Sekothrixide の全合成

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目次

略語表

Ac	acetyl
AcOEt	ethyl acetate
aq.	aqueous
Bn	benzyl
Bu	butyl
CBS	Corey-Bakshi-Shibata
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAH	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DIPT	diisopropylethylamine
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EE	ethoxyethyl
Et	ethyl
eq.	equivalent
Hex	hexyl
IBX	*o*-iodoxybenzoic acid
LAH	lithium aluminum hydride
LHMDS	lithium bis(trimethylsilyl)amide
m	meta
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
MNBA	2-methyl-6-nitrobenzoic anhydride
MOM	methoxymethyl

MS	molecular sieves
NaHMDS	sodium bis(trimethylsilyl)amide
n	normal
NMO	4-methylmorpholine *N*-oxide
NMR	nuclea magnetic resonance
Nu	nucleophile
o	ortho
p	para
Ph	phenyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
RCM	ring-closing metathesis
Red-Al	sodium *bis*(2-methoxyethoxy) aluminium hydride
sat.	saturated
SM	starting material
t	tertiary
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TS	transition state
Ts	tosyl

序論

人々は古来より長く健康で生活したいという希望から、病気や怪我に対しての様々な治療法を探してきた。特にガンは**table 1**に示すように日本人の死亡原因の第1位であり、そのガンは体内の様々な場所に発生するため、その治療は困難なことが多く日々治療法が研究されてきた。今日ガンの治療法は手術療法、放射線療法、化学療法の 3 種を軸に行われている。

Table 1. 死因順位別死亡数の年次推移 [1)]

死因順位	2006		2011		2012		2013	
	死因	死亡数	死因	死亡数	死因	死亡数	死因	死亡数
	全死因	1084450	全死因	1253066	全死因	1256359	全死因	1268436
第1位	悪性新生物	329314	悪性新生物	357305	悪性新生物	360963	悪性新生物	364872
第2位	心疾患	173024	心疾患	194926	心疾患	198836	心疾患	196723
第3位	脳血管疾患	128268	肺炎	124749	肺炎	123925	肺炎	122969
第4位	肺炎	107242	脳血管疾患	123867	脳血管疾患	121602	脳血管疾患	118347

現在、比較的早期のガンで転移がなければ手術療法や放射線療法といった局所療法が選択される場合が多い。しかし、ある程度進行した転移ガンには局所治療よりも、抗ガン剤の投与による治療がカギを握る。それは、投与された抗ガン剤が血液を通して体内を巡るため、ごく小さなガン細胞や様々な部分に転移したガン細胞にも効果を発揮するためである。また、抗ガン剤の投与により、ガン細胞をある程度縮小させてから局所療法に臨むといった相補的な使用も行われる。

従来、抗ガン剤による治療は、嘔吐、下痢、脱毛といった副作用が現れやすく、患者に大きな負担を強いる治療法であった。しかし、最近では吐き気を和らげたり、白血球の減少を抑える薬を併用したりすることで、副作用を軽減できるようになった。また、ガン細胞に選択的に効く分子標的薬が実用化されてきており、化学療法は著しく進歩している。しかし一方で、治療効果を妨げる深

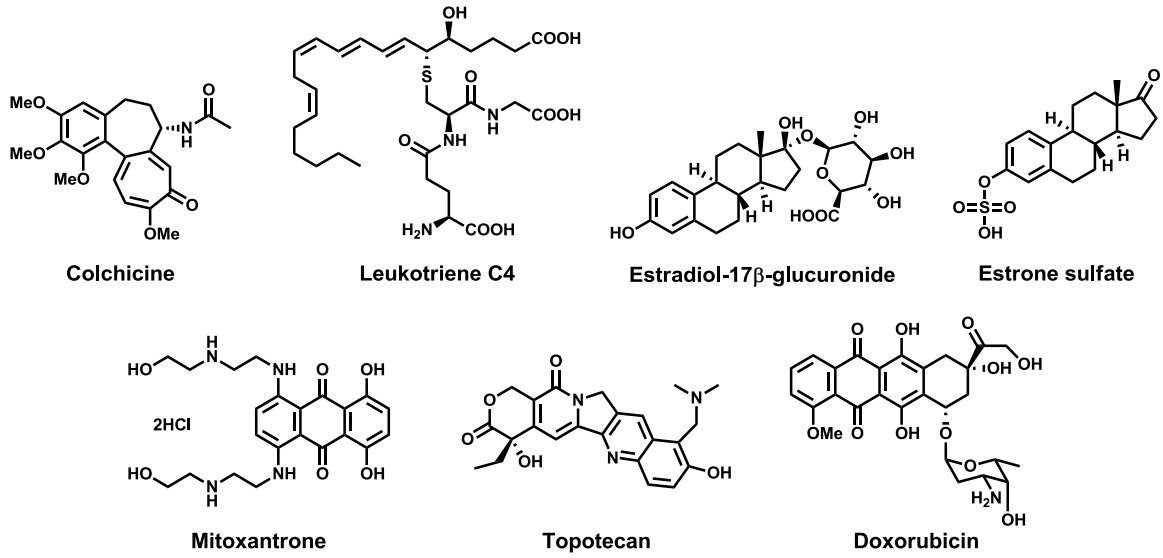
刻な要因としてガン細胞の多剤耐性といった問題がある。その多剤耐性の原因は様々あり、例えば、多剤排出トランスポーターの高発現化 [2] があげられる。多剤排出トランスポーターとは、細胞膜上に存在する膜タンパク質であり、

・Permeability-glycoprotein (P-gp)： P-糖タンパク質

・Multidrug Resistance Protein (MRP)： 多剤耐性タンパク質

・Breast Cancer Resistance Protein (BCRP)： 乳がん耐性タンパク質

の 3 種類がよく知られている。これらの基本的な作用は細胞内に侵入してきた化合物を細胞外へ排出すること [3] であり、タンパク質ごとにおおよその化合物群が分かっている(**Figure 1**)。特に P-gp は様々な抗ガン剤を細胞外へと排出することから、重要な研究対象であり研究が進んでいる。



P-gp：Colchicine といった植物アルカロイドや抗ガン剤を含む多くの疎水性化合物
MRP：Leukotriene C4、Estradiol-17β-glucuronide、Estrone sulfate 等の親水性分子
BCRP：Mitoxantrone、Topotecan、Doxorubicin 等の抗ガン剤

Figure 1. 多剤排出トランスポーターの基質 [4-9]

ヒトの P-gp 構造はまだ完全に解明されていないが、ハツカネズミ由来の P-gp の X 線結晶解析[10] がなされている(阻害剤 QZ59 との共結晶)。その大きさは幅約 70Å、長さ約 136Å である(Figure 2)。

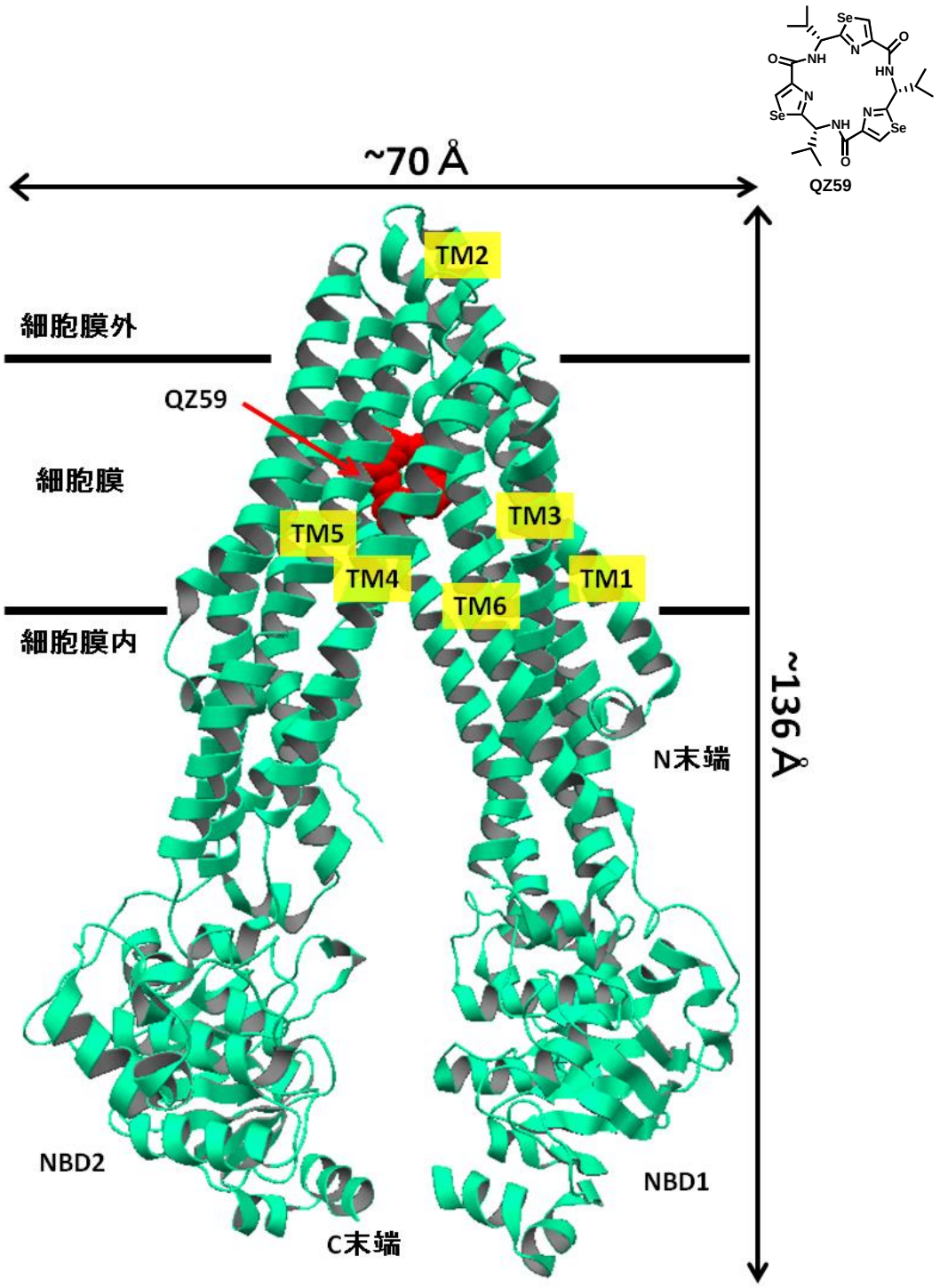


Figure 2. X 線結晶解析によるハツカネズミ由来の P-gp の構造

ハツカネズミ P-gp の細胞膜上での構造模式図 [10] を **figure 3** に示す。Trans Membrane (TM)と呼ばれるαヘリックス構造のアミノ酸残基が、細胞膜を貫通する膜貫通領域(Trans-Membrane Domain: TMD)と、2 つのヌクレオチド結合ドメイン(Nucleotide Binding Domain: NBD)からなる構造である。P-gp の TM は合計 12 回細胞膜を貫通し、TM1-TM12 まであることが分かっている。

