル環化反応が開発された(Scheme 4-20)[50]。本反応は、分子内反応においては比較的高濃度条件下(1–0.1M)においても分子間反応による副生成物は得られてこないこと、また、近年有機合成化学において注目を集めているアトムエコノミーの観点から、出発物と生成物の間で原子の損失がない原子効率の良い変換反応であることから、有機合成上非常に興味深い反応であり、実際 Stoltz らによる(–)-cyanthiwigin F の全合成において A 環構築に用いられている[51]。本反応の radical–acceptor としてアルケニルスルホンを用いれば、得られる生成物は SmI_2 を用いた還元的カップリング反応における生成物と同様、(+)-ophiobolin A の全合成に必要な 1 炭素ユニットを有することから、本反応についても(+)-ophiobolin A の B 環構築に適用することとした。

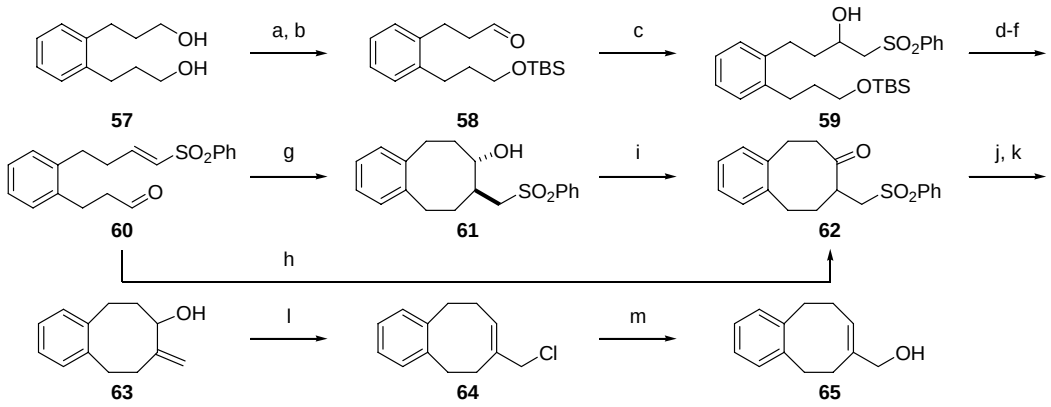
Scheme 4-20. Plausible Mechanism for the Acyl Radical Cyclization and Its Application to Total Synthesis of (–)-Cyanthiwigin F



しかしながら、両環化反応を用いた 8 員環構築については未だ報告例がないため、まず単純なモデル基質を用いて検討することとした(Scheme4-21)。市販のジオール **57** の一方の水酸基を TBS 基で保護した後、残りの水酸基を Dess–Martin 酸化、続いて $MeSO_2Ph$ のアニオンを付加させることでアルコール **59** へと変換した。生じた水酸基を脱水しアルケニルスルホンへと変換後、PPTS を用いた TBS 基の脱保護、最後に Dess–Martin 酸化を行うことで環化前駆体 **60** を合成した。環化前駆体 **60** に対し proton source として *t*–BuOH 存在下、4 当量の SmI_2 を用いて反応を行ったところ、反応は速やかに進行し、期待通り 8 員環環化成績体 **61** を良好な収率にて得ることに成功した。

環化体 **61** は Dess–Martin 酸化することでケトン **62** へと変換した。また、環化前駆体 **60** に対し、thiol を触媒とするアシルラジカル環化反応を行ったところ、触媒量では原料の残存が見られるものの、ラジカル開始剤、thiol ともに量論量以上用いて反応を行うことにより、原料は完全に消失し、中程度の収率ではあるが 8 員環環化成績体 **62** を合成することに成功した。(+)-ophiobolin A の全合成を達成するには環化により得られたケトン **62** を α,β–不飽和アルデヒドへ変換する必要がある。そこで、(+)-ophiobolin A の全合成を見据え、更なる官能基変換を行った。すなわち、環化体 **62** を DBU で処理した後、Luche 還元の条件に付すことでアリルアルコール **63** を合成した。得られたアリルアルコール **63** を $SOCl_2$、Py と反応させることでアリルクロリド **64** へと変換後、酸処理することでアリルアルコール **65** を合成することに成功した。

Scheme 4-21. Construction of the Eight–Membered Ring and Further Transformations

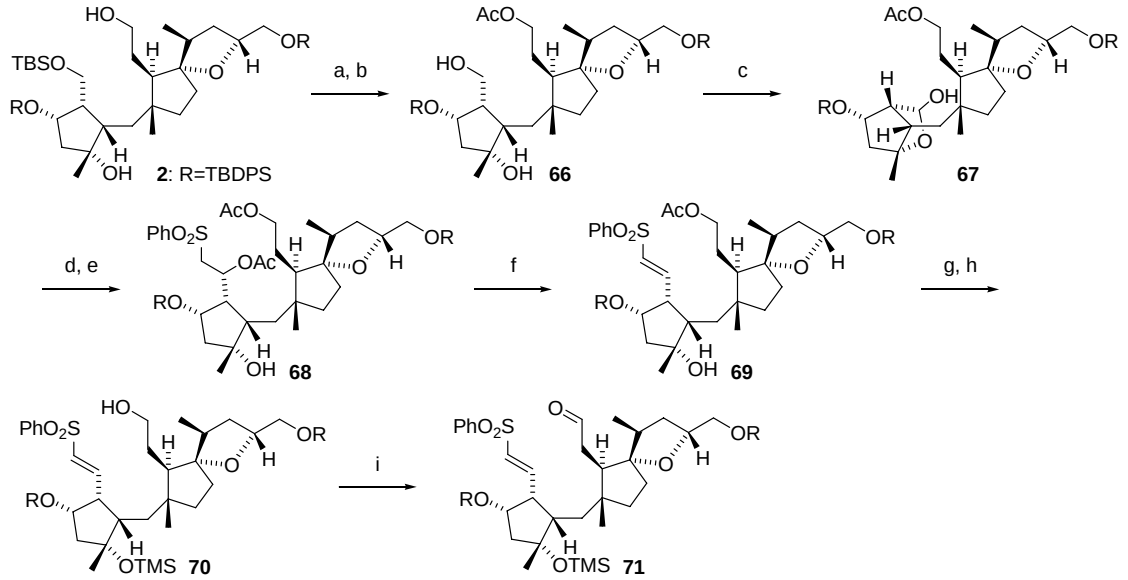


Reagents and conditions: (a) TBSCl, Et_3N, CH_2Cl_2, 0 ºC, 2 h, 64%; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h, 92%; (c) $MeSO_2Ph$, *n*–BuLi, THF, −78 ºC, 3 h, 100%; (d) MsCl, Et_3N, CH_2Cl_2, rt, 12 h, 98%; (e) PPTS, EtOH, rt, 12 h, 100%; (f) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, 100%; (g) SmI_2, *t*–BuOH, THF, 0 ºC to rt, 1.5 h, 67%; (h) *t*–$C_{12}H_{25}SH$, 1,1'–azobis(cyclohexanecarbonitrile), toluene, reflux, 3 d, 57%; (i) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, 96%; (j) DBU, benzene, 60 ºC, 18 h, 88%; (k) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, 0 ºC, 1.5 h, 100%; (l) $SOCl_2$, Py, toluene, 0 ºC to rt, 2 h, 94%; (m) 1N HCl/DMF (1:1), 60 ºC, 3 h, 97%.

モデル基質ではあるが、両環化反応が 8 員環構築においても有効な手法となり得ること、またその後の官能基変換は効率的に進行することが確認できたので、実際の系に活用することとし、基質合成を開始した(Scheme 4-22)。鍵中間体として設定した **2** の 1 級水酸基を Ac 基で保護、続く PPTS を用いた TBS 基の脱保護を行いジオール **66** へと変換後、IBX で処理することによりラクトール **67** を得た。ラクトール **67** に対し、$MeSO_2Ph$ のアニオンを付加させ、生じた水酸基を Ac 基で保護することにより **68** へと

変換後、DBU で処理することでアルケニルスルホン **69** を得た。続いて 3 級水酸基を TMS エーテルとして保護した後、DIBAL を用いた Ac 基の除去を行い **70** へと変換後、生じた水酸基を Ley 酸化の条件に付すことで環化前駆体 **71** を合成した。

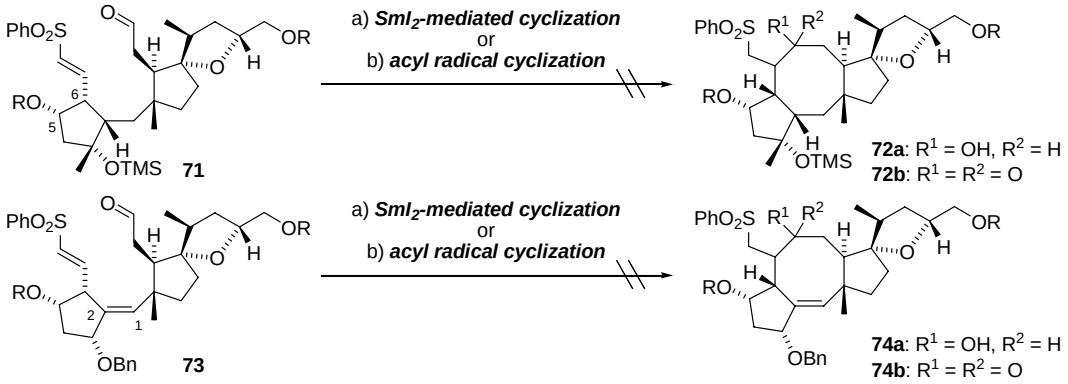
Scheme 4-22. Preparation of the Substrate for SmI_2–Mediated Cyclization and Acyl Radical Cyclization



Reagents and conditions: (a) Ac_2O, Py, DMAP, CH_2Cl_2, rt, 4 h, 99%; (b) PPTS, EtOH, rt, 12 h, 99%; (c) IBX, DMSO, rt, 2 h; (d) $MeSO_2Ph$, *n*–BuLi, THF, 0 ºC, 1.5 h; (e) Ac_2O, Py, DMAP, CH_2Cl_2, rt, 12 h, 88% (3 steps); (f) DBU, CH_2Cl_2, 0 ºC, 2 h, 77%; (g) TMSCl, imidazole, DMF, rt, 12 h, 83%; (h) DIBAL–H, CH_2Cl_2, −78 ºC, 2 h; (i) TPAP, NMO, MS4A, CH_2Cl_2, rt, 4.5 h, 93% (2 steps).

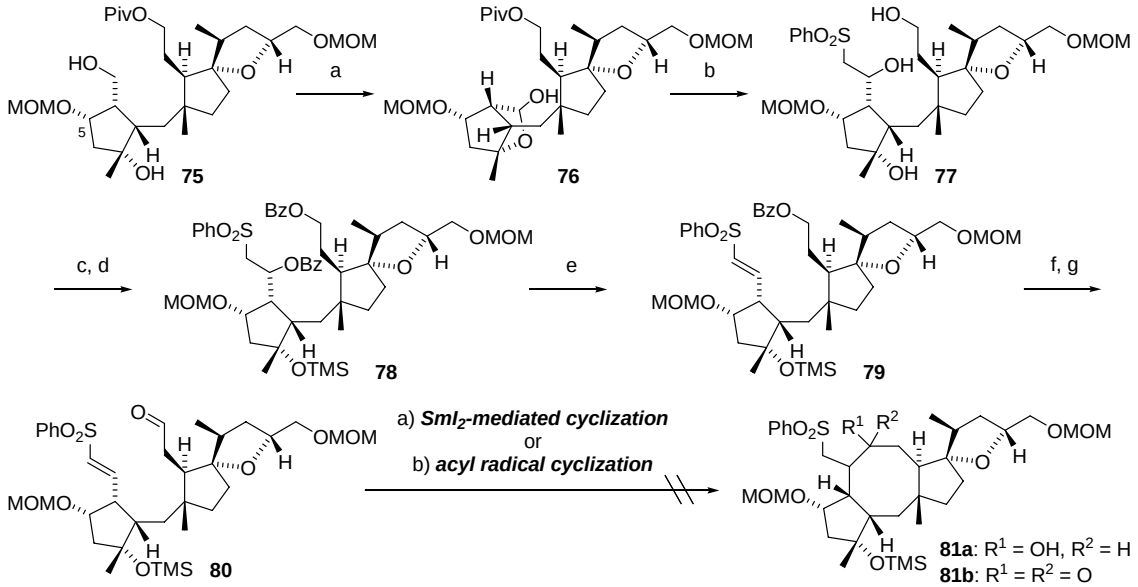
環化前駆体 **71** に対し、種々の条件（proton source の有無、添加剤として HMPA の添加、反応温度等）にて SmI_2 を用いた還元的カップリングを行ったが、所望の 8 員環環化成績体 **72a** は全く得られず、アルデヒドが還元された **70** が得られるのみであった (Scheme 4-23)。また、アシルラジカル環化の条件に付したところ、反応は全く進行せず主として原料が回収されるのみであった。さらに、渡環相互作用を緩和することを目的とし、C1–C2 位間がオレフィンである環化前駆体 **73** を合成し両環化反応を行ったが、この場合も同様の結果を与えるのみであった。

Scheme 4-23. Attempted Construction of the Eight-Membered Ring via SmI_2-Mediated Cyclization and Acyl Radical Cyclization



以上の実験結果を踏まえ、分子モデリングによる考察を行ったところ、反応点が存在する C6 位側鎖と同じ α 面に配向している C5 位 2 級水酸基の保護基である嵩高い TBDPS 基の立体障害により反応面が遮蔽されており、そのために環化反応が進行しないことが予想された。そこで、C5 位 2 級水酸基の保護基を嵩高い TBDPS 基から嵩の小さい保護基へと変換し、再度両環化反応を行うこととした(Scheme 4-24)。鍵中間体 **2** から数工程の保護基の変換により得られる C5 位が嵩の小さい MOM 基で保護されたジオール **75** に対し、前述と同様、IBX で処理、$MeSO_2Ph$ のアニオンを付加させた後、生じた水酸基を Ac 化、続いて DBU で処理したところ、反応は非常に緩慢であり、徐々に基質が分解していく結果となってしまった。そこで Ac 基ではなく、より脱離能の高い Bz 基を脱離基として用いることとし、トリオール **77** の 1 級および 2 級水酸基を Bz 化した後、残った 3 級水酸基を TMS 基で保護することで **78** へと変換後、DBU で処理したところ、期待通り速やかに反応は進行し、高収率にてアルケニルスルホン **79** を得ることに成功した。最後に脱保護、酸化の 2 工程を経て環化前駆体 **80** を合成した。得られた環化前駆体 **80** に対し、SmI_2 を用いた還元的カップリング反応を行ったところ、アルデヒドが還元された生成物とともに、C5 位が TBDPS 基で保護された基質とは異なり同定不可能な副生成物も得られてきた。この副生成物は、NMR 解析により脱スルホン化が進行していることが確認されたことから、C5 位 2 級水酸基の保護基による立体障害が反応点に大きく影響を与えていることが示唆された。また、アシルラジカル環化の条件に付した場合には、基質が分解するのみであり所望の 8 員環環化成績体 **81b** は全く得られなかった。

Scheme 4-24. Attempted Construction of the Eight-Membered Ring via SmI_2-Mediated Cyclization and Acyl Radical Cyclization



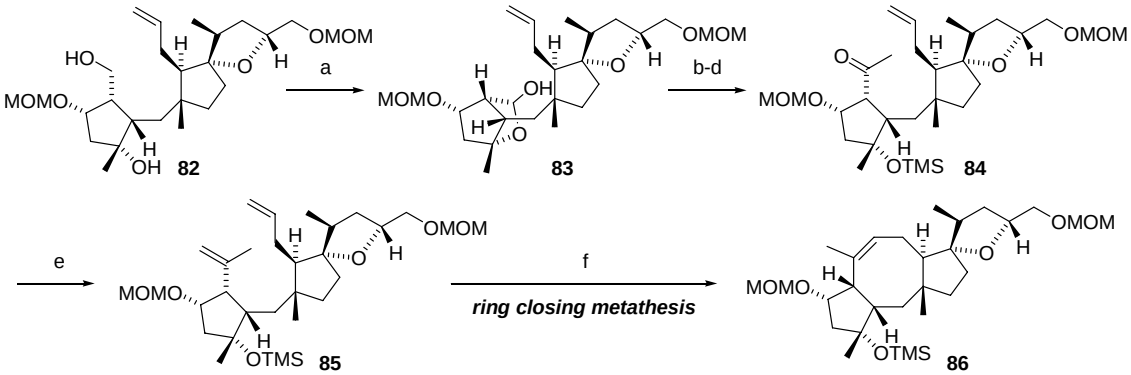
Reagents and conditions: (a) IBX, DMSO, rt, 2 h; (b) $MeSO_2Ph$, *n*-BuLi, THF, 0 ºC, 2 h; (c) BzCl, Et_3N, DMAP, CH_2Cl_2, rt, 12 h, 100% (3 steps); (d) TMSCl, imidazole, DMF, rt, 12 h, 85%; (e) DBU, CH_2Cl_2, rt, 4 h, 97%; (f) DIBAL-H, CH_2Cl_2, −78 ºC, 1 h; (g) TPAP, NMO, MS4A, CH_2Cl_2, rt, 4 h, 82% (2 steps).

閉環メタセシスによる 8 員環構築の検討：

以上のように C5 位 2 級水酸基の保護基による立体障害が反応点に大きく影響を与えていることが示唆されたため、再度閉環メタセシスによる 8 員環構築について検討を行うこととした(Scheme 4-25)。前述と同様、TBDPS 基から MOM 基へ保護基を変換することにより得られるジオール **82** に対し、IBX で処理、続くメチル基の付加、生じた 2 級水酸基を Dess-Martin 酸化、残った 3 級水酸基を TMS 基で保護することで **84** を得た。ここで、メチルケトン **84** をエノールトリフラートへと変換後、Pd 触媒を用いた一酸化炭素の挿入、DIBAL 還元によりヒドロキシメチル基の置換した 1,1-二置換オレフィンを導入する予定であったが、モデル基質における検討の際、メチルケトンから生成するエノールトリフラートが非常に不安定であり、カラムクロマトグラフィーにより分解してしまうという知見が得られていた。そこで、まず、メチル基の置換した 1,1-二置換オレフィンを合成し、本系における閉環メタセシスによる 8 員環構築の有用性を確認することとした。すなわち、メチルケトン **84** に対し高井試薬[52]を用いることでオレフィンを導入し、環化前駆体 **85** を合成した。環化前駆体 **85** に対し、閉環メタセシスによる 8 員環構築について種々検討を行ったところ toluene 中、加熱条件下、50 mol% の第二世代 Hoveyda-Grubbs 触媒を用いた際、最も収率よく所望の 8 員環環化成績体

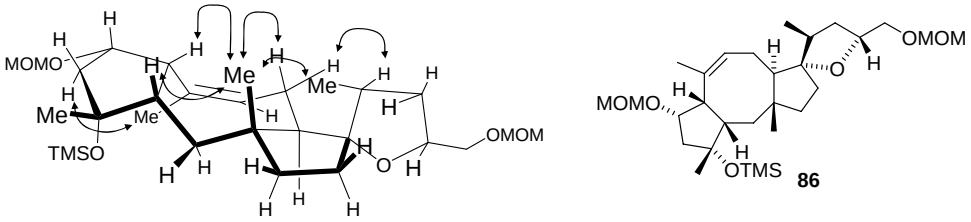
86 を与え、(+)-ophiobolin A が有する C14 位オキサスピロ環を含む 5–8–5 員環が縮環した 4 環式骨格の構築に初めて成功した。これにより全合成における問題点③を解決する糸口をつかむことができた。

Scheme 4-25. Construction of the Eight-Membered Ring via Ring Closing Metathesis



Reagents and conditions: (a) IBX, DMSO, rt, 2 h; (b) MeLi, Et_2O, rt, 6 h; (c) Dess–Martin periodinane, CH_2Cl_2, rt, 3 h, 94% (3 steps); (d) TMSCl, imidazole, DMF, rt, 12 h, 93%; (e) Zn, $PbCl_2$, CH_2I_2, $TiCl_4$, THF, rt, 4 h, 93%; (f) Hoveyda–Grubbs cat. 2nd, toluene, 100 °C, 2 d, 72%.

Figure 4-9. NOESY experiment on compound **86**.



今後、合成することに成功した 8 員環環化成績体 **86** からアリル位の酸化による水酸基の導入、また、併行してヒドロキシメチル基の置換した 1,1–二置換オレフィンの合成および閉環メタセシスによる 8 員環構築を行い、D 環側鎖の伸長および脱保護、酸化の工程を経ることで、(+)-ophiobolin A の世界初の不斉全合成を達成することが強く期待される。

第５章　総括

本論文を以下のように総括する。

第 2 章では、種々の官能基導入が可能となるハロゲン原子をオルト位に有するアリール置換メチルマロネートに対する PLE を用いた不斉加水分解により高エナンチオ選択的に不斉 4 級炭素を構築することに成功した。また、官能基変換可能な 2 炭素等価体、すなわちシンナミル基を側鎖に有するプロキラルなメチルマロネートに対する PLE を用いた不斉加水分解、続く前例のない PLE を用いた速度論的光学分割を見出し、高エナンチオ選択的に不斉 4 級炭素を構築することに成功した。

これら新規キラルビルディングブロックは不斉 4 級炭素に加え、区別できるカルボキシル基とエステル基を有しているため誘導体は両鏡像異性体として利用可能であることから様々な天然物合成への活用が期待される。

第 3 章では、第 2 章で得られたベンジル位不斉 4 級炭素を有する新規キラルビルディングブロックを出発物質とし、Buchwald らが報告した CuI を媒介とした分子内芳香族アミド化反応を骨格構築の鍵として用いることで、(−)-physostigmine の形式不斉全合成を達成し、新規キラルビルディングブロックの有用性を立証した。また、より汎用性の高い芳香環上に酸素原子を有する新規キラルビルディングブロックを合成し、(−)-physostigmine のより効率的な合成ルートを確立した。

第 4 章では、第 2 章で得られた 2 炭素等価体を側鎖に有する新規キラルビルディングブロックを(+)-ophiobolin A の C11 位不斉 4 級炭素源とし、不斉全合成研究を行った。アリルシランおよびヘミケタールを同一分子内に有する基質に対する Hosomi–Sakurai 反応は反応溶媒の選択が収率および選択性に大きく影響を与えることを見出し、Et_2O/toluene (1:1)の混合溶媒中で反応を行うことで良好な収率(68%)および選択性(4:1)にて所望の 1–oxaspiro[4.4]nonane 骨格を構築することに成功した。

また、得られた CD 環フラグメントと別途不斉合成した A 環フラグメントとのカップリングは、内本らの手法を用いることで高収率にて進行することが分かった。さらに、A 環上の適切な立体配置を備えた 2 つの置換基による遮蔽効果を利用することで、C2 位および C3 位不斉中心を高ジアステレオ選択的(C2: 35:1, C3: single isomer)に構築することに成功した。

本不斉全合成において最難関であると考えられる 8 員環構築の検討においては、C5 位 2 級水酸基の保護基である TBDPS 基の嵩高さが環化反応に大きく影響していることを見出し、保護基を嵩の小さい MOM 基へと変換した基質において閉環メタセシスを行うことで、期待通り 8 員環環化成績体を与え、(+)-ophiobolin A が有する C14 位オキサスピロ環を含む 5–8–5 員環が縮環した 4 環式骨格の構築に初めて成功した。

本研究に基づく更なる検討により、(+)-ophiobolin A の世界初の不斉全合成が達成できるものと考える。

第６章　実験項

General Information.

^{1}H and ^{13}C NMR spectra were recorded on a JEOL AL-400 and AL-300 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).

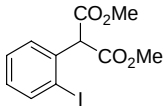
Materials.

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 1 節　PLE を用いた不斉加水分解による不斉 4 級炭素の構築

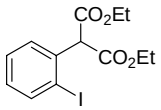
dimethyl 2−aryl−2−methylmalonate の不斉加水分解：

Dimethyl 2-(2-iodophenyl)malonate (5a)



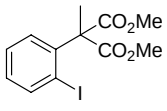
To a suspension of NaH (89.5 mg, 2.24 mmol) in THF (5 mL) was added a solution of **4a** (206 mg, 0.746 mmol) in THF (2 mL) dropwise at 0 ºC, and the reaction mixture was stirred for 30 min. Then, to the reaction mixture was added $(MeO)_2CO$ (0.188 mL, 2.24 mmol) at 0 ºC, and strring was continued at 50 ºC. After the starting material disappeared, the reaction 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 dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=20/1) to afford **5a** (235 mg, 94%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (1H, dd, *J*= 7.8, 1.2 Hz), 7.47 (1H, dd, *J*= 7.8, 1.7 Hz), 7.38 (1H, ddd, *J*= 7.8, 7.3, 1.2 Hz), 7.03 (1H, ddd, *J*= 7.8, 7.3, 1.7 Hz), 5.18 (1H, s), 3.79 (6H, s).

Diethyl 2-(2-iodophenyl)malonate (5b)



5b was prepared in 82% yield according to the procedure for **5a**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (1H, dd, *J*= 8.1, 1.2 Hz), 7.47 (1H, dd, *J*= 8.1, 1.7 Hz), 7.37 (1H, ddd, *J*= 8.1, 7.6, 1.2 Hz), 7.02 (1H, ddd, *J*= 8.1, 7.6, 1.7 Hz), 5.12 (1H, s), 4.27 (2H, dq, *J*= 10.7, 7.1 Hz), 4.23 (2H, dq, *J*= 10.7, 7.1 Hz), 1.29 (6H, t, *J*=7.1 Hz).

Dimethyl 2-(2-iodophenyl)-2-methylmalonate (6a)

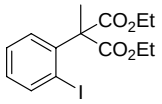


To a suspension of NaH (41.9 mg, 1.05 mmol) in THF (5 mL) was added a solution of **5a** (250 mg, 0.749 mmol) in THF (2 mL) dropwise at 0 ºC, and the reaction mixture was stirred for 30 min. Then, to the reaction mixture was added MeI (0.070 mL, 1.12 mmol)

at 0 ºC, and strring was continued at room temperature. After the starting material disappeared, the reaction 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 dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=20/1) to afford **6a** (210 mg, 80%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, dd, *J* = 7.8, 1.5 Hz), 7.33 (1H, ddd, *J* = 7.8, 7.6, 1.5 Hz), 7.07 (1H, dd, *J* = 7.8, 1.5 Hz), 6.96 (1H, ddd, *J* = 7.8, 7.6, 1.5 Hz), 3.81 (6H, s), 1.98 (3H, s).

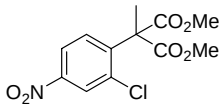
Diethyl 2-(2-iodophenyl)-2-methylmalonate (6b)



6b was prepared in 51% yield according to the procedure for **6a**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, dd, *J* = 7.8, 1.5 Hz), 7.32 (1H, ddd, *J* = 7.8, 7.6, 1.5 Hz), 7.10 (1H, dd, *J* = 7.8, 1.5 Hz), 6.95 (1H, ddd, *J* = 7.8, 7.6, 1.5 Hz), 4.33 (2H, dq, *J* = 11.0, 7.1 Hz), 4.24 (2H, dq, *J* = 11.0, 7.1 Hz), 1.97 (3H, s), 1.29 (6H, t, *J* = 7.1 Hz).

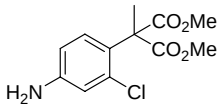
Dimethyl 2-(2-chloro-4-nitrophenyl)-2-methylmalonate (7)



To a suspension of NaH (62.5 mg, 1.56 mmol) in DMF (10 mL) was added a solution of dimethyl methylmalonate (0.347 mL, 2.60 mmol) dropwise at 0 ºC, and the reaction mixture was stirred for 30 min. Then, to the reaction mixture was added 1,2−dichloro−4−nitrobenzene (250 mg, 1.30 mmol) in DMF (3 mL) at 0 ºC, and strring was continued at 70 ºC. After the starting material disappeared, the reaction was quenched with saturated aqueous NH_4Cl solution (20 mL). The aqueous layer was extracted with Et_2O (20 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=8/1) to afford **7** (248 mg, 63%) as a pale yellow solid.

mp 83.1−85.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (1H, d, *J* = 2.4 Hz), 8.12 (1H, dd, *J* = 8.8, 2.4 Hz), 7.40 (1H, d, *J* = 8.8 Hz), 3.82 (6H, s), 1.96 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 147.3, 144.3, 135.1, 129.1, 126.0, 121.8, 59.7, 53.4, 21.8; IR (neat) ν_{max} 3089, 2955, 1751, 1529, 1346 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{12}H_{13}ClNO_6$: 302.0431, found: 302.0428.

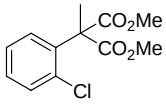
Dimethyl 2-(4-amino-2-chlorophenyl)-2-methylmalonate (7')



A mixture of **7** (1.49 g, 4.94 mmol), 10% Pd/C and AcOEt (50 mL) was stirred under H_2 atmospere (1 atm) at room temperature. After the reaction was completed, the mixture was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=2/1) to afford **7'** (1.34 g, 100%) as a white solid.

mp 85.5–86.4 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (1H, d, J = 8.5 Hz), 6.73 (1H, d, J = 2.4 Hz), 6.54 (1H, dd, J = 8.5, 2.4 Hz), 3.78 (6H, s), 1.88 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 146.8, 134.2, 128.7, 126.8, 117.1, 113.2, 59.0, 53.0, 22.3; IR (KBr) ν_{max} 3470, 3371, 2949, 1750, 1625, 1504 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{12}H_{15}ClNO_4$: 272.0690, found: 272.0680.

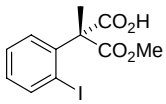
Dimethyl 2-(2-chlorophenyl)-2-methylmalonate (6c)



To a stirred solution of **7'** (1.31 g, 4.81 mmol) in aqueous 50% H_3PO_2 (40 mL) was added $NaNO_2$ (830 mg, 12.0 mmol) at 0 ºC. After the reaction was completed, K_2CO_3 was added to the reaction mixture. The aqueous layer was extracted with Et_2O (40 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **6c** (1.15 g, 93%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (1H, dd, J = 5.9, 3.4 Hz), 7.28–7.23 (2H, m), 7.13 (1H, dd, J = 5.9, 3.4 Hz), 3.80 (6H, s), 1.93 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 137.4, 133.6, 131.0, 128.8, 128.1, 126.9, 59.8, 53.0, 21.8; IR (KBr) ν_{max} 3008, 2956, 1748 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{12}H_{14}ClO_4$: 257.0581, found: 257.0575.

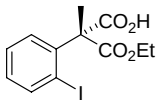
(*R*)-2-(Methoxycarbonyl)-2-(2-iodophenyl)propanoic acid (8a)



To a suspension of diester **6a** (737 mg, 2.11 mmol) in pH 8 phosphate buffer (50 mL) was added PLE (500 units), and the reaction mixture was stirred at 30 ºC. After **6a**

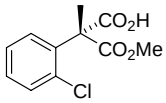
disappeared, to the reaction mixture was added 2*N* HCl to make pH of the solution to pH 3. The aqueous layer was extracted with EtOAc (30 mL × 2), dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **8a** (410 mg, 58%, 99% ee) as a colorless liquid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, dd, *J* = 7.8, 1.2 Hz), 7.51–7.41 (2H, m), 7.07 (1H, ddd, *J* = 7.8, 6.1, 2.9 Hz), 3.80 (3H, s), 2.04 (3H, s). (For the determination of ee, see the experiment for **8a'**.).

(*R*)-2-(Ethoxycarbonyl)-2-(2-iodophenyl)propanoic acid (8b)



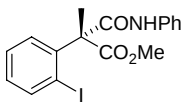
8b was prepared in 63% yield, 44% ee according to the procedure for **8a**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (1H, dd, *J* = 7.8, 1.0 Hz), 7.48–7.42 (2H, m), 7.06 (1H, ddd, *J* = 7.8, 5.9, 3.2 Hz), 4.29 (1H, dq, *J* = 10.7, 7.1 Hz), 4.26 (1H, dq, *J* = 10.7, 7.1 Hz), 2.03 (3H, s), 1.20 (3H, t, *J* = 7.1 Hz). (For the determination of ee, see the experiment for **8b'**.).

(*R*)-2-(Methoxycarbonyl)-2-(2-chlorophenyl)propanoic acid (8c)



8c was prepared in 92% yield, 99% ee according to the procedure for **8a**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, dd, *J* = 7.6, 1.7 Hz), 7.40 (1H, dd, *J* = 7.6, 1.7 Hz), 7.35 (1H, ddd, *J* = 7.6, 7.6, 1.7 Hz), 7.33 (1H, ddd, *J* = 7.6, 7.6, 1.7 Hz), 3.78 (3H, s), 2.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 172.0, 136.3, 133.8, 130.1, 129.5, 128.2, 127.1, 56.6, 54.2, 23.3; IR (KBr) ν_{max} 2960, 1742 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{11}H_{12}ClO_4$: 243.0424, found: 243.0424; $[\alpha]_D^{28}$ +14.6 (*c* 0.56, $CHCl_3$).

(*R*)-Methyl 2-(phenylcarbamoyl)-2-(2-iodophenyl)propanoate (8a')

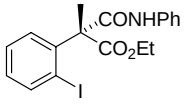


To a stirred solution of **8a** (7.5 mg, 0.0224 mmol) in CH_2Cl_2 (0.5 mL) was added $(COCl)_2$ (0.006 mL, 0.673 mmol) and a catalytic amount of DMF, and the reaction mixture was stirred at room temperature. After evolution of gas ceased, all volatile materials were

removed under reduced pressure affording the crude carboxylic acid chloride, which was used without further purification. To a solution of the carboxylic acid chloride in CH_2Cl_2 (0.5 mL) was added aniline (0.010 mL, 0.112 mmol) at 0 ºC, and the reaction mixture was stirred at room temperature. After the reaction was completed, to the reaction mixture was added H_2O (1 mL), and the aqueous layer was extracted with ether (1 mL × 3). The combined organic layer was washed with 2*N* HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by PTLC (hexane/ethyl acetate=2/1) to afford **8a'** (7.3 mg, 81% (2 steps)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48 (1H, s), 7.88 (1H, d, *J* = 7.8 Hz), 7.63 (2H, d, *J* = 7.6 Hz), 7.48–7.40 (2H, m), 7.33 (2H, dd, *J* = 7.6, 7.6 Hz), 7.12 (1H, dd, *J* = 7.6, 7.6 Hz), 7.03 (1H, ddd, *J* = 7.8, 5.4, 3.7 Hz), 3.75 (3H, s), 2.06 (3H, s); 99% ee; ee was determined by HPLC; DICEL CHIRALPAK AS–H 0.46 cm ϕ × 25 cm; hexane/isopropanol=9/1; flow rate=0.4 mL/min; retention time: 23.1, 25.0 min.

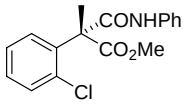
(*R*)-Ethyl 2-(phenylcarbamoyl)-2-(2-iodophenyl)propanoate (8b')



8b' was prepared in 17% yield according to the procedure for **8a'**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (1H, s), 7.88 (1H, dd, *J* = 7.9, 1.0 Hz), 7.63 (2H, dd, *J* = 8.8, 1.0 Hz), 7.43–7.42 (2H, m), 7.33 (2H, dd, *J* = 8.8, 7.8 Hz), 7.11 (1H, dd, *J* = 7.8, 7.8 Hz), 7.02 (1H, ddd, *J* = 7.9, 5.9, 3.4 Hz), 4.25 (1H, dq, *J* = 10.7, 7.3 Hz), 4.22 (1H, dq, *J* = 10.7, 7.3 Hz), 2.05 (3H, s), 1.22 (3H, t, *J* = 7.3 Hz); 44% ee; ee was determined by HPLC; DICEL CHIRALPAK AS–H 0.46 cm ϕ × 25 cm; hexane/isopropanol=9/1; flow rate=0.4 mL/min; retention time: 19.4, 20.8 min.

(*R*)-Methyl 2-(phenylcarbamoyl)-2-(2-chlorophenyl)propanoate (8c')



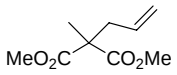
8c' was prepared in 75% yield according to the procedure for **8a'**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (1H, s), 7.60 (2H, dd, *J* = 7.6, 1.0 Hz), 7.46 (1H, dd, *J* = 7.6, 1.7 Hz), 7.40–7.25 (5H, m), 7.11 (1H, ddd, *J* = 7.6, 7.6, 1.0 Hz), 3.75 (3H, s), 2.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 168.2, 138.2, 137.9, 133.9, 130.0, 129.0, 128.9, 128.6, 127.0, 124.3, 120.0, 57.9, 53.5, 24.0; IR (KBr) ν_{max} 3304, 2956, 1724, 1684, 1600, 1540 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{17}H_{17}ClNO_3$: 318.0897, found:

318.0896; $[\alpha]_D^{25}$ +9.9 (*c* 0.91, $CHCl_3$); 99% ee; ee was determined by HPLC; DICEL CHIRALPAK AS-H 0.46 cm ϕ × 25 cm; hexane/isopropanol=9/1; flow rate=0.3 mL/min; retention time: 22.1 min for (*R*)-methyl 2-(phenylcarbamoyl)-2-(2-chlorophenyl) propanoate, 23.5 min for (*S*)-methyl 2-(phenylcarbamoyl)-2-(2-chlorophenyl) propanoate.

dimethyl 2-alkyl-2-methylmalonate の不斉加水分解：

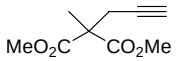
2-Allyl-2-methylmalonic acid dimethyl ester (13a)



To a suspension of NaH (329 mg, 7.97 mmol) in THF (60 mL) was added 2-methylmalonic acid dimethyl ester (1.09 g, 7.24 mmol) dropwise at 0 °C. After stirring for 30 min at room temperature, allyl bromide (0.771 mL, 8.91 mmol) was added dropwise at 0 °C. Then the reaction mixture was warmed up to room temperature and was stirred. After the reaction was completed, saturated aqueous NH_4Cl solution (60 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (40 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=20/1) to afford the titled diester **13a** (1.19 g, 86%) as a colorless liquid.

R_f = 0.53 (hexane/ethyl acetate=4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.69 (1H, ddt, *J* = 16.6, 11.2, 7.3 Hz), 5.14-5.09 (2H, m), 3.72 (6H, s), 2.62 (2H, d, *J* = 7.3 Hz), 1.41 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 132.4, 119.1, 53.6, 52.5, 40.2, 19.9; IR (neat) ν_{max} 2992, 2960, 2336, 1738, 1458, 1436, 1296, 1250, 1214, 1150, 1116 cm^{-1}.

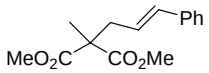
2-Methyl-2-(2-propynyl)malonic acid dimethyl ester (13b)



13b was prepared in 88% yield according to the procedure for **13a**.

R_f = 0.40 (hexane/ethyl acetate=4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 3.75 (6H, s), 2.80 (2H, d, *J* = 2.7 Hz), 2.03 (1H, t, *J* = 2.7 Hz), 1.56 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 79.0, 71.3, 53.1, 52.8, 25.9, 19.8; IR (neat) ν_{max} 3292, 3008, 2960, 1740, 1454, 1438, 1298, 1254, 1208, 1120 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_9H_{13}O_4$: 185.0814, found: 185.0809.

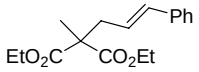
2-Methyl-2-(3-phenyl-2-propenyl)malonic acid dimethyl ester (13c)



13c was prepared in 97% yield according to the procedure for **13a**.

R_f = 0.48 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.19 (5H, m), 6.45 (1H, d, *J*= 15.6 Hz), 6.08 (1H, dt, *J*= 15.6, 7.6 Hz), 3.73 (6H, s), 2.77 (2H, dd, *J*= 7.6, 1.2 Hz), 1.46 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 137.0, 134.0, 128.4, 127.3, 126.1, 124.0, 54.0, 52.6, 39.5, 20.1; IR (neat) ν_{max} 3032, 3004, 2956, 1734, 1456, 1436, 1294, 1276, 1246, 1202, 1112, 970, 744, 696 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{15}H_{19}O_4$: 263.1283, found: 263.1283.

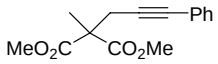
2-Methyl-2-(3-phenyl-2-propenyl)malonic acid diethyl ester (13c')



13c' was prepared in 100% yield according to the procedure for **13a**.

R_f = 0.30 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.18 (5H, m), 6.44 (1H, d, *J*= 15.6 Hz), 6.10 (1H, dt, *J*= 15.6, 7.6 Hz), 4.20 (4H, q, *J*= 7.1 Hz), 2.77 (2H, dd, *J*= 7.6, 1.0 Hz), 1.44 (3H, s), 1.25 (6H, t, *J*= 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 137.0, 133.9, 128.4, 127.2, 126.1, 124.2, 61.3, 53.9, 39.4, 20.0, 14.1; IR (neat) ν_{max} 2988, 2944, 1730, 1464, 1450, 1380, 1300, 1274, 1244, 1194, 1108, 970, 744, 694 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{17}H_{23}O_4$: 291.1596, found: 291.1594.

2-Methyl-2-(3-phenyl-2-propynyl)malonic acid dimethyl ester (13d)



13d was prepared in 92% yield according to the procedure for **13a**.

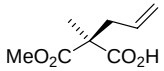
R_f = 0.39 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (2H, m), 7.29–7.25 (3H, m), 3.76 (6H, s), 3.01 (2H, s), 1.62 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 131.5, 128.1, 127.8, 123.1, 84.4, 83.4, 53.5, 52.8, 26.9, 20.1; IR (neat) ν_{max} 2956, 1738, 1250, 1118 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{15}H_{17}O_4$: 261.1127, found: 261.1125.

PLE-mediated asymmetric hydrolysis of 13c

To a suspension of diester **13c** (30.0 mg, 0.114 mmol) in pH 8 phosphate buffer (3 mL) was added PLE (15 units), and the reaction mixture was stirred at 30 ºC. After **13c** disappeared, to the reaction mixture was added 2*N* HCl to make pH of the solution to

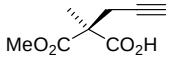
pH 3. The aqueous layer was extracted with EtOAc (1.5 mL × 2), dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **14c** (28.3 mg, 100%, 89% ee) as a colorless liquid.
In a large scale, to a suspension of PLE (2500 units) in pH 8 potassium phosphate buffer (1500 mL) was added diester **13c** (5.39 g, 20.5 mmol) via a syringe pump at 30 ºC for 24 h. After **13c** disappeared, to the reaction mixture was added 2*N* HCl to make pH of the solution to pH 3. The aqueous layer was extracted with EtOAc (500 mL × 3), dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **14c** (5.10 g, 100%, 88% ee) as a colorless liquid.
PLE-mediated asymmetric hydrolysis of **13a**, **13b**, **13c'**, **13d** was carried out according to the above procedure. In the experiments in Table 2-3, organic co-solvent (10%) was added to the above reaction mixture.

(*S*)-2-Allyl-2-methylmalonic acid monomethyl ester (14a)



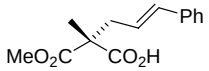
R_f = 0.45 (dichloromethane/methanol=5/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (1H, dddd, *J* = 16.6, 10.5, 7.6, 7.3 Hz), 5.14 (1H, ddd, *J* = 16.6, 3.2, 1.5 Hz), 5.13 (1H, ddd, *J* = 10.5, 1.5, 1.0 Hz), 3.77 (3H, s), 2.67 (1H, dddd, *J* = 13.9, 7.3, 1.2, 1.0 Hz), 2.62 (1H, dddd, *J* = 13.9, 7.6, 1.2, 1.0 Hz), 1.46 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 172.0, 132.1, 119.5, 53.6, 52.7, 40.2, 19.9; IR (neat) ν_{max} 2992, 2960, 1718, 1458, 1248 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_8H_{13}O_4$: 173.0814, found: 173.0817; $[\alpha]_D^{23}$ −3.2 (*c* 0.6, $CHCl_3$); 65% ee (For the determination of ee, see the experiment for **18a**.). For the structure determinateon, see the experiment for **15**.

(*S*)-2-Methyl-2-(2-propynyl)malonic acid monomethyl ester (14b)



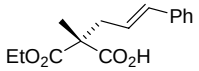
R_f = 0.24 (dichloromethane/methanol=10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (3H, s), 2.84 (1H, dd, *J* = 16.8, 2.7 Hz), 2.80 (1H, dd, *J* = 16.8, 2.7 Hz), 2.06 (1H, t, *J* = 2.7 Hz), 1.60 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 171.1, 78.8, 71.6, 53.0, 25.8, 19.8; IR (neat) ν_{max} 3300, 2960, 1740, 1728, 1462, 1440, 1298, 1258, 1124 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_8H_{11}O_4$: 171.0657, found: 171.0658; $[\alpha]_D^{30}$ −5.7 (*c* 1.3, $CHCl_3$); 77% ee (For the determination of ee, see the experiment for **18b**). For the structure determination, see the experiment from **14b** to **15**.

(*R*)-2-Methyl-2-(3-phenyl-2-propenyl)malonic acid monomethyl ester (14c)



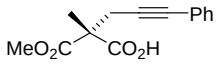
R_f = 0.33 (dichloromethane/methanol=10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.20 (5H, m), 6.47 (1H, d, *J* = 15.6 Hz), 6.10 (1H, dt, *J* = 15.6, 7.6 Hz), 3.75 (3H, s), 2.82 (1H, dd, *J* = 13.9, 7.6 Hz), 2.76 (1H, dd, *J* = 13.9, 7.6 Hz), 1.49 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 172.1, 136.9, 134.4, 128.4, 127.4, 126.2, 123.6, 54.0, 52.8, 39.5, 20.1; IR (neat) ν_{max} 2956, 2360, 1736, 1112 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{14}H_{17}NO_4$: 249.1127, found: 249.1127; $[\alpha]_D^{28}$ +4.9 (*c* 0.9, MeOH); 89% ee (For the determination of ee, see the experiment for **18c**). For the structure determination, see the experiments for **16** and **17**.

(*R*)-2-Methyl-2-(3-phenyl-2-propenyl)malonic acid monoethyl ester (14c')



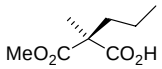
R_f = 0.30 (dichloromethane/methanol=10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.19 (5H, m), 6.47 (1H, d, *J* = 15.6 Hz), 6.11 (1H, dt, *J* = 15.6, 7.6 Hz), 4.22 (2H, q, *J* = 7.1 Hz), 2.83 (1H, ddd, *J* = 13.9, 7.6, 1.2 Hz), 2.75 (1H, ddd, *J* = 13.9, 7.6, 1.2 Hz), 1.49 (3H, s), 1.26 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 171.7, 136.9, 134.3, 128.4, 127.4, 126.2, 123.7, 61.8, 53.9, 39.5, 20.2, 14.1; IR (neat) ν_{max} 2988, 1712, 1240, 1112 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{15}H_{19}O_4$: 263.1283, found: 263.1278; $[\alpha]_D^{26}$ +5.8 (*c* 0.5, $CHCl_3$); 76% ee (For the determination of ee, see the experiment for **18c'**).

(*R*)-2-Methyl-2-(3-phenyl-2-propynyl)malonic acid monomethyl ester (14d)



R_f = 0.27 (dichloromethane/methanol=10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.35 (2H, m), 7.29–7.25 (3H, m), 3.78 (3H, s), 3.05 (1H, d, *J* = 16.8 Hz), 3.01 (1H, d, *J* = 16.8 Hz), 1.65 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 171.0, 131.6, 128.1, 128.0, 123.0, 84.1, 83.7, 53.6, 53.0, 26.9, 20.1; IR (KBr) ν_{max} 3001, 1751, 1719, 1298, 1205, 1101 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{14}H_{15}O_4$: 247.0970, found: 247.0967; $[\alpha]_D^{31}$ +2.0 (*c* 1.2, $CHCl_3$); 13% ee (For the determination of ee, see the experiment for **18d**). For the structure determination, see the experiments for **18e**.

(*S*)-2-Methyl-2-propylmalonic acid monomethyl ester (15)



To a stirred solution of **14a** (26.5 mg, 0.154 mmol) in EtOH (1.5 mL) was added a catalytic amount of 10% Pd/C under an atmosphere of Ar, and the reaction mixture was stirred under an atmosphere of hydrogen. The mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **15** (23.5 mg, 86%) as a colorless liquid.

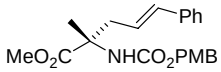
R_f = 0.40 (dichloromethane/methanol=10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (3H, s), 1.92–1.79 (2H, m), 1.45 (3H, s), 1.34–1.24 (2H, m), 0.94 (3H, t, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 173.0, 53.7, 52.6, 38.0, 20.1, 17.8, 14.2; IR (neat) ν_{max} 2968, 2880, 1738, 1718, 1242, 1160, 1138 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_8H_{15}O_4$: 175.0970, found: 175.0977; $[\alpha]_D^{27}$ −0.6 (*c* 1.3, $CHCl_3$).

conversion from **14b** to **15**.

To a stirred solution of **14b** (28.4 mg, 0.167 mmol) in EtOH (1.5 mL) was added a catalytic amount of 10% Pd/C under an atmosphere of Ar, and the reaction mixture was stirred under an atmosphere of hydrogen. The mixture was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **15** (23.7 mg, 81%) as a colorless liquid.

$[\alpha]_D^{25}$ −0.8 (*c* 1.1, $CHCl_3$)

(*S*)-2-(4-Methoxybenzyloxycarbonylamino)-2-methyl-5-phenyl-4-pentenoic acid methyl ester (16)

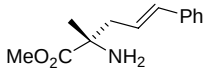


To a stirred solution of **14c** (51.2 mg, 0.206 mmol) in 1,2–dichloroethane (1 mL) was successively added Et_3N (0.049 mL, 0.350 mmol) and diphenylphosphorylazide (0.053 mL, 0.247 mmol). The reaction mixture was stirred at room temperature for 15 min and then was refluxed for 3 h. After checking that **14c** had been converted completely to the isocyanate by TLC, *p*–methoxybenzyl alcohol (0.044 mL, 0.350 mmol) was added to the solution and the reaction mixture was refluxed for 24 h. The solution was concentrated giving a yellow oil, which was purified by PTLC (hexane/ethyl acetate=4/1). This gave **16** (71.8 mg, 91%) as a clear colorless oil.

R_f = 0.20 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.18 (7H, m), 6.85 (2H, AA'XX' pattern, J = 8.5 Hz), 6.40 (1H, d, J = 15.6 Hz), 6.00 (1H, dt, J = 15.6, 7.6 Hz), 5.51 (1H, br), 5.05 (1H, d, J = 12.0 Hz), 5.00 (1H, d, J = 12.0 Hz), 3.79 (3H, s), 3.75

(3H, br), 2.95 (1H, br), 2.74 (1H, dd, J = 14.2, 7.6 Hz), 1.61 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 159.4, 154.7, 136.8, 134.3, 129.8, 128.4, 127.4, 126.2, 123.4, 113.8, 66.3, 59.9, 55.3, 52.7, 40.5, 23.4; IR (neat) ν_{max} 3364, 3028, 3004, 2956, 1736, 1724, 1518, 1304, 1248, 1178, 1036 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{22}H_{26}NO_5$: 384.1811, found: 384.1800; $[\alpha]_D^{31}$ +9.7 (c 1.1, $CHCl_3$).

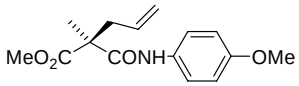
(*S*)-2-Amino-2-methyl-5-phenyl-4-pentenoic acid methyl ester (17)



To a stirred solution of **16** (49.1 mg, 0.128 mmol) in CH_2Cl_2 (1.35 mL) was added TFA (0.15 mL) at room temperature. The solution developed a purple color, and after 10min the reaction was completed. Addition of H_2O (1 mL), with stirring, discharged the color. The aqueous layer was extracted with hexane, and the resulting aqueous layer was made to pH 9 with aqueous ammonia. The mixture was extracted twice with CH_2Cl_2, and the combined extracts was dried over Na_2SO_4 and filtered. The solution was evaporated and the residue was purified by flash chromatography (dichloromethane/methanol=50/1), giving the product **17** (20.8 mg, 74%) as a clear colorless liquid.

$[\alpha]_D^{33}$ +13.8 (c 0.9, EtOH), lit. $[\alpha]_D^{20}$ +10.6 (c 0.8, EtOH).

(*S*)-2-(4-Methoxyphenylcarbamoyl)-2-methyl-4-pentenoic acid methyl ester (18a)

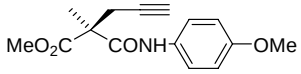


To a solution of **14a** (4.0 mg, 0.0232 mmol) in CH_2Cl_2 (0.5 mL) was added EDCI (6.7 mg, 0.0350 mmol) and DMAP (1.4 mg, 0.0115 mmol) at 0 ºC. To this reaction mixture was added amine (11.4 mg, 0.0926 mmol) at 0 ºC, and the reaction mixture was stirred at room temperature. To the reaction mixture was added H_2O (1 mL), and the aqueous layer was extracted with ether (1 mL × 3). The combined organic layer was washed with 2N HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by PTLC (hexane/ethyl acetate=4/1) to afford amide **18a** (3.9 mg, 61%).

R_f = 0.25 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (1H, s), 7.43 (2H, AA'XX' pattern, J = 9.0 Hz), 6.85 (2H, AA'XX' pattern, J = 9.0 Hz), 5.72 (1H, ddt, J = 17.1, 10.0, 7.3 Hz), 5.16–5.09 (2H, m), 3.78 (6H, s), 2.79 (1H, dddd, J = 13.7, 7.1, 1.2, 1.0 Hz), 2.63 (1H, dddd, J = 13.7, 7.6, 1.0, 1.0 Hz), 1.52 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 168.4, 156.3, 132.6, 130.7, 121.8, 119.1, 114.0, 55.5, 54.1, 52.8, 42.6, 20.9; IR

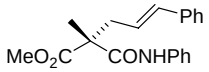
(neat) ν_{max} 3336, 2956, 1740, 1666, 1514, 1246 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{15}H_{20}NO_4$: 278.1392, found: 278.1392; $[\alpha]_D^{31}$ −22.7 (*c* 0.5, $CHCl_3$); 65% ee; ee was determined by HPLC; DICEL CHIRALPAK AS-H 0.46 cm ϕ × 25 cm; hexane/isopropanol=9/1; flow rate=0.5 mL/min; retention time: 33.9 min for (*R*)-2-(4-Methoxyphe nylcarbamoyl)-2-methyl-4-pentenoic acid methyl ester, 37.6 min for (*S*)-2-(4-Methoxyphenylcarba moyl)-2-methyl-4-pentenoic acid methyl ester.

(*S*)-2-(4-Methoxyphenylcarbamoyl)-2-methyl-4-pentynoic acid methyl ester (18b)



18b was prepared from **14b** in 52% yield according to the procedure for **18a**.
R_f = 0.18 (hexane/ethyl acetate=4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (1H, s), 7.43 (2H, AA'XX' pattern, *J* = 9.0 Hz), 6.86 (2H, AA'XX' pattern, *J* = 9.0 Hz), 3.82 (3H, s), 3.79 (3H, s), 2.94 (1H, dd, *J* = 16.8, 2.7 Hz), 2.84 (1H, dd, *J* = 16.8, 2.7 Hz), 2.07 (1H, t, *J* = 2.7 Hz), 1.65 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 167.4, 156.5, 130.5, 121.8, 114.0, 79.8, 71.4, 55.5, 53.8, 53.1, 26.8, 21.6; IR (neat) ν_{max} 3296, 2960, 1738, 1670, 1516, 1246 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{15}H_{18}NO_4$: 276.1236, found: 276.1232; $[\alpha]_D^{36}$ −19.7 (*c* 0.8, $CHCl_3$); 77% ee; ee was determined by HPLC; DICEL CHIRALCEL OD-H 0.46 cm ϕ × 25 cm; hexane/isopropanol=9/1; flow rate=0.4 mL/min; retention time: 28.3 min for (*S*)-2-(4-Methoxyphenylcarbamoyl)-2-methyl-4-pentynoic acid methyl ester, 30.4 min for (*R*)-2-(4-Methoxyphenylcarbamoyl)-2-methyl-4-pentynoic acid methyl ester.

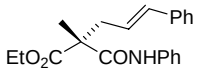
(*R*)-2-Methyl-5-phenyl-2-phenylcarbamoyl-4-pentenoic acid methyl ester (18c)



18c was prepared from **14c** in 54% yield according to the procedure for **18a**.
R_f = 0.48 (hexane/ethyl acetate=2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (1H, s), 7.54 (2H, d, *J* = 8.5 Hz), 7.34-7.18 (7H, m), 7.11 (1H, t, *J* = 7.6 Hz), 6.48 (1H, d, *J* = 15.9 Hz), 6.10 (1H, dt, *J* = 15.9, 7.6 Hz), 3.79 (3H, s), 2.96 (1H, ddd, *J* = 13.9, 7.3, 1.2 Hz), 2.79 (1H, ddd, *J* = 13.9, 7.6, 1.2 Hz), 1.58 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 168.6, 137.5, 136.8, 134.2, 128.9, 128.4, 127.4, 126.2, 124.4, 124.0, 120.1, 54.6, 52.9, 41.8, 21.1; IR (neat) ν_{max} 3352, 2956, 1738, 1674, 1542, 1248 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{20}H_{22}NO_3$: 324.1600, found: 324.1603; $[\alpha]_D^{27}$ +42.0 (*c* 0.3, $CHCl_3$); 89% ee; ee was determined by HPLC; DICEL CHIRALPAK AS-H 0.46 cm ϕ × 25 cm; hexane/isopropanol=9/1; flow rate=0.5 mL/min; retention time: 16.8 min for (*S*)-2-Methyl-5-phenyl-2-phenylcarbamoyl-4-pentenoic acid methyl ester, 17.9 min

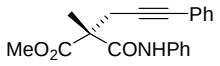
for (*R*)−2−Methyl−5−phenyl−2−phenylcarbamoyl−4−pentenoic acid methyl ester.

(*R*)-2-Methyl-5-phenyl-2-phenylcarbamoyl-4-pentenoic acid ethyl ester (18c')



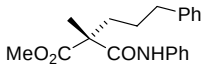
18c' was prepared from **14c'** in 74% yield according to the procedure for **18a**.
R_f = 0.58 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (1H, s), 7.54 (2H, d, *J* = 8.5 Hz), 7.34−7.18 (7H, m), 7.11 (1H, t, *J* = 7.6 Hz), 6.48 (1H, d, *J* = 15.6 Hz), 6.11 (1H, dt, *J* = 15.6, 7.3 Hz), 4.32−4.19 (2H, m), 2.97 (1H, ddd, *J* = 13.7, 7.3, 1.0 Hz), 2.78 (1H, ddd, *J* = 13.7, 7.6, 1.0 Hz), 1.58 (3H, s), 1.30 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 168.7, 137.6, 136.9, 134.1, 128.8, 128.4, 127.4, 126.1, 124.3, 124.1, 120.0, 62.0, 54.5, 41.8, 21.3, 14.2; IR (neat) ν_{max} 3348, 2984, 2940, 1710, 1600, 1538, 1244 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{21}H_{24}NO_3$: 338.1756, found: 338.1760; $[\alpha]_D^{31}$ +35.0 (*c* 0.7, $CHCl_3$); 76% ee; ee was determined by HPLC; DICEL CHIRALPAK AS−H 0.46 cm ϕ × 25 cm; hexane/isopropanol=9/1; flow rate=0.2 mL/min; retention time: 42.3 min for (*S*)−2−Methyl−5−phenyl−2−phenylcarbamoyl−4−pentenoic acid ethyl ester, 44.8 min for (*R*)−2−Methyl−5−phenyl−2−phenylcarbamoyl−4−pentenoic acid ethyl ester.

(*R*)-2-Methyl-5-phenyl-2-phenylcarbamoyl-4-pentynoic acid methyl ester (18d)



18d was prepared from **14d** in 49% yield according to the procedure for **18a**.
R_f = 0.29 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (1H, s), 7.53 (2H, d, *J* = 8.1 Hz), 7.36−7.26 (7H, m), 7.12 (1H, t, *J* = 7.6 Hz), 3.84 (3H, s), 3.15 (1H, d, *J* = 16.8 Hz), 3.05 (1H, d, *J* = 16.8 Hz), 1.71 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 167.9, 137.4, 131.6, 128.9, 128.2, 128.0, 124.5, 122.9, 120.1, 85.0, 83.8, 54.4, 53.2, 28.1, 21.6; IR (neat) ν_{max} 3356, 2956, 1738, 1678, 1602, 1538, 1444, 1244 cm^{-1}; HRMS (FAB) [M+H]$^+$ calculated for $C_{20}H_{20}NO_3$: 322.1443, found: 322.1443; $[\alpha]_D^{35}$ +7.8 (*c* 0.3, $CHCl_3$); 13% ee; ee was determined by HPLC; DICEL CHIRALPAK AS−H 0.46 cm ϕ × 25 cm; hexane/isopropanol=9/1; flow rate=0.2 mL/min; retention time: 44.2 min for (*S*)−2−Methyl−5−phenyl−2−phenylcarbamoyl−4−pentynoic acid methyl ester, 45.8 min for (*R*)−2−Methyl−5−phenyl−2−phenylcarbamoyl−4−pentynoic acid methyl ester.

(*R*)-2-Methyl-5-phenyl-2-phenylcarbamoylpentanonic acid methyl ester (18e)



18e was prepared from **18c** in 74% yield according to the procedure for **15**.

$[\alpha]_D^{28}$ +23.3 (*c* 1.0, $CHCl_3$)

18e was prepared from **18d** in 78% yield according to the procedure for **15**.

$[\alpha]_D^{28}$ +4.2 (*c* 0.4, $CHCl_3$)

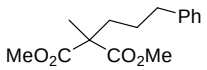
R_f = 0.57 (hexane/ethyl acetate=2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.11 (1H, s), 7.53–7.51 (2H, m), 7.33–7.23 (4H, m), 7.18–7.08 (4H, m), 3.75 (3H, s), 2.68–2.54 (2H, m), 2.10 (1H, ddd, *J* = 13.4, 11.2, 5.1 Hz), 1.92 (1H, ddd, *J* = 13.4, 11.2, 5.1 Hz), 1.68–1.53 (2H, m), 1.51 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 169.0, 141.5, 137.7, 128.8, 128.3, 125.8, 124.3, 120.0, 54.2, 52.8, 38.3, 35.8, 26.9, 21.2; IR (neat) ν_{max} 3348, 3060, 3028, 2952, 1734, 1716, 1676, 1600, 1540, 1246, 1118cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{20}H_{24}NO_3$: 326.1756, found: 326.1758.

<u>PLE を用いた速度論的光学分割</u>：

PLE-mediated kinetic resolution of 14c

To a suspension of PLE (350 units) in pH 8 potassium phosphate buffer (250 mL) was added a suspension of monoester **14c** (791 mg, 3.19 mmol, 89% ee) in pH 8 potassium phosphate buffer (30 mL) via a syringe pump at 30 ºC for 72 h. After a week from the addition of **14c**, to the reaction mixture was added 2*N* HCl to make pH of the solution to pH 3. The aqueous layer was extracted with EtOAc (200 mL × 3), dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **14c** (508 mg, 88%, 96% ee) as a colorless liquid.

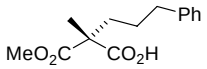
2-Methyl-2-(3-phenylpropyl)malonic acid dimethyl ester (13e)



13e was prepared from **13c** in 91% yield according to the procedure for **15**.

R_f = 0.44 (hexane/ethyl acetate=4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (2H, m), 7.19–7.15 (3H, m), 3.69 (6H, s), 2.62 (2H, t, *J* = 7.6 Hz), 1.93–1.89 (2H, m), 1.60–1.52 (2H, m), 1.40 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 141.6, 128.2, 125.7, 53.6, 52.4, 35.9, 35.3, 26.2, 20.0; IR (neat) ν_{max} 3000, 2956, 1736, 1268, 1116 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{15}H_{21}O_4$: 265.1440, found: 265.1440.

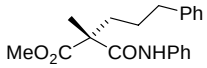
(*R*)-2-Methyl-2-(3-phenylpropyl)malonic acid monomethyl ester (14e)



14e was prepared in 59% yield according to the procedure for PLE-mediated kinetic resolution of **14c**.

R_f = 0.33 (dichloromethane/methanol=10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.26 (2H, m), 7.20–7.16 (3H, m), 3.73 (3H, s), 2.63 (2H, t, *J* = 7.3 Hz), 2.00–1.86 (2H, m), 1.68–1.55 (2H, m), 1.44 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 172.6, 141.5, 128.3, 125.8, 53.6, 52.7, 36.0, 35.5, 26.3, 20.2; IR (neat) ν_{max} 3028, 2996, 2956, 1736, 1718, 1454, 1268 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{14}H_{19}O_4$: 251.1283, found: 251.1288; $[\alpha]^{26}_D$ +0.7 (*c* 0.8, $CHCl_3$); 36% ee. (**14e** was converted to **18e** according to the procedure for **18a**, and the ee was determined by HPLC.).

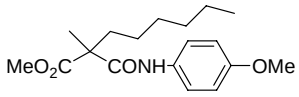
(*R*)-2-Methyl-5-phenyl-2-phenylcarbamoylpentanonic acid methyl ester (18e)



18e was prepared from **14e** in 52% yield according to the procedure for **18a**.

$[\alpha]_D^{36}$ +11.9 (*c* 0.5, $CHCl_3$); 36% ee; ee was determined by HPLC; DICEL CHIRALCEL OD-H 0.46 cm ϕ × 25 cm; hexane/isopropanol=9/1; flow rate=0.3 mL/min; retention time: 27.2 min for (*S*)-2-Methyl-5-phenyl-2-phenylcarbamoylpentanoic acid methyl ester, 29.1 min for (*R*)-2-Methyl-5-phenyl-2-phenylcarbamoylpentanoic acid methyl ester.

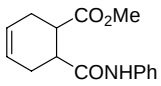
2-(4-Methoxyphenylcarbamoyl)-2-methyloctanoic acid methyl ester (18f)



18f was prepared from **14f** in 52% yield according to the procedure for **18a**.

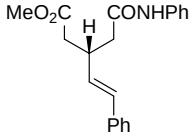
R_f = 0.57 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (1H, s), 7.45 (2H, AA'XX' pattern, *J* = 9.0 Hz), 6.85 (2H, AA'XX' pattern, *J* = 9.0 Hz), 3.78 (6H, s), 2.03 (1H, dt, *J* = 15.4, 7.6 Hz), 1.86 (1H, dt, *J* = 15.4, 7.6 Hz), 1.51 (3H, s), 1.26–1.19 (8H, m), 0.86 (3H, t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 169.0, 156.2, 130.9, 121.6, 114.0, 55.4, 54.1, 52.7, 38.9, 31.5, 29.4, 25.1, 22.5, 21.1, 14.0; IR (neat) ν_{max} 3336, 2932, 1714, 1666, 1602, 1516, 1246 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{18}H_{28}NO_4$: 322.2018, found: 322.2005; racemic mixture; ee was determined by HPLC; DICEL CHIRALCEL OD-H 0.46 cm ϕ × 25 cm; hexane/isopropanol=19/1; flow rate=0.4 mL/min; retention time : 20.0, 22.0 min.

6-Phenylcarbamoyl-3-cyclohexenecarboxylic acid methyl ester (18g)



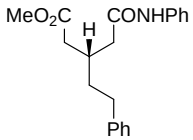
18g was prepared from **14g** in 45 %yield according to the procedure for **18a**.
R_f = 0.14 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (1H, s), 7.50 (2H, d, *J* = 8.3 Hz), 7.29 (2H, dd, *J* = 8.3, 7.3 Hz), 7.08 (1H, t, *J* = 7.3 Hz), 5.77 (2H, s), 3.72 (3H, s), 3.14–3.05 (2H, m), 2.76–2.27 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 170.9, 137.9, 128.8, 125.6, 124.8, 124.0, 119.8, 52.1, 41.6, 40.6, 26.9, 26.0; IR (neat) ν_{max} 3324, 3032, 2952, 1730, 1666, 1602, 1538, 1442, 1250, 1206 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{15}H_{18}NO_3$: 260.1287, found: 260.1279; racemic mixture; ee was determined by HPLC; DICEL CHIRALPAK AS–H 0.46 cm ϕ × 25 cm; hexane/isopropanol=3/1; flow rate=0.3 mL/min; retention time: 31.5, 36.6 min.

(*S*)-5-Phenyl-3-phenylcarbamoylmethyl-4-pentenoic acid methyl ester (18h)



18h was prepared from **14h** in 34% yield according to the procedure for **18a**.
R_f = 0.22 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (1H, s), 7.49 (2H, d, *J* = 7.8 Hz), 7.33–7.19 (7H, m), 7.08 (1H, t, *J* = 7.3 Hz), 6.50 (1H, d, *J* = 15.9 Hz), 6.18 (1H, dd, *J* = 15.9, 8.1 Hz), 3.67 (3H, s), 3.28 (1H, dtt, *J* = 8.1, 7.1, 6.8 Hz), 2.67–2.51 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 169.2, 137.7, 136.7, 131.1, 130.5, 128.9, 128.4, 127.4, 126.2, 124.2, 119.8, 51.8, 42.3, 38.8, 36.7; IR (KBr) ν_{max} 3345, 1736, 1655, 1600, 1527, 1256 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{20}H_{22}NO_3$: 324.1600, found: 324.1591; $[\alpha]_D^{27}$ −27.4 (*c* 0.3, $CHCl_3$); 98% ee; ee was determined by HPLC; DICEL CHIRALPAK AS–H 0.46 cm ϕ × 25 cm; hexane/isopropanol=3/1; flow rate=0.4 mL/min; retention time: 42.8 min for (*R*)–5–Phenyl–3–phenylcarbamoylmethyl–4–pentenoic acid methyl ester, 47.2 min for (*S*)–5–Phenyl–3–phenylcarbamoylmethyl–4–pentenoic acid methyl ester.

(*S*)-5-Phenyl-3-phenylcarbamoylmethylpentanoic acid methyl ester (18i)



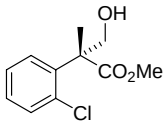
18i was prepared from **14i** in 49% yield according to the procedure for **18a**.
R_f = 0.16 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, s), 7.52 (2H,

d, J = 7.8 Hz), 7.33–7.17 (7H, m), 7.09 (1H, t, J = 7.6 Hz), 3.71 (3H, s), 2.71 (2H, t, J = 7.3 Hz), 2.56–2.38 (5H, m), 1.84–1.64 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 169.9, 141.5, 137.9, 128.9, 128.4, 128.3, 125.9, 124.1, 119.6, 51.8, 41.9, 37.7, 36.2, 33.3, 33.1; IR (KBr) ν_{max} 3312, 3023, 2944, 2856, 1730, 1659, 1598, 1523, 1441, 1207, 1153 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{20}H_{24}NO_3$: 326.1756, found: 326.1751; $[\alpha]_D^{28}$ +4.0 (*c* 0.5, $CHCl_3$); 30% ee; ee was determined by HPLC; DICEL CHIRALCEL OD–H 0.46 cm ϕ × 25 cm; hexane/isopropanol=3/1; flow rate=0.3 mL/min; retention time: 26.2 min for (*S*)–5–Phenyl–3–phenylcarbamoylmethylpentanoic acid methyl ester, 29.4 min for (*R*)–5–Phenyl–3–phenylcarbamoylmethylpentanoic acid methyl ester.