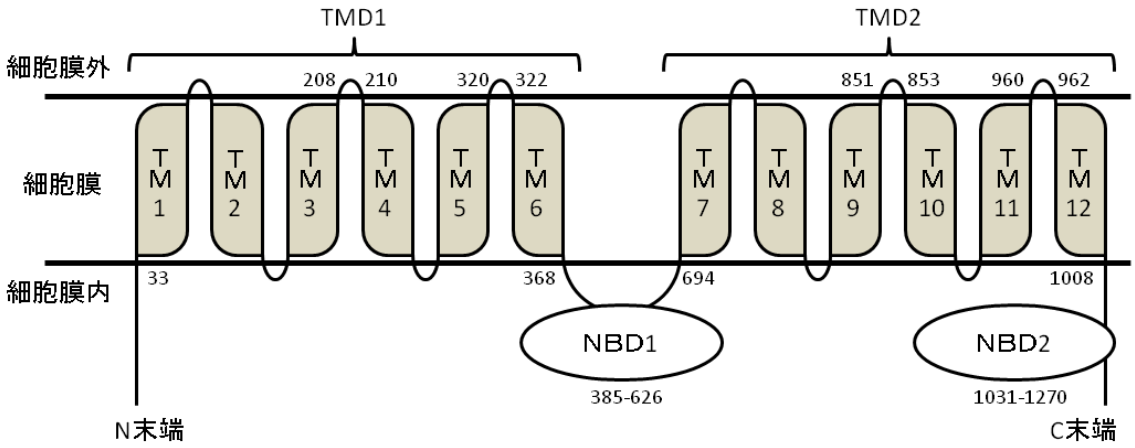


Figure 3. ハツカネズミ P-gp の細胞膜上での構造模式図

さらにヒト P-gp と基質の結合領域に関する研究 [11-14] もなされている。基質には **figure 4** に示す verapamil やその誘導体(MethaneThioSulfonate (MTS)-verapamil)があり、それらを用いた実験により、verapamil 結合領域は、TM4:S222、TM6:L339, A342、TM10:I868、TM11:F942, T945、TM12:G984 に囲まれるあたりであることが推定されている (**Figure 5**)。このように P-gp と基質の結合領域が特定できると、P-gp の多剤排出トランスポーター機能を阻害する薬剤開発の大きな手助けとなるであろう。

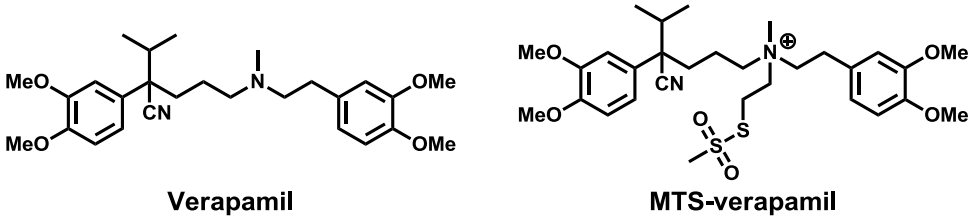


Figure 4. Verapamil と MTS-verapamil の構造

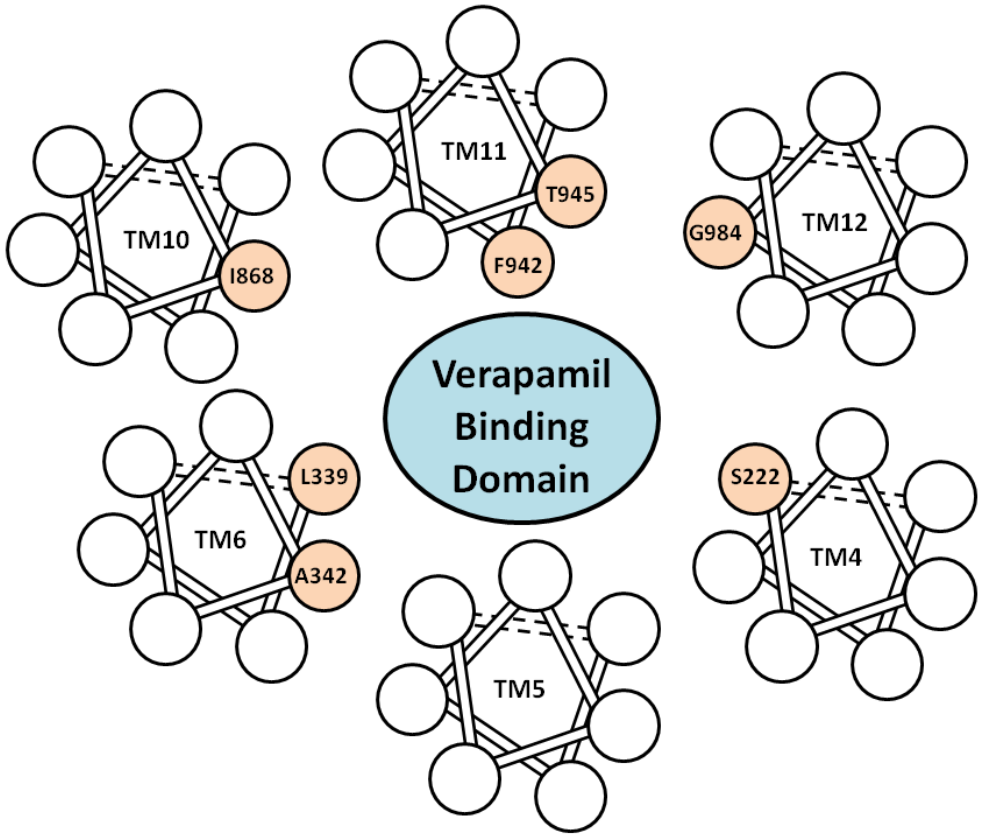


Figure 5. ヒト P-gp に対する verapamil の推定結合領域

これまで P-gp の排出機能を阻害する様々な薬剤(cyclosporin、ritonavir、MK571、Hoechst 33342)が発見[15-20]されているが、これらすべてに関して詳細な結合領域の特定及び作用機構の解明まではされていない。なお、各種阻害剤の化学構造上の傾向として Ph 基といった疎水性の官能基を多く含む化合物である点があげられる(**Figure 6**)。

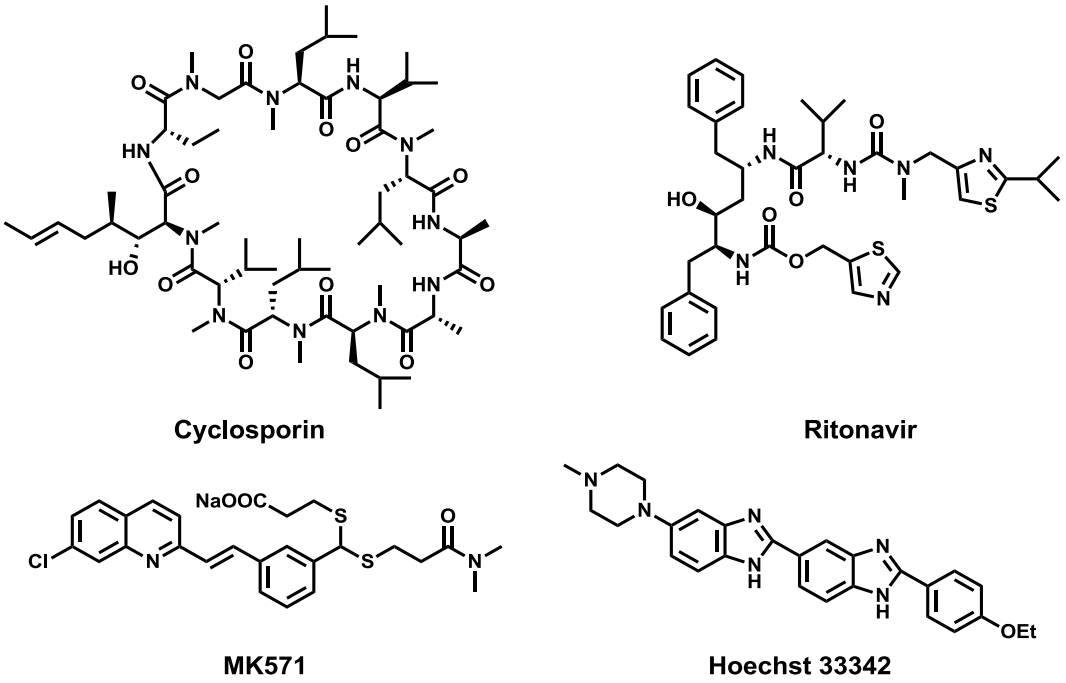
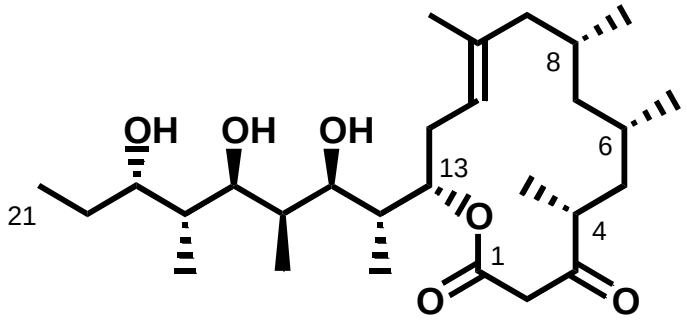


Figure 6. P-gp の各種阻害剤

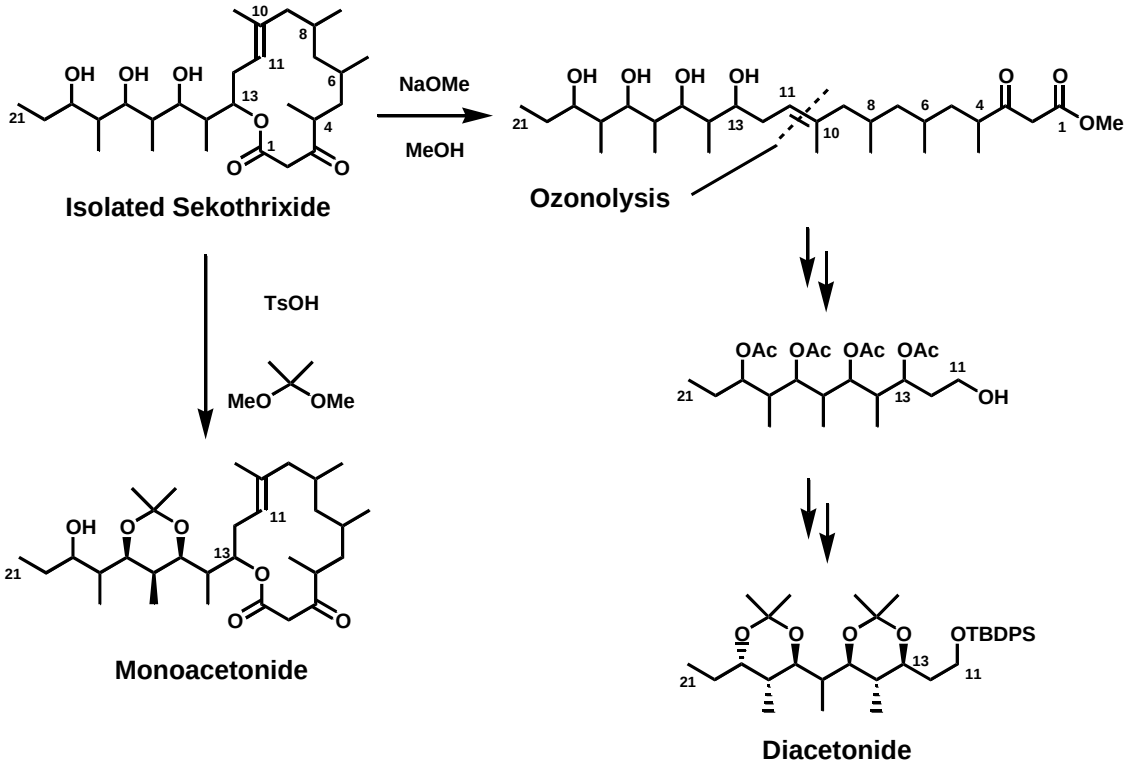
この様な背景において、東京大学の瀬戸教授らは colchicine 耐性を獲得した KB-C2 細胞[21]の増殖抑制活性を指標とする、新しい多剤耐性克服薬の探索を行った。その一連の研究の中で埼玉県秩父郡横瀬付近の土壌に生息している微生物 *Saccharothrixide* sp. CF24 を大量培養し、その抽出液から化合物を単離してスクリーニングをかけた。その結果、新しい多剤耐性克服薬となりうる 14 員環ケトライド sekothrixide を 1991 年に発見した。[22]



Sekothrixide
(Proposed Structure)

この sekothrixide を単独で使用した場合の IC_{50} 値は 6.5 μg/mL であり、また 1.5 μg/mL の colchicine 溶液を同時に添加した時の IC_{50} 値は 1.0 μg/mL を示し、相乗効果を誘導することが報告されている。[22] その化学構造上の特徴として、側鎖の 7 連続不斉中心を有するポリプロピオネート構造と、3 つのメチル基及び 1 つの三置換オレフィンのみで構築されたケトライド環があげられる。側鎖には水酸基が多く並び親水性、ケトライド環は疎水性であるという、側鎖と環ではっきりとその極性が二分されている。また、他の 14 員環マクロラクトン化合物は、糖鎖を有していることが多いが sekothrixide には無いといった特徴がある。この様な興味深い生理活性とユニークな化学構造から、筆者は sekothrixide を全合成のターゲットとして相応しいと考え合成検討を行うこととした。

瀬戸先生らによる sekothrixide の構造解析は次のようにして行われた。[23] 側鎖のポリプロピオネート構造の相対立体化学は **scheme 1** のような化学変換を経て高い信頼性で決定された。まず、sekothrixide をモノアセトニド体へと変換し C15-C17 位の立体配置を明らかとした。次にラクトン環を開環後、ジアセトニド体へと誘導し C13-C15 及び C17-C19 位の立体配置を決定した。これらモノアセトニド体とジアセトニド体の各種スペクトルデータを組み合わせて側鎖部全体の相対立体配置が決定された。



Scheme 1

ラクトン環上の C4,6,8 位のメチル基の立体化学の解析[24] は、DADAS90 (Distance Analysis in Dihedral Angle Space)[25] と呼ばれるプログラムを用い行われた。その方法はモノアセトニド体のモデルデータを作成後、MM2 レベルで構造最適化を行う。その最適化構造と、モノアセトニド体のカップリング定数からとりうる範囲の 2 面角と、NOE 相関を制約条件として用い DADAS90 に入力する。プログラム内部で構造の 2 面角を制約条件内でランダムに変化させた後、それぞれを構造最適化する。それらいくつもの出力結果を統計学的に処理し、最も相似性が高い、すなわち RMSD (Root Mean Square Deviation)の値が小さいものを解とした。その解は C4 位が *R*、C6 位が *S*、C8 位が *R* の配置をとる ***4R 6S 8R*** であった(**Figure 7**)。しかし、構造最適化は MM2 レベルの計算であり、制約条件は sekothrixide そのもののデータを用いておらずモノアセトニド体のスペクトルデータを基にしており、あいまいさが残る。

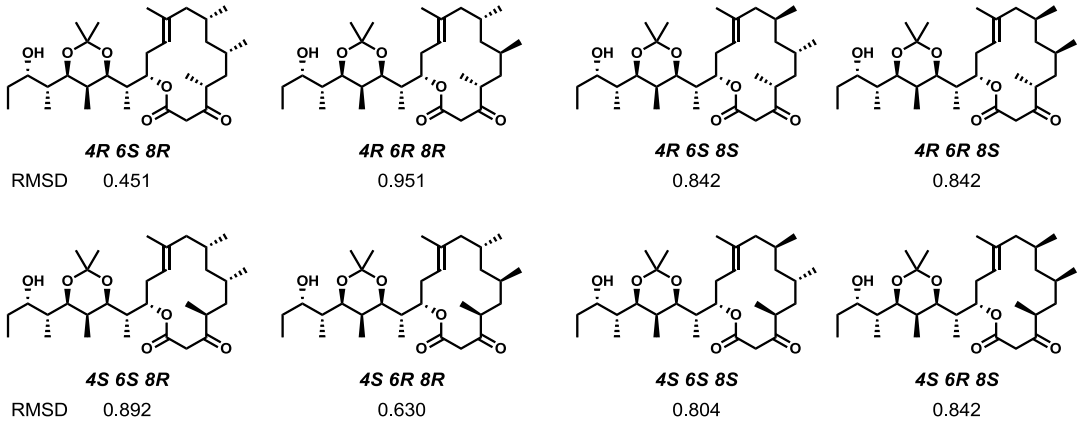
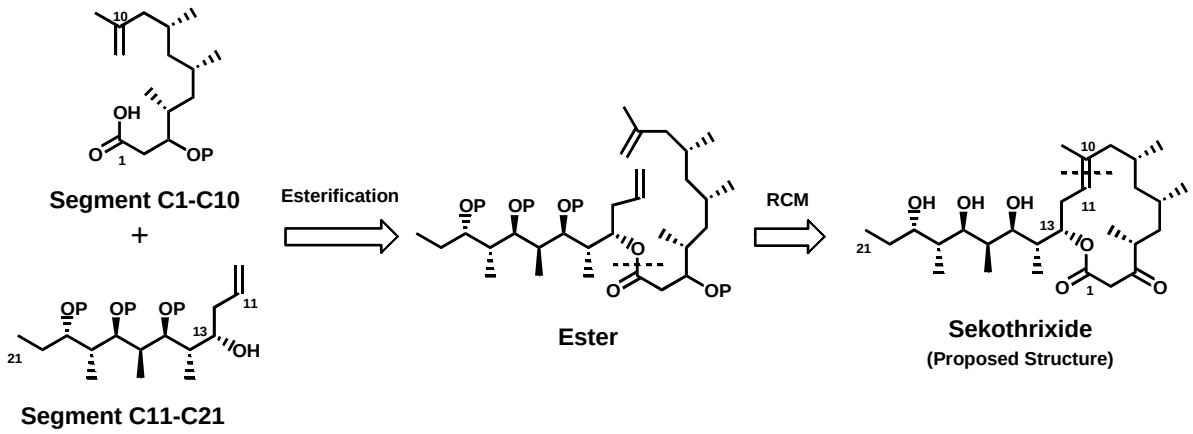


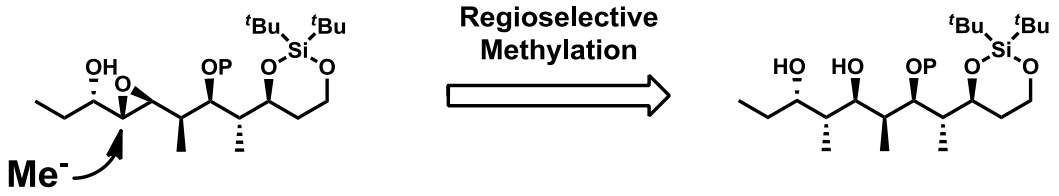
Figure 7. DADAS90 による結果と各種ジアステレオマーとの構造類似性比較

このようなマクロラクトン上のメチル基の立体化学に関するあいまいさから、著者は sekothrixide の合成研究において提唱構造体と天然物が異なる立体化学であったとしても対処しやすい、合成スキームを立案した(**Scheme 2**)。それは、segment C1-C10 と segment C11-C21 を合成し、両者をエステル化、そして閉環メタセシス反応[26-30]に付し sekothrixide の構築を達成するスキームである。この方法であれば segment C1-C10 を変更するだけで、最終化合物の C4,6,8 位のメチル基の立体化学の作り分けが可能となる。



Scheme 2

ところで Segment C11-C21 の合成時に鍵工程となる、第二級のエポキシアルコールに対する位置選択的メチル化反応はこれまでほとんど報告[31-34]されていない(Scheme 3)。そこでまず、第一章ではこの様な反応に関する検討を行った。