第２節　(−)-physostigmine の形式不斉全合成

(−)-physostigmine の形式不斉全合成：

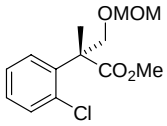
(*R*)-Methyl 2-(2-chlorophenyl)-3-hydroxy-2-methylpropanoate (5)



To a stirred solution of **4** (850 mg, 3.50 mmol) in CH_2Cl_2 (35 mL) was added $(COCl)_2$ (0.917 mL, 10.5 mmol) and a catalytic amount of DMF, and the reaction mixture was stirred at room temperature. After evolution of gas ceased, all volatile materials were removed under reduced pressure affording the crude carboxylic acid chloride, which was used without further purification. To a solution of the carboxylic acid chloride in THF (35 mL) was added $NaBH_4$ (663 mg, 17.5 mmol) portionwise at −30 ºC, and then was added MeOH (4.2 mL) at this temperature for 1.5 h. After the reaction was completed, 2*N*HCl was slowly added to the reaction mixture to adjust the solution to pH 2, and the aqueous layer was extracted with Et_2O (20 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=2/1) to afford **5** (688 mg, 86% (2 steps)) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (1H, dd, *J* = 7.8, 1.7 Hz), 7.36 (1H, dd, *J* = 7.8, 1.7 Hz), 7.31 (1H, ddd, *J* = 7.8, 7.8, 1.7 Hz), 7.24 (1H, ddd, *J* = 7.8, 7.8, 1.7 Hz), 4.34 (1H, d, *J* = 11.5 Hz), 3.72 (3H, s), 3.57 (1H, d, *J* = 11.5 Hz), 2.75 (1H, br), 1.73 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 138.2, 133.6, 130.6, 128.6, 128.2, 127.0, 67.0, 52.3, 51.5, 21.2; IR (neat) ν_{max} 3468, 2956, 1732 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{11}H_{14}ClO_3$: 229.0631, found: 229.0632; $[\alpha]_D^{26}$ +48.9 (*c* 1.00, $CHCl_3$).

(*R*)-Methyl 2-(2-chlorophenyl)-3-(methoxymethoxy)-2-methylpropanoate (6)

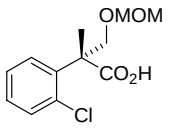


To a stirred solution of **5** (882 mg, 3.85 mmol) in CH_2Cl_2 (30 mL) was added NaI (57.8 mg, 0.385 mmol), DIPEA (4.03 mL, 23.1 mmol), and MOMCl (0.969 mL, 11.6 mmol) successively at room temperature, and the mixture was refluxed. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (20 mL) was slowly added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (15 mL × 2). The

combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=8/1) to afford **6** (955 mg, 91%) as a white solid.

mp 60.9–62.3 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, dd, *J* = 7.3, 1.5 Hz), 7.36 (1H, dd, *J* = 7.3, 1.5 Hz), 7.28 (1H, ddd, *J* = 7.3, 7.3, 1.5 Hz), 7.22 (1H, ddd, *J* = 7.3, 7.3, 1.5 Hz), 4.58 (1H, d, *J* = 6.6 Hz), 4.51 (1H, d, *J* = 6.6 Hz), 4.15 (1H, d, *J* = 9.5 Hz), 4.03 (1H, d, *J* = 9.5 Hz), 3.70 (3H, s), 3.20 (3H, s), 1.70 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 139.1, 133.5, 130.6, 128.4, 128.3, 126.8, 96.5, 71.2, 55.2, 52.4, 50.9, 21.8; IR (neat) ν_{max} 2952, 2894, 1726 cm^{-1}; HRMS (FAB) [M+H]$^+$ caluculated for $C_{13}H_{18}ClO_4$: 273.0894, found: 273.0894; $[\alpha]_D^{29}$ +38.6 (*c* 0.90, $CHCl_3$).

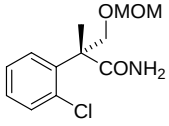
(*R*)-2-(2-Chlorophenyl)-3-(methoxymethoxy)-2-methylpropanoic acid (7)



To a stirred solution of **6** (875 mg, 3.21 mmol) in MeOH (30 mL) was added 1M NaOH (30 mL) at room temperature, and the mixture was refluxed. After the reaction was completed, the mixture was concentrated under reduced pressure. 2*N* HCl was slowly added to the aqueous layer to adjust the solution to pH 3, and the aqueous layer was extracted with Et_2O (70 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=2/1) to afford **7** (742 mg, 89%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (1H, dd, *J* = 7.6, 1.7 Hz), 7.37 (1H, dd, *J* = 7.6, 1.7 Hz), 7.27 (1H, ddd, *J* = 7.6, 7.6, 1.7 Hz), 7.22 (1H, ddd, *J* = 7.6, 7.6, 1.7 Hz), 4.60 (1H, d, *J* = 6.6 Hz), 4.53 (1H, d, *J* = 6.6 Hz), 4.15 (1H, d, *J* = 9.5 Hz), 4.05 (1H, d, *J* = 9.5 Hz), 3.22 (3H, s), 1.74 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 138.5, 133.6, 130.7, 128.5, 128.4, 126.8, 96.4, 70.9, 55.2, 50.9, 21.7; IR (neat) ν_{max} 2952, 1708 cm^{-1}; HRMS (FAB) [M+Na]$^+$ caluculated for $C_{12}H_{15}ClO_4Na$: 281.0557, found: 281.0564; $[\alpha]_D^{30}$ +34.1 (*c* 0.94, $CHCl_3$).

(*R*)-2-(2-Chlorophenyl)-3-(methoxymethoxy)-2-methylpropanamide (3)

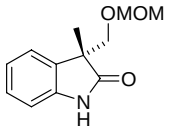


To a stirred solution of **7** (700 mg, 2.71 mmol) in CH_2Cl_2 (20 mL) was added $(COCl)_2$ (0.713 mL, 8.12 mmol) and a catalytic amount of DMF, and the reaction mixture was

stirred at room temperature. After evolution of gas ceased, all volatile materials were removed under reduced pressure affording the crude carboxylic acid chloride, which was used without further purification. Into a stirred solution of the carboxylic acid chloride in THF (35 mL) was bubbled NH_3 at 0 °C. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=1/2) to afford **3** (539 mg, 77% (2 steps)) as a white solid.

mp 118.1–122.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, dd, *J* = 7.6, 1.7 Hz), 7.40 (1H, dd, *J* = 7.6, 1.7 Hz), 7.30 (1H, ddd, *J* = 7.6, 7.6, 1.7 Hz), 7.25 (1H, ddd, *J* = 7.6, 7.6, 1.7 Hz), 5.90 (1H, br), 5.51 (1H, br), 4.65 (1H, d, *J* = 6.6 Hz), 4.60 (1H, d, *J* = 6.6 Hz), 4.19 (1H, d, *J* = 10.0 Hz), 3.90 (1H, d, *J* = 10.0 Hz), 3.30 (3H, s), 1.70 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 138.8, 134.3, 131.2, 129.0, 128.7, 127.0, 96.6, 71.4, 55.5, 51.4, 22.1; IR (neat) ν_{max} 3400, 3193, 2945, 1685, 1618 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{12}H_{17}ClNO_3$: 258.0897, found: 258.0900; $[\alpha]_D^{25}$ +42.9 (*c* 0.52, $CHCl_3$).

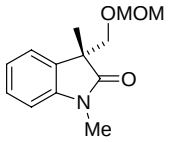
(*R*)-3-((Methoxymethoxy)methyl)-3-methylindolin-2-one (8)



To a stirred solution of **3** (58.9 mg, 0.229 mmol) in DMF (4 mL) was added K_2CO_3 (63.2 mg, 0.457 mmol), CuI (21.8 mg, 0.114 mmol), and *N*,*N*'-dimethylethylenediamine (0.024 mL, 0.229 mmol) successively at room temperature, and the mixture was refluxed. After the reaction was completed, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=2/1) to afford **8** (38.6 mg, 76%) as a white solid.

mp 103.5–103.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (1H, br), 7.25 (1H, dd, *J* = 7.6, 1.0 Hz), 7.22 (1H, ddd, *J* = 7.6, 7.6, 1.0 Hz), 7.05 (1H, ddd, *J* = 7.6, 7.6, 1.0 Hz), 6.92 (1H, dd, *J* = 7.6, 1.0 Hz), 4.51 (1H, d, *J* = 6.6 Hz), 4.45 (1H, d, *J* = 6.6 Hz), 3.85 (1H, d, *J* = 9.3 Hz), 3.78 (1H, d, *J* = 9.3 Hz), 3.15 (3H, s), 1.38 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.8, 140.9, 133.1, 128.0, 123.0, 122.3, 109.9, 96.2, 71.6, 55.0, 49.5, 19.6; IR (KBr) ν_{max} 3437, 3170, 2963, 1719, 1679 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{12}H_{16}NO_3$: 222.1130, found: 222.1129; $[\alpha]_D^{27}$ −25.1 (*c* 0.93, $CHCl_3$).

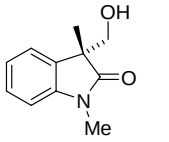
(*R*)-3-((Methoxymethoxy)methyl)-1,3-dimethylindolin-2-one (9)



To a suspension of NaH (43.4 mg, 1.08 mmol) in THF (8 mL) was added a solution of **8** (185 mg, 0.834 mmol) in THF (2 mL) dropwise at 0 ºC, and the reaction mixture was stirred for 30 min. Then, to the reaction mixture was added MeI (0.078 mL, 1.25 mmol) at 0 ºC, and strring was continued at 0 ºC. After the starting material disappeared, the reaction 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 dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=3/1) to afford **9** (190 mg, 97%) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (2H, m), 7.07 (1H, ddd, *J* = 7.6, 7.6, 1.0 Hz), 6.86 (1H, dd, *J* = 7.6, 1.0 Hz), 4.49 (1H, d, *J* = 6.6 Hz), 4.43 (1H, d, *J* = 6.6 Hz), 3.81 (1H, d, *J* = 9.3 Hz), 3.78 (1H, d, *J* = 9.3 Hz), 3.23 (3H, s), 3.14 (3H, s), 1.35 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 143.5, 132.6, 127.9, 122.7, 122.3, 107.9, 96.1, 71.6, 55.0, 48.9, 26.2, 19.7; IR (neat) ν_{max} 3060, 2936, 1716 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{13}H_{18}NO_3$: 236.1287, found: 236.1293; $[\alpha]_D^{31}$ −17.6 (*c* 0.76, $CHCl_3$).

(*R*)-3-(Hydroxymethyl)-1,3-dimethylindolin-2-one (2)

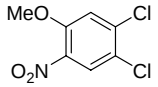


To a stirred solution of **9** (61.0 mg, 0.259 mmol) in MeOH (3 mL) was added a catalytic amount of conc. HCl, and the reaction mixture was stirred at 50 ºC. After the starting material disappeared, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (3 mL). The aqueous layer was extracted with AcOEt (3 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=1/1) to afford **2** (40.0 mg, 81%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (1H, dd, *J* = 7.8, 7.8 Hz), 7.23 (1H, d, *J* = 7.3 Hz), 7.10 (1H, dd, *J* = 7.3, 7.3 Hz), 6.87 (1H, d, *J* = 7.8 Hz), 3.86 (1H, d, *J* = 11.0 Hz), 3.75 (1H, d, *J* = 11.0 Hz), 3.23 (3H, s), 2.27 (1H, br), 1.42 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 143.6, 131.7, 128.3, 122.7, 122.7, 108.3, 67.6, 49.9, 26.2, 19.0; IR (KBr) ν_{max} 3363, 1691 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{11}H_{14}NO_2$: 192.0946, found: 192.1024; $[\alpha]_D^{26}$ −8.6 (*c* 0.42, $CHCl_3$), lit. $[\alpha]_D^{29}$ −8.5 (*c* 0.42, $CHCl_3$).

(−)-physostigmine の改良形式不斉全合成：

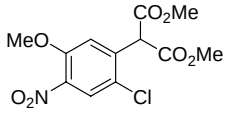
1,2-Dichloro-4-methoxy-5-nitrobenzene (12)



To a stirred solution of 4,5−dichloro−2−nitrophenol (3.17 g, 15.2 mmol) in acetone (80 mL) was added K_2CO_3 (4.21 g, 30.4 mmol), MeI (2.85 mL, 45.6 mmol) successively at room temperature. After the reaction was completed, saturated aqueous NH_4Cl solution (80 mL) was added to the reaction mixture. The resultant solution was concentrated under reduced pressure, and the residue was extracted with Et_2O (80 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=30/1) to afford **12** (3.32 g, 99%) as a yellow solid.

R_f = 0.44 (hexane/ethyl acetate=4/1); mp 66.4−71.4 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (1H, s), 7.20 (1H, s), 3.98 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 138.6, 137.9, 127.0, 123.9, 115.6, 57.1; IR (KBr) ν_{max} 1515, 1343, 1269, 933 cm^{-1}.

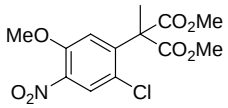
Dimethyl 2-(2-chloro-5-methoxy-4-nitrophenyl)malonate (12')



To a suspension of NaH (1.03 g, 25.8 mmol) in DMF (100 mL) was added dimethyl malonate (3.69 mL, 32.3 mmol) dropwise at 0 ºC, and the reaction mixture was stirred for 30 min. Then, to the reaction mixture was added a solution of **12** (2.84 g, 12.9 mmol) in DMF (10 mL) via a cannula at 0 ºC, and strring was continued at 100 ºC. After the starting material disappeared, the reaction was quenched with saturated aqueous NH_4Cl solution (100 mL). The aqueous layer was extracted with Et_2O (100 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was used in the next step without further purification.

R_f = 0.32 (hexane/ethyl acetate=2/1); mp 93.3−96.1 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (1H, s), 7.37 (1H, s), 5.28 (1H, s), 3.98 (3H, s), 3.82 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 151.5, 139.1, 136.6, 126.1, 125.2, 115.8, 56.9, 53.5, 53.4; IR (KBr) ν_{max} 1770, 1739, 1573, 1526, 1271, 1221, 1144 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{12}H_{13}ClNO_7$: 318.0381, found: 318.0374.

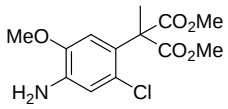
Dimethyl 2-(2-chloro-5-methoxy-4-nitrophenyl)-2-methylmalonate (13)



To a suspension of NaH (723 mg, 18.1 mmol) in THF (100 mL) was added a solution of **12'** in THF (10 mL) dropwise at 0 ºC, and the reaction mixture was stirred for 30 min. Then, to the reaction mixture was added MeI (1.21 mL, 19.4 mmol) at 0 ºC, and strring was continued at 40 ºC. After the starting material disappeared, the reaction was quenched with saturated aqueous NH_4Cl solution (100 mL). The aqueous layer was extracted with Et_2O (100 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=8/1) to afford **13** (3.38 g, 79% (2 steps)) as a yellow solid.

R_f = 0.28 (hexane/ethyl acetate=2/1); mp 101.2–104.4 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (1H, s), 7.01 (1H, s), 3.95 (3H, s), 3.82 (6H, s), 1.95 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 151.4, 143.7, 138.1, 127.8, 124.8, 114.0, 59.7, 56.6, 53.4, 21.9; IR (KBr) ν_{max} 1752, 1728, 1570, 1509, 1266, 1222, 1113 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{13}H_{15}ClNO_7$: 332.0537, found: 332.0551.

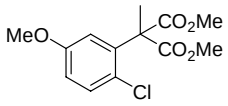
Dimethyl 2-(4-amino-2-chloro-5-methoxyphenyl)-2-methylmalonate (14)



A mixture of **13** (3.35 g, 10.1 mmol), 10% Pd/C and AcOEt (100 mL) was stirred under H_2 atmospere (1 atm) at room temperature. After the reaction was completed, the mixture was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=8/1) to afford **14** (2.99 g, 98%) as a white solid.

R_f = 0.21 (hexane/ethyl acetate=2/1); mp 105.6–107.9 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (1H, s), 6.55 (1H, s), 3.80 (3H, s), 3.79 (6H, s), 1.89 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 145.4, 136.6, 126.1, 125.3, 116.5, 110.1, 59.2, 55.5, 53.0, 22.4; IR (KBr) ν_{max} 3441, 3358, 2958, 1730, 1578, 1514, 1259, 1229, 1114, 1035 cm^{-1}; HRMS (FAB) $[M]^+$ caluculated for $C_{13}H_{16}ClNO_5$: 301.0717, found: 301.0720.

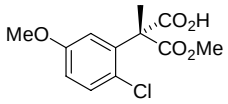
Dimethyl 2-(2-chloro-5-methoxyphenyl)-2-methylmalonate (15)



To a stirred solution of **14** (2.99 g, 9.91 mmol) in aqueous 50% H_3PO_2 (80 mL) was added $NaNO_2$ (1.71 g, 25.7 mmol) at 0 °C. After the reaction was completed, K_2CO_3 was added to the reaction mixture. The aqueous layer was extracted with Et_2O (60 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=8/1) to afford **15** (2.27 g, 80%) as a white solid.

R_f = 0.21 (hexane/ethyl acetate=4/1); mp 70.6–71.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (1H, d, *J* = 8.8 Hz), 6.77 (1H, dd, *J* = 8.8, 2.9 Hz), 6.71 (1H, d, *J* = 2.9 Hz), 3.80 (6H, s), 3.78 (3H, s), 1.91 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 158.0, 138.1, 131.4, 124.6, 115.1, 112.8, 59.6, 55.1, 52.8, 21.6; IR (KBr) ν_{max} 2958, 1751, 1723, 1602, 1576, 1295, 1253, 1113, 1045 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{13}H_{16}ClO_5$: 287.0686, found: 287.0699.

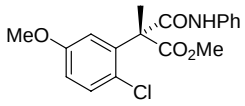
(*R*)-2-(Methoxycarbonyl)-2-(2-chloro-5-methoxyphenyl)propanoic acid (11)



To a suspension of **15** (2.27 g, 7.92 mmol) in pH 8 phosphate buffer (190 mL) was added PLE (1900 units), and the reaction mixture was stirred at 30 °C. After the reaction was completed, to the reaction mixture was added 2*N* HCl to make pH of the solution to pH 3. The aqueous layer was extracted with EtOAc (50 mL × 2), dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **11** (1.86 g, 86%) as a colorless oil.

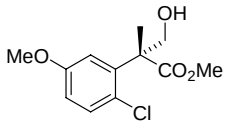
R_f = 0.18 (dichloromethane/methanol=10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.35 (1H, br), 7.29 (1H, d, *J* = 8.8 Hz), 7.02 (1H, d, *J* = 2.9 Hz), 6.84 (1H, dd, *J* = 8.8, 2.9 Hz), 3.83 (3H, s), 3.79 (3H, s), 1.98 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 171.8, 158.4, 137.2, 130.5, 124.9, 115.6, 113.5, 56.5, 55.5, 54.2, 23.2; IR (neat) ν_{max} 2956, 1744, 1604, 1578, 1414, 1296, 1250, 1114, 1044 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{12}H_{14}ClO_5$: 273.0530, found: 273.0540; $[\alpha]_D^{21}$ +27.1 (*c* 1.44, $CHCl_3$); 99% ee (For the determination of ee, see the experiment for **11'**.).

(*R*)-Methyl 2-(phenylcarbamoyl)-2-(2-chloro-5-methoxyphenyl)propanoate (11')



To a stirred solution of **11** (72.2 mg, 0.265 mmol) in CH_2Cl_2 (2 mL) was added $(COCl)_2$ (0.069 mL, 0.794 mmol) and a catalytic amount of DMF, and the reaction mixture was stirred at room temperature. After evolution of gas ceased, all volatile materials were removed under reduced pressure affording the crude carboxylic acid chloride, which was used without further purification. To a solution of the carboxylic acid chloride in CH_2Cl_2 (2 mL) was added aniline (0.073 mL, 0.794 mmol) at 0 ºC, and the reaction mixture was stirred at room temperature. After the reaction was completed, to the reaction mixture was added H_2O (1 mL), and the aqueous layer was extracted with ether (1 mL × 3). The combined organic layer was washed with 2*N* HCl, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified by PTLC (hexane/ethyl acetate=2/1) to afford **11'** (87.3 mg, 95% (2 steps)) as a pale yellow solid.
R_f = 0.43 (hexane/ethyl acetate=2/1); mp 104.6–106.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (1H, s), 7.60 (2H, dd, *J* = 8.3, 1.2 Hz), 7.32 (2H, dd, *J* = 8.3, 7.3 Hz), 7.26 (1H, d, *J* = 8.5 Hz), 7.10 (1H, tt, *J* = 7.3, 1.2 Hz), 7.02 (1H, d, *J* = 2.9 Hz), 6.80 (1H, dd, *J* = 8.5, 2.9 Hz), 3.80 (3H, s), 3.74 (3H, s), 1.99 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 168.1, 158.4, 139.1, 137.9, 130.4, 128.9, 125.2, 124.3, 120.0, 115.8, 113.1, 57.8, 55.4, 53.5, 24.0; IR (KBr) ν_{max} 2951, 1720, 1678, 1599, 1549, 1298, 1270, 1126, 1038 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{18}H_{19}NClO_4$: 348.1003, found: 348.1001; $[\alpha]_D^{21}$ −16.5 (*c* 1.49, $CHCl_3$); 99% ee; ee was determined by HPLC; DICEL CHIRALCEL OD–H 0.46 cm ϕ × 25 cm; hexane/isopropanol=9/1; flow rate=0.5 mL/min; retention time: 16.6 min for (*S*)–methyl 2–(phenylcarbamoyl)–2–(2–chloro–5–methoxyphenyl)propanoate, 19.3 min for (*R*)–methyl 2–(phenylcarbamoyl)–2–(2–chloro–5–methoxyphenyl)propanoate.

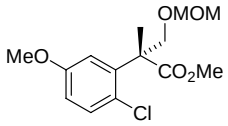
(*R*)-Methyl 2-(2-chloro-5-methoxyphenyl)-3-hydroxy-2-methylpropanoate (16)



16 was prepared from **11** in 93%yield (2 steps) according to the procedure for **5**.
R_f = 0.22 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, d, *J* = 8.8 Hz), 6.98 (1H, d, *J* = 2.9 Hz), 6.77 (1H, dd, *J* = 8.8, 2.9 Hz), 4.32 (1H, d, *J* = 11.5 Hz), 3.81 (3H, s), 3.72 (3H, s), 3.55 (1H, d, *J* = 11.5 Hz), 2.76 (1H, br), 1.71 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 158.5, 139.1, 131.3, 125.0, 115.2, 113.0, 67.2, 55.5, 52.5, 51.6, 21.2;

IR (neat) ν_{max} 3444, 2952, 1732, 1602, 1576, 1414, 1296, 1246, 1114, 1048 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{12}H_{16}ClO_4$: 259.0737, found: 259.0734; $[\alpha]_D^{22}$ +52.3 (*c* 1.61, $CHCl_3$).

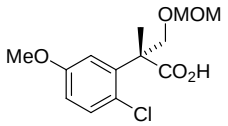
(*R*)-Methyl 2-(2-chloro-5-methoxyphenyl)-3-(methoxymethoxy)-2-methylpropanoate (17)



17 was prepared from **16** in 93% yield according to the procedure for **6**.

R_f = 0.44 (hexane/ethyl acetate=2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (1H, d, *J* = 8.5 Hz), 6.94 (1H, d, *J* = 2.9 Hz), 6.75 (1H, dd, *J* = 8.5, 2.9 Hz), 4.58 (1H, d, *J* = 6.6 Hz), 4.52 (1H, d, *J* = 6.6 Hz), 4.12 (1H, d, *J* = 9.5 Hz), 4.01 (1H, d, *J* = 9.5 Hz), 3.80 (3H, s), 3.70 (3H, s), 3.23 (3H, s), 1.67 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 158.2, 140.2, 131.1, 124.9, 115.6, 112.5, 96.5, 71.2, 55.4, 55.2, 52.4, 50.9, 21.7; IR (neat) ν_{max} 2948, 1736, 1602, 1576, 1470, 1296, 1250, 1110, 1046 cm^{-1}; HRMS (FAB) $[M]^+$ caluculated for $C_{14}H_{19}ClO_5$: 302.0921, found: 302.0912; $[\alpha]_D^{22}$ +10.5 (*c* 0.84, $CHCl_3$).

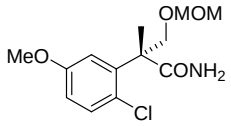
(*R*)-2-(2-Chloro-5-methoxyphenyl)-3-(methoxymethoxy)-2-methylpropanoic acid (18)



18 was prepared from **17** in 97% yield according to the procedure for **7**.

R_f = 0.50 (dichloromethane/methanol=2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, d, *J* = 8.8 Hz), 6.94 (1H, d, *J* = 2.9 Hz), 6.76 (1H, dd, *J* = 8.8, 2.9 Hz), 4.60 (1H, d, *J* = 6.6 Hz), 4.54 (1H, d, *J* = 6.6 Hz), 4.12 (1H, d, *J* = 9.5 Hz), 4.03 (1H, d, *J* = 9.5 Hz), 3.80 (3H, s), 3.24 (3H, s), 1.72 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 158.2, 139.4, 131.2, 125.0, 115.6, 112.8, 96.5, 70.9, 55.5, 55.3, 50.9, 21.6; IR (neat) ν_{max} 3084, 2944, 1710, 1602, 1576, 1472, 1294, 1244, 1152, 1046 cm^{-1}; HRMS (FAB) $[M]^+$ caluculated for $C_{13}H_{17}ClO_5$: 288.0765, found: 288.0755; $[\alpha]_D^{24}$ +10.9 (*c* 1.92, $CHCl_3$).

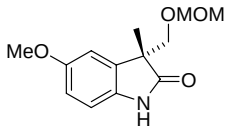
(*R*)-2-(2-Chloro-5-methoxyphenyl)-3-(methoxymethoxy)-2-methylpropanamide (19)



19 was prepared from **18** according to the procedure for **3**.

The crude amide **19** was used for the next step without further purification.

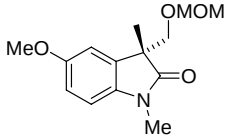
(*R*)-5-Methoxy-3-((methoxymethoxy)methyl)-3-methylindolin-2-one (20)



20 was prepared from **19** in 96% yield (3 steps) according to the procedure for **8**.

R_f = 0.20 (hexane/ethyl acetate=1/1); mp 77.4–79.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (1H, s), 6.87 (1H, d, *J* = 2.4 Hz), 6.86 (1H, d, *J* = 8.3 Hz), 6.74 (1H, dd, *J* = 8.3, 2.4 Hz), 4.52 (1H, d, *J* = 6.6 Hz), 4.48 (1H, d, *J* = 6.6 Hz), 3.83 (1H, d, *J* = 9.3 Hz), 3.79 (3H, s), 3.78 (1H, d, *J* = 9.3 Hz), 3.24 (3H, s), 1.37 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.7, 155.7, 134.5, 134.3, 112.3, 110.4, 110.2, 96.2, 71.6, 55.7, 55.1, 50.0, 19.7; IR (KBr) ν_{max} 3283, 1721, 1682, 1493, 1200, 1116, 1049, 1030 cm^{-1}; HRMS (FAB) $[M]^+$ caluculated for $C_{13}H_{17}NO_4$: 251.1158, found: 251.1161; $[\alpha]_D^{21}$ −36.6 (*c* 1.34, $CHCl_3$).

(*R*)-5-Methoxy-3-((methoxymethoxy)methyl)-1,3-dimethylindolin-2-one (20')

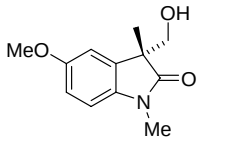


20' was prepared from **20** according to the procedure for **9**.

The crude **20'** was sufficiently pure, and was used for the next step without further purification.

R_f = 0.30 (hexane/ethyl acetate=1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (1H, d, *J* = 2.4 Hz), 6.80 (1H, dd, *J* = 8.3, 2.4 Hz), 6.76 (1H, d, *J* = 2.4 Hz), 4.50 (1H, d, *J* = 6.6 Hz), 4.45 (1H, d, *J* = 6.6 Hz), 3.80 (3H, s), 3.78 (1H, d, *J* = 9.3 Hz), 3.77 (1H, d, *J* = 9.3 Hz), 3.21 (3H, s), 3.17 (3H, s), 1.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 155.9, 137.1, 134.1, 111.9, 110.6, 108.1, 96.3, 71.7, 55.8, 55.1, 49.3, 26.3, 19.8; IR (neat) ν_{max} 2944, 1712, 1500, 1148, 1112, 1042 cm^{-1}; HRMS (FAB) $[M]^+$ caluculated for $C_{14}H_{19}NO_4$: 265.1314, found: 265.1311; $[\alpha]_D^{26}$ −47.3 (*c* 1.32, $CHCl_3$).

(*R*)-3-(Hydroxymethyl)-5-methoxy-1,3-dimethylindolin-2-one (21)

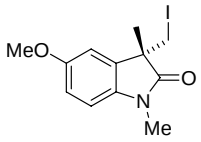


21 was prepared from **20'** in 73% yield (2 steps) according to the procedure for **2**.

R_f = 0.11 (hexane/ethyl acetate=1/1); mp 133.7–139.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (1H, d, *J* = 2.4 Hz), 6.82 (1H, dd, *J* = 8.3, 2.4 Hz), 6.78 (1H, d, *J* = 8.3 Hz), 3.83 (1H, d, *J* = 10.7 Hz), 3.80 (3H, s), 3.73 (1H, d, *J* = 10.7 Hz), 3.20 (3H, s), 1.40 (3H, s); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 179.5, 156.2, 137.0, 133.1, 112.2, 110.5, 108.5, 67.6, 55.8, 50.3, 26.3, 19.0; IR (KBr) ν_{max} 3385, 2927, 1686, 1493, 1294, 1042 cm^{-1}; HRMS (FAB) $[M]^+$ caluculated for $C_{12}H_{15}NO_3$: 221.1052, found: 221.1048; $[\alpha]_D^{26}$ −15.7 (*c* 0.84, $CHCl_3$).

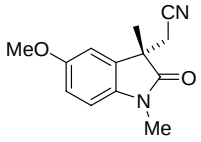
(*S*)-3-(Iodomethyl)-5-methoxy-1,3-dimethylindolin-2-one (22)



To a stirred solution of **21** (127 mg, 0.574 mmol) in toluene (5 mL) was added imidazole (117 mg, 1.72 mmol), PPh_3 (452 mg, 1.72 mmol), and I_2 (364 mg, 1.44 mmol) successively at room temperature, and the mixture was refluxed. After the reaction was completed, a mixture of saturated aqueous $NaHCO_3$ solution (3 mL) and saturated aqueous $Na_2S_2O_3$ solution (3 mL) were added to the reaction mixture, and the aqueous layer was extracted with Et_2O (5 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **22** (125 mg, 66%) as a colorless solid.

R_f = 0.52 (hexane/ethyl acetate=1/1); mp 114.0−116.0 ºC; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (1H, d, *J* = 2.4 Hz), 6.86 (1H, dd, *J* = 8.5, 2.4 Hz), 6.79 (1H, d, *J* = 8.5 Hz), 3.82 (3H, s), 3.51 (1H, d, *J* = 9.8 Hz), 3.41 (1H, d, *J* = 9.8 Hz), 3.23 (3H, s), 1.51 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 156.0, 136.6, 133.9, 112.5, 110.3, 108.5, 55.8, 48.9, 26.4, 23.0, 10.8; IR (KBr) ν_{max} 1705, 1693, 1498, 1224 cm^{-1}; HRMS (FAB) $[M]^+$ caluculated for $C_{12}H_{14}INO_2$: 331.0069, found: 331.0070; $[\alpha]_D^{28}$ −17.3 (*c* 1.35, $CHCl_3$).

2-((*S*)-5-Methoxy-1,3-dimethyl-2-oxoindolin-3-yl)acetonitrile (10)



To a stirred solution of **22** (75.3 mg, 0.227 mmol) in DMSO (3 mL) was added a NaCN (44.6 mg, 0.910 mmol), and the reaction mixture was stirred at 80 ºC. After the starting material disappeared, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (3 mL). The aqueous layer was extracted with Et_2O (5 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=2/1) to afford **10** (45.0 mg, 86%) as a colorless oil.

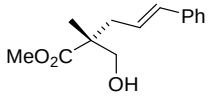
R_f = 0.35 (hexane/ethyl acetate=1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.10 (1H, d, *J* = 2.4

Hz), 6.87 (1H, dd, J = 8.5, 2.4 Hz), 6.82 (1H, d, J = 8.5 Hz), 3.82 (3H, s), 3.23 (3H, s), 2.85 (1H, d, J = 16.6 Hz), 2.57 (1H, d, J = 16.6 Hz), 1.52 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 156.4, 136.0, 132.2, 116.5, 113.4, 110.4, 109.1, 55.8, 45.2, 26.5, 26.3, 22.1; IR (neat) ν_{max} 1712, 1602, 1506, 1454, 1292, 1042 cm^{-1}; HRMS (FAB) $[M]^+$ caluculated for $C_{13}H_{14}N_2O_2$: 230.1055, found: 230.1055; $[\alpha]_D^{25}$ +58.9 (*c* 1.42, $CHCl_3$), lit. $[\alpha]_D$ +57.5 (*c* 0.50, $CHCl_3$).

第３節　抗腫瘍細胞性セスタテルペノイド(+)-ophiobolin A の不斉全合成研究

1-oxaspiro[4.4]nonane 骨格の構築：

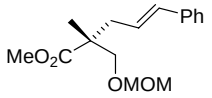
(*E*)-(*R*)-2-Hydroxymethyl-2-methyl-5-phenylpent-4-enoic acid methyl ester (7)



To a stirred solution of **6** (20.8 g, 83.8 mmol) in CH_2Cl_2 (250 mL) was added $(COCl)_2$ (21.9 mL, 251 mmol) and a catalytic amount of DMF, and the reaction mixture was stirred at room temperature. After evolution of gas ceased, all volatile materials were removed under reduced pressure affording the crude carboxylic acid chloride, which was used without further purification. To a solution of the carboxylic acid chloride in THF (500 mL) was added $NaBH_4$ (9.51 g, 251 mmol) portionwise at −30 ºC, and then was added MeOH (50 mL) at this temperature for 1.5 h. After the reaction was completed, 2*N* HCl was slowly added to the reaction mixture to adjust the solution to pH 2, and the aqueous layer was extracted with Et_2O (300 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **7** (16.2 g, 83% (2 steps)) as an oil.

R_f = 0.27 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.20 (5H, m), 6.44 (1H, d, *J* = 15.6 Hz), 6.15 (1H, ddd, *J* = 15.6, 7.6, 7.6 Hz), 3.73 (3H, s), 3.72 (1H, dd, *J* = 11.5, 7.1 Hz), 3.61 (1H, dd, *J* = 11.5, 6.3 Hz), 2.51 (2H, d, *J* = 7.6 Hz), 2.31 (1H, dd, *J* = 7.1, 6.3 Hz), 1.22 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 137.2, 133.5, 128.5, 127.3, 126.1, 124.8, 67.8, 52.0, 48.2, 39.0, 19.5; IR (neat) ν_{max} 3420, 2956, 2364, 1732, 1212, 1126, 1040, 970, 744, 694 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{14}H_{19}O_3$: 235.1334, found: 235.1329; $[\alpha]_D^{35}$ +10.5 (*c* 1.2, $CHCl_3$).