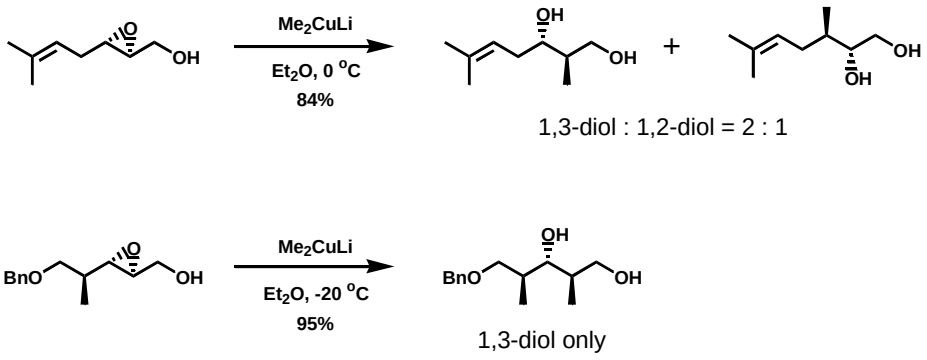
Scheme 3

第一章　第二級エポキシアルコール類の求核置換反応開発

第一節　背景

エポキシドの置換反応は、有機合成化学における有用な方法論として認識され、多くの複雑な天然物合成にも利用されている。その主な理由として、二つのことが挙げられる。第一に、香月-Sharpless不斉エポキシ化[35] のような優れた反応が開発されたことで、望みの立体配置を有する種々のエポキシドを容易に入手できるようになったことである。第二に、エポキシドの置換反応は通常S_N2で進行するため、生成物の立体化学はエポキシドの配置によって一義的に決まることである。しかし、エポキシドには2つの反応点が存在し、位置選択性をいかに発現させるかということが重要な問題となる。その解決には、適切な求核剤の選択や反応条件の設定だけでなく、基質そのものの工夫が必要となる。

そのような試みの一例として、第一級エポキシアルコールに対する有機銅試薬[36-43] の求核置換反応がある(Scheme 4)。この場合、求核剤は水酸基に隣接した側のエポキシドの反応点に攻撃し、1,3-ジオールの生成が優先する傾向にある。特に水酸基の反対側にメチル基を有するような基質では、立体効果の影響があり高い位置選択性が見られる。[44,45]



Scheme 4

一方、第二級アルコールに隣接するエポキシドを有機銅試薬による求核置換反応に用いた例は少ない。もし、第一級エポキシアルコールの場合と同様に、その反応点の制御が可能であれば、sekothrixide のようなポリプロピオネート系天然物合成にも応用しうる新たな鎖状立体制御法となるであろう(**Figure 8**)。そこで、比較的合成容易な第二級エポキシアルコールを用いて有機銅試薬との反応を検討した。

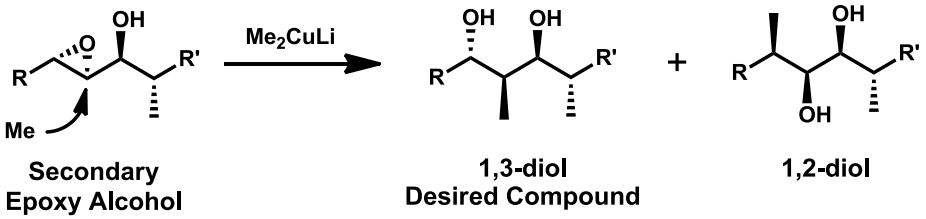


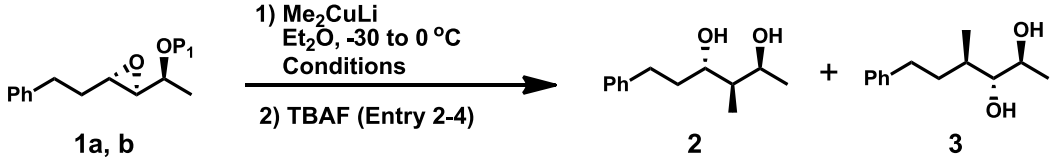
Figure 8. 第二級エポキシアルコールに対する位置選択的反応

第二節 *anti*-エポキシアルコールとメチル銅試薬の反応における位置選択性

第二級エポキシアルコールの場合、エポキシドに対する水酸基の相対配置が 2 種類考えられ、それぞれの立体化学が位置選択性に与える影響は同じであるとは限らない。まず、*anti* 配置のエポキシアルコール **1a**[46] を選択し以下反応検討に用いた。

メチル基を有機基とする Gilman 試薬(Me_2CuLi)用いて置換反応を検討した(**Table 2**)。Gilman 試薬(5 当量)をエーテル溶媒中で調製後、-30℃において **1a** を滴下したのち、徐々に 0℃まで昇温した。その結果、1,3-ジオール **2** と 1,2-ジオール **3** が混合物として得られ、その生成比は約 1:3 であった(**Entry 1**)。

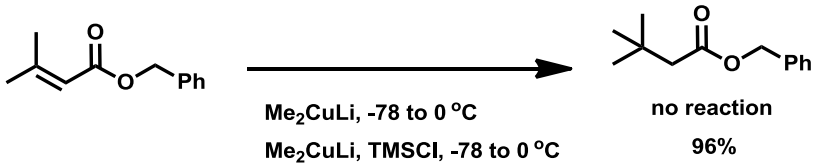
Table 2



1a, b **2** **3**

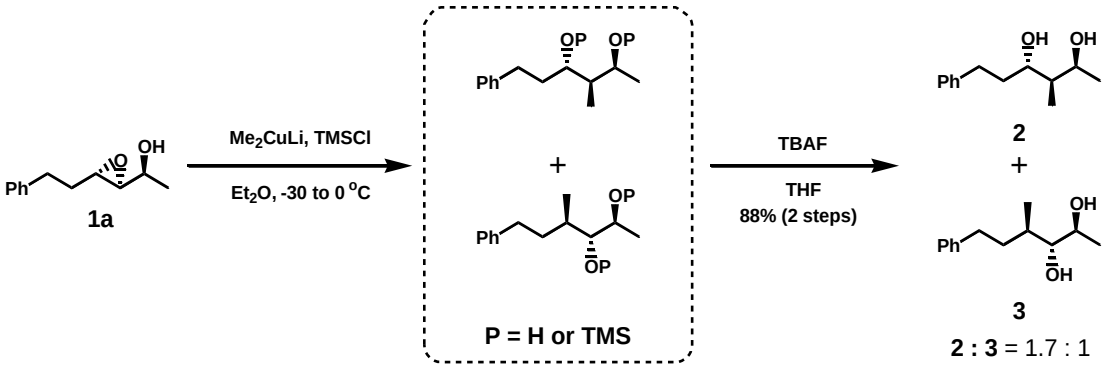
Entry	Sub	P_1	Additive reagent	Ratio 2 : 3	Yield (%) 2 + 3
1	1a	H	None	1 : 3	75
2	1a	H	TMSCl	1.7 : 1	88
3	1b	TMS	None	3 : 1	81
4	1b	TMS	TMSCl	2.5 : 1	90

ポリプロピオネート構造の合成に本反応を利用するとき、1,3-ジオール体が優先的に生成することが望まれる。そこで、位置選択性を逆転させるための検討として、反応系に影響を及ぼす試薬の添加を考えた。種々の試薬が考えられる中、エノンに対する有機銅試薬の 1,4 付加反応[47]においてよく用いられる TMSCl に着目した(**Scheme 5**)。



Scheme 5

Gilman 試薬と TMSCl をそれぞれ 5 当量用い反応を行った(**Table 2, Entry 2**)。その結果、いくつかの開環体が得られたが、その一部の水酸基はシリル化されていた。そこで、これらをそのまま TBAF で処理したところ、ジオール **2** および **3** の混合物を 2 工程収率 88%で得た(**Scheme 6**)。また、興味深いことに、TMSCl を加えることにより、わずかに **2** の生成が優先することが分かった。



Scheme 6

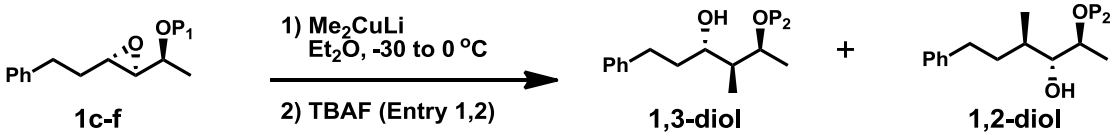
置換反応によって得られた生成物に一部シリル基が結合していたことから、置換反応の前にエポキシアルコールの水酸基がシリル化されることが位置選択性に影響を与えたのではないかと考えた。そこで、あらかじめ水酸基をTMS基で保護した**1b**を基質として、Gilman試薬によるメチル化を行った。その結果、**2**の選択性が約3:1にまで向上した。

Entry 4 では、**entry 3** の反応に、さらに TMSCl を加えて行った。この時の選択性は約 2.5:1 であり、**entry 3** の結果と比べて殆ど差はなかった。よって位置選択性の逆転は TMSCl の添加による効果ではなく、水酸基がシリル基と結合したことによる影響であることがわかった。ここで興味深いことは、水酸基がシリル基と結合する場合、その周囲は立体的に込み入った環境になっているにもかかわらず、それに近い側のエポキシド炭素にメチル基が反応しやすい点である。

第三節　他の保護基の影響

他の保護基でも同様の結果が得られるのかを検討した(**Table 3**)。シリル系の保護基の場合、その嵩高さに応じて反応が遅くなると同時に、1,3-ジオールの選択性が低下した(**Entry 1**,**2**)。これらの結果より、選択性発現にはあまり嵩高くない保護基が望ましいものと考え、メチル基で保護した基質**1e**で反応を行った(**Entry 3**)。しかし予期に反し選択性は全く発現しなかった。次に他のエーテル系保護基を入れた基質で検討したところ、MOM基の場合に良好な選択性が見られた(**Entry 4**)。これは、二つの酸素原子による錯体中の金属（CuまたはLi）への配位が影響しているものと考えられる。