(*E*)-(*R*)-2-Methoxymethoxymethyl-2-methyl-5-phenylpent-4-enoic acid methyl ester (8)

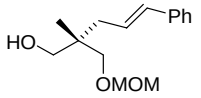


To a stirred solution of **7** (16.2 g, 69.2 mmol) in CH_2Cl_2 (400 mL) was added NaI (2.07 g, 13.8 mmol), DIPEA (72.3 mL, 415 mmol), and MOMCl (21.0 mL, 277 mmol) successively at room temperature, and the mixture was refluxed. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (300 mL) was slowly added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (200 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was

purified by flash chromatography (hexane/ethyl acetate=8/1) to afford the titled MOM ether **8** (19.1 g, 99%) as an oil.

R_f = 0.37 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.19 (5H, m), 6.43 (1H, d, *J* = 15.6 Hz), 6.12 (1H, ddd, *J* = 15.6, 7.8, 7.6 Hz), 4.61 (2H, s), 3.70 (3H, s), 3.66 (1H, d, *J* = 9.3 Hz), 3.55 (1H, d, *J* = 9.3 Hz), 3.35 (3H, s), 2.56 (1H, dd, *J* = 13.7, 7.6 Hz), 2.45 (1H, dd, *J* = 13.7, 7.8 Hz), 1.26 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 137.3, 133.4, 128.5, 127.2, 126.1, 125.0, 96.6, 72.7, 55.2, 51.8, 47.4, 39.1, 19.8; IR (neat) ν_{max} 3032, 2952, 2888, 1732, 1458, 1436, 1216, 1150, 1112, 1048, 970, 920, 744, 694 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{16}H_{23}O_4$: 279.1596, found: 279.1596; $[\alpha]_D^{24}$ +5.4 (*c* 1.1, $CHCl_3$).

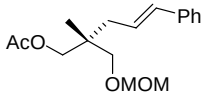
(*E*)-(*S*)-2-Methoxymethoxymethyl-2-methyl-5-phenylpent-4-en-1-ol (8')



To a stirred solution of $LiAlH_4$ (2.44 g, 51.5 mmol) in Et_2O (350 mL) was added a solution of **8** (19.1 g, 68.6 mmol) in Et_2O (30 mL) dropwise at 0 ºC, and the reaction mixture was stirred at room temperature. After the reaction was completed, saturated aqueous Na_2SO_4 solution was slowly added dropwise to the reaction mixture till no gas evolution was observed, and the precipitated solid was filtered off through a Celite pad. The filtrate and washings were combined, and concentrated under reduced pressure. The residue, crude **8'**, was used without further purification.

R_f = 0.28 (hexane/ethyl acetate=2/1).

(*E*)-(*R*)-Acetic acid 2-methoxymethoxymethyl-2-methyl-5-phenylpent-4-enyl ester (9)

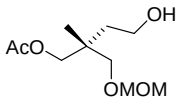


To a stirred solution of crude **8'** obtained as above in CH_2Cl_2 (400 mL) was added pyridine (6.66 mL, 82.4 mmol), DMAP (839 mg, 6.86 mmol), Ac_2O (7.77 mL, 82.4 mmol) successively at room temperature. After the reaction was completed, saturated aqueous NH_4Cl solution (300 mL) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (200 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=8/1) to afford the titled acetate **9** (19.2 g, 96% (2 steps)) as an oil.

R_f = 0.34 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.18 (5H, m), 6.41 (1H, d, *J* = 15.6 Hz), 6.19 (1H, ddd, *J* = 15.6, 7.6, 7.6 Hz), 4.61 (2H, s), 3.99 (2H, s),

3.38 (1H, d, J = 9.3 Hz), 3.36 (1H, d, J = 9.3 Hz), 3.35 (3H, s), 2.27 (1H, ddd, J = 13.7, 7.6, 1.2 Hz), 2.25 (1H, ddd, J = 13.7, 7.6, 1.2 Hz), 2.07 (3H, s), 0.98 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 137.4, 133.2, 128.5, 127.1, 126.0, 125.3, 96.7, 71.7, 68.4, 55.2, 38.5, 38.3, 20.9, 19.3; IR (neat) ν_{max} 2936, 2888, 1740, 1242, 1150, 1112, 1048, 970, 918, 744, 694 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{17}H_{25}O_4$: 293.1753, found: 293.1752; $[\alpha]_D^{24}$ +2.4 (c 1.1, $CHCl_3$).

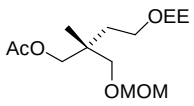
(*R*)-Acetic acid 4-hydroxy-2-methoxymethoxymethyl-2-methylbutyl ester (10)



Into a stirred solution of **9** (5.14 g, 17.6 mmol) in MeOH (150 mL) was bubbled O_3 at −78 °C till the starting material was consumed. Then, $NaBH_4$ (1.66 g, 43.9 mmol) was added portionwise to the reaction mixture and the reaction mixture was wormed up to 0 °C with stirring. After the reaction was completed, saturated aqueous NH_4Cl solution (100 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (100 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=8/1) to afford **10** (3.65 g, 94% (2 steps)) as an oil.

R_f = 0.23 (hexane/ethyl acetate=1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.61 (2H, s), 3.98 (1H, d, J = 11.0 Hz), 3.96 (1H, d, J = 11.0 Hz), 3.73 (1H, ddd, J = 13.2, 6.6, 6.6 Hz), 3.72 (1H, ddd, J = 13.2, 6.6, 6.6 Hz), 3.40 (2H, s), 3.35 (3H, s), 2.07 (3H, s), 1.68 (1H, ddd, J = 14.2, 6.6, 6.6 Hz), 1.63 (1H, ddd, J = 14.2, 6.6, 6.6 Hz), 0.98 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 96.7, 72.2, 68.7, 58.6, 55.4, 38.2, 37.2, 20.9, 19.9; IR (neat) ν_{max} 3400, 2944, 2892, 1742, 1248, 1150, 1114, 1048 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{10}H_{21}O_5$: 221.1389, found: 221.1386; $[\alpha]_D^{25}$ −1.2 (c 1.1, $CHCl_3$).

(*R*)-Acetic acid 4-(1-ethoxyethoxy)-2-methoxymethoxymethyl-2-methylbutyl ester (11)

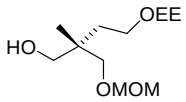


To a stirred solution of **10** (15.4 g, 70.0 mmol) in CH_2Cl_2 (400 mL) was added ethyl vinyl ether (10.1 mL, 105 mmol), PPTS (1.76 g, 7.00 mmol) successively at room temperature. After the reaction was completed, triethylamine (1.2 mL) was added to the reaction mixture, and the resultant mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=8/1) to afford the

titled ethoxyethylether **11** (19.6 g, 96%) as an oil.

R_f = 0.48 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (1H, q, J = 5.4 Hz), 4.59 (2H, s), 3.96 (2H, s), 3.70–3.58 (2H, m), 3.52–3.44 (2H, m), 3.37–3.30 (2H, m), 3.34 (3H, s), 2.06 (3H, s), 1.60–1.70 (2H, m), 1.30 (3H, d, J = 5.4 Hz), 1.20 (3H, t, J = 7.1 Hz), 0.97 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 99.6, 99.5, 96.6, 72.0, 68.5, 61.2, 60.6, 55.1, 37.0, 34.4, 20.8, 19.8, 19.5, 15.3; IR (neat) ν_{max} 2980, 2936, 2888, 1742, 1242, 1150, 1132, 1112, 1048 cm^{-1}; HRMS (FAB) $[M-EtO]^+$ calculated for $C_{12}H_{23}O_5$: 247.1545, found: 247.1545.

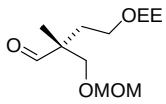
(*S*)-4-(1-Ethoxyethoxy)-2-methoxymethoxymethyl-2-methylbutan-1-ol (11')



To a stirred solution of **11** (4.62 g, 15.8 mmol) in MeOH (120 mL) was added K_2CO_3 (6.55 g, 47.4 mmol) at room temperature. After the reaction was completed, saturated aqueous NH_4Cl solution (80 mL) was added to the reaction mixture. The resultant solution was concentrated under reduced pressure, and the residue was extracted with Et_2O (80 mL × 2). The combined organic layer was dried (Na_2SO_4), and purified by flash chromatography (hexane/ethyl acetate=2/1) to afford the titled alcohol **11'** (3.91 g, 99%) as an oil.

R_f = 0.24 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (1H, q, J = 5.4 Hz), 4.61 (2H, s), 3.72 (1H, m), 3.64 (1H, m), 3.55–3.36 (6H, m), 3.36 (3H, s), 3.06 (1/2H, t, J = 6.8 Hz), 3.05 (1/2H, t, J = 6.8 Hz), 1.71 (1H, m), 1.59 (1H, m), 1.32 (3H, d, J = 5.4 Hz), 1.21 (3H, t, J = 7.1 Hz), 0.93 (3/2H, s), 0.92 (3/2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.7, 96.7, 74.2, 68.4, 61.6, 61.3, 60.9, 55.2, 38.6, 34.7, 34.6, 19.8, 19.7, 15.4; IR (neat) ν_{max} 3476, 2980, 2936, 2884, 1384, 1148, 1110, 1046 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{12}H_{27}O_5$: 251.1858, found: 251.1858.

(*R*)-4-(1-Ethoxyethoxy)-2-methoxymethoxymethyl-2-methylbutyraldehyde (12)

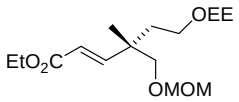


To a stirred solution of **11'** (3.87 g, 15.5 mmol) in CH_2Cl_2 (120 mL) was added DMSO (21.9 mL, 309 mmol), Et_3N (21.5 mL, 155 mmol), and SO_3·Py (12.3 g, 77.3 mmol) successively at 0 °C. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (200 mL) was slowly added to the reaction mixture and the aqueous layer was

extracted with Et_2O (200 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=6/1) to afford **12** (3.76 g, 98%) as an oil.

R_f = 0.44 (hexane/ethyl acetate=2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.55 (1H, s), 4.63 (1/2H, q, *J* = 5.4 Hz), 4.61 (1/2H, q, *J* = 5.4 Hz), 4.59 (2H, s), 3.69–3.51 (4H, m), 3.49–3.41 (2H, m), 3.34 (3H, s), 2.04–1.94 (1H, m), 1.79–1.70 (1H, m), 1.26 (3/2H, d, *J* = 5.4 Hz), 1.25 (3/2H, d, *J* = 5.4 Hz), 1.19 (3H, t, *J* = 7.1 Hz), 1.14 (3/2H, s), 1.13 (3/2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 99.7, 99.5, 96.6, 71.3, 71.2, 60.7, 60.5, 55.3, 48.9, 48.8, 33.4, 19.5, 16.7, 16.5, 15.3; IR (neat) ν_{max} 2984, 2940, 2892, 1730, 1382, 1148, 1112, 1048 cm^{-1}; HRMS (FAB) $[M+Na]^+$ calculated for $C_{12}H_{24}O_5Na$: 271.1521, found: 271.1516.

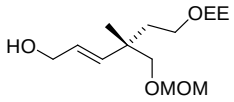
(*E*)-(*S*)-6-(1-Ethoxyethoxy)-4-methoxymethoxymethyl-4-methylhex-2-enoic acid ethyl ester (12')



To a stirred solution of *t*–BuOK (2.94 g, 26.2 mmol) in THF (100 mL) was added triethyl phosphonoacetate (7.81 mL, 39.4 mmol) at 0 ºC. After stirring for 10 min, a solution of **12** in THF (10 mL) was added dropwise at −78 ºC. Then the reaction mixture was warmed up to room temperature and was stirred. After the reaction was completed, saturated aqueous NH_4Cl solution (80 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (80 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=8/1) to afford the titled ester **12'** (4.18 g, 100%) as an oil.

R_f = 0.49 (hexane/ethyl acetate=2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (1H, d, *J* = 16.1 Hz), 5.81 (1H, d, *J* = 16.1 Hz), 4.65 (1/2H, q, *J* = 5.4 Hz), 4.64 (1/2H, q, *J* = 5.4 Hz), 4.60 (2H, s), 4.19 (2H, q, *J* = 7.3 Hz), 3.64–3.54 (2H, m), 3.52–3.35 (4H, m), 3.34 (3H, s), 1.85–1.71 (2H, m), 1.29 (3H, t, *J* = 7.3 Hz), 1.28 (3H, d, *J* = 5.4 Hz), 1.19 (3H, t, *J* = 7.1 Hz), 1.13 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 154.0, 119.8, 99.6, 99.5, 96.6, 74.6, 74.5, 61.5, 61.4, 60.5, 60.2, 55.3, 40.0, 37.0, 21.2, 21.1, 19.8, 15.3, 14.2; IR (neat) ν_{max} 2984, 2940, 2888, 1722, 1370, 1148, 1112, 1050 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{16}H_{31}O_6$: 319.2121, found: 319.2122.

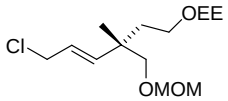
(*E*)-(*S*)-6-(1-Ethoxyethoxy)-4-methoxymethoxymethyl-4-methylhex-2-en-1-ol (13)



To a stirred solution of **12'** (6.37 g, 20.0 mmol) in CH_2Cl_2 (150 mL) was added a solution of DIBAL–H in toluene (53.2 mL, 0.94 M) at −78 ºC. After the reaction was completed, MeOH was added to the reaction mixture at −78 ºC till no gas evolution was observed. Then, saturated aqueous Rochelle salt solution (100 mL) was added to the reaction mixture and the resultant solution was stirred vigorously at room temperature. After 30 min, the aqueous layer was extracted with CH_2Cl_2 (80 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=2/1) to afford the titled alcohol **13** (5.45 g, 100%) as an oil.

R_f = 0.18 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (1H, d, *J* = 15.9 Hz), 5.65 (1H, dt, *J* = 15.9, 5.1 Hz), 4.65 (1H, q, *J* = 5.4 Hz), 4.60 (2H, s), 4.14 (2H, dd, *J* = 5.4, 5.1 Hz), 3.65–3.56 (2H, m), 3.51–3.37 (2H, m), 3.35 (3H, s), 3.33 (2H, s), 1.74–1.69 (2H, m), 1.29 (3H, d, *J* = 5.4 Hz), 1.20 (3H, t, *J* = 7.1 Hz), 1.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 127.6, 99.6, 99.5, 96.7, 75.6, 63.8, 61.8, 60.6, 60.5, 55.2, 38.9, 37.3, 21.6, 19.9, 19.8, 15.3; IR (neat) ν_{max} 3436, 2980, 2936, 2884, 1384, 1148, 1110, 1048 cm^{-1}; HRMS (FAB) $[M-EtO]^+$ calculated for $C_{12}H_{23}O_4$: 231.1596, found: 231.1596.

(*E*)-(*S*)-1-Chloro-6-(1-ethoxyethoxy)-4-methoxymethoxymethyl-4-methylhex-2-ene (14)

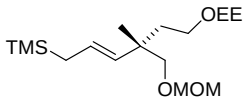


To a stirred solution of **13** (5.45 g, 19.7 mmol) in DMF (120 mL) was added LiCl (3.34 g, 78.9 mmol), 2,6–lutidine (9.19 mL, 78.9 mmol), MsCl (3.05 mL, 39.4 mmol) successively at 0 ºC. After the reaction was completed, saturated aqueous NH_4Cl solution (80 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (200 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=20/1) to afford **14** (5.60 g, 96%) as an oil.

R_f = 0.42 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (1H, d, *J* = 15.6 Hz), 5.62 (1H, dt, *J* = 15.6, 6.8 Hz), 4.65 (1H, q, *J* = 5.4 Hz), 4.60 (2H, s), 4.06 (2H, d, *J* = 6.8 Hz), 3.66–3.55 (2H, m), 3.51–3.38 (2H, m), 3.35 (3H, s), 3.33 (2H, s), 1.78–1.67 (2H, m), 1.29 (3H, d, *J* = 5.4 Hz), 1.20 (3H, t, *J* = 7.1 Hz), 1.08 (3H, s); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 141.0, 124.6, 99.6, 96.7, 75.3, 61.7, 60.6, 55.2, 45.5, 39.2, 37.2, 21.5, 19.8, 15.3; IR (neat) ν_{max} 2980, 2940, 2888, 1382, 1150, 1132, 1112, 1048 cm^{-1}; HRMS (FAB) $[M-EtO]^+$ calculated for $C_{12}H_{22}ClO_3$: 249.1257, found: 249.1258.

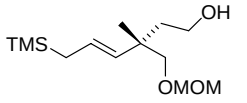
(*E*)-(*S*)-[6-(1-Ethoxyethoxy)-4-methoxymethoxymethyl-4-methylhex-2-enyl]trimethylsilane (15)



To a stirred solution of hexamethyldisilane (2.47 mL, 12.1 mmol) in HMPA (5 mL) was added a solution of MeLi in Et_2O (13.1 mL, 0.92 M) dropwise at 0 °C, and the resultant red solution was stirred at this temperature for 3 min. Then the solution was diluted with Et_2O (20 mL) and the diluted solution was cooled to −60 °C. After 5 min, a solution of **14** (1.19 g, 4.02 mmol) in Et_2O (3 mL) was added to the reaction mixture dropwise, and stirring was continued at the same temperature. After the reaction was completed, saturated aqueous NH_4Cl solution (15 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=20/1) to afford the titled allyltrimethylsilane **15** (1.14 g, 86%) as an oil.

R_f = 0.56 (hexane/ethyl acetate=4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.40 (1H, dt, J= 15.6, 7.8 Hz), 5.24 (1H, d, J= 15.6 Hz), 4.67 (1H, q, J= 5.4 Hz), 4.61 (2H, s), 3.68−3.57 (2H, m), 3.52−3.41 (2H, m), 3.36 (3H, s), 3.29 (1H, d, J = 9.3 Hz), 3.27 (1H, d, J = 9.3 Hz), 1.73−1.68 (2H, m), 1.45 (2H, d, J= 7.8 Hz), 1.30 (3H, d, J= 5.4 Hz), 1.21 (3H, t, J= 7.1 Hz), 1.05 (3H, s), 0.00 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 124.8, 99.6, 96.7, 76.3, 62.2, 62.1, 60.6, 55.1, 39.0, 37.6, 23.0, 22.0, 19.9, 15.3, −2.0; IR (neat) ν_{max} 2960, 2884, 2364, 1382, 1250, 1150, 1112, 1052, 854 cm^{-1}; HRMS (FAB) $[M-EtO]^+$ calculated for $C_{15}H_{31}O_3Si$: 287.2042, found: 287.2043.

(*E*)-(*S*)-3-Methoxymethoxymethyl-3-methyl-6-trimethylsilanylhex-4-en-1-ol (16)

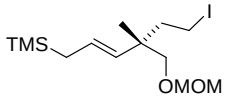


To a stirred solution of **15** (3.89 g, 11.7 mmol) in EtOH (80 mL) was added PPTS (2.94 g, 11.7 mmol) at room temperature. After the reaction was completed, triethylamine (2.0 mL) was added to the reaction mixture, and the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl

acetate=4/1) to afford the titled alcohol **16** (3.05 g, 100%) as an oil.

R_f = 0.44 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (1H, dt, *J* = 15.6, 7.8 Hz), 5.29 (1H, d, *J* = 15.6 Hz), 4.63 (2H, s), 3.69 (2H, dd, *J* = 6.6, 6.6 Hz), 3.37 (3H, s), 3.36 (1H, d, *J* = 9.3 Hz), 3.29 (1H, d, *J* = 9.3 Hz), 2.08 (1H, br), 1.71 (2H, ddd, *J* = 6.6, 6.6, 1.5 Hz), 1.46 (2H, dd, *J* = 7.8, 0.7 Hz), 1.06 (3H, s), 0.00 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.1, 125.0, 96.8, 76.2, 59.7, 55.3, 41.5, 39.2, 23.1, 22.4, −2.0; IR (neat) ν_{max} 3364, 2956, 2888, 1250, 1150, 1112, 1050, 856 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{13}H_{29}O_3Si$: 261.1886, found: 261.1893; $[\alpha]_D^{23}$ +7.3 (*c* 1.0, $CHCl_3$).

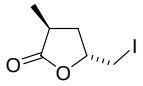
(*E*)-(*S*)-(6-Iodo-4-methoxymethoxymethyl-4-methylhex-2-enyl)trimethylsilane (Fragment A)



Imidazole (3.19 g, 46.8 mmol), PPh_3 (5.83 g, 22.2 mmol), and I_2 (5.94 g, 23.4 mmol) was added to benzene (90 mL) at room temperature with stirring, and the resultant suspension was stirred at room temperature for 30 min. Then, to the reaction mixture was added a solution of **16** (3.05 g, 11.7 mmol) in benzene (10 mL), and the resultant solution was stirred at room temperature. After the reaction was completed, a mixture of saturated aqueous $NaHCO_3$ solution (60 mL) and saturated aqueous $Na_2S_2O_3$ solution (60 mL) were added to the reaction mixture, and the aqueous layer was extracted with Et_2O (100 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=120/1) to afford **Fragment A** (3.97 g, 92%) as an oil.

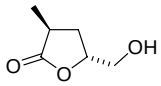
R_f = 0.53 (hexane/ethyl acetate=20/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (1H, dt, *J* = 15.9, 8.1 Hz), 5.18 (1H, d, *J* = 15.9 Hz), 4.61 (2H, s), 3.36 (3H, s), 3.29 (1H, d, *J* = 9.3 Hz), 3.24 (1H, d, *J* = 9.3 Hz), 3.13 (2H, dd, *J* = 8.5, 7.8 Hz), 2.10 (1H, ddd, *J* = 9.3, 8.5, 7.8 Hz), 2.07 (1H, ddd, *J* = 9.3, 8.5, 7.8 Hz), 1.46 (2H, dd, *J* = 8.1, 0.7 Hz), 1.02 (3H, s), 0.00 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.4, 125.9, 96.7, 75.4, 55.3, 43.5, 42.5, 23.1, 21.4, 1.0, −2.0; IR (neat) ν_{max} 2956, 2888, 1248, 1152, 1112, 1052, 852, 840 cm^{-1}; HRMS (FAB) $[M+Na]^+$ calculated for $C_{13}H_{27}IO_2SiNa$: 393.0723, found: 393.0732; $[\alpha]_D^{25}$ −6.4 (*c* 1.0, $CHCl_3$).

(3*S*,5*R*)-5-Iodomethyl-3-methyldihydrofuran-2(3*H*)-one (28)



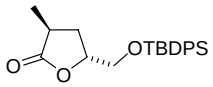
To a stirred solution of 4-isopropyl-3-(2-methylpent-4-enoyl)-oxazolidin-2-one (**27**) (376 mg, 1.67 mmol) in a mixture of ethyl acetate (12 mL) and H_2O (6 mL) was added NCS (0.379 g, 2.84 mmol), $NaHCO_3$ (351 mg, 4.17 mmol), and NaI (425 mg, 2.84 mmol) successively at room temperature. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (10 mL) and saturated aqueous $Na_2S_2O_3$ solution (10 mL) were added to the reaction mixture, and the aqueous layer was extracted with Et_2O (15 mL × 2). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford the known iodide **28** (369 mg, 92%) as an oil.

(3*S*,5*R*)-5-Hydroxymethyl-3-methyldihydrofuran-2(3*H*)-one (25)



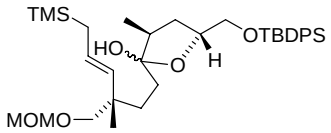
To a stirred solution of the iodide **28** (344 mg, 1.43 mmol) in DMF (14 mL) was added CF_3CO_2Na (292 mg, 2.15 mmol) at 90 ºC till the starting material was consumed. Then diethylamine (0.445 mL, 4.29 mmol) was added dropwise to the reaction mixture at room temperature, and the resultant solution was stirred at the same temperature. After the reaction was completed, H_2O (10 mL) and ethyl acetate (20 mL) were added to the reaction mixture, and the aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=2/1) to afford the known alcohol **25** (117 mg, 63%) as an oil.

(3*S*,5*R*)-5-(*tert*-Butyldiphenylsilyloxymethyl)-3-methyldihydrofuran-2(3*H*)-one (Fragment B)



To a stirred solution of the alcohol **25** (116 mg, 0.892 mmol) in CH_2Cl_2 (10 mL) was added imidazole (122 mg, 1.78 mmol) and TBDPSCl (0.278 mL, 1.07 mmol) successively at room temperature. After the reaction was completed, saturated aqueous NH_4Cl (10 mL) was added to the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2 (8 mL × 2). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=20/1) to afford **Fragment B** (319 mg, 97%) as a white solid.

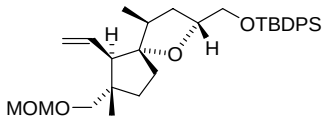
(3*S*,5*R*)-5-(*tert*-Butyldiphenylsilanyloxymethyl)-2-[(*E*)-(3*S*)-3-methoxymethoxymethyl-3-methyl-6-trimethylsilanyl-hex-4-enyl]-3-methyltetrahydrofuran-2-ol (5)



To a stirred solution of **Fragment A** (867 mg, 2.34 mmol) in Et_2O (5 mL) was added a solution of *t*–BuLi in pentane (3.14 mL, 1.49 M) dropwise at −78 ºC, and the resultant solution was stirred at this temperature for 15 min. Then, to the reaction mixture was added **Fragment B** (820 mg, 2.22 mmol) in Et_2O (2 mL) dropwise, and stirring was continued at the same temperature. After the reaction was completed, saturated aqueous NH_4Cl solution (10 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=15/1) to afford **5** (1.17 g, 86%) as a mixture of diastereomers.

R_f = 0.50 (hexane/ethyl acetate=4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74−7.64 (4H, m), 7.47−7.38 (6H, m), 5.40 (1H, dt, *J*= 15.9, 7.8 Hz), 5.18 (1H, dt, *J*= 15.9, 1.2 Hz), 4.62 (2H, s), 3.68−3.59 (2H, m), 3.44 (1H, m), 3.36 (3H, s), 3.30 (1H, d, *J*= 9.3 Hz), 3.28 (1H, d, *J*= 9.3 Hz), 2.89 (1H, m), 2.59(1H, br), 2.52−2.36 (2H, m), 1.78−1.52 (3H, m), 1.46 (2H, dd, *J* = 7.8, 1.2 Hz), 1.40−1.33 (1H, m), 1.07 (9H, s), 1.07 (3H, d, *J*= 7.1 Hz), 1.01 (3H, s), 0.00 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 133.6, 133.1, 129.8, 127.8, 125.4, 106.8, 96.7, 76.1, 69.8, 68.2, 55.1, 42.4, 39.5, 37.0, 35.7, 31.4, 26.8, 23.1, 21.6, 19.2, 17.8, −2.0; IR (neat) ν_{max} 3420, 2960, 2936, 2892, 2860, 2336, 1248, 1150, 1114, 1048, 854, 736, 702 cm^{-1}; HRMS (FAB) $[M+Na]^+$ calculated for $C_{35}H_{56}O_5Si_2Na$: 635.3564, found: 635.3582.

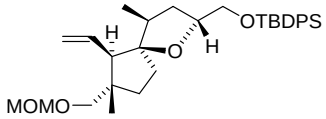
***tert*-Butyl-[(2*R*,4*S*,5*S*,6*R*,7*S*)-7-methoxymethoxymethyl-4,7-dimethyl-6-vinyl-1-oxaspiro[4.4]non-2-ylmethoxy]diphenylsilane (29a)**



To a stirred solution of **5** (10.0 mg, 0.0163 mmol) in CH_2Cl_2 (1 mL) was added a solution of $TiCl_3(Oi\text{–}Pr)$ in CH_2Cl_2 (0.049 mL, 1.0 M) at −78 ºC. After 4 h, the reaction was completed and was quenched with adding triethylamine (0.010 mL). H_2O (1 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (1 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl

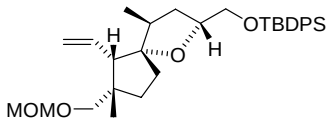
acetate=130/1) to afford **29a** (2.5 mg, 29%), **29b** (2.6 mg, 31%), and **29c** (3.4 mg, 40%). R_f = 0.33 (hexane/ethyl acetate=10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (4H, m), 7.44–7.35 (6H, m), 5.61 (1H, ddd, *J* = 16.8, 10.7, 10.0 Hz), 4.98 (1H, dd, *J* = 10.0, 2.4 Hz), 4.84 (1H, dd, *J* = 16.8, 2.4 Hz), 4.58 (2H, s), 4.03 (1H, m), 3.65 (1H, dd, *J* = 10.0, 4.4 Hz), 3.52 (1H, dd, *J* = 10.0, 6.3 Hz), 3.35–3.26 (2H, m), 3.31 (3H, s), 2.38 (1H, d, *J* = 10.7 Hz), 2.18–2.09 (1H, m), 2.05–1.99 (1H, m), 1.86–1.72 (2H, m), 1.68–1.58 (2H, m), 1.41 (1H, m), 1.04 (9H, s), 0.99 (3H, d, *J* = 7.1 Hz), 0.87 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 135.6, 133.8, 129.5, 127.6, 117.6, 96.6, 96.0, 76.5, 76.0, 66.9, 60.7, 55.0, 45.1, 37.0, 36.3, 34.6, 30.9, 26.9, 20.3, 19.2, 15.8; IR (neat) ν_{max} 2960, 2936, 2864, 1150, 1114, 1050, 704 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{32}H_{47}O_4Si$: 523.3244, found: 523.3253; $[\alpha]_D^{24}$ −13.7 (*c* 1.1, $CHCl_3$).

***tert*-Butyl-[(2*R*,4*S*,5*R*,6*R*,7*S*)-7-methoxymethoxymethyl-4,7-dimethyl-6-vinyl-1-oxaspiro[4.4]non-2-ylmethoxy]diphenylsilane (29b)**



R_f = 0.45 (hexane/ethyl acetate=10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.65 (4H, m), 7.40–7.32 (6H, m), 5.91 (1H, ddd, *J* = 17.3, 10.0, 10.0 Hz), 5.02 (1H, dd, *J* = 10.0, 2.4 Hz), 4.94 (1H, dd, *J* = 17.3, 2.4 Hz), 4.58 (2H, s), 4.09 (1H, m), 3.55 (1H, dd, *J* = 10.0, 4.4 Hz), 3.51 (1H, dd, *J* = 10.0, 5.9 Hz), 3.33 (3H, s), 3.16 (1H, d, *J* = 9.0 Hz), 3.14 (1H, d, *J* = 9.0 Hz), 2.27 (1H, d, *J* = 10.0 Hz), 2.10 (1H, m), 1.94–1.89 (1H, m), 1.75–1.65 (3H, m), 1.53 (1H, m), 1.20 (1H, m), 1.02 (9H, s), 0.95 (3H, d, *J* = 6.8 Hz), 0.94 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 135.6, 133.8, 129.4, 127.5, 116.5, 96.7, 95.8, 78.0, 75.2, 67.2, 55.1, 53.2, 46.2, 40.5, 38.0, 36.2, 34.4, 26.9, 21.0, 19.3, 14.2; IR (neat) ν_{max} 2960, 2936, 2864, 1148, 1114, 1046, 702 cm^{-1}; HRMS (FAB) $[M]^+$ calculated for $C_{32}H_{46}O_4Si$: 522.3165, found: 522.3139; $[\alpha]_D^{26}$ +4.0 (*c* 1.1, $CHCl_3$).

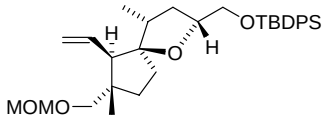
***tert*-Butyl-[(2*R*,4*S*,5*S*,6*S*,7*S*)-7-methoxymethoxymethyl-4,7-dimethyl-6-vinyl-1-oxaspiro[4.4]non-2-ylmethoxy]diphenylsilane (29c)**



R_f = 0.39 (hexane/ethyl acetate=10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.65 (4H, m), 7.44–7.35 (6H, m), 5.73 (1H, ddd, *J* = 17.1, 10.3, 10.3 Hz), 4.97 (1H, dd, *J* = 10.3, 2.4 Hz), 4.92 (1H, dd, *J* = 17.1, 2.4 Hz), 4.60 (2H, s), 4.02 (1H, m), 3.64 (1H, d, *J* = 9.0 Hz), 3.55

(1H, dd, J = 10.3, 5.1 Hz), 3.47 (1H, dd, J = 10.3, 6.1 Hz), 3.33 (3H, s), 3.29 (1H, d, J = 9.0 Hz), 2.02–1.83 (2H, m), 1.89 (1H, d, J = 10.3 Hz), 1.69–1.50 (3H, m), 1.31–1.23 (2H, m), 1.06 (3H, s), 1.04 (9H, s), 0.91 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 134.6, 133.8, 133.7, 129.5, 129.4, 127.5, 117.8, 96.7, 94.7, 76.0, 73.4, 66.3, 61.1, 55.0, 45.1, 36.2, 35.3, 34.6, 30.2, 26.9, 25.1, 19.3, 14.2; IR (neat) ν_{max} 2960, 2936, 2872, 1146, 1114, 1050, 738, 704 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{32}H_{47}O_4Si$: 523.3244, found: 523.3229; $[\alpha]_D^{23}$ −22.2 (*c* 0.6, $CHCl_3$).

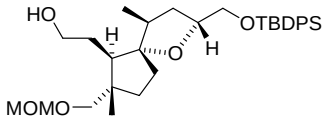
tert-Butyl[(2*R*,4*R*,5*R*,6*R*,7*S*)-7-methoxymethoxymethyl-4,7-dimethyl-6-vinyl-1-oxaspiro[4.4]non-2-ylmethoxy]diphenylsilane (29d)



To a stirred solution of **5** (9.5 mg, 0.0155 mmol) in CH_2Cl_2 (1 mL) was added a solution of $TiCl(O\textit{i}\text{-}Pr)_3$ in CH_2Cl_2 (0.047 mL, 1.0 M) at −78 °C. Stirring was continued at −78 °C at 4 h, then at −50 °C for 2 h, and finally at −20 °C for 12 h. After the reaction was completed, the reaction was quenched with triethylamine (0.010 mL). H_2O (1 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (1 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=30/1) to afford **29d** (6.8 mg, 84%).

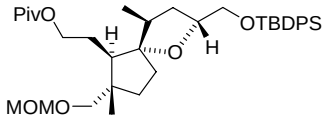
R_f = 0.42 (hexane/ethyl acetate=10/1); mp 94–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.70 (4H, m), 7.43–7.35 (6H, m), 5.91 (1H, ddd, J = 17.3, 10.0, 9.8 Hz), 5.12 (1H, dd, J = 10.0, 2.4 Hz), 4.95 (1H, dd, J = 17.3, 2.4 Hz), 4.62 (2H, s), 3.91 (1H, m), 3.67 (1H, dd, J = 10.5, 4.4 Hz), 3.62 (1H, dd, J = 10.5, 4.6 Hz), 3.36 (3H, s), 3.22 (2H, s), 2.09 (1H, m), 2.09 (1H, d, J = 9.8 Hz), 1.95–1.89 (1H, m), 1.73–1.56 (4H, m), 1.47 (1H, m), 1.04 (9H, s), 1.03 (3H, s), 0.96 (3H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 135.6, 133.8, 133.7, 129.4, 127.5, 117.8, 96.7, 94.8, 78.6, 75.8, 66.7, 56.3, 55.1, 44.6, 38.5, 36.4, 34.8, 32.8, 26.8, 20.9, 19.3, 14.4; IR (KBr) ν_{max} 2952, 2866, 1464, 1427, 1385, 1107, 1047, 1003, 916, 812, 744, 706 cm^{-1}; HRMS (FAB) $[M]^+$ calculated for $C_{32}H_{46}O_4Si$: 522.3165, found: 522.3152; $[\alpha]_D^{24}$ +35.8 (*c* 0.5, $CHCl_3$).

2-[(2*R*,4*S*,5*S*,6*R*,7*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-7-methoxymethoxymethyl-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethanol (29a')



To a stirred solution of **29a** (31.5 mg, 0.0603mmol) in THF (1 mL) was added a solution of 9−BBN in THF (0.362 mL, 0.5 M) dropwise at 0 ºC, and the resultant solution was stirred at room temperature. After the starting material disappeared, 3*N* NaOH solution (0.2 mL) and 30 % H_2O_2 solution (0.2 mL) was added to the reaction mixture and the resultant mixture was stirred at room temperature. After the reaction was completed, H_2O (1 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (1 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **29a'** (32.5 mg, 100%) as an oil.
R_f = 0.35 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.65 (4H, m), 7.43−7.34 (6H, m), 4.61 (2H, s), 3.92 (1H, m), 3.66 (1H, dd, *J* = 10.3, 4.6 Hz), 3.63−3.55 (2H, m), 3.59 (1H, dd, *J* = 10.3, 5.9 Hz), 3.34 (3H, s), 3.31 (1H, d, *J* = 9.0 Hz), 3.29 (1H, d, *J* = 9.0 Hz), 2.27−2.17 (1H, m), 2.12−2.06 (2H, m), 1.82−1.47 (6H, m), 1.31 (1H, m), 1.06 (9H, s), 1.03 (3H, d, *J* = 6.8 Hz), 0.87 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 133.7, 133.5, 129.5, 127.5, 96.6, 95.3, 74.9, 66.4, 62.7, 55.2, 48.8, 43.3, 37.2, 34.7, 29.9, 28.9, 26.9, 19.7, 19.4, 15.3; IR (neat) ν_{max} 3468, 2940, 2864, 1114, 1046, 704 cm^{-1}; HRMS (FAB) $[M+Na]^+$ calculated for $C_{32}H_{48}O_5SiNa$: 563.3169, found: 563.3160; $[\alpha]_D^{24}$ −9.0 (*c* 0.7, $CHCl_3$).

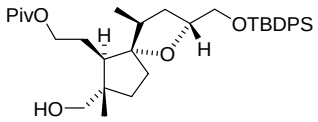
2-{(2*R*,4*S*,5*S*,6*R*,7*S*)-2-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-7-[(methoxymethoxy)methyl]-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl}ethyl pivalate (30)



To a stirred solution of **29a'** (1.72 g, 3.19 mmol) in CH_2Cl_2 (30 mL) was added pyridine (1.03 mL, 12.8 mmol), DMAP (390 mg, 3.19 mmol), PivCl (0.982 mL, 7.97 mmol) successively at room temperature. After the reaction was completed, saturated aqueous NH_4Cl solution (30 mL) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **30** (1.99 g, 100%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (4H, m), 7.42–7.34 (6H, m), 4.60 (2H, s), 4.05 (1H, ddd, *J* = 10.3, 6.2, 6.0 Hz), 4.02 (1H, ddd, *J* = 10.3, 6.6, 6.0 Hz), 3.94–3.89 (1H, m), 3.64 (1H, dd, *J* = 10.3, 4.2 Hz), 3.57 (1H, dd, *J* = 10.3, 6.2 Hz), 3.34 (3H, s), 3.30 (1H, d, *J* = 9.2 Hz), 3.28 (1H, d, *J* = 9.2 Hz), 2.22–2.10 (2H, m), 1.99 (1H, dd, *J* = 7.1, 7.1 Hz), 1.79–1.53 (5H, m), 1.50 (1H, dd, *J* = 11.5, 6.5 Hz), 1.33 (1H, dd, *J* = 11.0, 5.5 Hz), 1.14 (9H, s), 1.05 (9H, s), 1.03 (3H, d, *J* = 6.8 Hz), 0.88 (3H, s).

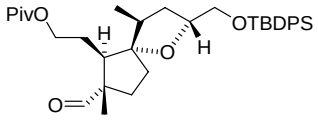
2-[(2*R*,4*S*,5*S*,6*R*,7*S*)-2-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-7-(hydroxymethyl)-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethyl pivalate (30')



To a stirred solution of **30** (1.92 g, 3.08 mmol) in a mixture of CH_2Cl_2 (20 mL) and Me_2S (10 mL) was added $BF_3{\cdot}OEt_2$ (1.93 mL, 15.4 mmol) at −30 °C. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (20 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (20 mL × 2). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **30'** (1.65 g, 92%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (4H, m), 7.43–7.35 (6H, m), 4.06–4.03 (2H, m), 3.95–3.91 (1H, m), 3.63 (1H, dd, *J* = 10.3, 4.4 Hz), 3.56 (1H, dd, *J* = 10.3, 6.0 Hz), 3.42 (1H, d, *J* = 10.6 Hz), 3.39 (1H, d, *J* = 10.6 Hz), 2.21–2.09 (2H, m), 1.92 (1H, dd, *J* = 7.1, 7.1 Hz), 1.81–1.65 (5H, m), 1.61–1.48 (2H, m), 1.31–1.26 (1H, m), 1.15 (9H, s), 1.05 (9H, s), 1.03 (3H, d, *J* = 6.8 Hz), 0.88 (3H, s).

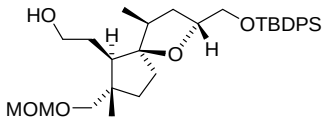
2-[(2*R*,4*S*,5*S*,6*R*,7*S*)-2-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-7-formyl-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethyl pivalate (4)



To a stirred solution of **30'** (1.63 g, 2.80 mmol) in CH_2Cl_2 (30 mL) was added Dess–Martin periodinane (3.56 g, 8.40 mmol) at room temperature. After the reaction was completed, Et_2O (50 mL) and a mixture of saturated aqueous $NaHCO_3$ solution (60 mL) and saturated aqueous $Na_2S_2O_3$ solution (60 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (50 mL × 2). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **4** (1.52 g, 94%) as an oil.

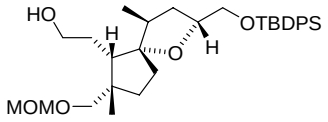
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (1H, s), 7.68–7.65 (4H, m), 7.44–7.35 (6H, m), 4.01–3.94 (2H, m), 3.82 (1H, ddd, *J* = 11.0, 7.7, 7.3 Hz), 3.64 (1H, dd, *J* = 10.4, 4.4 Hz), 3.60 (1H, dd, *J* = 10.4, 5.5 Hz), 2.39 (1H, dd, *J* = 9.0, 5.5 Hz), 2.25–2.18 (1H, m), 2.16–2.08 (2H, m), 1.83 (1H, ddd, *J* = 13.5, 9.3, 8.2 Hz), 1.77–1.60 (3H, m), 1.55–1.47 (1H, m), 1.34 (1H, ddd, *J* = 12.3, 8.2, 3.7 Hz), 1.14 (9H, s), 1.06 (9H, s), 1.03 (3H, d, *J* = 6.8 Hz), 1.02 (3H, s).

2-[(2*R*,4*S*,5*R*,6*R*,7*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-7-methoxymethoxymethyl-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethanol (29b')



29b' was prepared from **29b** in 85% yield according to the procedure for **29a'**.
R_f = 0.27 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.67 (4H, m), 7.44–7.35 (6H, m), 4.63 (2H, s), 4.19 (1H, m), 3.72–3.65 (2H, m), 3.58–3.57 (2H, m), 3.37 (3H, s), 3.30 (1H, d, *J* = 9.3 Hz), 3.30 (1H, d, *J* = 9.3 Hz), 2.48 (1H, br), 2.19 (1H, m), 2.08 (1H, m), 1.88 (1H, dd, *J* = 6.6, 6.3 Hz), 1.80–1.56 (5H, m), 1.52–1.48 (2H, m), 1.05 (3H, s), 1.04 (9H, s), 1.03 (3H, d, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 133.8, 133.7, 129.5, 127.6, 96.7, 96.2, 78.3, 77.5, 67.1, 62.1, 55.4, 44.7, 44.2, 40.9, 39.2, 36.5, 36.2, 29.7, 26.8, 21.1, 19.2, 15.2; IR (neat) ν_{max} 3436, 2960, 2880, 1148, 1114, 1046, 704 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{32}H_{49}O_5Si$: 541.3349, found: 541.3354; $[\alpha]_D^{23}$ −3.2 (*c* 1.0, $CHCl_3$).

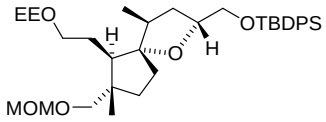
2-[(2*R*,4*S*,5*S*,6*S*,7*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-7-methoxymethoxymethyl-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethanol (29c')



29c' was prepared from **29c** in 100% yield according to the procedure for **29a'**.
R_f = 0.42 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.66 (4H, m), 7.44–7.36 (6H, m), 4.62 (1H, d, *J* = 6.6 Hz), 4.61 (1H, d, *J* = 6.6 Hz), 3.96 (1H, m), 3.64–3.54 (4H, m), 3.48 (1H, d, *J* = 9.3 Hz), 3.44 (1H, d, *J* = 9.3 Hz), 3.35 (3H, s), 2.01–1.87 (2H, m), 1.86–1.53 (6H, m), 1.49–1.41 (2H, m), 1.16–1.08 (1H, m), 1.12 (3H, s), 1.05 (9H, s), 0.95 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.9, 133.6, 129.6, 127.6, 96.7, 94.4, 75.6, 72.3, 66.5, 63.2, 55.2, 50.6, 44.2, 37.8, 35.4, 35.0, 29.9, 27.3, 26.8, 25.4, 19.3, 13.9; IR (neat) ν_{max} 3456, 2956, 2936, 2868, 1146, 1114, 1048, 704 cm^{-1};

HRMS (FAB) $[M+H]^+$ calculated for $C_{32}H_{49}O_5Si$: 541.3349, found: 541.3354; $[\alpha]_D^{27}$ −11.4 (*c* 1.1, $CHCl_3$).

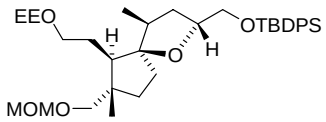
***tert*-Butyl-{(2*R*,4*S*,5*S*,6*R*,7*S*)-6-[2-(1-ethoxyethoxy)ethyl]-7-methoxymethoxymethyl-4,7-dimethyl-1-oxaspiro[4.4]non-2-ylmethoxy}diphenylsilane (31a)**



To a stirred solution of **29a'** (391 mg, 0.724 mmol) in CH_2Cl_2 (7 mL) was added ethyl vinyl ether (0.104 mL, 1.08 mmol), PPTS (18.2 mg, 0.0724 mmol) successively at room temperature. After the reaction was completed, triethylamine (0.12 mL) was added to the reaction mixture, and the resultant mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=8/1) to afford the titled ethoxyethylether **31a** (412 mg, 93%) as an oil.

R_f = 0.42 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (4H, m), 7.43–7.34 (6H, m), 4.60 (2H, s), 4.54 (1/2H, q, *J* = 5.4 Hz), 4.48 (1/2H, q, *J* = 5.4 Hz), 3.94 (1H, m), 3.70–3.65 (1H, m), 3.56–3.45 (3H, m), 3.39–3.30 (2H, m), 3.33 (3H, s), 3.30 (1H, d, *J* = 9.0 Hz), 3.28 (1H, d, *J* = 9.0 Hz), 2.17–2.04 (2H, m), 1.91 (1H, dd, *J* = 7.1, 7.1 Hz), 1.80–1.67 (3H, m), 1.62–1.56 (2H, m), 1.50 (1H, m), 1.33 (1H, m), 1.21 (3/2H, d, *J* = 5.4 Hz), 1.19 (3/2H, d, *J* = 5.4 Hz), 1.11 (3/2H, t, *J* = 7.1 Hz), 1.10 (3/2H, t, *J* = 7.1 Hz), 1.05 (9H, s), 1.03 (3H, d, *J* = 6.8 Hz), 0.85 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 133.7, 133.6, 133.5, 129.5, 127.5, 99.6, 96.6, 95.3, 74.9, 66.7, 66.6, 65.7, 65.5, 60.9, 55.0, 48.6, 43.8, 37.5, 37.4, 34.6, 29.9, 26.9, 26.8, 20.0, 19.3, 18.9, 15.5, 15.4; IR (neat) ν_{max} 2936, 2884, 1114, 1050, 704 cm^{-1}; HRMS (FAB) $[M]^+$ calculated for $C_{36}H_{56}O_6Si$: 612.3846, found: 612.3848.

***tert*-Butyl-{(2*R*,4*S*,5*R*,6*R*,7*S*)-6-[2-(1-ethoxyethoxy)ethyl]-7-methoxymethoxymethyl-4,7-dimethyl-1-oxaspiro[4.4]non-2-ylmethoxy}diphenylsilane (31b)**

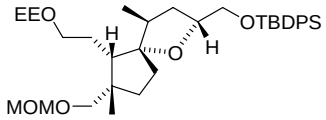


31b was prepared from **29b'** in 100% yield according to the procedure for **31a**.

R_f = 0.34 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.67 (4H, m), 7.43–7.34 (6H, m), 4.69 (1/2H, q, *J* = 5.4 Hz), 4.67 (1/2H, q, *J* = 5.4 Hz), 4.60 (2H, s), 4.19 (1H, m), 3.69–3.59 (2H, m), 3.58–3.56 (2H, m), 3.55–3.44 (2H, m), 3.35 (3H, s), 3.25 (1/2H, d, *J* = 9.0 Hz), 3.24 (1/2H, d, *J* = 9.0 Hz), 3.22 (1/2H, d, *J* = 9.0 Hz), 3.21 (1/2H, d, *J* = 9.0

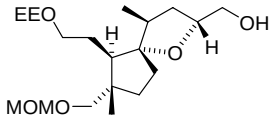
Hz), 2.18 (1H, m), 2.07 (1H, m), 1.81–1.46 (8H, m), 1.30 (3H, d, J = 5.4 Hz), 1.20 (3H, t, J = 7.1 Hz), 1.04 (9H, s), 1.03 (3H, s), 1.02 (3H, d, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 133.8, 129.5, 127.6, 99.6, 99.3, 96.7, 96.0, 78.3, 67.1, 65.1, 64.6, 60.7, 60.6, 55.1, 44.9, 44.6, 40.9, 39.5, 36.5, 35.8, 26.8, 20.6, 19.9, 19.2, 15.4, 15.1; IR (neat) ν_{max} 2960, 2930, 2880, 1132, 1112, 1046, 704 cm^{-1}; HRMS (FAB) $[M+Na]^+$ calculated for $C_{36}H_{56}O_6SiNa$: 635.3744, found: 635.3732.

tert-Butyl-{(2*R*,4*S*,5*S*,6*S*,7*S*)-6-[2-(1-ethoxyethoxy)ethyl]-7-methoxymethoxymethyl-4,7-dimethyl-1-oxaspiro[4.4]non-2-ylmethoxy}diphenylsilane (31c)



31c was prepared from **29c'** in 93% yield according to the procedure for **31a**.
R_f = 0.41 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.65 (4H, m), 7.43–7.35 (6H, m), 4.60 (2H, s), 4.58 (1/2H, q, J = 5.4 Hz), 4.57 (1/2H, q, J = 5.4 Hz), 3.97 (1H, m), 3.64–3.48 (5H, m), 3.45–3.36 (3H, m), 3.33 (3H, s), 1.97–1.84 (3H, m), 1.70 (1H, m), 1.64–1.53 (3H, m), 1.51–1.42 (2H, m), 1.24 (3/2H, d, J = 5.4 Hz), 1.23 (3/2H, d, J = 5.4 Hz), 1.16 (3/2H, t, J = 7.1 Hz), 1.15 (3/2H, t, J = 7.1 Hz), 1.12–1.07 (1H, m), 1.10 (3H, s), 1.04 (9H, s), 0.93 (3H, d, J = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 133.9, 133.7, 129.5, 127.6, 99.5, 96.8, 94.1, 94.0, 75.5, 72.3, 72.2, 66.7, 65.5, 65.3, 60.7, 60.4, 55.0, 50.1, 44.3, 44.2, 37.5, 37.4, 35.2, 30.2, 30.1, 26.8, 25.5, 25.4, 24.2, 24.1, 19.9, 19.2, 15.3, 13.9; IR (neat) ν_{max} 2960, 2936, 2872, 1134, 1114, 1048, 704 cm^{-1}; HRMS (FAB) $[M+Na]^+$ calculated for $C_{36}H_{56}O_6SiNa$: 635.3744, found: 635.3752.

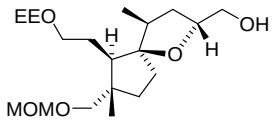
{(2*R*,4*S*,5*S*,6*R*,7*S*)-6-[2-(1-Ethoxyethoxy)ethyl]-7-methoxymethoxymethyl-4,7-dimethyl-1-oxaspiro[4.4]non-2-yl}methanol (31a')



To a stirred solution of **31a** (412 mg, 0.672 mmol) in THF (7 mL) was added a solution of TBAF in THF (1.34 mL, 1.0 M) at room temperature. After the reaction was completed, saturated aqueous NH_4Cl solution (5 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (5 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford the titled alcohol **31a'** (251 mg, 100%) as an oil.

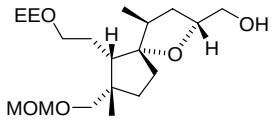
R_f = 0.13 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (1/2H, q, J = 5.4 Hz), 4.68 (1/2H, q, J = 5.4 Hz), 4.62 (2H, s), 3.93 (1H, m), 3.70–3.58 (3H, m), 3.54–3.43 (3H, m), 3.36 (3H, s), 3.33 (1H, d, J = 9.0 Hz), 3.30 (1H, d, J = 9.0 Hz), 2.19 (1H, m), 2.04 (1H, m), 1.99–1.92 (1H, m), 1.82–1.73 (2H, m), 1.71–1.57 (3H, m), 1.52 (1H, m), 1.34 (1H, m), 1.30 (3H, d, J = 5.4 Hz), 1.21 (3H, t, J = 7.1 Hz), 1.04 (3H, d, J = 6.8 Hz), 0.86 (3/2H, s), 0.85 (3/2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.4, 96.6, 95.8, 76.6, 76.5, 74.7, 65.7, 65.1, 64.6, 60.9, 60.8, 55.1, 48.8, 48.7, 44.0, 43.9, 36.7, 35.7, 34.5, 34.4, 29.8, 26.6, 26.5, 19.9, 19.8, 19.0, 18.9, 15.6, 15.3; IR (neat) ν_{max} 3456, 2948, 2880, 1110, 1048 cm^{-1}; HRMS (FAB) $[M+Na]^+$ calculated for $C_{20}H_{38}O_6Na$: 397.2566, found: 397.2562.

{(2*R*,4*S*,5*R*,6*R*,7*S*)-6-[2-(1-Ethoxyethoxy)ethyl]-7-methoxymethoxymethyl-4,7-dimethyl-1-oxaspiro[4.4]non-2-yl}methanol (31b')



31b' was prepared from **31b** in 98% yield according to the procedure for **31a'**.
R_f = 0.22 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (1/2H, q, J = 5.4 Hz), 4.67 (1/2H, q, J = 5.4 Hz), 4.61 (2H, s), 4.19 (1H, m), 3.70–3.32 (6H, m), 3.36 (3H, s), 3.26 (1/2H, d, J = 9.0 Hz), 3.25 (1/2H, d, J = 9.0 Hz), 3.23 (1/2H, d, J = 9.0 Hz), 3.22 (1/2H, d, J = 9.0 Hz), 2.20 (1H, m), 2.05 (1H, br), 1.90–1.49 (9H, m), 1.30 (3H, d, J = 5.4 Hz), 1.20 (3H, t, J = 7.1 Hz), 1.04 (3H, d, J = 6.8 Hz), 1.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.6, 99.3, 96.7, 96.3, 77.9, 76.9, 76.8, 66.4, 64.9, 64.4, 60.7, 60.5, 55.1, 44.9, 44.4, 41.4, 39.9, 36.2, 35.8, 26.7, 20.7, 19.9, 15.3, 15.0; IR (neat) ν_{max} 3468, 2956, 2880, 1146, 1110, 1044 cm^{-1}; HRMS (FAB) $[M-EtO]^+$ calculated for $C_{18}H_{33}O_5$: 329.2328, found: 329.2318.

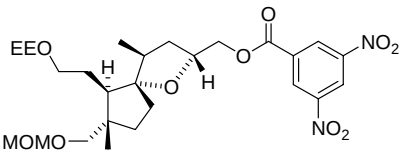
{(2*R*,4*S*,5*S*,6*S*,7*S*)-6-[2-(1-Ethoxyethoxy)ethyl]-7-methoxymethoxymethyl-4,7-dimethyl-1-oxaspiro[4.4]non-2-yl}methanol (31c')



31c' was prepared from **31c** in 97% yield according to the procedure for **31a'**.
R_f = 0.13 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (1/2H, q, J = 5.4 Hz), 4.65 (1/2H, q, J = 5.4 Hz), 4.58 (2H, s), 3.93 (1H, m), 3.65–3.53 (3H, m), 3.50–3.29 (5H, m), 3.31 (3H, s), 2.15 (1H, br), 1.95–1.67 (4H, m), 1.64–1.50 (3H, m), 1.48–1.39 (2H, m), 1.26 (3H, d, J = 5.4 Hz), 1.17 (3H, t, J = 7.1 Hz), 1.10–1.01 (1H, m), 1.07 (3/2H, s), 1.06 (3/2H, s), 0.91 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.4, 99.2, 96.7,

94.2, 94.1, 75.2, 71.8, 71.7, 65.8, 65.2, 64.8, 60.6, 60.4, 55.0, 50.5, 50.3, 44.5, 44.4, 38.9, 38.6, 35.0, 34.5, 34.4, 30.4, 30.3, 25.1, 25.0, 24.4, 24.3, 19.8, 19.7, 15.3, 13.8, 13.7; IR (neat) ν_{max} 3472, 2940, 2876, 1134, 1108, 1048 cm^{-1}; HRMS (FAB) $[M+Na]^+$ calculated for $C_{20}H_{38}O_6Na$: 397.2566, found: 397.2573.

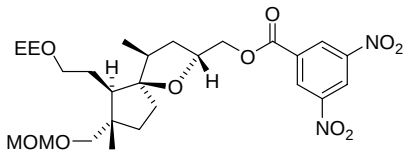
3,5-Dinitrobenzoic acid (2*R*,4*S*,5*S*,6*R*,7*S*)-6-[2-(1-ethoxyethoxy)ethyl]-7-methoxymethoxy methyl-4,7-dimethyl-1-oxaspiro[4.4]non-2-ylmethyl ester (32a)



To a stirred solution of **31a'** (251 mg, 0.671 mmol) in CH_2Cl_2 (7 mL) was added triethylamine (0.187 ml, 1.34 mmol), DMAP (8.2 mg, 0.0670 mmol), and 3,5-$(NO_2)_2$BzCl (232 mg, 1.01 mmol)) successively at room temperature. After the reaction was completed, saturated aqueous NH_4Cl solution (5 mL) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (5 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=8/1) to afford the titled 3,5-dinitrobenzoate **32a** (381 mg, 100%) as an oil.

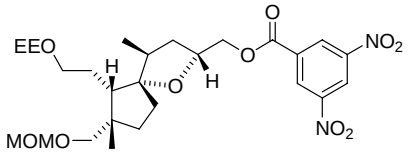
R_f = 0.47 (hexane/ethyl acetate=2/1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.23 (1H, t, *J* = 2.0 Hz), 9.17 (2H, d, *J* = 2.0 Hz), 4.61 (1H, q, *J* = 5.4 Hz), 4.60 (2H, s), 4.45-4.36 (2H, m), 4.23 (1H, m), 3.63-3.51 (2H, m), 3.49-3.37 (2H, m), 3.34 (3H, s), 3.31 (1H, d, *J* = 9.3 Hz), 3.29 (1H, d, *J* = 9.3 Hz), 2.26 (1H, m), 2.02 (1H, m), 2.00 (1H, dd, *J* = 7.3, 6.8 Hz), 1.90-1.77 (3H, m), 1.67-1.53 (3H, m), 1.34 (1H, m), 1.24 (3/2H, d, *J* = 5.4 Hz), 1.23 (3/2H, d, *J* = 5.4 Hz), 1.17 (3/2H, t, *J* = 7.1 Hz), 1.15 (3/2H, t, *J* = 7.1 Hz), 1.10 (3H, d, *J* = 6.8 Hz), 0.88 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 148.5, 133.7, 129.5, 122.3, 99.5, 99.4, 96.6, 96.2, 76.6, 71.7, 69.3, 65.3, 65.1, 60.7, 60.6, 55.1, 48.5, 48.4, 43.6, 37.4, 35.1, 34.5, 30.0, 26.7, 26.6, 19.9, 19.2, 15.4; IR (neat) ν_{max} 2960, 2884, 1738, 1550, 1348, 1280, 1170, 1150, 1112, 1046 cm^{-1}; HRMS (FAB) $[M-EtO]^+$ calculated for $C_{25}H_{35}N_2O_{10}$: 523.2292, found: 523.2294.

3,5-Dinitrobenzoic acid (2*R*,4*S*,5*R*,6*R*,7*S*)-6-[2-(1-ethoxyethoxy)ethyl]-7-methoxymethoxy methyl-4,7-dimethyl-1-oxaspiro[4.4]non-2-ylmethyl ester (32b)



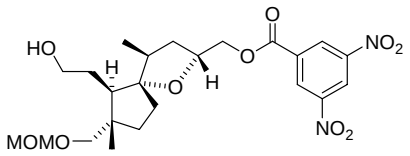
32b was prepared from **31b'** in 100% yield according to the procedure for **32a**.
R_f = 0.41 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (1H, t, *J* = 2.0 Hz), 9.18 (2H, d, *J* = 2.0 Hz), 4.69 (1/2H, q, *J* = 5.4 Hz), 4.67 (1/2H, q, *J* = 5.4 Hz), 4.61 (2H, s), 4.50–4.40 (1H, m), 4.42 (1H, dd, *J* = 10.7, 5.4 Hz), 4.35 (1H, dd, *J* = 10.7, 4.4 Hz), 3.73–3.59 (2H, m), 3.55–3.45 (2H, m), 3.36 (3H, s), 3.27 (1H, d, *J* = 9.3 Hz), 3.23 (1/2H, d, *J* = 9.3 Hz), 3.22 (1/2H, d, *J* = 9.3 Hz), 2.28 (1H, m), 2.05–1.91 (2H, m), 1.80–1.58 (6H, m), 1.51 (1H, m), 1.30 (3H, d, *J* = 5.4 Hz), 1.20 (3H, t, *J* = 7.1 Hz), 1.09 (3H, d, *J* = 7.1 Hz), 1.02 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 148.7, 134.0, 129.5, 122.4, 99.6, 99.4, 96.7, 74.9, 69.5, 64.9, 64.4, 60.7, 60.6, 55.2, 45.0, 44.4, 41.4, 39.8, 36.6, 35.7, 26.8, 20.5, 19.9, 15.4, 15.0, 14.2; IR (neat) ν_{max} 2960, 2884, 1738, 1552, 1348, 1280, 1170, 1146, 1132, 1110, 1048, 722 cm^{-1}; HRMS (FAB) $[M+Na]^+$ calculated for $C_{27}H_{40}N_2O_{11}Na$: 591.2530, found: 591.2540.

3,5-Dinitrobenzoic acid (2*R*,4*S*,5*S*,6*S*,7*S*)-6-[2-(1-ethoxyethoxy)ethyl]-7-methoxymethoxy methyl-4,7-dimethyl-1-oxaspiro[4.4]non-2-ylmethyl ester (32c)



32c was prepared from **31c'** in 100% yield according to the procedure for **32a**.
R_f = 0.48 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (1H, t, *J* = 2.0 Hz), 9.15 (2H, d, *J* = 2.0 Hz), 4.60 (1/2H, q, *J* = 5.4 Hz), 4.59 (1/2H, q, *J* = 5.4 Hz), 4.57 (1H, d, *J* = 6.8 Hz), 4.56 (1H, d, *J* = 5.4 Hz), 4.44–4.33 (2H, m), 4.25 (1H, m), 3.65–3.36 (6H, m), 3.30 (3H, s), 2.08–2.00 (1H, m), 1.98–1.85 (2H, m), 1.80–1.69 (2H, m), 1.67–1.45 (4H, m), 1.23 (3/2H, d, *J* = 5.4 Hz), 1.22 (3/2H, d, *J* = 5.4 Hz), 1.20–1.12 (1H, m), 1.17 (3H, t, *J* = 7.1 Hz), 1.11 (3H, s), 1.00 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 148.7, 133.9, 129.5, 122.3, 99.5, 99.4, 96.7, 95.1, 72.2, 72.1, 69.0, 65.2, 65.0, 60.6, 60.5, 55.0, 50.1, 44.3, 44.2, 37.7, 35.3, 35.1, 30.1, 30.0, 25.5, 25.4, 24.2, 19.8, 15.3, 13.8; IR (neat) ν_{max} 2960, 2880, 1738, 1550, 1348, 1282, 1168, 1136, 1110, 1048, 722 cm^{-1}; HRMS (FAB) $[M+Na]^+$ calculated for $C_{27}H_{40}N_2O_{11}Na$: 591.2530, found: 591.2518.

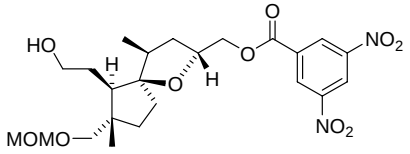
3,5-Dinitrobenzoic acid (2*R*,4*S*,5*S*,6*R*,7*S*)-6-(2-hydroxyethyl)-7-methoxymethoxymethyl-4,7-dimethyl-1-oxaspiro[4.4]non-2-ylmethyl ester (32a')



To a stirred solution of **32a** (381 mg, 0.671 mmol) in EtOH (5 mL) was added PPTS (169 mg, 0.671 mmol) at room temperature. After the reaction was completed, triethylamine (0.11 mL) was added to the reaction mixture and the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **32a'** (292 mg, 88%) as an oil.

R_f = 0.44 (hexane/ethyl acetate=1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (2H, d, *J* = 2.2 Hz), 9.22 (1H, t, *J* = 2.2 Hz), 4.62 (1H, d, *J* = 6.6 Hz), 4.61 (1H, d, *J* = 6.6 Hz), 4.50 (1H, dd, *J* = 11.7, 5.1 Hz), 4.43 (1H, dd, *J* = 11.7, 3.4 Hz), 4.24 (1H, m), 3.73 (1H, ddd, *J* = 11.0, 5.6, 5.4 Hz), 3.60 (1H, ddd, *J* = 11.0, 7.8, 5.6 Hz), 3.35 (3H, s), 3.32 (1H, d, *J* = 9.0 Hz), 3.31 (1H, d, *J* = 9.0 Hz), 2.74 (1H, br), 2.41 (1H, m), 2.17 (1H, dd, *J* = 8.5, 4.6 Hz), 2.05 (1H, ddd, *J* = 12.7, 8.1, 4.6 Hz), 1.90–1.78 (3H, m), 1.74–1.55 (3H, m), 1.37 (1H, m), 1.09 (3H, d, *J* = 6.8 Hz), 0.88 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 148.5, 133.6, 129.8, 122.3, 96.6, 96.2, 76.6, 72.0, 68.4, 62.9, 55.2, 49.3, 43.6, 36.6, 35.5, 34.5, 29.5, 28.6, 19.6, 15.2; IR (neat) ν_{max} 3476, 2952, 2884, 1736, 1544, 1348, 1282, 1170, 1148, 1112, 1046 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{23}H_{33}N_2O_{10}$: 497.2135, found: 497.2150; $[\alpha]_D^{28}$ −5.9 (*c* 1.5, $CHCl_3$).

3,5-Dinitrobenzoic acid (2*R*,4*S*,5*R*,6*R*,7*S*)-6-(2-hydroxyethyl)-7-methoxymethoxymethyl-4,7-dimethyl-1-oxaspiro[4.4]non-2-ylmethyl ester (32b')

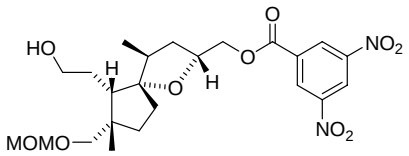


32b' was prepared from **32b** in 64% yield according to the procedure for **32a'**.

R_f = 0.23 (hexane/ethyl acetate=1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (1H, t, *J* = 2.0 Hz), 9.18 (2H, d, *J* = 2.0 Hz), 4.63 (2H, s), 4.50–4.44 (1H, m), 4.42 (1H, dd, *J* = 11.0, 5.6 Hz), 4.36 (1H, dd, *J* = 11.0, 4.1 Hz), 3.72–3.68 (2H, m), 3.38 (3H, s), 3.32 (1H, d, *J* = 9.8 Hz), 3.31 (1H, d, *J* = 9.8 Hz), 2.43 (1H, br), 2.30 (1H, m), 2.04 (1H, ddd, *J* = 12.7, 8.0, 4.4 Hz), 1.98–1.91 (2H, m), 1.78–1.68 (4H, m), 1.60–1.47 (2H, m), 1.11 (3H, d, *J* = 7.1 Hz), 1.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 148.7, 133.9, 129.5, 122.4, 96.9, 96.7,

77.3, 74.9, 69.5, 61.8, 55.4, 44.8, 43.9, 41.3, 39.5, 36.7, 36.1, 29.7, 20.9, 15.0; IR (neat) ν_{max} 3456, 2960, 2884, 1738, 1552, 1348, 1280, 1170, 1148, 1110, 1046, 722 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{23}H_{33}N_2O_{10}$: 497.2135, found: 497.2111; $[\alpha]_D^{32}$ +2.1 (*c* 0.7, MeOH).

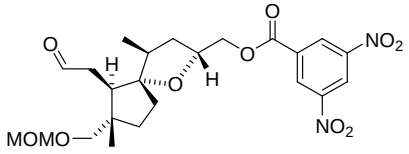
3,5-Dinitrobenzoic acid (2*R*,4*S*,5*S*,6*S*,7*S*)-6-(2-hydroxyethyl)-7-methoxymethoxymethyl-4,7-dimethyl-1-oxaspiro[4.4]non-2-ylmethyl ester (32c')



32c' was prepared from **32c** in 74% yield according to the procedure for **32a'**.

R_f = 0.41 (hexane/ethyl acetate=1/1); ^1H NMR (400 MHz, $CDCl_3$) δ 9.23 (1H, t, *J* = 2.0 Hz), 9.19 (2H, d, *J* = 2.0 Hz), 4.58 (1H, d, *J* = 6.6 Hz), 4.56 (1H, d, *J* = 6.6 Hz), 4.47 (1H, dd, *J* = 11.5, 5.6 Hz), 4.39 (1H, dd, *J* = 11.5, 3.9 Hz), 4.26 (1H, m), 3.72–3.62 (2H, m), 3.46 (1H, d, *J* = 9.3 Hz), 3.38 (1H, d, *J* = 9.3 Hz), 3.31 (3H, s), 2.07 (1H, m), 1.96–1.83 (3H, m), 1.80–1.72 (2H, m), 1.66 (1H, ddd, *J* = 14.1, 7.3, 6.8 Hz), 1.62 (1H, ddd, *J* = 14.1, 7.3, 6.3 Hz), 1.56–1.46 (2H, m), 1.19–1.12 (1H, m), 1.12 (3H, s), 1.01 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 148.7, 133.8, 129.6, 122.4, 96.7, 95.1, 72.4, 72.0, 68.7, 62.9, 55.1, 50.6, 44.3, 38.3, 35.2, 34.9, 30.0, 27.3, 25.3, 13.8; IR (neat) ν_{max} 3476, 2960, 2880, 1738, 1550, 1348, 1282, 1168, 1108, 1046, 722 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{23}H_{33}N_2O_{10}$: 497.2135, found: 497.2130; $[\alpha]_D^{32}$ +5.0 (*c* 0.7, MeOH).