Table 3



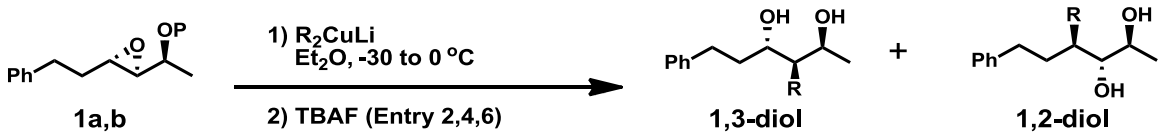
1c-f　　1,3-diol　　1,2-diol

Entry	Sub	P_1	P_2	Ratio 1,3-diol : 1,2-diol	Yield (%) 1,3-diol + 1,2-diol
1	1c	TES	H	1.6 : 1	73
2	1d	TBS	H	1 : 1	66
3	1e	Me	Me	1 : 1	86
4	1f	MOM	MOM	3 : 1	92

第四節　Gilman 試薬における有機基の検討

さらに求核基を Me 基から他のものに変え、選択性の変化を観察した(Table 4)。いずれの場合も、Me_2CuLi のときと同様、エポキシアルコール **1a** では 1,2-ジオールが主として得られ、TMS 保護した **1b** の場合は 1,3-ジオールが主生成物であった。

Table 4

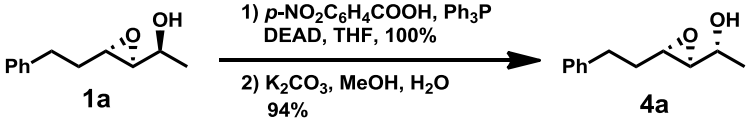


Entry	Sub	P	R	Ratio 1,3-diol : 1,2-diol	Yield (%) 1,3-diol + 1,2-diol
1	1a	H	^{n}Bu	1 : 4.4	90
2	1b	TMS	^{n}Bu	2.5 : 1	60
3	1a	H	^{n}Hex	1 : 4.4	87
4	1b	TMS	^{n}Hex	2.2 : 1	57
5	1a	H	allyl	1 : 1.5	86
6	1b	TMS	allyl	2 : 1	74

よってアルキル求核基の場合では基質の水酸基の保護の有無によって、その位置選択性に規則性があることが明らかとなった。

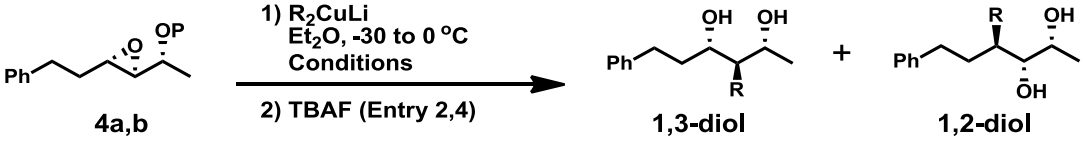
第五節 *syn*-エポキシアルコールの置換反応

次にアルコールとエポキシドの相対配置が、*syn* の基質 **4a** を合成した(**Scheme 7**)。得られた **4a** およびその TMS 保護を行った **4b** に対し、Me, ^{n}Bu 基を求核基とする置換反応を行った(**Table 5**)。興味あることに TMS 基の有無にかかわりなく、ほぼ完全な位置選択性で反応は進行し、1,2-ジオールが主生成物として得られた。よって TMS 基の位置選択性への効果は、*anti* 体に限られることが分かった。



Scheme 7

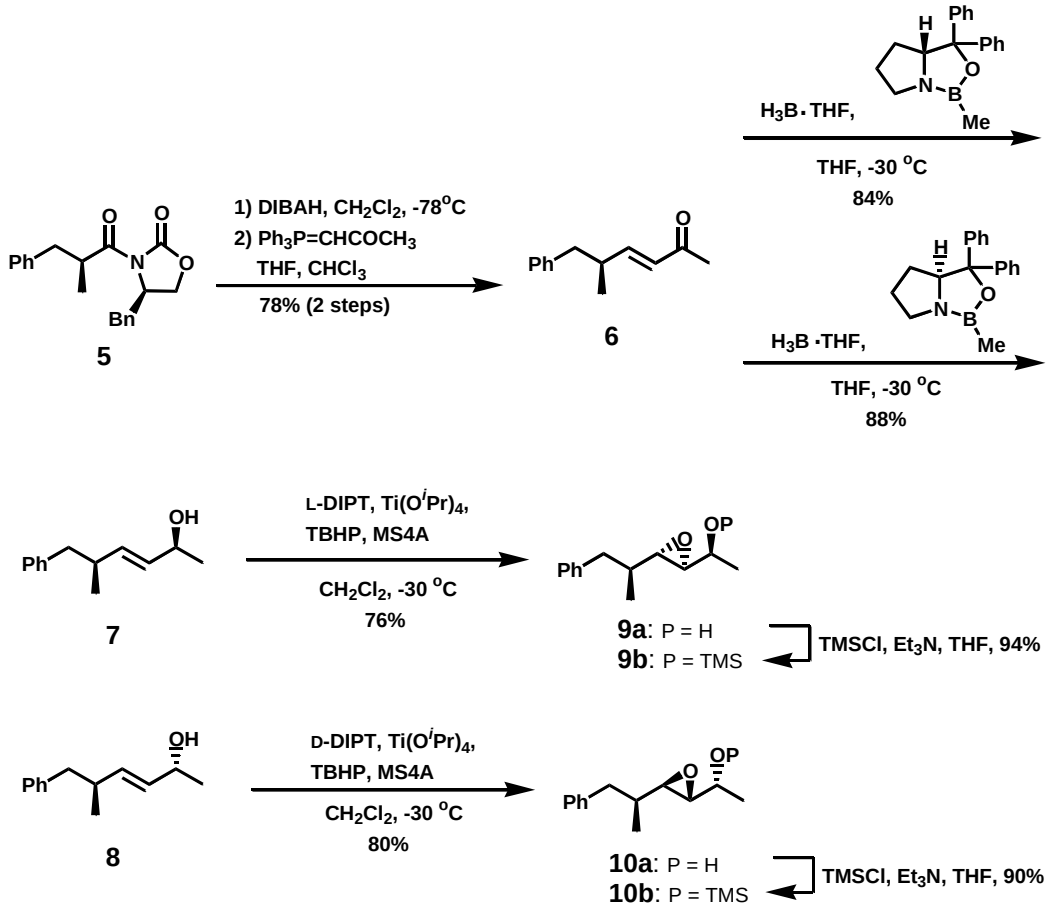
Table 5



Entry	Sub	P	R	Ratio 1,3-diol : 1,2-diol	Yield (%) 1,2-diol	Recovered SM (%)
1	4a	H	Me	trace : 1	43	40
2	4b	TMS	Me	trace : 1	88	—
3	4a	H	^{n}Bu	trace : 1	92	—
4	4b	TMS	^{n}Bu	trace : 1	85	—

第六節　基質の置換基による影響

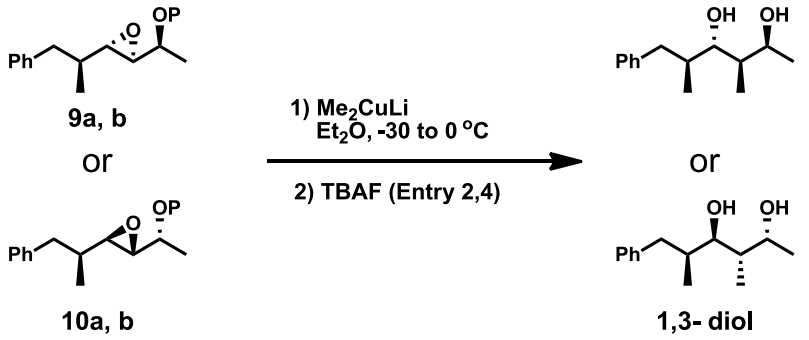
基質の立体障害を利用した 1,3-ジオール体の生成比向上を期待し、エポキシドの隣にメチル基を有する化合物 **9**, **10** を用いて検討した。基質の合成は以下のように行った(**Scheme 8**)。化合物 **5**[48] の DIBAH 還元によりアルデヒドを得、Wittig 反応を行うことによりエノン **6** を合成し、CBS 還元からアリルアルコール **7** 及び **8** へ導いた。アリルアルコールを香月-Sharpless 酸化に付し、エポキシアルコール **9a**, **10a** をそれぞれ合成した。



Scheme 8

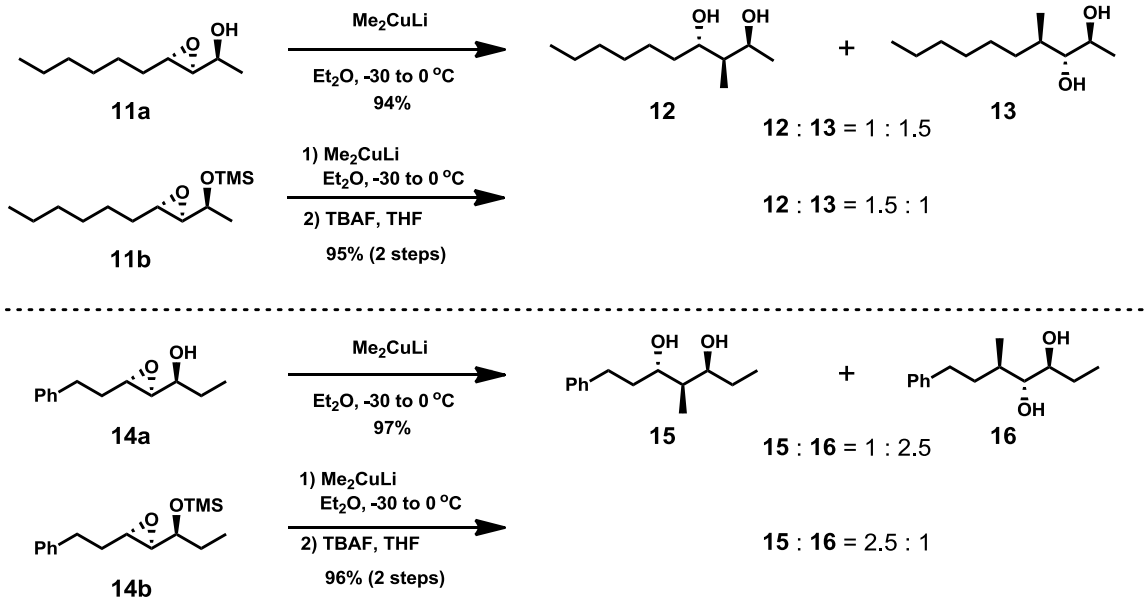
エポキシドの隣にメチル基を有する基質 **9, 10** にて反応を行った結果 1,3-ジオール体が主生成物として得られ、それらの収率は **table 2** 場合と比較するといずれも向上していた。加えて TMS 基によるさらなる収率向上も認められた(**Table 6**)。

Table 6



Entry	Sub	P	Yield (%) 1,3-diol	Recovered SM (%)
1	9a	H	32	57
2	9b	TMS	77	—
3	10a	H	27	67
4	10b	TMS	84	—

さらに基質の適応範囲を検討するため *anti* 配置の基質 **11**, **14** にて反応を行った(**Scheme 9**)。どちらの基質もエポキシアルコール体では 1,2-ジオールが、TMS 保護体では 1,3-ジオールが優先して得られるというこれまでの傾向と同じであった。よって、この反応の基質一般性がうかがえた。



Scheme 9

第七節　反応の遷移状態の考察

第七節ではこれまで行ってきた求核置換反応の位置選択性について考察する。中村らは B3LYP/631A レベルの基底関数を用いた量子化学計算によってエチレンオキシドと Me_2CuLi との遷移状態を解析した。[49,50] それによれば、求核反応時の遷移状態は **figure 9** に示すように、Gilman 試薬の Li がエポキシドに配位し、錯体がエポキシドを取り囲むような形になる。このとき錯体末端の Me^a と銅と Me^b がほぼ直線状に並び、Me^a と銅の中心がエポキシドの C-O 結合の後ろ側に位置している。

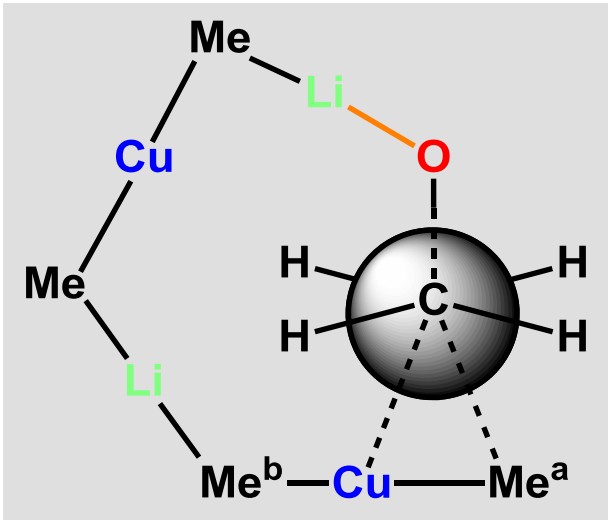


Figure 9.　求核反応時の遷移状態

この報告を参考に、著者らが行ってきた第二級エポキシアルコールに対する求核置換反応の遷移状態を考えた。まず *anti* 体のエポキシアルコール **1a** は Gilman 試薬と反応しリチウムアルコキシドとなり **figure 10** の様なキレート構造をとるものと考えた。一方、TMS 保護体 **1b** は非キレート構造をとっていると考えた。

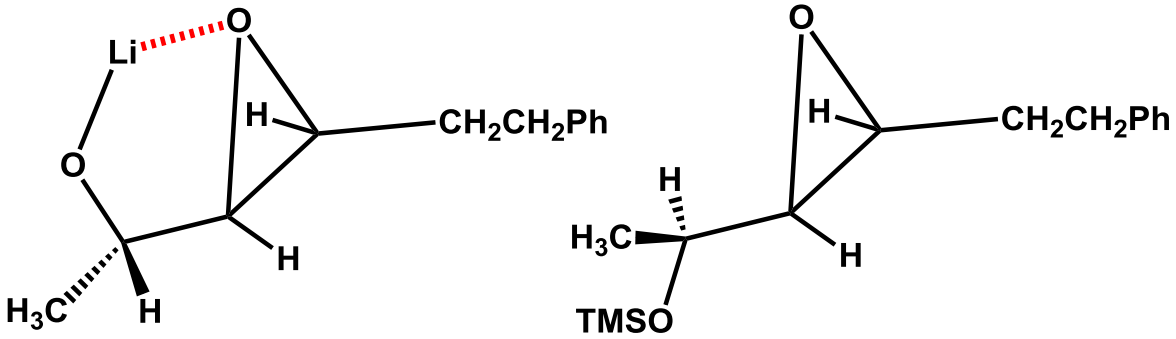


Figure 10

また、syn 体の **4a,b** も *anti* 体と同様のキレート構造及び非キレート構造になっていると考えた (**Figure 11**)。

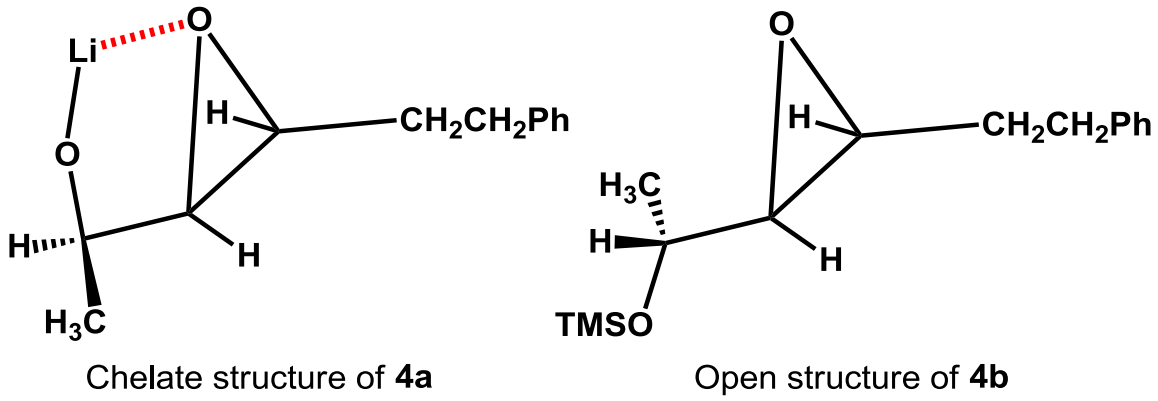


Figure 11

まず **figure 10** のキレート構造を基に、**1a** に対する反応の位置選択性について考察した (**Figure 12**, **13**)。1,3-ジオール **2** が生成するには、C3 位に対しメチル基が導入されなければならない。C3 位で Gilman 試薬が反応する場合、TS-I の様な遷移状態をとるものと推測され、この時 C1 のメチル基により Gilman 試薬の Me^a に立体反発が生じる。一方、1,2-ジオール **3** が生成するときは C4 位で反応するため、これは TS-II の様な遷移状態をとるであろう。

したがって、TS-I と TS-II を比較した場合、C1 位の立体障害を避けるように TS-II からの反応が優先し、1,2-ジオール **3** が主生成物として得られてきたものと考えた。

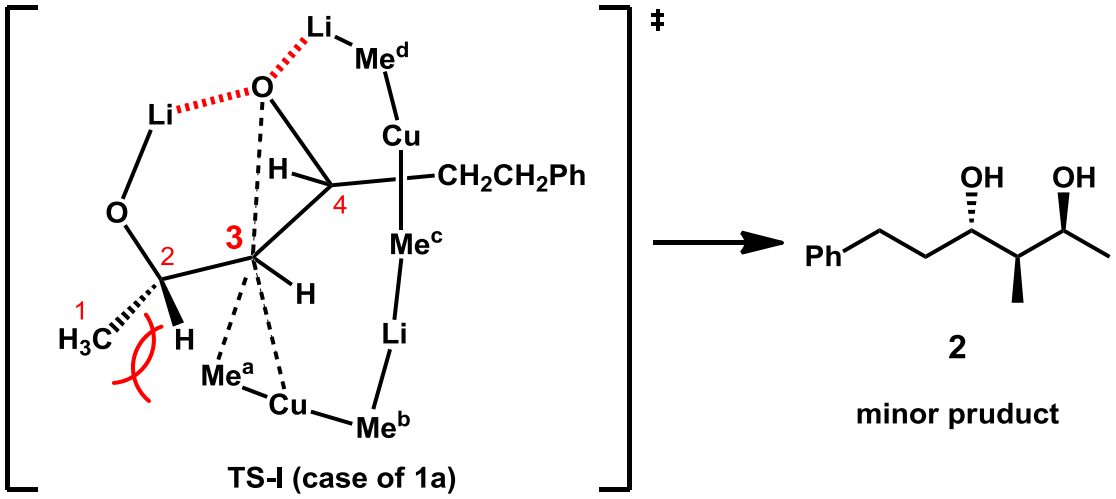


Figure 12

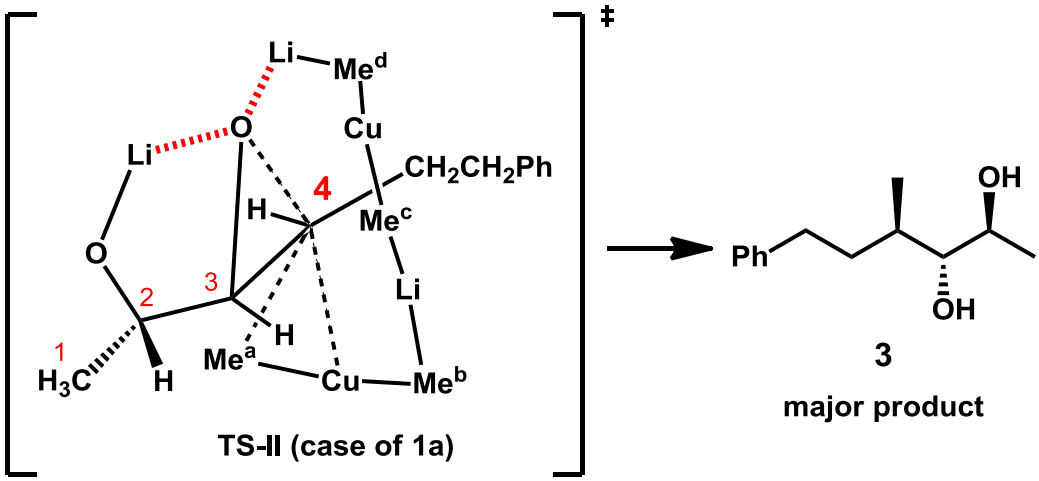


Figure 13

また、*syn* 体の **4a** の場合も *anti* 体の時と同様に、遷移状態 TS-IV が TS-III より有利であり 1,2-ジオール体が主生成物として得られたものと推測した(**Figure 14, 15**)。