3,5-Dinitrobenzoic acid (2*R*,4*S*,5*S*,6*R*,7*S*)-7-methoxymethoxymethyl-4,7-dimethyl-6-(2-oxoethyl)-1-oxaspiro[4.4]non-2-ylmethyl ester (33a)

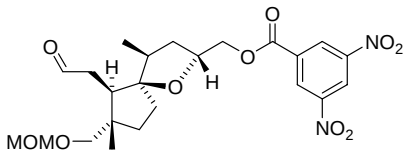


To a stirred solution of **32a'** (26.1 mg, 0.0526 mmol) in CH_2Cl_2 (5 mL) was added Dess–Martin periodinane (33.4 mg, 0.0787 mmol) at room temperature. After the reaction was completed, Et_2O (10 mL) and a mixture of saturated aqueous $NaHCO_3$ solution (10 mL) and saturated aqueous $Na_2S_2O_3$ solution (10 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (10 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=6/1) to afford

the titled aldehyde **33a** (25.7 mg, 99%) as an oil.

R_f = 0.44 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (1H, dd, *J* = 3.9, 1.7 Hz), 9.23 (1H, t, *J* = 2.2 Hz), 9.17 (2H, d, *J* = 2.2 Hz), 4.60 (1H, d, *J* = 6.6 Hz), 4.59 (1H, d, *J* = 6.6 Hz), 4.42 (1H, dd, *J* = 11.5, 3.9 Hz), 4.36 (1H, dd, *J* = 11.5, 5.6 Hz), 4.22 (1H, m), 3.38 (1H, d, *J* = 9.0 Hz), 3.34 (1H, d, *J* = 9.0 Hz), 3.34 (3H, s), 2.75 (1H, dd, *J* = 9.3, 5.6 Hz), 2.45 (1H, ddd, *J* = 15.9, 5.6, 1.7 Hz), 2.36 (1H, ddd, *J* = 15.9, 9.3, 3.9 Hz), 2.12 (1H, m), 2.03–1.97 (1H, m), 1.87–1.77 (3H, m), 1.61 (1H, m), 1.36 (1H, m), 1.08 (3H, d, *J* = 6.8 Hz), 0.90 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 162.4, 148.5, 133.7, 129.5, 122.3, 96.6, 95.6, 72.3, 68.6, 55.2, 47.4, 42.8, 41.9, 37.1, 35.6, 34.5, 30.2, 20.3, 15.4; IR (neat) ν_{max} 2964, 2888, 1734, 1550, 1348, 1284, 1170, 1112, 1046 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{23}H_{31}N_2O_{10}$: 495.1979, found: 495.1977; $[\alpha]_D^{25}$ −30.8 (*c* 1.2, $CHCl_3$).

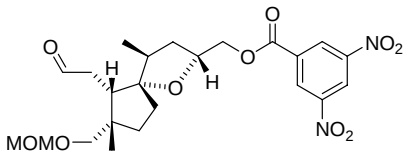
3,5-Dinitrobenzoic acid (2*R*,4*S*,5*R*,6*R*,7*S*)-7-methoxymethoxymethyl-4,7-dimethyl-6-(2-oxo ethyl)-1-oxaspiro[4.4]non-2-ylmethyl ester (33b)



33b was prepared from **32b'** in 100% yield according to the procedure for **33a**.

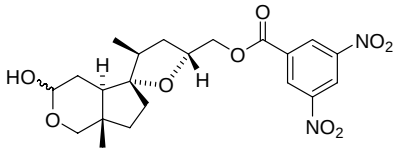
R_f = 0.41 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (1H, dd, *J* = 1.5, 1.2 Hz), 9.24 (1H, t, *J* = 2.0 Hz), 9.18 (2H, d, *J* = 2.0 Hz), 4.58 (2H, s), 4.43–4.35 (3H, m), 3.34 (3H, s), 3.26 (2H, s), 2.54–2.48 (3H, m), 2.28 (1H, ddd, *J* = 13.9, 13.9, 6.8 Hz), 2.03 (1H, m), 1.90 (1H, ddd, *J* = 13.2, 8.3, 8.3 Hz), 1.84–1.77 (2H, m), 1.61–1.43 (2H, m), 1.08 (3H, d, *J* = 7.1 Hz), 1.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 162.4, 148.7, 133.9, 129.5, 122.4, 96.7, 95.3, 76.1, 74.7, 69.2, 55.2, 45.1, 43.2, 42.3, 41.9, 40.0, 36.2, 34.9, 20.4, 15.3; IR (neat) ν_{max} 2960, 2884, 1732, 1550, 1348, 1282, 1170, 1110, 1046, 722 cm^{-1}; HRMS (FAB) $[M+Na]^+$ calculated for $C_{23}H_{30}N_2O_{10}Na$: 517.1798, found: 517.1801; $[\alpha]_D^{23}$ +22.4 (*c* 0.8, $CHCl_3$).

3,5-Dinitrobenzoic acid (2*R*,4*S*,5*S*,6*S*,7*S*)-7-methoxymethoxymethyl-4,7-dimethyl-6-(2-oxo ethyl)-1-oxaspiro[4.4]non-2-ylmethyl ester (33c)



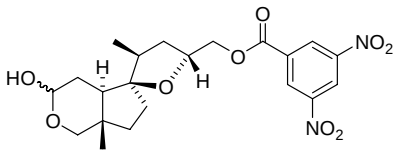
33c was prepared from **32c'** in 95% yield according to the procedure for **33a**.
R_f = 0.47 (hexane/ethyl acetate=2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (1H, dd, *J* = 1.7, 1.5 Hz), 9.23 (1H, t, *J* = 2.0 Hz), 9.15 (2H, d, *J* = 2.0 Hz), 4.54 (1H, d, *J* = 6.3 Hz), 4.52 (1H, d, *J* = 6.3 Hz), 4.39 (1H, dd, *J* = 11.2, 6.1 Hz), 4.35 (1H, dd, *J* = 11.2, 4.1 Hz), 4.27 (1H, m), 3.38 (1H, d, *J* = 9.3 Hz), 3.36 (1H, d, *J* = 9.3 Hz), 3.29 (3H, s), 2.57 (1H, ddd, *J* = 17.6, 6.6, 1.5 Hz), 2.49 (1H, ddd, *J* = 17.6, 6.6, 1.7 Hz), 2.16 (1H, dd, *J* = 6.6, 6.6 Hz), 1.96–1.88 (2H, m), 1.83–1.72 (3H, m), 1.56–1.48 (1H, m), 1.29–1.24 (1H, m), 1.11 (3H, s), 1.03 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 162.4, 148.7, 133.8, 129.5, 122.4, 96.7, 94.8, 72.5, 68.7, 55.2, 47.1, 44.0, 39.0, 37.6, 35.1, 35.0, 29.7, 25.2, 13.7; IR (neat) ν_{max} 2960, 2884, 1734, 1550, 1348, 1282, 1168, 1110, 1048, 732 cm^{-1}; HRMS (FAB) $[M+Na]^+$ calculated for $C_{23}H_{30}N_2O_{10}Na$: 517.1798, found: 517.1773; $[\alpha]_D^{27}$ +2.3 (*c* 1.2, $CHCl_3$).

3,5-Dinitrobenzoic acid (3*RS*,4a*R*,5*S*,7a*S*,3'*S*,5'*R*)-3-hydroxy-7a-methyloctahydrocyclopenta[c] pyran-5-spiro-2'-(3'-methyltetrahydrofuran)-5'-ylmethyl ester (33a')



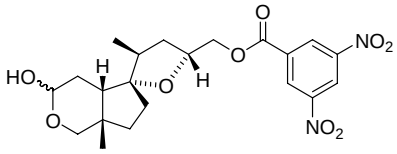
To a stirred solution of **33a** (24.6 mg, 0.497 mmol) in THF (2 mL) was added 2*N* HCl (1 mL), and the mixture was refluxed. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (1 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (1 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by short flash chromatography (hexane/ethyl acetate=4/1) to afford the titled crude lactol **33a'** as a solid. This was used for next step without further purification.

3,5-Dinitrobenzoic acid (3*RS*,4a*R*,5*R*,7a*S*,3'*S*,5'*R*)-3-hydroxy-7a-methyloctahydrocyclopenta[c] pyran-5-spiro-2'-(3'-methyltetrahydrofuran)-5'-ylmethyl ester (33b')



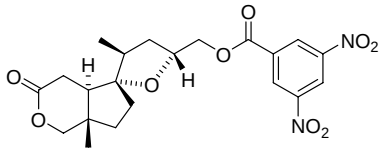
33b' was prepared from **33b** according to the procedure for **33a'**.

3,5-Dinitrobenzoic acid (3*RS*,4a*S*,5*S*,7a*S*,3'*S*,5'*R*)-3-hydroxy-7a-methyloctahydrocyclopenta[c] pyran-5-spiro-2'-(3'-methyltetrahydrofuran)-5'-ylmethyl ester (33c')



33c' was prepared from **33c** according to the procedure for **33a'**.

3,5-Dinitrobenzoic acid (4a*R*,5*S*,7a*S*,3'*S*,5'*R*)-7a-methylhexahydrocyclopenta[c]pyran-3(1*H*)-one-5-spiro-2'-(3'-methyltetrahydrofuran)-5'-ylmethyl ester (34a)

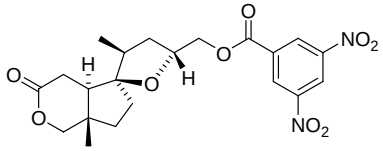


To a stirred solution of crude **33a'** in benzene (3 mL) was added Fetizon reagent (503 mg, 0.838 mmol), and the mixture was refluxed. After the reaction was completed, the mixture was filtered through a Celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by short flash chromatography (hexane/ethyl acetate=4/1) to afford **34a** (14.6 mg, 66% (2steps)) as a solid.

R_f = 0.20 (hexane/ethyl acetate=2/1); mp 157 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (1H, t, *J*= 2.2 Hz), 9.16 (2H, d, *J*= 2.2 Hz), 4.46 (1H, dd, *J*= 11.2, 3.4 Hz), 4.37 (1H, dd, *J*= 11.2, 6.1 Hz), 4.31 (1H, m), 4.21 (1H, d, *J*= 10.3 Hz), 4.16 (1H, d, *J*= 10.3 Hz), 2.68 (1H, dd, *J* = 16.8, 4.9 Hz), 2.41 (1H, dd, *J*= 16.8, 14.6 Hz), 2.31 (1H, dd, *J*= 14.6, 4.9 Hz), 2.23 (1H, ddd, *J*= 14.6, 11.8, 7.1 Hz), 2.17 (1H, dq, *J*= 7.1, 5.8 Hz), 1.93 (1H, dd, *J*= 14.6, 8.1 Hz), 1.86 (2H, dd, *J*= 7.4, 5.8 Hz), 1.65 (1H, ddd, *J*= 11.8, 11.7, 8.1 Hz), 1.59 (1H, dd, *J*= 11.7, 7.1 Hz), 1.12 (3H, d, *J*= 7.1 Hz), 0.96 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 162.4, 148.7, 133.6, 129.5, 122.5, 93.3, 81.8, 72.8, 68.9, 53.3, 39.8, 37.1, 36.5, 33.8, 32.8, 30.3, 16.2, 15.8; IR (KBr) ν_{max} 1735, 1544, 1345, 1277, 1168 cm^{-1}; HRMS (FAB) $[M+H]^+$

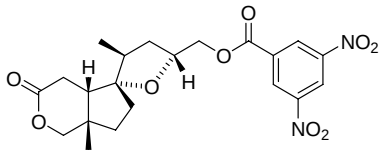
calculated for $C_{21}H_{25}N_2O_9$: 449.1560, found: 449.1571; $[\alpha]_D^{27}$ −68.1 (*c* 0.5, $CHCl_3$).

3,5-Dinitrobenzoic acid (4a*R*,5*R*,7a*S*,3'*S*,5'*R*)-7a-methylhexahydrocyclopenta[c]pyran-3(1*H*)-one-5-spiro-2'-(3'-methyltetrahydrofuran)-5'-ylmethyl ester (34b)



34b was prepared from **33b'** in 57% yield according to the procedure for **34a**.
R_f = 0.36 (hexane/ethyl acetate=1/1); mp 47−50 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (1H, t, *J* = 2.0 Hz), 9.18 (2H, d, *J* = 2.0 Hz), 4.47 (1H, dd, *J* = 10.5, 5.1 Hz), 4.41 (1H, m), 4.38 (1H, dd, *J* = 10.5, 4.4 Hz), 4.23 (1H, d, *J* = 10.2 Hz), 4.09 (1H, d, *J* = 10.2 Hz), 2.75 (1H, dd, *J* = 17.9, 13.6 Hz), 2.61 (1H, dd, *J* = 17.9, 5.6 Hz), 2.33−2.26 (2H, m), 2.06 (1H, dd, *J* = 14.6, 10.5 Hz), 2.02 (1H, ddd, *J* = 12.8, 7.2, 4.9 Hz), 1.87 (1H, dd, *J* = 13.6, 5.6 Hz), 1.77 (1H, ddd, *J* = 12.8, 8.2, 7.9 Hz), 1.66 (1H, dd, *J* = 12.3, 8.7 Hz), 1.30 (1H, ddd, *J* = 12.3, 11.3, 10.5 Hz), 1.19 (3H, s), 1.06 (3H, d, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 162.4, 148.7, 133.8, 129.4, 122.5, 92.7, 81.8, 75.1, 69.2, 47.1, 42.6, 40.6, 40.5, 36.1, 34.4, 30.9, 16.7, 15.2; IR (KBr) ν_{max} 1732, 1547, 1346, 1281, 1172 cm^{-1}; HRMS (FAB) $[M+H]^+$ calculated for $C_{21}H_{25}N_2O_9$: 449.1560, found: 449.1555; $[\alpha]_D^{21}$ −12.0 (*c* 0.6, $CHCl_3$).

3,5-Dinitrobenzoic acid (4a*S*,5*S*,7a*S*,3'*S*,5'*R*)-7a-methylhexahydrocyclopenta[c]pyran-3(1*H*)-one-5-spiro-2'-(3'-methyltetrahydrofuran)-5'-ylmethyl ester (34c)

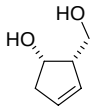


34c was prepared from **33c'** in 53% yield according to the procedure for **34a**.
R_f = 0.45 (hexane/ethyl acetate=1/1); mp 45−46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24−9.20 (3H, m), 4.42 (1H, dd, *J* = 11.0, 6.1 Hz), 4.37 (1H, dd, *J* = 11.0, 3.8 Hz), 4.35 (1H, m), 4.04 (1H, d, *J* = 11.5 Hz), 3.88 (1H, d, *J* = 11.5 Hz), 2.53 (1H, dd, *J* = 15.6, 4.9 Hz), 2.33 (1H, dd, *J* = 15.6, 7.7 Hz), 2.07 (1H, m), 2.05−1.97 (1H, m), 1.89 (1H, dd, *J* = 7.7, 4.9 Hz), 1.85 (1H, ddd, *J* = 12.5, 10.8, 10.5 Hz), 1.63−1.55 (2H, m), 1.48 (1H, dd, *J* = 12.0, 5.6 Hz), 1.09 (3H, s), 1.03 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 163.3, 149.3, 134.7, 130.4, 123.0, 96.3, 75.3, 73.7, 69.3, 48.7, 40.7, 37.3, 36.3, 34.6, 29.9, 28.5, 26.2, 14.9; IR (KBr) ν_{max} 1738, 1547, 1346, 1283, 1171 cm^{-1}; HRMS (FAB) $[M+H]^+$

calculated for $C_{21}H_{25}N_2O_9$: 449.1560, found: 449.1563; $[\alpha]_D^{22}$ −21.0 (*c* 0.8, $CHCl_3$).

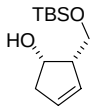
C2 位および C3 位不斉中心の構築：

(1*S*,2*S*)-2-(Hydroxymethyl)cyclopent-3-enol (36)



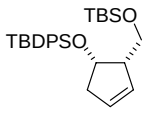
To a stirred solution of **35** (3.15 g, 22.2 mmol) in CH_2Cl_2 (1000 mL) was added Grubbs cat. 2nd (376 mg, 0.443 mmol) in CH_2Cl_2 (20 mL) at room temperature. After the reaction was completed, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to afford the known diol **36** (2.33 g, 92%) as an oil.

(1*S*,2*S*)-2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)cyclopent-3-en-1-ol (36')



To a stirred solution of **36** (1.76 g, 15.4 mmol) in CH_2Cl_2 (160 mL) was added imidazole (1.37 g, 20.1 mmol) and TBSCl (2.64 g, 17.0 mmol) successively at 0 ºC. After the reaction was completed, saturated aqueous NH_4Cl (100 mL) was added to the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2 (80 mL × 2). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **36'** (3.07 g, 87%) as an oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81–5.79 (1H, m), 5.49–5.48 (1H, m), 4.64–4.58 (1H, m), 3.93 (1H, dd, *J* = 10.2, 4.4 Hz), 3.81 (1H, dd, *J* = 10.2, 7.6 Hz), 3.19–3.17 (1H, m), 2.85 (1H, br), 2.70–2.64 (1H, m), 2.37–2.33 (1H, m), 0.90 (9H, s), 0.08 (3H, s), 0.07 (3H, s).

***tert*-Butyl{[(1*S*,2*S*)-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)cyclopent-3-en-1-yl]oxy}diphenyl silane (37)**

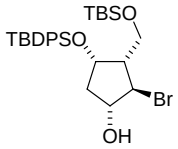


To a stirred solution of **36'** (2.97 g, 13.0 mmol) in a mixture of CH_2Cl_2 (80 mL) and DMF (8 mL) was added imidazole (2.66 g, 39.1 mmol), DMAP (318 mg, 2.60 mmol) and TBDPSCl (6.77 mL, 26.0 mmol) successively at room temperature. After the reaction

was completed, saturated aqueous NH_4Cl (50 mL) was added to the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2 (50 mL × 2). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **37** (5.96 g, 98%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (4H, m), 7.45–7.34 (6H, m), 5.75–5.74 (1H, m), 5.64–5.62 (1H, m), 4.57 (1H, ddd, *J* = 7.1, 6.8, 6.3 Hz), 3.96 (1H, dd, *J* = 9.8, 5.6 Hz), 3.76 (1H, dd, *J* = 9.8, 9.5 Hz), 2.65–2.64 (1H, m), 2.32–2.27 (1H, m), 2.24–2.17 (1H, m), 1.06 (9H, s), 0.90 (9H, s), 0.05 (3H, s), 0.03 (3H, s).

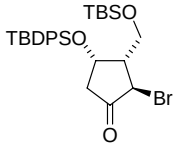
(1*R*,2*R*,3*S*,4*S*)-2-Bromo-3-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4-{[*tert*-butyl(diphenyl)silyl]oxy}cyclopentanol (38)



To a stirred solution of **37** (5.69 g, 12.2 mmol) in a mixture of acetone (90 mL) and H_2O (30 mL) was added NBS (4.34 g, 24.4 mmol) at room temperature. After the reaction was completed, saturated aqueous $NaHCO_3$ (50 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (80 mL × 2). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **38** (3.99 g, 58%) as an oil and inseparable mixture of **38'** and **39** (1.72 g, 25%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.65 (4H, m), 7.45–7.35 (6H, m), 4.66–4.65 (1H, m), 4.49 (1H, ddd, *J* = 7.6, 7.6, 6.6 Hz), 4.15 (1H, dd, *J* = 5.9, 3.7 Hz), 4.02 (1H, dd, *J* = 10.0, 6.3 Hz), 3.83 (1H, dd, *J* = 10.0, 4.6 Hz), 2.36–2.29 (1H, m), 2.28 (1H, ddd, *J* = 14.4, 7.6, 4.9 Hz), 1.80 (1H, br), 1.74 (1H, ddd, *J* = 14.4, 7.6, 2.9 Hz), 1.07 (9H, s), 0.91 (9H, s), 0.09 (3H, s), 0.06 (3H, s).

(2*R*,3*S*,4*S*)-2-Bromo-3-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4-{[*tert*-butyl(diphenyl)silyl]oxy}cyclopentanone (Fragment C)

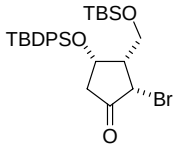


To a stirred solution of **38** (3.64 g, 6.46 mmol) in CH_2Cl_2 (60 mL) was added Dess–Martin periodinane (8.21 g, 19.4 mmol) at room temperature. After the reaction

was completed, Et_2O (80 mL) and a mixture of saturated aqueous $NaHCO_3$ solution (80 mL) and saturated aqueous $Na_2S_2O_3$ solution (80 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (60 mL × 2). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **Fragment C** (3.55 g, 98%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.64 (4H, m), 7.48–7.36 (6H, m), 4.48 (1H, ddd, *J* = 8.0, 7.3, 6.3 Hz), 4.27 (1H, dd, *J* = 10.0, 2.9 Hz), 4.25 (1H, d, *J* = 7.3 Hz), 3.89 (1H, dd, *J* = 10.0, 3.4 Hz), 2.58 (1H, dd, *J* = 18.8, 7.3 Hz), 2.40–2.35 (1H, m), 2.27 (1H, dd, *J* = 18.8, 8.0 Hz), 1.09 (9H, s), 0.90 (9H, s), 0.12 (3H, s), 0.08 (3H, s).

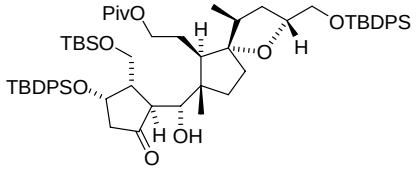
(2*S*,3*S*,4*S*)-2-Bromo-3-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4-{[*tert*-butyl(diphenyl)silyl]oxy} cyclopentanone (Fragment C')



To a stirred solution of **38'** and **39** (1.65 g, 2.93 mmol) in CH_2Cl_2 (30 mL) was added Dess–Martin periodinane (3.11 g, 7.32 mmol) at room temperature. After the reaction was completed, Et_2O (50 mL) and a mixture of saturated aqueous $NaHCO_3$ solution (50 mL) and saturated aqueous $Na_2S_2O_3$ solution (50 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (50 mL × 2). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **Fragment C'** (1.00 g, 61%) as an oil and **40** (559 mg, 34%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.59 (4H, m), 7.48–7.36 (6H, m), 4.80 (1H, ddd, *J* = 6.1, 5.6, 4.9 Hz), 4.25 (1H, d, *J* = 7.1 Hz), 4.07 (1H, dd, *J* = 10.2, 4.1 Hz), 4.01 (1H, dd, *J* = 10.2, 6.8 Hz), 2.39–2.34 (1H, m), 2.32 (1H, dd, *J* = 18.8, 4.9 Hz), 2.25 (1H, dd, *J* = 18.8, 6.1 Hz), 1.07 (9H, s), 0.90 (9H, s), 0.10 (3H, s), 0.08 (3H, s).

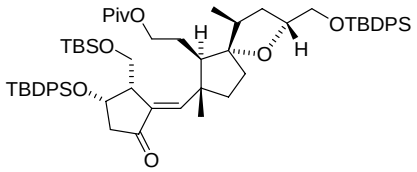
2-[(2*R*,4*S*,5*S*,6*R*,7*S*)-7-[(*R*)-((1*S*,2*S*,3*S*)-2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-5-oxocyclopentyl)(hydroxy)methyl]-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethyl 2,2-dimethylpropanoate (41)



To a stirred solution of **4** (1.39 g, 2.41 mmol) and **Fragment C** (2.71 g, 4.81 mmol) in benzene (25 mL) was added a solution of Et_3B in hexane (5.25 mL, 1.01 M) and Ph_3SnH (1.69 g, 4.81 mmol) in benzene (10 mL) successively at room temperature. After the reaction was completed, saturated aqueous KF (50 mL) was added to the reaction mixture, and the aqueous layer was extracted with AcOEt (50 mL × 2). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **41** (2.30 g, 90%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.63 (6H, m), 7.59–7.58 (2H, m), 7.44–7.33 (12H, m), 4.66 (1H, ddd, *J* = 4.6, 4.6, 4.1 Hz), 4.17 (1H, ddd, *J* = 10.5, 10.5, 5.4 Hz), 4.00–3.96 (2H, m), 3.93–3.89 (1H, m), 3.84 (1H, dd, *J* = 10.0, 5.6 Hz), 3.62 (1H, dd, *J* = 10.2, 4.6 Hz), 3.51 (1H, dd, *J* = 7.7, 1.8 Hz), 3.50 (1H, dd, *J* = 10.2, 6.7 Hz), 3.11 (1H, d, *J* = 7.7 Hz), 2.50 (1H, dd, *J* = 8.2, 1.8 Hz), 2.34–2.29 (1H, m), 2.26–2.19 (1H, m), 2.14–2.12 (2H, m), 2.08 (1H, ddd, *J* = 12.5, 7.9, 4.6 Hz), 2.01 (1H, dd, *J* = 8.4, 4.4 Hz), 1.80–1.73 (1H, m), 1.70–1.54 (4H, m), 1.46–1.43 (1H, m), 1.27–1.22 (1H, m), 1.14 (9H, s), 1.05 (9H, s), 1.03 (3H, d, *J* = 6.7 Hz), 1.02 (9H, s), 0.95 (3H, s), 0.88 (9H, s), 0.04 (6H, s).

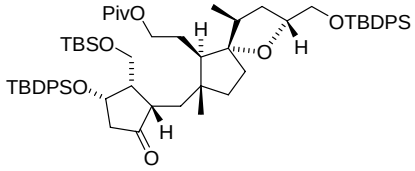
2-[(2*R*,4*S*,5*S*,6*R*,7*R*)-7-[(*E*)-((2*S*,3*S*)-2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-5-oxocyclopentylidene)methyl]-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethyl 2,2-dimethylpropanoate (3)



To a stirred solution of **41** (2.22 g, 2.09 mmol) in benzene (20 mL) was added Burgess reagent (1.49 g, 6.27 mmol) in benzene (5 mL) at room temperature. After the reaction was completed, saturated aqueous $NaHCO_3$ (50 mL) was added to the reaction mixture, and the aqueous layer was extracted with AcOEt (20 mL × 2). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **3** (2.01 g, 92%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.63 (8H, m), 7.43–7.33 (12H, m), 6.59 (1H, s), 4.34 (1H, dd, *J* = 9.5, 2.3 Hz), 4.34–4.29 (1H, m), 4.04 (1H, ddd, *J* = 10.8, 9.2, 5.9 Hz), 3.88–3.80 (2H, m), 3.81 (1H, dd, *J* = 9.5, 3.1 Hz), 3.61 (1H, dd, *J* = 10.2, 4.4 Hz), 3.52 (1H, dd, *J* = 10.2, 6.7 Hz), 3.04–3.03 (1H, m), 2.68 (1H, dd, *J* = 17.7, 10.5 Hz), 2.22–2.09 (2H, m), 2.17 (1H, dd, *J* = 17.7, 7.9 Hz), 1.98 (1H, dd, *J* = 8.2, 5.9 Hz), 1.76–1.57 (5H, m), 1.54–1.44 (2H, m), 1.12 (9H, s), 1.10 (9H, s), 1.03 (9H, s), 1.02 (3H, d, *J* = 6.7 Hz), 0.93 (3H, s), 0.85 (9H, s), 0.06 (3H, s), −0.02 (3H,s).

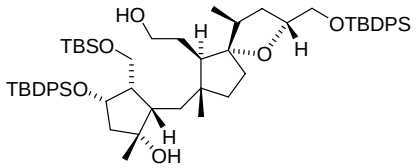
2-[(2*R*,4*S*,5*S*,6*R*,7*R*)-7-[((1*S*,2*S*,3*S*)-2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-5-oxocyclopentyl)methyl]-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethyl 2,2-dimethylpropanoate (42a)



To a stirred solution of **3** (29.8 mg, 0.0286 mmol) in a mixture of MeOH (1 mL) and THF (1 mL) was added a catalytic amount of Ranney Ni under an atmosphere of Ar, and the reaction mixture was stirred under an atmosphere of hydrogen. After the reaction was completed, to the mixture was added acetone (3 mL) and stirred for 1 h. Then the mixture was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography to afford **42a** (24.6 mg, 82%) as a white solid and **42b** (0.7 mg, 2%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.63 (8H, m), 7.45–7.33 (12H, m), 4.38 (1H, ddd, *J* = 9.0, 9.0, 6.7 Hz), 4.38–4.33 (1H, m), 4.04–3.93 (2H, m), 3.86–3.83 (1H, m), 3.73 (1H, dd, *J* = 10.2, 3.1 Hz), 3.61 (1H, dd, *J* = 10.2, 4.4 Hz), 3.51 (1H, dd, *J* = 10.2, 6.7 Hz), 2.41 (1H, dd, *J* = 18.4, 9.7 Hz), 2.26–2.24 (1H, m), 2.19–2.07 (3H, m), 2.00 (1H, dd, *J* = 14.8, 2.0 Hz), 1.87–1.85 (1H, m), 1.73 (1H, dd, *J* = 7.9, 6.1 Hz), 1.68–1.61 (2H, m), 1.57–1.40 (5H, m), 1.20–1.16 (1H, m), 1.12 (9H, s), 1.09 (9H, s), 1.03 (9H, s), 1.00 (3H, d, *J* = 6.7 Hz), 0.86 (9H, s), 0.72 (3H, s), 0.09 (3H, s), 0.03 (3H,s).

(1*R*,2*S*,3*S*,4*S*)-3-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4-{[*tert*-butyl(diphenyl)silyl]oxy}-2-{[(2*R*,4*S*,5*S*,6*R*,7*R*)-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-6-(2-hydroxyethyl)-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl]methyl}-1-methylcyclopentanol (2)

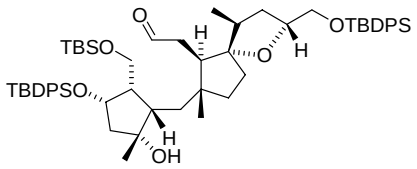


To a stirred solution of **42a** (188 mg, 0.180 mmol) in Et_2O (7 mL) was added a solution of MeLi in Et_2O (0.797 mL, 1.13 M) at −78 ºC. Stirring was continued at −78 ºC at 2 h, then at 0 ºC for 30 min. After the reaction was completed, saturated aqueous NH_4Cl (5 mL) was added to the reaction mixture, and the aqueous layer was extracted with AcOEt (5 mL × 2). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **2** (173 mg, 98%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.63 (8H, m), 7.44−7.34 (12H, m), 4.40 (1H, br), 4.28 (1H, dd, J = 10.4, 1.3 Hz), 4.08 (1H, ddd, J = 9.3, 9.3, 7.3 Hz), 3.90−3.85 (1H, m), 3.71 (1H, dd, J = 10.4, 3.1 Hz), 3.64 (1H, dd, J = 10.3, 4.6 Hz), 3.56 (1H, dd, J = 10.3, 6.2 Hz), 3.54−3.48 (2H, m), 2.22 (1H, ddd, J = 10.4, 7.5, 7.3 Hz), 2.05 (1H, ddd, J = 12.1, 8.1, 3.8 Hz), 1.97−1.84 (4H, m), 1.76 (1H, dd, J = 9.3, 3.1 Hz), 1.70−1.59 (3H, m), 1.54−1.41 (6H, m), 1.29−1.25 (1H, m), 1.07 (9H, s), 1.04 (9H, s), 1.03 (3H, s), 1.01 (3H, d, J = 6.8 Hz), 0.96 (9H, s), 0.65 (3H, s), 0.18 (3H, s), 0.17 (3H,s).

8 員環構築の検討：

[(2*R*,4*S*,5*S*,6*R*,7*R*)-7-[((1*S*,2*R*,4*S*,5*S*)-5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4-{[*tert*-butyl(diphenyl)silyl]oxy}-2-hydroxy-2-methylcyclopentyl)methyl]-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]acetaldehyde (43)

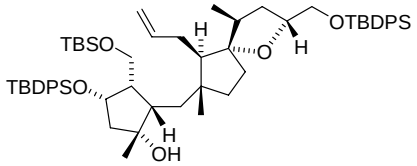


To a stirred solution of $(COCl)_2$ (0.020 mL, 0.281 mmol) in CH_2Cl_2 (5 mL) was added DMSO (0.020 mL, 0.225 mmol) at −78 ºC, and the mixture was stirred at this temperature for 30 min. Then, a solution of **2** (27.5 mg, 0.0281 mmol) in CH_2Cl_2 (1 mL) was added dropwise at −78 ºC. After 30 min, Et_3N (0.078 mL, 0.563 mmol) was added to the reaction mixture at −78 ºC, and the reaction mixture was warmed up to room

temperature. After the reaction was completed, H_2O (5 mL) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (5 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **43** (27.4 mg, 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (1H, dd, *J* = 2.9, 2.9 Hz), 7.67–7.63 (8H, m), 7.44–7.33 (12H, m), 4.44 (1H, br), 4.26 (1H, dd, *J* = 10.6, 1.3 Hz), 4.06 (1H, ddd, *J* = 9.7, 9.2, 7.1 Hz), 3.92–3.87 (1H, m), 3.64 (1H, dd, *J* = 10.6, 2.9 Hz), 3.60 (1H, dd, *J* = 10.3, 4.6 Hz), 3.48 (1H, dd, *J* = 10.3, 6.0 Hz), 2.41 (1H, dd, *J* = 7.7, 7.1 Hz), 2.32 (1H, ddd, *J* = 15.2, 8.1, 2.9 Hz), 2.18 (1H, ddd, *J* = 15.2, 6.8, 2.9 Hz), 2.03–1.84 (5H, m), 1.69–1.40 (7H, m), 1.30–1.22 (1H, m), 1.07 (9H, s), 1.04 (3H, s), 1.03 (9H, s), 0.97 (3H, d, *J* = 6.6 Hz), 0.96 (9H, s), 0.64 (3H, s), 0.19 (3H, s), 0.18 (3H,s).

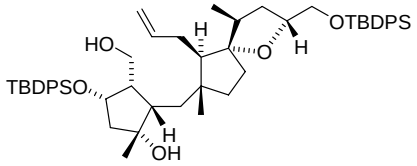
(1*R*,2*S*,3*S*,4*S*)-2-{[(2*R*,4*S*,5*S*,6*R*,7*R*)-6-Allyl-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl]methyl}-3-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-4-{[*tert*-butyl(diphenyl)silyl]oxy}-1-methylcyclopentanol (44)



To a suspension of $Ph_3P^+MeBr^-$ (87.0 mg, 0.239 mmol) in THF (3 mL) was added a solution of *t*–BuOK (29.7 mg, 0.225 mmol) in THF (2 mL) dropwise at room temperature, and the reaction mixture was stirred for 1 h. Then, to the reaction mixture was added **43** (27.4 mg, 0.0281 mmol) in THF (1 mL) at 0 °C. After the starting material disappeared, the reaction 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 dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography to afford **44** (27.3 mg, 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.63 (8H, m), 7.44–7.33 (12H, m), 5.73 (1H, dddd, *J* = 17.2, 10.3, 6.8, 6.2 Hz), 4.94 (1H, dd, *J* = 17.2, 1.8 Hz), 4.78 (1H, dd, *J* = 10.3, 1.8 Hz), 4.42 (1H, br), 4.25 (1H, dd, *J* = 10.3, 1.1 Hz), 4.07 (1H, ddd, *J* = 9.5, 9.3, 7.1 Hz), 3.92–3.87 (1H, m), 3.71 (1H, dd, *J* = 10.3, 2.9 Hz), 3.61 (1H, dd, *J* = 10.1, 4.4 Hz), 3.48 (1H, dd, *J* = 10.1, 6.8 Hz), 2.22–2.15 (1H, m), 2.13–1.99 (3H, m), 1.96–1.84 (4H, m), 1.66–1.59 (2H, m), 1.53–1.52 (2H, m), 1.49–1.36 (3H, m), 1.22–1.16 (1H, m), 1.07 (9H, s), 1.03 (9H, s), 1.02 (3H, s), 0.99 (3H, d, *J* = 6.8 Hz), 0.96 (9H, s), 0.67 (3H, s), 0.18 (3H, s), 0.17 (3H,s).

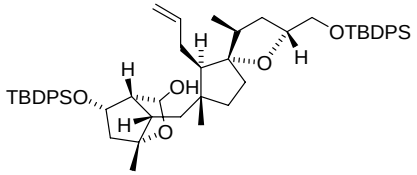
(1*R*,2*S*,3*S*,4*S*)-2-{[(2*R*,4*S*,5*S*,6*R*,7*R*)-6-Allyl-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl]methyl}-4-{[*tert*-butyl(diphenyl)silyl]oxy}-3-(hydroxymethyl)-1-methylcyclopentanol (45)



To a stirred solution of **44** (25.7 mg, 0.0264 mmol) in EtOH (3 mL) was added PPTS (1.3 mg, 5.28 × 10^{-3} mmol) at room temperature. After the reaction was completed, Et_3N (0.004 mL, 0.0264 mmol) was added to the reaction mixture, and the resultant solution was concentrated under reduced pressure. The residue was purified by flash chromatography to afford **45** (22.7 mg, 100%).

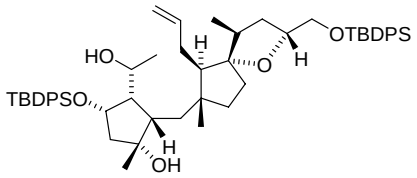
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.63 (8H, m), 7.46–7.33 (12H, m), 5.74 (1H, dddd, *J* = 17.0, 10.3, 6.8, 6.4 Hz), 4.96 (1H, dd, *J* = 17.0, 1.8 Hz), 4.81 (1H, dd, *J* = 10.3, 1.8 Hz), 4.42 (1H, ddd, *J* = 9.7, 7.5, 6.6 Hz), 4.06 (1H, dd, *J* = 12.1, 3.3 Hz), 3.92–3.87 (1H, m), 3.83 (1H, dd, *J* = 12.1, 2.2 Hz), 3.61 (1H, dd, *J* = 10.1, 4.4 Hz), 3.47 (1H, dd, *J* = 10.1, 6.8 Hz), 2.23–2.15 (1H, m), 2.13–1.96 (5H, m), 1.89 (1H, dd, *J* = 8.2, 6.4 Hz), 1.80 (1H, dd, *J* = 15.0, 6.4 Hz), 1.69–1.59 (3H, m), 1.48–1.36 (4H, m), 1.22–1.18 (1H, m), 1.08 (9H, s), 1.06 (3H, s), 1.03 (9H, s), 0.99 (3H, d, *J* = 6.6 Hz), 0.67 (3H, s).

(1*R*,4*R*,5*S*,7*S*)-7-{[(2*R*,4*S*,5*S*,6*R*,7*R*)-6-Allyl-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl]methyl}-5-{[*tert*-butyl(diphenyl)silyl]oxy}-1-methyl-2-oxabicyclo[2.2.1]heptan-3-ol (48)



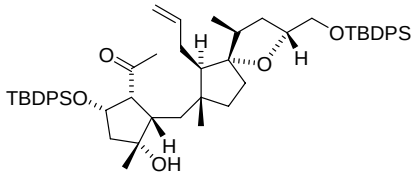
To a stirred solution of **45** (81.3 mg, 0.0946 mmol) in DMSO (5 mL) was added IBX (79.5 mg, 0.284 mmol) at room temperature. After the reaction was completed, Et_2O (10 mL) and a mixture of saturated aqueous $NaHCO_3$ solution (5 mL) and saturated aqueous $Na_2S_2O_3$ solution (5 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (5 mL × 2). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The crude lactol **48** was used for the next step without further purification.

(1*R*,2*S*,3*S*,4*S*)-2-{[(2*R*,4*S*,5*S*,6*R*,7*R*)-6-Allyl-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl]methyl}-4-{[*tert*-butyl(diphenyl)silyl]oxy}-3-(1-hydroxyethyl)-1-methylcyclopentanol (49)



To a stirred solution of **48** in Et_2O (4.5 mL) was added a solution of MeLi in Et_2O (0.586 mL, 1.13 M) at 0 ºC. After the reaction was completed, saturated aqueous NH_4Cl (5 mL) was added to the reaction mixture, and the aqueous layer was extracted with AcOEt (5 mL × 2). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude alcohol **49** was used for the next step without further purification.

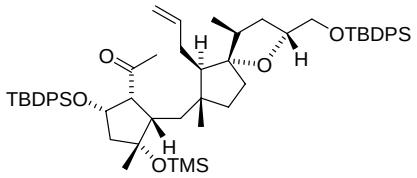
1-((1*R*,2*S*,3*R*,5*S*)-2-{[(2*R*,4*S*,5*S*,6*R*,7*R*)-6-Allyl-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl]methyl}-5-{[*tert*-butyl(diphenyl)silyl]oxy}-3-hydroxy-3-methylcyclopentyl)ethanone (49')



To a stirred solution of **49** (24.1 mg, 0.0276 mmol) in CH_2Cl_2 (4.5 mL) was added Dess–Martin periodinane (80.3 mg, 0.189 mmol) at room temperature. After the reaction was completed, Et_2O (5 mL) and a mixture of saturated aqueous $NaHCO_3$ solution (5 mL) and saturated aqueous $Na_2S_2O_3$ solution (5 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (5 mL × 2). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **49'** (82.4 mg, 100% (3 steps)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.58 (8H, m), 7.48–7.33 (12H, m), 5.67 (1H, dddd, J = 17.3, 10.7, 6.8, 6.3 Hz), 4.92 (1H, d, J = 17.3 Hz), 4.79 (1H, br), 4.77 (1H, d, J = 10.7 Hz), 4.30 (1H, ddd, J = 9.8, 7.8, 7.6 Hz), 3.93–3.87 (1H, m), 3.60 (1H, dd, J = 10.0, 4.6 Hz), 3.48–3.44 (1H, m), 3.47 (1H, dd, J = 10.0, 6.6 Hz), 2.35 (1H, dd, J = 7.3, 6.8 Hz), 2.27–2.15 (2H, m), 2.23 (3H, s), 2.10–1.79 (4H, m), 1.74–1.20 (8H, m), 1.04 (9H, s), 1.03 (9H, s), 0.99 (3H, d, J = 7.0 Hz), 0.98 (3H, s), 0.68 (3H, s).

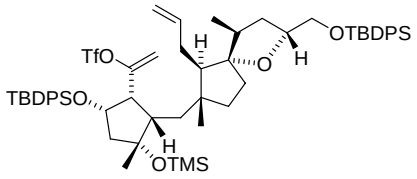
1-{(1*R*,2*S*,3*R*,5*S*)-2-{[(2*R*,4*S*,5*S*,6*R*,7*R*)-6-Allyl-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl]methyl}-5-{[*tert*-butyl(diphenyl)silyl]oxy}-3-methyl-3-[(trimethylsilyl)oxy]cyclopentyl}ethanone (50)



To a stirred solution of **49'** (23.7 mg, 0.0272 mmol) in DMF (1.5 mL) was added imidazole (55.6 mg, 0.816 mmol) and TMSCl (0.069 mL, 0.544 mmol) successively at room temperature. After the reaction was completed, saturated aqueous NaCl (5 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (3 mL × 2). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **50** (24.0 mg, 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.62 (8H, m), 7.46–7.32 (12H, m), 5.69 (1H, dddd, *J* = 17.1, 10.2, 6.8, 6.3 Hz), 4.94 (1H, dd, *J* = 17.1, 1.7 Hz), 4.77 (1H, dd, *J* = 10.2, 1.7 Hz), 4.18 (1H, ddd, *J* = 9.3, 7.8, 7.3 Hz), 3.92–3.86 (1H, m), 3.61 (1H, dd, *J* = 10.0, 4.4 Hz), 3.47 (1H, dd, *J* = 10.0, 7.1 Hz), 3.06 (1H, dd, *J* = 7.3, 6.8 Hz), 2.39 (3H, s), 2.29 (1H, dd, *J* = 13.9, 9.5 Hz), 2.23–2.14 (1H, m), 2.07–1.95 (3H, m), 1.87 (1H, dd, *J* = 13.9, 8.5 Hz), 1.79 (1H, dd, *J* = 8.5, 6.8 Hz), 1.74–1.35 (7H, m), 1.32–1.19 (1H, m), 1.07 (3H, s), 1.03 (9H, s), 1.01 (9H, s), 0.99 (3H, d, *J* = 6.8 Hz), 0.68 (3H, s), 0.08 (9H, s).

1-{(1*R*,2*S*,3*R*,5*S*)-2-{[(2*R*,4*S*,5*S*,6*R*,7*R*)-6-Allyl-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl]methyl}-5-{[*tert*-butyl(diphenyl)silyl]oxy}-3-methyl-3-[(trimethylsilyl)oxy]cyclopentyl}vinyl trifluoromethanesulfonate (51)

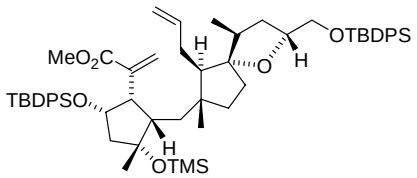


To a stirred solution of **50** (25.2 mg, 0.0267 mmol) in THF (1.5 mL) was added a solution of KHMDS in toluene (0.534 mL, 0.5 M) at −78 °C, and the mixture was stirred at this temperature for 30 min. Then, a solution of Comins' reagent (95.7 mg, 0.267 mmol) in THF (0.5 mL) was added dropwise at −78 °C. After the reaction was completed, saturated aqueous NaCl (2 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (2 mL × 2). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash

chromatography to afford **51** (23.5 mg, 82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.63 (8H, m), 7.46–7.33 (12H, m), 5.71 (1H, dddd, *J* = 17.1, 10.2, 6.6, 6.1 Hz), 5.59 (1H, d, *J* = 3.4 Hz), 5.42 (1H, d, *J* = 3.4 Hz), 4.95 (1H, dd, *J* = 17.1, 1.5 Hz), 4.75 (1H, dd, *J* = 10.2, 1.5 Hz), 4.10 (1H, ddd, *J* = 10.5, 7.1, 6.8 Hz), 3.93–3.87 (1H, m), 3.61 (1H, dd, *J* = 10.0, 4.4 Hz), 3.47 (1H, dd, *J* = 10.0, 7.1 Hz), 2.89 (1H, dd, *J* = 6.8, 6.6 Hz), 2.23–2.15 (1H, m), 2.08–2.00 (4H, m), 1.94 (1H, dd, *J* = 13.4, 11.0 Hz), 1.80 (1H, dd, *J* = 8.5, 6.6 Hz), 1.73–1.20 (8H, m), 1.04 (9H, s), 1.03 (9H, s), 1.00 (3H, d, *J* = 6.6 Hz), 1.00 (3H, s), 0.68 (3H, s), 0.03 (9H, s).

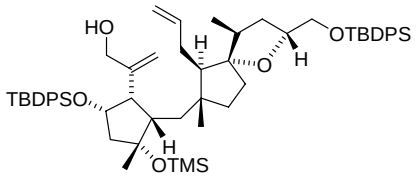
Methyl 2-{(1*S*,2*S*,3*R*,5*S*)-2-{[(2*R*,4*S*,5*S*,6*R*,7*R*)-6-allyl-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl]methyl}-5-{[*tert*-butyl(diphenyl)silyl]oxy}-3-methyl-3-[(trimethylsilyl)oxy]cyclopentyl}acrylate (51')



To a stirred solution of **51** (9.5 mg, 8.83 × 10^{-3} mmol) in MeOH (3 mL) was added Et_3N (0.019 mL, 0.132 mmol) and $Pd(PPh_3)_4$ (10.2 mg, 8.83 × 10^{-3} mmol) successively at room temperature under an atmosphere of Ar, and the reaction mixture was stirred at 50 °C under an atmosphere of CO. After the reaction was completed, saturated aqueous NH_4Cl solution (3 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (5 mL × 2). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **51'** (7.7 mg, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (8H, m), 7.43–7.33 (12H, m), 6.56 (1H, d, *J* = 1.2 Hz), 6.15 (1H, d, *J* = 1.2 Hz), 5.70 (1H, dddd, *J* = 17.3, 10.2, 6.8, 6.3 Hz), 4.91 (1H, d, *J* = 17.3 Hz), 4.75 (1H, d, *J* = 10.2 Hz), 4.14–4.06 (1H, m), 3.93–3.87 (1H, m), 3.81 (1H, dd, *J* = 6.8, 6.8 Hz), 3.66 (3H, s), 3.62 (1H, dd, *J* = 10.0, 4.1 Hz), 3.48 (1H, dd, *J* = 10.0, 7.1 Hz), 2.21–2.14 (1H, m), 2.08–1.92 (4H, m), 1.83–1.73 (2H, m), 1.70–1.20 (8H, m), 1.03 (9H, s), 0.99 (3H, d, *J* = 6.8 Hz), 0.97 (9H, s), 0.97 (3H, s), 0.65 (3H, s), 0.00 (9H, s).

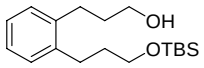
2-{(1*S*,2*S*,3*R*,5*S*)-2-{[(2*R*,4*S*,5*S*,6*R*,7*R*)-6-Allyl-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl]methyl}-5-{[*tert*-butyl(diphenyl)silyl]oxy}-3-methyl-3-[(trimethylsilyl)oxy]cyclopentyl}prop-2-en-1-ol (52)



To a stirred solution of **51'** (5.0 mg, 5.07×10^{-3} mmol) in hexane (0.7 mL) was added a solution of DIBAL–H in hexane (0.054 mL, 0.94 M) at −78 °C. After the reaction was completed, MeOH was added to the reaction mixture at −78 °C till no gas evolution was observed. Then, saturated aqueous Rochelle salt solution (3 mL) was added to the reaction mixture and the resultant solution was stirred vigorously at room temperature. After 30 min, the aqueous layer was extracted with AcOEt (3 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **52** (4.8 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.63 (8H, m), 7.44–7.33 (12H, m), 5.69 (1H, dddd, J = 17.2, 10.2, 6.8, 6.3 Hz), 5.36 (1H, d, J = 1.8 Hz), 5.08 (1H, d, J = 1.8 Hz), 4.91 (1H, dd, J = 17.2, 1.6 Hz), 4.74 (1H, dd, J = 10.2, 1.6 Hz), 4.16 (1H, brs), 4.16 (1H, brs), 4.12 (1H, ddd, 10.8, 7.5, 7.1 Hz), 3.92–3.87 (1H, m), 3.61 (1H, dd, J = 10.0, 4.4 Hz), 3.46 (1H, dd, J = 10.0, 7.1 Hz), 3.09 (1H, br), 2.88 (1H, dd, J = 7.3, 6.8 Hz), 2.21–2.14 (1H, m), 2.06–1.93 (5H, m), 1.80 (1H, dd, J = 8.6, 6.3 Hz), 1.75–1.20 (8H, m), 1.03 (9H, s), 1.03 (9H, s), 1.01 (3H, s), 0.99 (3H, d, J = 6.8 Hz), 0.63 (3H, s), 0.04 (9H, s).

2-[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]propyl]benzenepropanol (57')

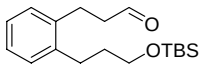


1,2–Benzenedipropanol (1.45 g, 7.46 mmol) in THF (20 mL) was added to a vigorously stirred suspension of NaH (299 mg,7.46 mmol) in THF (50 mL) at 0 °C. After stirring for 16 h, TBSCl (1.16 g, 7.46 mmol) was added and stirring was continued at room temperature. After the reaction was completed, saturated aqueous NH_4Cl solution (70 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (70 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=10/1) to afford **57'** (1.47 g, 64%) as a yellow oil.

R_f = 0.17 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.11 (4H, m), 3.70 (2H, dt, J = 6.1, 5.6 Hz), 3.67 (2H, t, J = 6.1 Hz), 2.73 (2H, t, J = 7.8 Hz), 2.70 (2H, t,

J = 8.0 Hz), 1.87 (2H, dt, J = 7.8, 6.1 Hz), 1.80 (2H, dt, J = 8.0, 6.1 Hz), 1.30 (1H, t, J = 5.6 Hz), 0.91 (9H, s), 0.07 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 139.6, 129.3, 129.2, 126.0, 125.9, 62.6, 62.5, 34.3, 34.0, 28.8, 28.7, 25.9, 18.3, −5.3; IR (neat) ν_{max} 3364, 2936, 2860, 1256, 1100, 838 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{18}H_{33}O_2Si$: 309.2250, found: 309.2241.

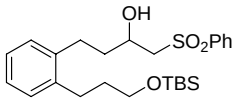
2-[3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]propyl]benzenepropanal (58)



To a stirred solution of **57'** (1.47 g, 4.76 mmol) in CH_2Cl_2 (40 mL) was added Dess−Martin periodinane (4.04 g, 9.52 mmol) at room temperature. After the reaction was completed, Et_2O (80 mL) and a mixture of saturated aqueous $NaHCO_3$ solution (80 mL) and saturated aqueous $Na_2S_2O_3$ solution (80 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (80 mL × 2). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=15/1) to afford **58** (1.34 g, 92%) as a yellow oil.

R_f = 0.37 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (1H, t, J = 1.5 Hz), 7.17−7.13 (4H, m), 3.67 (2H, t, J = 6.1 Hz), 2.98 (2H, t, J = 7.1 Hz), 2.74 (2H, dt, J = 7.1, 1.5 Hz), 2.69 (2H, t, J = 8.0 Hz), 1.79 (2H, tt, J = 8.0, 6.1 Hz), 0.91 (9H, s), 0.06 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 140.0, 138.0, 129.4, 128.9, 126.5, 126.2, 62.4, 44.9, 34.2, 28.8, 25.9, 24.8, 18.3, −5.3; IR (neat) ν_{max} 2956, 2860, 1728, 1100, 836 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{18}H_{31}O_2Si$: 307.2093, found: 307.2104.

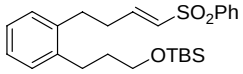
4-(2-(3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]propyl)phenyl)-1-(phenylsulfonyl)butan-2-ol (59)



To a stirred solution of $MeSO_2Ph$ (888 mg, 5.68 mmol) in THF (35 mL) was added a solution of *n*−BuLi in hexane (3.42 mL, 1.66 M) dropwise at −78 ºC, and the reaction mixture was stirred for 20 min. Then, to the reaction mixture was added a solution of **58** (1.34 g, 4.37 mmol) in THF (10 mL) via a cannula at −78 ºC, and strring was continued. After the reaction was completed, saturated aqueous NH_4Cl solution (40 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (40 mL × 2). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced

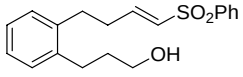
pressure. The residue was used in the next step without further purification.
R_f = 0.11 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, dd, *J* = 7.3, 1.2 Hz), 7.69 (1H, tt, *J* = 7.3, 1.2 Hz), 7.59 (2H, dd, *J* = 7.3, 7.3 Hz), 7.14–7.04 (4H, m), 4.24–4.17 (1H, m), 3.64 (2H, t, *J* = 6.2 Hz), 3.42 (1H, br), 3.25 (1H, dd, *J* = 14.1, 9.5 Hz), 3.16 (1H, dd, *J* = 14.1, 2.0 Hz), 2.84–2.67 (2H, m), 2.64 (2H, t, *J* = 7.9 Hz), 1.82–1.68 (4H, m), 0.90 (9H, s), 0.05 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 139.2, 138.8, 134.1, 129.5, 129.3, 129.2, 127.9, 126.2, 126.0, 65.4, 62.5, 62.3, 37.8, 34.2, 28.7, 27.9, 25.9, 18.3, −5.3; IR (neat) ν_{max} 3516, 2936, 2860, 1448, 1306, 1258, 1152, 1090, 836 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{25}H_{39}O_4SSi$: 463.2338, found: 463.2341.

(3-(2-((*E*)-4-(Phenylsulfonyl)but-3-enyl)phenyl)propoxy)(*tert*-butyl)dimethylsilane (59')



To a stirred solution of **59** in CH_2Cl_2 (40 mL) was added Et_3N (3.95 mL, 28.4 mmol), MsCl (0.676 mL, 8.73 mmol) successively at 0 °C, and the reaction mixture was stirred at room temperature. After the reaction was completed, saturated aqueous NH_4Cl solution (40 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (40 mL × 2). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=10/1) to afford **59'** (2.87 g, 98% (2 steps)) as a yellow oil.
R_f = 0.32 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, dd, *J* = 7.3, 2.2 Hz), 7.61 (1H, tt, *J* = 7.3, 2.2 Hz), 7.53 (2H, dd, *J* = 7.3, 7.3 Hz), 7.17–7.06 (4H, m), 7.02 (1H, dt, *J* = 15.1, 6.8 Hz), 6.31 (1H, dt, *J* = 15.1, 1.5 Hz), 3.63 (2H, t, *J* = 6.1 Hz), 2.80 (2H, t, *J* = 8.0 Hz), 2.63 (2H, t, *J* = 7.9 Hz), 2.52 (2H, ddt, *J* = 7.9, 6.8, 1.5 Hz), 1.75 (2H, tt, *J* = 8.0, 6.1 Hz), 0.89 (9H, s), 0.04 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 140.6, 140.0, 137.7, 133.2, 131.0, 129.4, 129.2, 129.1, 127.6, 126.6, 126.1, 62.3, 34.2, 32.8, 30.6, 28.7, 25.9, 18.3, 15.2, −5.3; IR (neat) ν_{max} 2956, 1322, 1146, 1088, 838, 778 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{25}H_{37}O_3SSi$: 445.2233, found: 445.2229.

3-(2-((*E*)-4-(Phenylsulfonyl)but-3-enyl)phenyl)propan-1-ol (59")

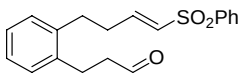


To a stirred solution of **59'** (2.87 g, 6.45 mmol) in EtOH (60 mL) was added PPTS (487 mg, 1.94 mmol) at room temperature. After the reaction was completed, Et_3N (0.45 mL, 1.94 mmol) was added to the reaction mixture, and the resultant solution was

concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=2/1) to afford **59"** (2.13 g, 100%) as an oil.

R_f = 0.22 (hexane/ethyl acetate=1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, dd, *J* = 7.3, 1.5 Hz), 7.63 (1H, tt, *J* = 7.3, 1.5 Hz), 7.53 (2H, dd, *J* = 7.3, 7.3 Hz), 7.19–7.06 (4H, m), 7.02 (1H, dt, *J* = 15.1, 7.1 Hz), 6.32 (1H, dt, *J* = 15.1, 1.5 Hz), 3.69 (2H, dt, *J* = 6.1, 3.6 Hz), 2.81 (2H, t, *J* = 8.0 Hz), 2.68 (2H, t, *J* = 7.8 Hz), 2.54 (2H, ddt, *J* = 7.8, 7.1, 1.5 Hz), 1.84 (2H, tt, *J* = 8.0, 6.1 Hz), 1.37 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0, 140.5, 140.0, 137.7, 133.3, 131.0, 129.4, 129.2, 129.1, 127.6, 126.7, 126.3, 62.2, 33.8, 32.8, 30.5, 28.6; IR (neat) ν_{max} 3516, 2940, 1448, 1308, 1146, 732 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{19}H_{23}O_3S$: 331.1368, found: 331.1366.

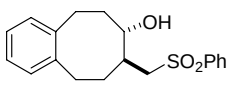
3-(2-((*E*)-4-(Phenylsulfonyl)but-3-enyl)phenyl)propanal (60)



To a stirred solution of **59"** (2.11 g, 6.39 mmol) in CH_2Cl_2 (60 mL) was added Dess–Martin periodinane (5.42 g, 12.8 mmol) at room temperature. After the reaction was completed, Et_2O (100 mL) and a mixture of saturated aqueous $NaHCO_3$ solution (100 mL) and saturated aqueous $Na_2S_2O_3$ solution (100 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (100 mL × 2). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **60** (2.10 g, 100%) as an oil.

R_f = 0.53 (hexane/ethyl acetate=1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (1H, t, *J* = 1.2 Hz), 7.85 (2H, dd, *J* = 7.3, 1.2 Hz), 7.62 (1H, tt, *J* = 7.3, 1.2 Hz), 7.54 (2H, dd, *J* = 7.3, 7.3 Hz), 7.18–7.07 (4H, m), 7.01 (1H, dt, *J* = 15.1, 7.1 Hz), 6.33 (1H, dt, *J* = 15.1, 1.5 Hz), 2.91 (2H, t, *J* = 8.0 Hz), 2.80 (2H, t, *J* = 8.0 Hz), 2.75 (2H, t, *J* = 7.3 Hz), 2.53 (2H, ddt, *J* = 7.3, 7.1, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 145.5, 140.5, 138.0, 137.7, 133.3, 131.2, 129.3, 129.2, 129.0, 127.6, 126.9, 126.7, 44.7, 32.6, 30.5, 24.4; IR (neat) ν_{max} 3060, 2940, 2840, 1722, 1308, 1290, 1146, 1086, 754 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{19}H_{21}O_3S$: 329.1211, found: 329.1220.

5,6,7,8,9,10-Hexahydro-8-((phenylsulfonyl)methyl)benzo[8]annulen-7-ol (61)

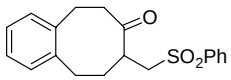


To a stirred solution of **60** (100 mg, 0.304 mmol) in degassed THF (30 mL) and *t*–BuOH (0.059 ml, 0.609 mmol) was added a solution of SmI_2 in THF (4.0 mL, 1.20 mmol, 0.30

M) at 0 °C, and the reaction mixture was stirred at room temperature. After the reaction was completed, stirred open to the air, then saturated aqueous NH_4Cl solution (10 mL) was added to the reaction mixture and the aqueous layer was extracted with AcOEt (10 mL × 2). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (benzene/ethyl acetate=20/1) to afford **61** (67.4 mg, 67%) as a white solid.

R_f = 0.48 (benzene/ethyl acetate=3/1); mp 66.5–68.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (2H, d, *J* = 7.6 Hz), 7.60 (1H, t, *J* = 7.6 Hz), 7.48 (2H, dd, *J* = 7.6, 7.6 Hz), 7.19–7.09 (3H, m), 6.99–6.97 (1H, m), 3.79 (1H, dd, *J* = 14.1, 8.5 Hz), 3.43–3.35 (1H, m), 3.03 (1H, d, *J* = 10.7 Hz), 2.89–2.83 (2H, m), 2.81 (1H, dd, *J* = 14.1, 2.2 Hz), 2.78–2.70 (2H, m), 2.25–2.17 (1H, m), 2.02–1.93 (1H, m), 1.82–1.72 (2H, m), 1.70–1.61 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 139.2, 138.8, 133.6, 129.3, 129.2, 128.9, 127.7, 126.9, 72.6, 59.1, 40.7, 37.7, 36.7, 31.0, 29.9; IR (KBr) ν_{max} 3477, 2911, 1447, 1292, 1155, 1128, 1079 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{19}H_{23}O_3S$: 331.1368, found: 331.1362.

5,6,9,10-Tetrahydro-8-((phenylsulfonyl)methyl)benzo[8]annulen-7(8*H*)-one (62)



To a stirred solution of **61** (67.4 mg, 0.204 mmol) in CH_2Cl_2 (2 mL) was added Dess–Martin periodinane (173 mg, 0.408 mmol) at room temperature. After the reaction was completed, Et_2O (4 mL) and a mixture of saturated aqueous $NaHCO_3$ solution (4 mL) and saturated aqueous $Na_2S_2O_3$ solution (4 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (4 mL × 2). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=4/1) to afford **62** (64.3 mg, 96%) as a white solid.

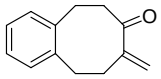
Acyl radical cyclization of 60

To a stirred solution of **60** (10.0 mg, 0.0304 mmol) in toluene (2 mL) was added 1,1'–azobis(cyclohexanecarbonitrile) (11.2 mg, 0.0457 mmol), *t*–$C_{12}H_{25}SH$ (0.022 mL, 0.0913 mmol) successively at room temperature. The solution was degassed three times by the freeze–thaw procedure, and the reaction mixture was stirred at 100 °C. After the reaction was completed, the reaction mixture was concentrated under reduced pressure. The residue was purified by PTLC (hexane/ethyl acetate=2/1) to afford **62** (5.7 mg, 57%).

R_f = 0.42 (hexane/ethyl acetate=1/1); mp 155.2–155.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* = 7.6 Hz), 7.63 (1H, t, *J* = 7.6 Hz), 7.52 (2H, dd, *J* = 7.6, 7.6 Hz), 7.23–7.16 (3H, m), 7.09–7.06 (1H, m), 3.69 (1H, dd, *J* = 13.4, 10.5 Hz), 3.13–3.00 (2H, m), 2.98–2.88

(3H, m), 2.80 (1H, ddd, J = 13.9, 4.9, 4.9 Hz), 2.69–2.57 (2H, m), 1.71–1.60 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5, 139.3, 138.9, 138.2, 133.8, 129.7, 129.4, 129.3, 127.8, 127.7, 127.4, 60.2, 48.5, 42.4, 34.0, 30.8, 29.6; IR (KBr) ν_{max} 2928, 2360, 1696, 1296, 1148, 1084 cm^{-1}; HRMS (FAB) $[M+H]^+$ caluculated for $C_{19}H_{21}O_3S$: 329.1211, found: 329.1216.

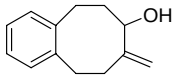
5,6,9,10-Tetrahydro-8-methylenebenzo[8]annulen-7(8*H*)-one (62')



To a stirred solution of **62** (55.6 mg, 0.169 mmol) in benzene (1.7 mL) was added DBU (0.405 mL, 2.71 mmol) at room temperature, and the mixture was stirred at 60 ºC. After the reaction was completed, saturated aqueous NH_4Cl solution (4 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (4 mL × 2). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=15/1) to afford **62'** (27.7 mg, 88%) as a white solid.

R_f = 0.35 (hexane/ethyl acetate=4/1); mp 38.2–39.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.09 (4H, m), 5.01 (1H, s), 4.98 (1H, s), 3.02–2.99 (2H, m), 2.83–2.75 (4H, m), 2.51–2.48 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 151.3, 139.4, 138.9, 130.0, 129.6, 127.2, 127.0, 113.4, 46.6, 36.0, 33.2, 30.0; IR (KBr) ν_{max} 2943, 1697, 1487, 1447, 1182, 1073, 926 cm^{-1}; HRMS (EI) $[M]^+$ caluculated for $C_{13}H_{14}O$: 186.1045, found: 186.1046.

5,6,7,8,9,10-Hexahydro-8-methylenebenzo[8]annulen-7-ol (63)

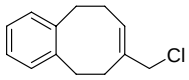


To a stirred solution of **62'** (27.7 mg, 0.149 mmol) in MeOH (1.5 mL) was added $CeCl_3 \cdot 7H_2O$ (61.0 mg, 0.164 mmol), $NaBH_4$ (6.2 mg, 0.164 mmol) at 0 ºC, and the mixture was stirred. After the reaction was completed, saturated aqueous NH_4Cl solution (3 mL) was added to the reaction mixture. The resultant solution was concentrated under reduced pressure, and the residue was extracted with Et_2O (3 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=10/1) to afford **63** (28.0 mg, 100%) as an oil.

R_f = 0.21 (hexane/ethyl acetate=4/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–7.08 (4H, m), 5.04 (1H, s), 4.82 (1H, s), 3.96–3.93 (1H, m), 2.86–2.68 (4H, m), 2.61–2.55 (1H, m), 2.38–2.33 (1H, m), 2.13–2.07 (1H, m), 1.81–1.74 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 140.2, 140.0, 129.1, 129.1, 126.6, 126.5, 112.0, 77.3, 77.0, 76.7, 72.8, 40.6, 39.3,

32.8, 29.1; IR (neat) ν_{max} 3384, 2932, 1452, 1040, 756 cm^{-1}; HRMS (EI) $[M]^+$ caluculated for $C_{13}H_{16}O$: 188.1201, found: 188.1202.

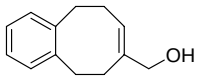
(*E*)-7-(Chloromethyl)-5,6,9,10-tetrahydrobenzo[8]annulene (64)



To a stirred solution of **63** (28.0 mg, 0.150 mmol) in toluene (1.5 mL) was added pyridine (0.061 mL, 0.752 mmol), $SOCl_2$ (0.027 mL, 0.376 mmol) at 0 °C, and the mixture was stirred at room temperature. After the reaction was completed, brine (3 mL) was added to the reaction mixture and the aqueous layer was extracted with Et_2O (3 mL × 2). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate=40/1) to afford **64** (29.2 mg, 94%) as an oil.

R_f = 0.44 (hexane/ethyl acetate=4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.12–7.08 (2H, m), 7.05–7.01 (2H, m), 5.59 (1H, dd, *J* = 7.3, 7.3 Hz), 3.84 (2H, s), 3.06 (2H, dd, *J* = 7.3, 7.3 Hz), 2.99 (2H, dd, *J* = 7.3, 7.3 Hz), 2.65 (2H, dd, *J* = 7.3, 7.3 Hz), 2.49 (2H, ddd, *J* = 7.3, 7.3, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 139.8, 136.9, 130.1, 129.7, 129.4, 126.2, 126.1, 52.1, 33.6, 33.4, 29.8, 28.3; IR (neat) ν_{max} 3016, 2948, 2892, 1494, 1454, 1262, 756 cm^{-1}; HRMS (EI) $[M]^+$ caluculated for $C_{13}H_{15}Cl$: 206.0862, found: 206.0861.

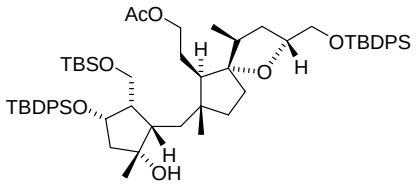
((*E*)-5,6,9,10-Tetrahydrobenzo[8]annulen-8-yl)methanol (65)



To a stirred solution of **64** (29.2 mg, 0.141 mmol) in DMF (0.7 mL) was added 1*N* HCl (0.7 mL) at room temperature, and the mixture was stirred at 60 °C. After the reaction was completed, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (2 mL). The aqueous layer was extracted with Et_2O (2 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by flash chromatography (hexane/ethyl acetate=10/1) to afford **65** (25.8 mg, 97%) as an oil.