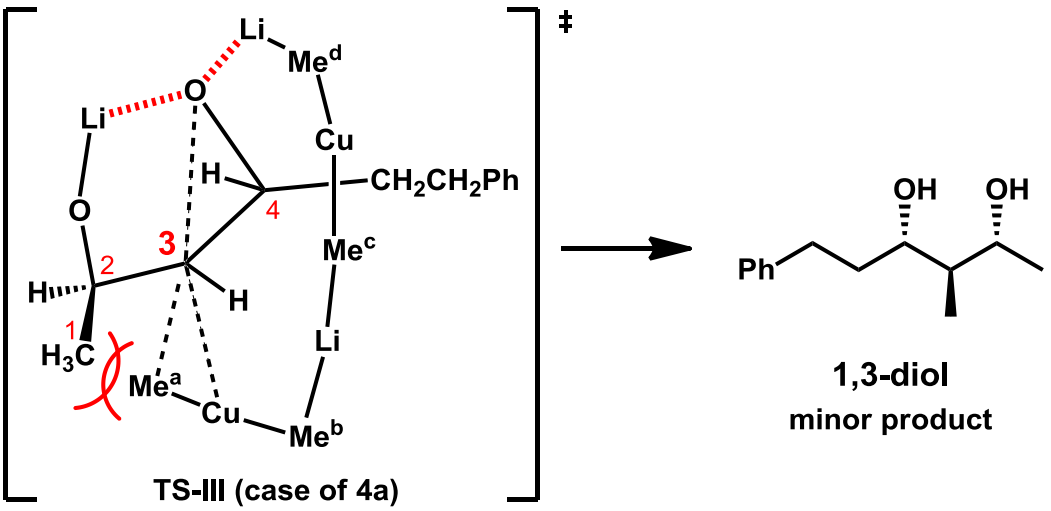


Figure 14

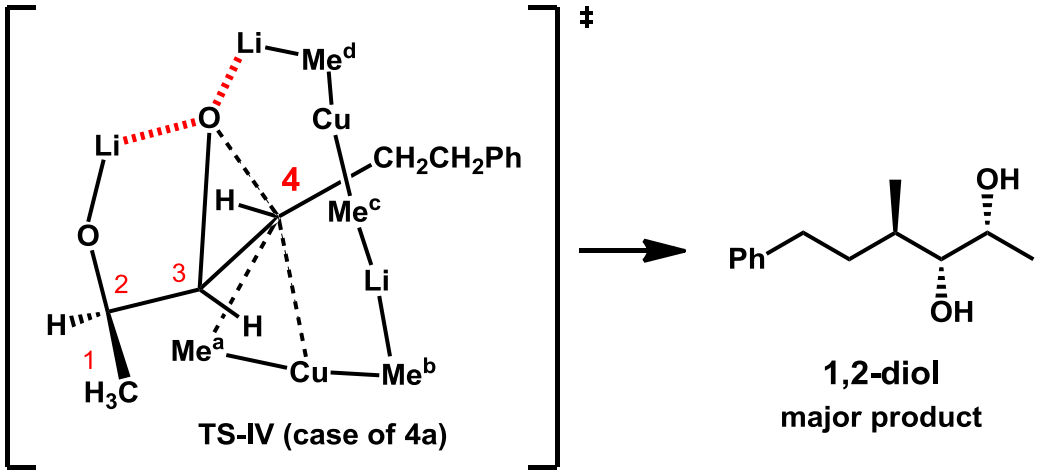


Figure 15

次に、*anti* 体の TMS 保護された **1b** の位置選択性について考察した。TMS 保護体では、水酸基フリーの時の様なキレート構造をとらないが Gilman 試薬の Me^b と Me^c に挟まれた Li 原子に対し基質のシリルオキシ基が配位[55]した遷移状態(**Figure 16**、TS-V)が有利であると考えれば、1,3-ジオール体が主生成物として得られたことを説明できる。このことは、**table 3, entry 1,2** においてシリル系保護基のかさ高さが増すに従って、1,3-ジオール体の生成比が減少したことの説明としても無理がない。つまり保護基のアルキル基と Gilman 試薬との立体障害が増すことにより、C2 位の酸素原子と Li との配位が弱まり Me^a が C4 位側へ移動するであろう。

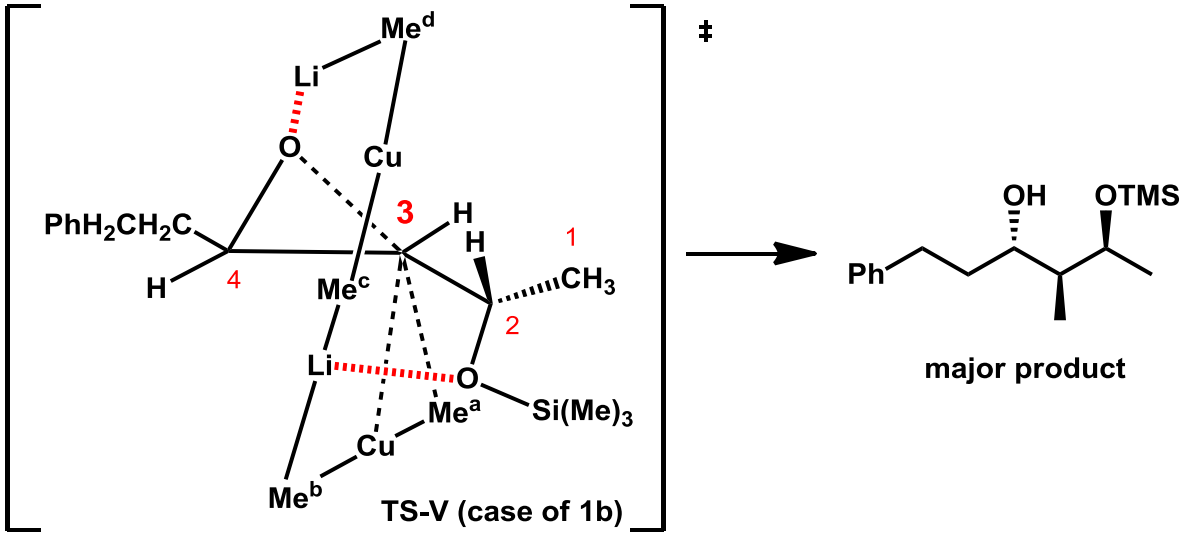


Figure 16

一方、*syn* 体の TMS 保護体 **4b** の場合、TS-VI のように Li に対して基質のシリルオキシ基が配位すると、C1 のメチル基と Gilman 試薬との間に大きな立体反発が生じる結果、1,3-ジオール体の生成比が低かったと考えられる(**Figure 17**)。今後は、高精度量子化学計算などを駆使して、遷移状態に関する考察を深めたいと考えている。

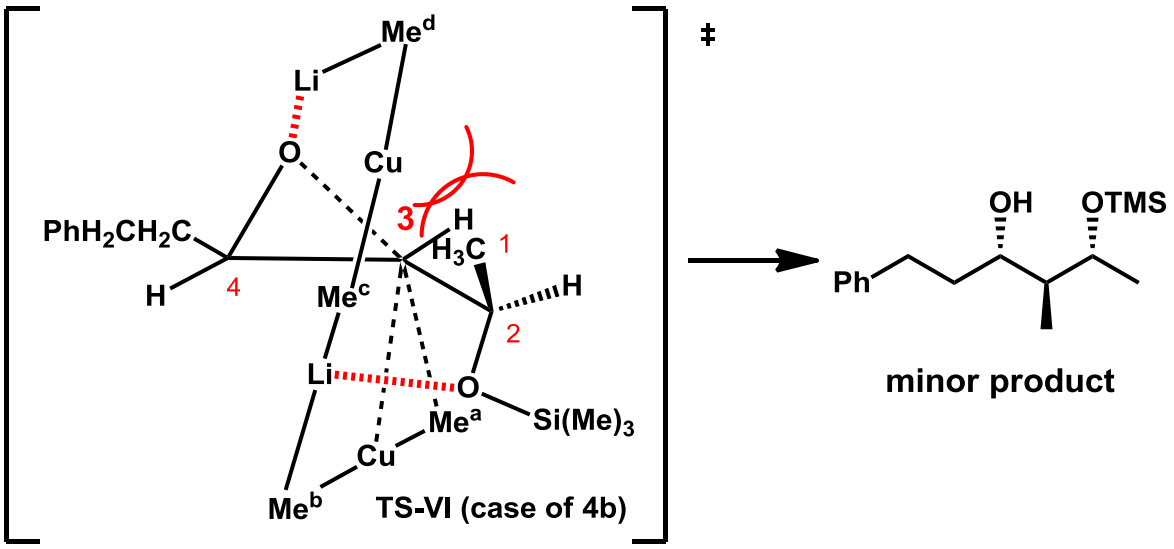
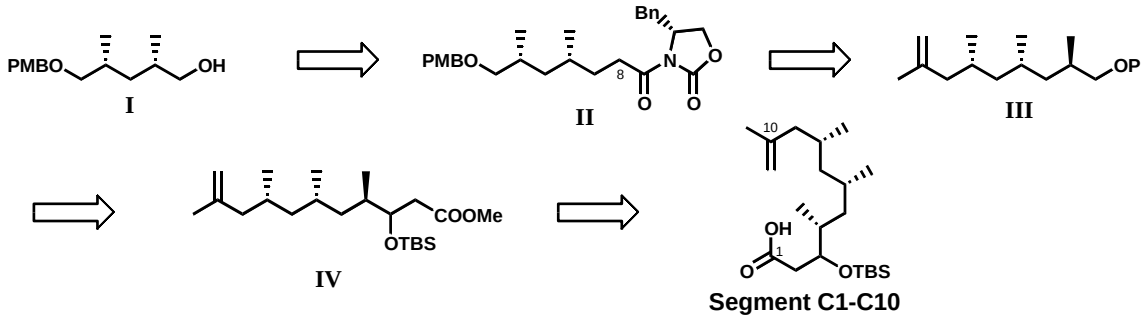