R_f = 0.13 (hexane/ethyl acetate=4/1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.11–7.09 (2H, m), 7.04–7.01 (2H, m), 5.44 (1H, dd, *J* = 7.1, 7.1 Hz), 3.79 (2H, d, *J* = 5.6 Hz), 3.03 (2H, dd, *J* = 7.1, 7.1 Hz), 2.99 (2H, dd, *J* = 7.1, 7.1 Hz), 2.58 (2H, dd, *J* = 7.1, 7.1 Hz), 2.48 (2H, ddd, *J* = 7.1, 7.1, 7.1 Hz), 0.81 (1H, br); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 140.1, 129.8, 129.6, 126.2, 126.2, 125.4, 68.9, 33.6, 33.6, 29.3, 27.8; IR (neat) ν_{max} 3592, 3344, 2924, 1492, 1454, 1004 cm^{-1}; HRMS (EI) $[M]^+$ caluculated for $C_{13}H_{16}O$: 188.1201, found: 188.1208.

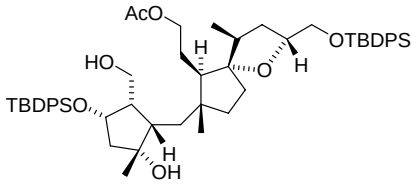
2-[(2*R*,4*S*,5*S*,6*R*,7*R*)-7-[((1*S*,2*R*,4*S*,5*S*)-5-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4-{[*tert*-butyl(diphenyl)silyl]oxy}-2-hydroxy-2-methylcyclopentyl)methyl]-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethyl acetate (2')



To a stirred solution of **2** (60.7 mg, 0.0621 mmol) in CH_2Cl_2 (2.5 mL) was added pyridine (0.025 mL, 0.310 mmol), DMAP (2.3 mg, 0.0186 mmol), Ac_2O (0.018 mL, 0.186 mmol) successively at room temperature. After the reaction was completed, saturated aqueous NH_4Cl solution (3 mL) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (3 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **2'** (57.0 mg, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.63 (8H, m), 7.44–7.33 (12H, m), 4.40 (1H, br), 4.28 (1H, dd, *J* = 10.4, 1.1 Hz), 4.10–4.01 (2H, m), 3.93 (1H, ddd, *J* = 9.2, 7.1, 7.1 Hz), 3.88–3.84 (1H, m), 3.72 (1H, dd, *J* = 10.4, 2.9 Hz), 3.62 (1H, dd, *J* = 10.3, 4.4 Hz), 3.53 (1H, dd, *J* = 10.3, 6.6 Hz), 2.15–2.06 (2H, m), 1.97–1.84 (4H, m), 1.94 (3H, s), 1.75 (1H, dd, *J* = 8.6, 4.9 Hz), 1.69–1.38 (8H, m), 1.29–1.25 (1H, m), 1.07 (9H, s), 1.04 (3H, s), 1.03 (9H, s), 1.01 (3H, d, *J* = 6.4 Hz), 0.96 (9H, s), 0.66 (3H, s), 0.18 (3H, s), 0.17 (3H,s).

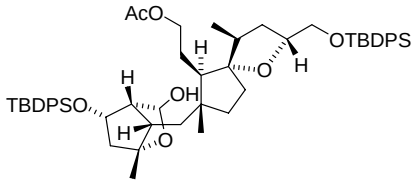
2-[(2*R*,4*S*,5*S*,6*R*,7*R*)-7-{[(1*S*,2*R*,4*S*,5*S*)-4-{[*tert*-Butyl(diphenyl)silyl]oxy}-2-hydroxy-5-(hydroxylmethyl)-2-methylcyclopentyl]methyl}-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethyl acetate (66)



66 was prepared from **2'** in 99% yield according to the procedure for **45**.

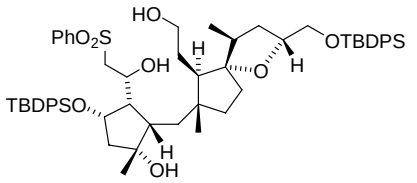
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.63 (8H, m), 7.46–7.33 (12H, m), 4.41 (1H, ddd, *J* = 9.5, 7.0, 7.0 Hz), 4.13–4.06 (2H, m), 3.93–3.82 (3H, m), 3.75 (1H, dd, *J* = 6.4, 6.1 Hz), 3.62 (1H, dd, *J* = 10.3, 4.4 Hz), 3.53 (1H, dd, *J* = 10.3, 6.6 Hz), 2.15–2.06 (3H, m), 2.00 (1H, dd, *J* = 15.0, 9.9 Hz), 1.97 (3H, s), 1.87–1.84 (1H, m), 1.81 (1H, dd, *J* = 15.0, 6.4 Hz), 1.73 (1H, dd, *J* = 8.2, 5.5 Hz), 1.65–1.55 (4H, m), 1.47–1.39 (4H, m), 1.27–1.24 (1H, m), 1.09 (9H, s), 1.08 (3H, s), 1.03 (9H, s), 1.01 (3H, d, *J* = 6.4 Hz), 0.65 (3H, s).

2-[(2*R*,4*S*,5*S*,6*R*,7*R*)-7-[((1*R*,4*R*,5*S*,7*S*)-5-{[*tert*-Butyl(diphenyl)silyl]oxy}-3-hydroxy-1-methyl-2-oxabicyclo[2.2.1]hept-7-yl)methyl]-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethyl acetate (67)



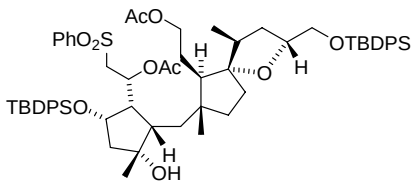
67 was prepared from **66** according to the procedure for **48**.
The crude lactol **67** was used for the next step without further purification.

(1*R*,2*S*,3*S*,4*S*)-4-{[*tert*-Butyl(diphenyl)silyl]oxy}-2-{[(2*R*,4*S*,5*S*,6*R*,7*R*)-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-6-(2-hydroxyethyl)-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl]methyl}-3-[1-hydroxy-2-(phenylsulfonyl)ethyl]-1-methylcyclopentanol (67')



To a stirred solution of $MeSO_2Ph$ (280 mg, 1.79 mmol) in THF (4 mL) was added a solution of *n*–BuLi in hexane (1.081 mL, 1.66 M) dropwise at −78 ºC, and the reaction mixture was stirred for 20 min. Then, to the reaction mixture was added a solution of **67** in THF (2 mL) via a cannula at −78 ºC, and the reaction mixture was warmed up to 0 ºC. After the reaction was completed, saturated aqueous NH_4Cl solution (5 mL) was added to the reaction mixture and the aqueous layer was extracted with AcOEt (5 mL × 2). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The crude triol **67'** was used for the next step without further purification.

1-((1*S*,2*S*,3*R*,5*S*)-2-{[(2*R*,4*S*,5*S*,6*R*,7*R*)-6-[2-(Acetyloxy)ethyl]-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl]methyl}-5-{[*tert*-butyl(diphenyl)silyl]oxy}-3-hydroxy-3-methylcyclopentyl)-2-(phenylsulfonyl)ethyl acetate (68)

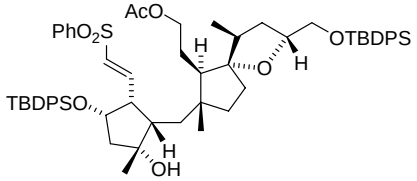


To a stirred solution of **67'** in CH_2Cl_2 (4 mL) was added pyridine (0.145 mL, 1.79 mmol), DMAP (14.6 mg, 0.120 mmol), Ac_2O (0.113 mL, 1.20 mmol) successively at room temperature. After the reaction was completed, saturated aqueous NH_4Cl solution (5

mL) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (4 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **68** (116 mg, 88% (3 steps)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.85 (2H, m), 7.65–7.59 (9H, m), 7.53–7.50 (2H, m), 7.44–7.33 (12H, m), 5.68–5.65 (1H, m), 4.54 (1H, dd, *J* = 14.8, 1.1 Hz), 4.32–4.25 (1H, m), 4.13–4.06 (1H, m), 3.99 (1H, dd, *J* = 14.8, 9.2 Hz), 3.91–3.82 (2H, m), 3.61 (1H, dd, *J* = 10.2, 4.4 Hz), 3.51 (1H, dd, *J* = 10.2, 6.8 Hz), 2.46–2.42 (1H, m), 2.18–2.05 (2H, m), 2.00 (3H, s), 1.78 (3H, s), 1.76–1.13 (13H, m), 1.08 (9H, s), 1.03 (3H, s), 1.03 (9H, s), 1.02 (3H, d, *J* = 6.8 Hz), 0.67 (3H, s).

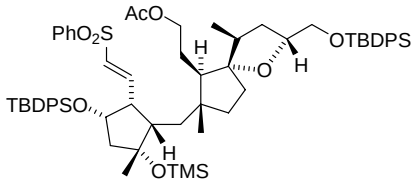
2-[(2*R*,4*S*,5*S*,6*R*,7*R*)-7-({(1*S*,2*R*,4*S*,5*S*)-4-{[*tert*-Butyl(diphenyl)silyl]oxy}-2-hydroxy-2-methyl-5-[(*E*)-2-(phenylsulfonyl)vinyl]cyclopentyl}methyl)-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethyl acetate (69)



To a stirred solution of **68** (25.7 mg, 0.0233 mmol) in CH_2Cl_2 (1.5 mL) was added DBU (0.020 mL, 0.140 mmol) at 0 °C. After the reaction was completed, saturated aqueous NaCl (3 mL) was added to the reaction mixture, and the aqueous layer was extracted with Et_2O (3 mL × 2). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **69** (18.6 mg, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.85 (2H, m), 7.65–7.28 (24H, m), 6.10 (1H, d, *J* = 15.2 Hz), 4.32–4.26 (1H, m), 3.95 (1H, ddd, *J* = 10.6, 10.6, 4.9 Hz), 3.86–3.81 (2H, m), 3.60 (1H, dd, *J* = 10.2, 4.4 Hz), 3.50 (1H, dd, *J* = 10.2, 6.8 Hz), 2.70–2.65 (1H, m), 2.12–1.92 (5H, m), 1.98 (3H, s), 1.67–1.19 (10H, m), 1.12 (3H, s), 1.02 (9H, s), 0.97 (3H, d, *J* = 6.8 Hz), 0.96 (9H, s), 0.50 (3H, s).

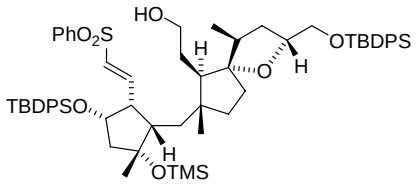
2-[(2*R*,4*S*,5*S*,6*R*,7*R*)-2-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-7-({(1*S*,2*R*,4*S*,5*S*)-4-{[*tert*-butyl (diphenyl)silyl]oxy}-2-methyl-5-[(*E*)-2-(phenylsulfonyl)vinyl]-2-[(trimethylsilyl)oxy]cyclo pentyl}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethyl acetate (69')



69' was prepared from **69** in 90% yield according to the procedure for **50**.

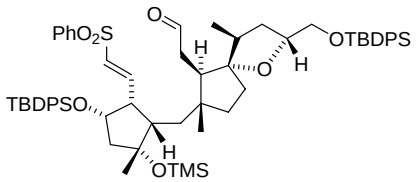
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.84 (2H, m), 7.65–7.28 (24H, m), 5.98 (1H, d, J = 15.4 Hz), 4.27 (1H, ddd, J = 8.8, 7.3, 7.3 Hz), 3.91 (1H, ddd, J = 10.0, 9.8, 4.4 Hz), 3.86–3.77 (2H, m), 3.61 (1H, dd, J = 10.2, 4.4 Hz), 3.50 (1H, dd, J = 10.2, 6.8 Hz), 2.58–2.52 (1H, m), 2.13–1.99 (5H, m), 1.97 (3H, s), 1.67–1.19 (10H, m), 1.15 (3H, s), 1.03 (9H, s), 0.96 (9H, s), 0.96 (3H, d, J = 6.8 Hz), 0.44 (3H, s), 0.19 (9H, s).

2-[(2*R*,4*S*,5*S*,6*R*,7*R*)-2-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-7-({(1*S*,2*R*,4*S*,5*S*)-4-{[*tert*-butyl (diphenyl)silyl]oxy}-2-methyl-5-[(*E*)-2-(phenylsulfonyl)vinyl]-2-[(trimethylsilyl)oxy]cyclo pentyl}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethanol (70)



To a stirred solution of **69'** (14.8 mg, 0.0133 mmol) in CH_2Cl_2 (1 mL) was added a solution of DIBAL–H in toluene (0.067 mL, 0.99 M) at −78 °C. After the reaction was completed, MeOH was added to the reaction mixture at −78 °C till no gas evolution was observed. Then, saturated aqueous Rochelle salt solution (3 mL) was added to the reaction mixture and the resultant solution was stirred vigorously at room temperature. After 30 min, the aqueous layer was extracted with AcOEt (3 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The crude alcohol **70** was used for the next step without further purification.

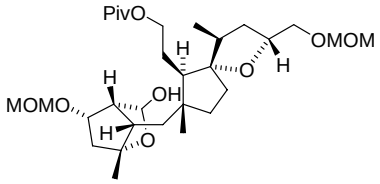
[(2*R*,4*S*,5*S*,6*R*,7*R*)-2-({[*tert*-Butyl(diphenyl)silyl]oxy}methyl)-7-({(1*S*,2*R*,4*S*,5*S*)-4-{[*tert*-butyl(diphenyl)silyl]oxy}-2-methyl-5-[(*E*)-2-(phenylsulfonyl)vinyl]-2-[(trimethylsilyl)oxy]cyclopentyl}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]acetaldehyde (71)



To a suspension of MS4A (13.3 mg, 0.5 g/mmol) in CH_2Cl_2 (0.2 mL) was added a solution of **70** in CH_2Cl_2 (0.5 mL), NMO (4.7 mg, 0.0398 mmol) and TPAP (2.3 mg, 6.63×10^{-3} mmol) at room temperature. After the reaction was completed, the mixture was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography to afford **71** (13.2 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (1H, dd, *J* = 3.9, 1.0 Hz), 7.87–7.84 (2H, m), 7.65–7.30 (24H, m), 5.92 (1H, d, *J* = 15.1 Hz), 4.28 (1H, ddd, *J* = 8.8, 7.1, 7.1 Hz), 3.87–3.81 (1H, m), 3.58 (1H, dd, *J* = 10.0, 4.6 Hz), 3.39 (1H, dd, *J* = 10.0, 7.1 Hz), 2.52–2.46 (1H, m), 2.19–1.94 (5H, m), 1.84–1.78 (1H, m), 1.70 (1H, dd, *J* = 15.6, 3.9 Hz), 1.63–1.20 (8H, m), 1.15 (3H, s), 1.02 (9H, s), 0.99 (9H, s), 0.92 (3H, d, *J* = 6.8 Hz), 0.39 (3H, s), 0.20 (9H, s).

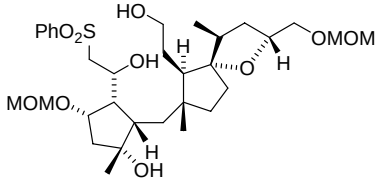
2-{(2*R*,4*S*,5*S*,6*R*,7*R*)-7-{[(1*R*,4*R*,5*S*,7*S*)-3-Hydroxy-5-(methoxymethoxy)-1-methyl-2-oxabicyclo[2.2.1]hept-7-yl]methyl}-2-[(methoxymethoxy)methyl]-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl}ethyl pivalate (76)



76 was prepared from **75** according to the procedure for **48**.

The crude lactol **76** was used for the next step without further purification.

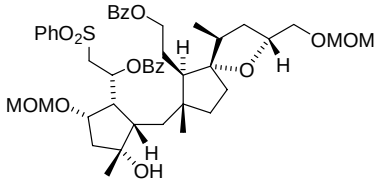
(1*R*,2*S*,3*S*,4*S*)-2-({(2*R*,4*S*,5*S*,6*R*,7*R*)-6-(2-Hydroxyethyl)-2-[(methoxymethoxy)methyl]-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl}methyl)-3-[1-hydroxy-2-(phenylsulfonyl)ethyl]-4-(methoxymethoxy)-1-methylcyclopentanol (77)



77 was prepared from **76** according to the procedure for **67'**.

The crude triol **77** was used for the next step without further purification.

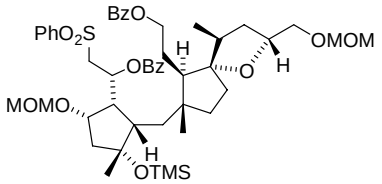
1-[(1*R*,2*S*,3*R*,5*S*)-2-({(2*R*,4*S*,5*S*,6*R*,7*R*)-6-[2-(Benzoyloxy)ethyl]-2-[(methoxymethoxy)methyl]-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl}methyl)-3-hydroxy-5-(methoxymethoxy)-3-methylcyclopentyl]-2-(phenylsulfonyl)ethyl benzoate (77')



To a stirred solution of **77** in CH_2Cl_2 (4 mL) was added Et_3N (0.163 mL, 1.17 mmol), DMAP (8.9 mg, 0.0729 mmol), BzCl (0.085 mL, 0.729 mmol) successively at room temperature. After the reaction was completed, saturated aqueous NH_4Cl solution (5 mL) was added to the reaction mixture and the aqueous layer was extracted with CH_2Cl_2 (4 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **79'** (122 mg, 100% (3 steps)).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02–8.00 (2H, m), 7.95–7.93 (2H, m), 7.86–7.81 (2H, m), 7.60–7.36 (9H, m), 5.83 (1H, ddd, J = 6.3, 3.4, 3.2 Hz), 4.72 (1H, d, J = 6.6 Hz), 4.70 (1H, d, J = 6.6 Hz), 4.64 (1H, d, J = 6.6 Hz), 4.62 (1H, d, J = 6.6 Hz), 4.54–4.46 (1H, m), 4.15–4.06 (1H, m), 4.02–3.95 (1H, m), 3.90 (1H, dd, J = 14.4, 6.6 Hz), 3.84 (1H, dd, J = 14.4, 5.9 Hz), 3.51–3.46 (2H, m), 3.41 (3H, s), 3.35–3.33 (1H, m), 3.33 (3H, s), 3.06 (1H, ddd, J = 10.0, 7.6, 3.2 Hz), 2.39–2.21 (2H, m), 2.10 (1H, dd, J = 14.4, 4.4 Hz), 1.97–1.08 (13H, m), 1.26 (3H, s), 1.05 (3H, d, J = 6.6 Hz), 0.66 (3H, s).

1-{(1*R*,2*S*,3*R*,5*S*)-2-({(2*R*,4*S*,5*S*,6*R*,7*R*)-6-[2-(Benzoyloxy)ethyl]-2-[(methoxymethoxy)methyl]-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl}methyl)-5-(methoxymethoxy)-3-methyl-3-[(trimethylsilyl)oxy]cyclopentyl}-2-(phenylsulfonyl)ethyl benzoate (78)

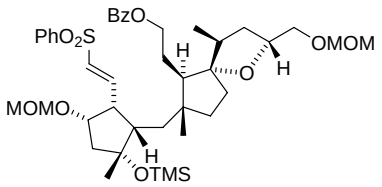


78 was prepared from **77'** in 85% yield according to the procedure for **50**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–8.12 (2H, m), 7.85–7.28 (13H, m), 5.86 (1H, ddd, J = 8.6, 3.4, 3.2 Hz), 4.65 (1H, d, J = 6.6 Hz), 4.64 (1H, d, J = 6.6 Hz), 4.60–4.55 (1H, m), 4.51 (1H, d, J = 6.8 Hz), 4.42 (1H, d, J = 6.8 Hz), 4.27–4.14 (2H, m), 3.99–3.90 (2H, m), 3.53–3.47 (2H, m), 3.36–3.33 (1H, m), 3.34 (3H, s), 3.31 (3H, s), 2.89 (1H, ddd, J = 8.5, 8.3,

3.7 Hz), 2.38–2.25 (1H, m), 2.23–2.17 (1H, m), 2.10–1.10 (13H, m), 1.29 (3H, s), 0.92 (3H, d, *J* = 6.6 Hz), 0.44 (3H, s), 0.10 (9H, s).

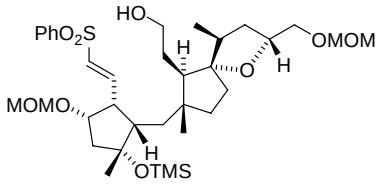
2-[(2*R*,4*S*,5*S*,6*R*,7*R*)-2-[(Methoxymethoxy)methyl]-7-({(1*S*,2*R*,4*S*,5*S*)-4-(methoxymethoxy)-2-methyl-5-[(*E*)-2-(phenylsulfonyl)vinyl]-2-[(trimethylsilyl)oxy]cyclopentyl}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethyl benzoate (79)



79 was prepared from **78** in 97% yield according to the procedure for **69**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07–8.04 (2H, m), 7.89–7.85 (2H, m), 7.59–7.33 (7H, m), 6.26 (1H, d, *J* = 15.1 Hz), 4.65 (1H, d, *J* = 6.6 Hz), 4.63 (1H, d, *J* = 6.6 Hz), 4.50 (1H, d, *J* = 6.8 Hz), 4.49 (1H, d, *J* = 6.8 Hz), 4.39–4.31 (1H, m), 4.23–4.16 (1H, m), 4.13–4.05 (1H, m), 4.01–3.95 (1H, m), 3.53–3.45 (2H, m), 3.36–3.31 (1H, m), 3.33 (3H, s), 3.26 (3H, s), 3.13–3.06 (1H, m), 2.34–2.09 (3H, m), 1.94–1.88 (1H, m), 1.83–1.08 (10H, m), 1.29 (3H, s), 1.02 (3H, d, *J* = 6.6 Hz), 0.60 (3H, s), 0.20 (9H, s).

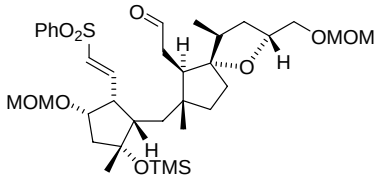
2-[(2*R*,4*S*,5*S*,6*R*,7*R*)-2-[(Methoxymethoxy)methyl]-7-({(1*S*,2*R*,4*S*,5*S*)-4-(methoxymethoxy)-2-methyl-5-[(*E*)-2-(phenylsulfonyl)vinyl]-2-[(trimethylsilyl)oxy]cyclopentyl}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]ethanol (79')



79' was prepared from **79** according to the procedure for **70**.

The crude alcohol **79'** was used for the next step without further purification.

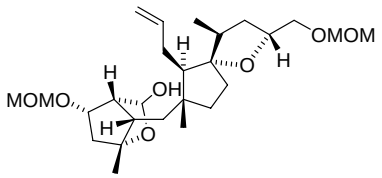
[(2*R*,4*S*,5*S*,6*R*,7*R*)-2-[(Methoxymethoxy)methyl]-7-({(1*S*,2*R*,4*S*,5*S*)-4-(methoxymethoxy)-2-methyl-5-[(*E*)-2-(phenylsulfonyl)vinyl]-2-[(trimethylsilyl)oxy]cyclopentyl}methyl)-4,7-dimethyl-1-oxaspiro[4.4]non-6-yl]acetaldehyde (80)



80 was prepared from **79'** in 82% yield (2 steps) according to the procedure for **71**.

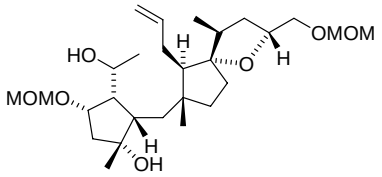
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (1H, d, *J* = 4.4 Hz), 7.91–7.88 (2H, m), 7.58–7.47 (3H, m), 7.39 (1H, dd, *J* = 15.4, 11.2 Hz), 6.21 (1H, d, *J* = 15.4 Hz), 4.63 (2H, s), 4.50 (2H, s), 4.19 (1H, ddd, *J* = 8.8, 7.3, 7.3 Hz), 4.00–3.94 (1H, m), 3.40 (1H, dd, *J* = 10.0, 4.6 Hz), 3.36–3.33 (1H, m), 3.35 (3H, s), 3.26 (3H, s), 3.08–3.02 (1H, m), 2.36–2.25 (2H, m), 2.20–2.12 (1H, m), 2.09–2.01 (1H, m), 1.95–1.89 (1H, m), 1.77 (1H, ddd, *J* = 12.2, 7.6, 4.1 Hz), 1.71–1.17 (9H, m), 1.28 (3H, s), 0.97 (3H, d, *J* = 6.8 Hz), 0.56 (3H, s), 0.21 (9H, s).

(1*R*,4*R*,5*S*,7*S*)-7-({(2*R*,4*S*,5*S*,6*R*,7*R*)-6-Allyl-2-[(methoxymethoxy)methyl]-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl}methyl)-5-(methoxymethoxy)-1-methyl-2-oxabicyclo[2.2.1]heptan-3-ol (83)



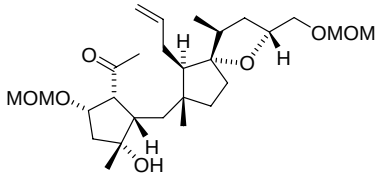
83 was prepared from **82** according to the procedure for **48**.
The crude lactol **83** was used for the next step without further purification.

(1*R*,2*S*,3*S*,4*S*)-2-({(2*R*,4*S*,5*S*,6*R*,7*R*)-6-Allyl-2-[(methoxymethoxy)methyl]-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl}methyl)-3-(1-hydroxyethyl)-4-(methoxymethoxy)-1-methylcyclopentanol (83')



83' was prepared from **83** according to the procedure for **49**.
The crude diol **83'** was used for the next step without further purification.

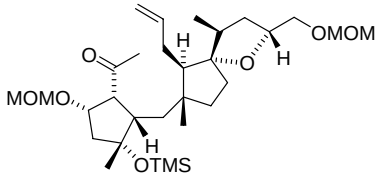
1-[(1*R*,2*S*,3*R*,5*S*)-2-({(2*R*,4*S*,5*S*,6*R*,7*R*)-6-Allyl-2-[(methoxymethoxy)methyl]-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl}methyl)-3-hydroxy-5-(methoxymethoxy)-3-methylcyclopentyl]ethanone (83")



83" was prepared from **83'** in 94% yield (3 steps) according to the procedure for **49'**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (1H, dddd, *J* = 17.3, 10.5, 6.6, 6.0 Hz), 5.06 (1H, dd, *J* = 17.3, 1.7 Hz), 4.95 (1H, dd, *J* = 10.5, 1.7 Hz), 4.75 (1H, br), 4.64 (2H, s), 4.62 (1H, d, *J* =

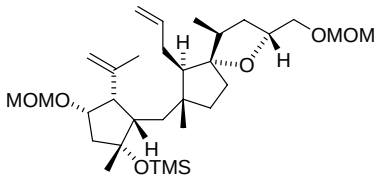
6.8 Hz), 4.59 (1H, d, *J* = 6.8 Hz), 4.23 (1H, ddd, *J* = 8.5, 7.8, 6.8 Hz), 4.03–3.97 (1H, m), 3.65 (1H, dd, *J* = 6.8, 6.6 Hz), 3.48 (1H, dd, *J* = 10.0, 6.3 Hz), 3.42 (1H, dd, *J* = 10.0, 5.1 Hz), 3.36 (3H, s), 3.35 (3H, s), 2.34 (1H, dd, *J* = 14.4, 8.3 Hz), 2.28–2.22 (1H, m), 2.25 (3H, s), 2.15–1.96 (3H, m), 1.90 (1H, dd, *J* = 14.4, 9.3 Hz), 1.87–1.81 (1H, m), 1.72–1.22 (8H, m), 1.19 (3H, s), 1.03 (3H, d, *J* = 6.6 Hz), 0.80 (3H, s).

1-{(1*R*,2*S*,3*R*,5*S*)-2-({(2*R*,4*S*,5*S*,6*R*,7*R*)-6-Allyl-2-[(methoxymethoxy)methyl]-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl}methyl)-5-(methoxymethoxy)-3-methyl-3-[(trimethylsilyl)oxy]cyclopentyl}ethanone (84)



84 was prepared from **83"** in 93% yield according to the procedure for **50**.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (1H, dddd, *J* = 17.3, 10.2, 6.8, 6.0 Hz), 5.08 (1H, dd, *J* = 17.3, 1.7 Hz), 4.95 (1H, dd, *J* = 10.2, 1.7 Hz), 4.65 (1H, d, *J* = 6.6 Hz), 4.64 (1H, d, *J* = 6.6 Hz), 4.60 (1H, d, *J* = 6.8 Hz), 4.57 (1H, d, *J* = 6.8 Hz), 4.17 (1H, ddd, *J* = 9.0, 7.8, 7.6 Hz), 4.03–3.97 (1H, m), 3.48 (1H, dd, *J* = 9.8, 6.6 Hz), 3.43 (1H, dd, *J* = 9.8, 5.1 Hz), 3.36 (3H, s), 3.32 (3H, s), 3.25 (1H, dd, *J* = 7.3, 6.8 Hz), 2.37–2.23 (3H, m), 2.30 (3H, s), 2.13–2.03 (2H, m), 1.95 (1H, dd, *J* = 9.0, 6.0 Hz), 1.86–1.79 (1H, m), 1.72–1.22 (8H, m), 1.29 (3H, s), 1.03 (3H, d, *J* = 6.8 Hz), 0.75 (3H, s), 0.13 (9H, s).

{[(1*R*,2*S*,3*S*,4*S*)-2-({(2*R*,4*S*,5*S*,6*R*,7*R*)-6-Allyl-2-[(methoxymethoxy)methyl]-4,7-dimethyl-1-oxaspiro[4.4]non-7-yl}methyl)-3-isopropenyl-4-(methoxymethoxy)-1-methylcyclopentyl]oxy}(trimethyl)silane (85)

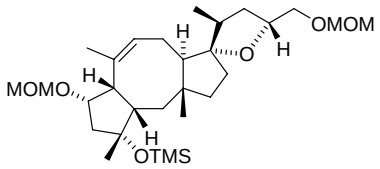


To a suspension of Zn powder (185 mg, 2.83 mmol) and $PbCl_2$ (15.7 mg, 0.0565 mmol) in degassed THF (1 mL) was added CH_2I_2 (0.114 mL, 1.41 mmol) and the reaction mixture was stirred at room temperature for 1 h. A solution of $TiCl_4$ in toluene (0.283 mL, 1.0 M) was added to the reaction mixture at 0 ºC and stirred at room temperature for 1 h. Then **84** (19.6 mg, 0.0353 mmol) in THF (1mL) was added to the mixture at 0 ºC. After the reaction was completed, saturated aqueous $NaHCO_3$ solution (0.5 mL) was added to the reaction mixture and the mixture was filtered through a plug of Celite. To the filterate

was added saturated aqueous $Na_2S_2O_3$ solution (1 mL) and the aqueous layer was extracted with AcOEt (2 mL × 2). The combined organic layer was dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **85** (18.1 mg, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (1H, dddd, *J* = 17.3, 10.2, 6.8, 6.3 Hz), 5.07 (1H, dd, *J* = 17.3, 1.7 Hz), 4.98 (1H, d, *J* = 2.4 Hz), 4.94 (1H, dd, *J* = 10.2, 1.7 Hz), 4.84 (1H, d, *J* = 2.4 Hz), 4.69 (1H, d, *J* = 6.8 Hz), 4.65 (1H, d, *J* = 6.6 Hz), 4.65 (1H, d, *J* = 6.6 Hz), 4.58 (1H, d, *J* = 6.8 Hz), 4.10 (1H, ddd, *J* = 11.0, 7.8, 7.6 Hz), 4.03–3.98 (1H, m), 3.49 (1H, dd, *J* = 10.0, 6.6 Hz), 3.43 (1H, dd, *J* = 10.0, 5.1 Hz), 3.37 (3H, s), 3.35 (3H, s), 2.95 (1H, dd, *J* = 7.3, 6.8 Hz), 2.37–2.13 (4H, m), 2.18 (3H, s), 2.10–2.06 (2H, m), 1.97 (1H, dd, *J* = 8.8, 6.3 Hz), 1.86–1.21 (8H, m), 1.28 (3H, s), 1.03 (3H, d, *J* = 6.8 Hz), 0.71 (3H, s), 0.09 (9H, s).

({(3*S*,3'*S*,3a*R*,5'*R*,6a*S*,7*S*,9*R*,9a*S*,10a*R*)-7-(Methoxymethoxy)-5'-[(methoxymethoxy)methyl]-3',6,9,10a-tetramethyl-1,3a,4,4',5',6a,7,8,9,9a,10,10a-dodecahydro-2*H*,3'*H*-spiro[dicyclopenta[*a*,*d*][8]annulene-3,2'-furan]-9-yl}oxy)(trimethyl)silane (86)



To a stirred solution of **85** (2.6 mg, 4.70 × 10^{-3} mmol) in toluene (1 mL) was added Hoveyda–Grubbs cat. 2nd (1.5 mg, 2.35 × 10^{-3} mmol) in toluene (0.2 mL) at 100 ºC. After the reaction was completed, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography to afford **86** (1.8 mg, 72%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (1H, dd, *J* = 8.2, 7.9 Hz), 4.68 (1H, d, *J* = 6.6 Hz), 4.66 (1H, d, *J* = 6.6 Hz), 4.66 (1H, d, *J* = 6.7 Hz), 4.62 (1H, d, *J* = 6.7 Hz), 4.12 (1H, ddd, *J* = 10.8, 9.0, 6.7 Hz), 3.95 (1H, dddd, *J* = 6.9, 6.7, 6.4, 4.1 Hz), 3.56 (1H, dd, *J* = 10.2, 4.1 Hz), 3.49 (1H, dd, *J* = 10.2, 6.4 Hz), 3.38 (3H, s), 3.35 (3H, s), 3.20 (1H, dd, *J* = 6.9, 6.7 Hz), 2.27 (1H, dd, *J* = 13.6, 9.0 Hz), 2.20 (1H, dd, *J* = 13.6, 10.8 Hz), 2.12–2.06 (1H, m), 1.95 (3H, s), 1.94–1.81 (4H, m), 1.72–1.60 (4H, m), 1.55–1.46 (2H, m), 1.33–1.25 (2H, m), 1.30 (3H, s), 1.00 (3H, d, *J* = 6.9 Hz), 0.75 (3H, s), 0.06 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 129.9, 96.6, 96.0, 96.0, 79.8, 78.2, 72.8, 70.8, 61.4, 55.5, 55.1, 52.0, 49.3, 44.9, 42.7, 41.2, 38.4, 36.2, 35.9, 30.5, 29.5, 23.1, 22.1, 17.9, 16.9, 2.2; HRMS (FAB) $[M+Na]^+$ calculated for $C_{29}H_{52}O_6SiNa$: 547.3431, found: 547.3440.

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(a) Toone, E. J.; Jones, J. B. *Tetrahedron: Asymmetry* **1991**, *2*, 1041–1052. (b) Canet, J.-L.; Fadel, A.; Salaün, J. *J. Org. Chem.* **1992**, *57*, 3463–3473. (c) Fadel, A.; Canet, J.-L.; Salaün, J. *Tetrahedron: Asymmetry* **1993**, *4*, 27–30. (d) Provencher, L.; Wynn, H.; Jones, J. B. *Tetrahedron: Asymmetry* **1993**, *4*, 2025–2040. (e) Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 893–900. (f) Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 371–374. (g) Arzel, P.; Fredia, V.; Weber, P.; Fadel, A. *Tetrahedron: Asymmetry* **1999**, *10*, 3877–3881. (h) Fadel, A.; Vandromme, L. *Tetrahedron: Asymmetry* **1999**, *10*, 1153–1162. (i) Dominguez de María, P.; Kossmann, B.; Potgrave, N.; Buchholz, S.; Trauthwein, H.; May, O.; Gröger, H. *Synlett* **2005**, *11*, 1746–1748.

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