Figure 17

第二章 Sekothrixide の合成研究

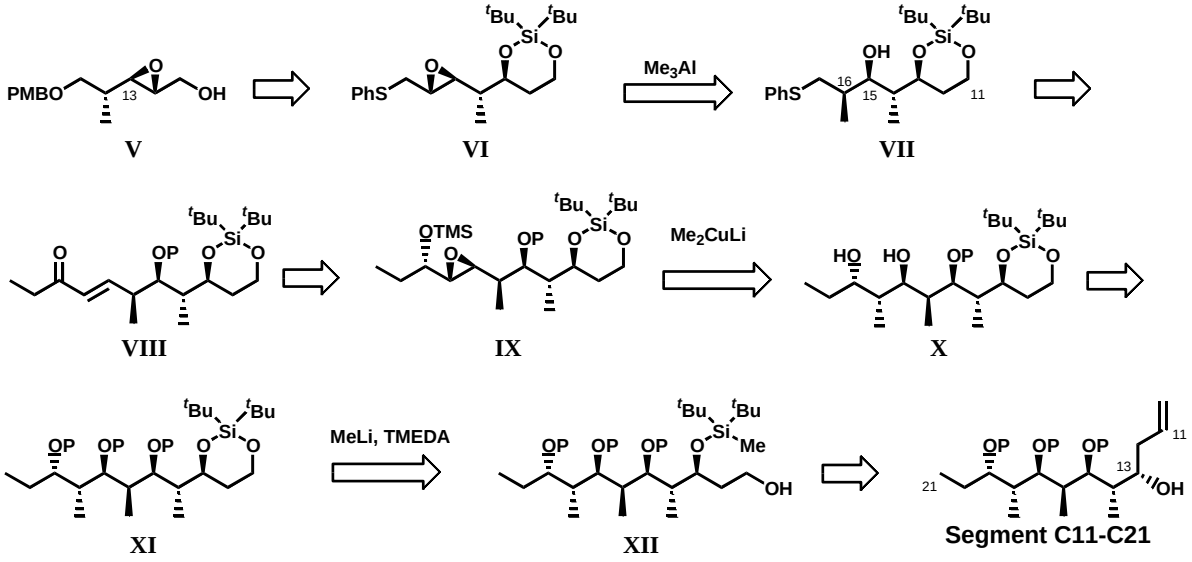
第一節 合成計画

第二章では、前章で確立した方法を用いて14員環ケトライド sekothrixide の全合成研究について述べる。序論で述べたように、sekothrixide のマクロラクトン部の立体化学の決定法に、信頼性の面で疑問が残る。そのため全合成を行うにあたり、segment C1-C10 と segment C11-C21 を別々に合成し、それらをエステル化と閉環メタセシスにより連結する収束的合成経路を立案した。Segment C1-C10 の合成は、次の様に計画した(**Scheme 10**)。既知のアルコール **I**[51-53] から誘導したアミド II に対し立体選択的にメチル化を行う。次に、閉環メタセシス反応に必要なイソプロペニル基の導入などにより **III** を合成し、向山アルドール反応 [54] とアルカリ加水分解により segment C1-C10 へと誘導する。



Scheme 10

一方、segment C11-C21 の合成に関しては、既知のアルコール **V**[55] を出発基質とし、以下のように計画を立てた(**Scheme 11**)。C15-C16 位の水酸基とメチル基が *syn* 配置の **VII** は、エポキシスルフィド **VI** に対する二重立体反転を伴うメチル化 [56-58] から得られるものと考えた。そこからエノン **VIII** へ変換後、CBS 還元、香月-Sharpless エポキシ化により第二級のエポキシアルコールのシリル化体 **IX** を合成する。このものに対し、位置選択的メチル化により、所望の 1,3-ジオール **X** が得られるものと考えた。さらにシリレン **XI** を位置選択的に脱保護し、得られる **XII** の第一級水酸基を末端オレフィンへ変換すれば、segment C11-C21 が構築できるものと考えた。

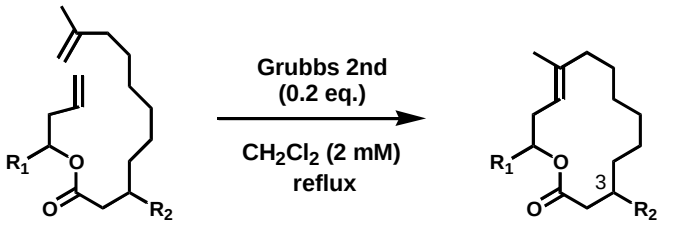

PMBO
OH
13
V
PhS
VI
Me3Al
PhS
OH
16
15
11
VII
VIII
OTMS
IX
Me2CuLi
HO
HO
OP
X
MeLi, TMEDA
Me
XI
XII
21
Segment C11-C21

Scheme 11

第二節　大環状閉環メタセシスの予備実験

Scheme 2 に示した合成計画の重要な課題の一つに、閉環メタセシス反応によって構築される三置換オレフィン部の立体化学制御があげられる。そこでモデル化合物を用いて予備実験を行った(**Table 7**)。**Entry 1** では、ホモアリルアルコールとβ位に置換基のないカルボン酸から導いたエステルに対し、第二世代Grubbs触媒を用いて閉環メタセシス反応を行った。その結果、目的とするラクトン体の収率は 47%にとどまった。次に R_1 にフェニルエチル基を導入したエステルで反応を行ったが、この場合の収率は 51%であった(**Entry 2**)。

Table 7



Entry	R_1	R_2	Yield (%)[a]
1	H	H	47
2	Ph$\frown$CH$_2$	H	51
3	Ph$\frown$CH$_2$	OTBS	93[b]

a: *E*-geometry yield, b: Diastereo mixture.

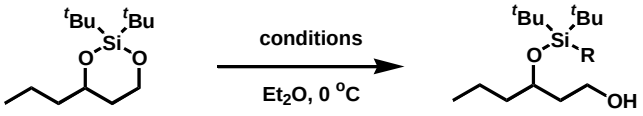
Entry 3 の R_2 にシリルオキシ基を有するエステルでの閉環メタセシス反応は、収率が 93%と大幅に向上した。この理由はわかっていないが、著者は第二級のTBSエーテルにより周りとの立体障害が生じ、炭素鎖が直線状ではなく弧を描くようなコンフォメーションをとり、オレフィン部が接近しやすくなり収率が向上したものと考えている。得られた化合物の三置換オレフィン部の立体化学は ^{13}C-NMR のケミカルシフトによって決定した。Stothers の報告[59] によると、三置換オレフィン上のメチル基の ^{13}C-NMR ケミカルシフトは *E* 体の場合、周りの置換基の立体圧縮効果により 11-18 ppm に高磁場シフトする。一方 *Z* 体の場合は 21-28 ppm である。**Entry 3** の閉環メタセシス成績体の対応するメチル基のケミカルシフトは、15.8 と 16.2 ppm であったことから *E* 体である

と決定した。なお天然物 sekothrixide のケミカルシフトは、16.6 ppm であった。以上の予備実験より、3 位にシリルオキシ基があれば環化反応が飛躍的に改善されることが明らかになり、sekothrixide の全合成を行う上で重要な知見となった。

第三節　シリレンの位置選択的開裂の予備実験

合成研究を始める前に保護基の架け替えによる工程数の増加を抑える目的から、シリレンの位置選択的開裂反応[60]について検討した(**Table 8**)。まず求核剤としてMeLiを用い反応を行ったところ、原料回収に終わった(**Entry 1**)。**Entry 2**ではTMEDAを加えMeLiによる反応を試みたところ、位置選択的にシリレンの開環反応が進行し、第一級アルコールが 71%の収率で得られた。また、^{n}BuLi/ TMEDA の条件で行ったところ求核基の立体障害からか収率は顕著に低下した(**Entry 3**)。

Table 8



Entry	RLi (5 eq.)	additive (5 eq.)	yield (%)
1	Me	none	-
2	Me	TMEDA	71
3	^{n}Bu	TMEDA	15

この反応の遷移状態は**figure 18**のような配位をし、シリレンの空いている側から求核攻撃が起こり、第一級アルコールが主として生成したものと考えられる。

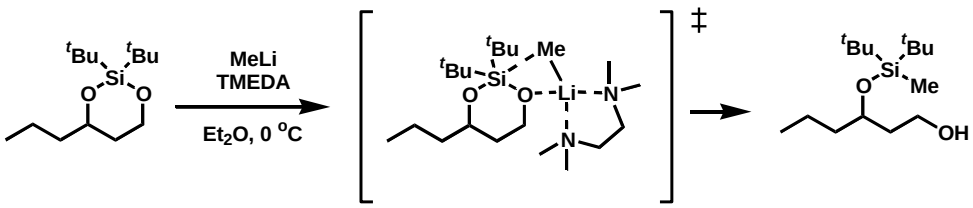
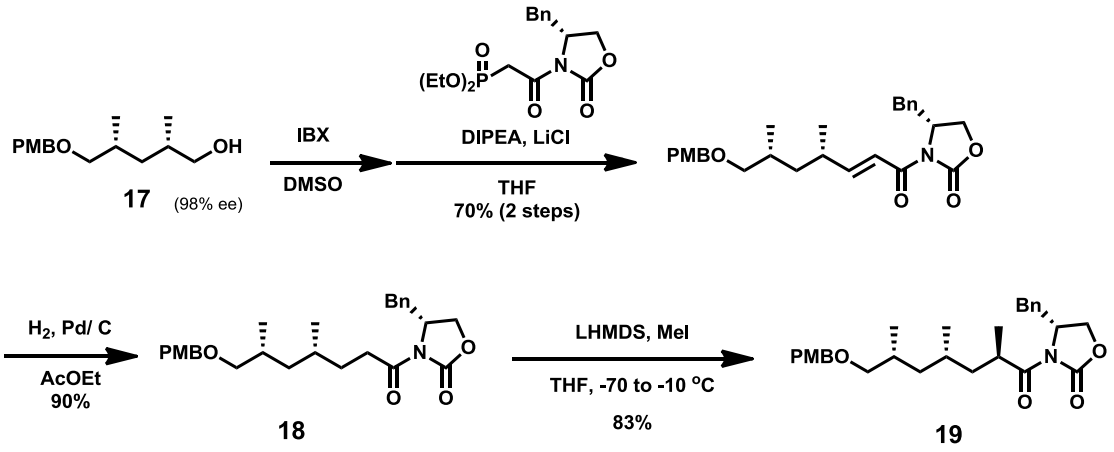


Figure 18.　位置選択的シリレンの開環反応の推定遷移状態

第四節　Segment C1-C10 の合成

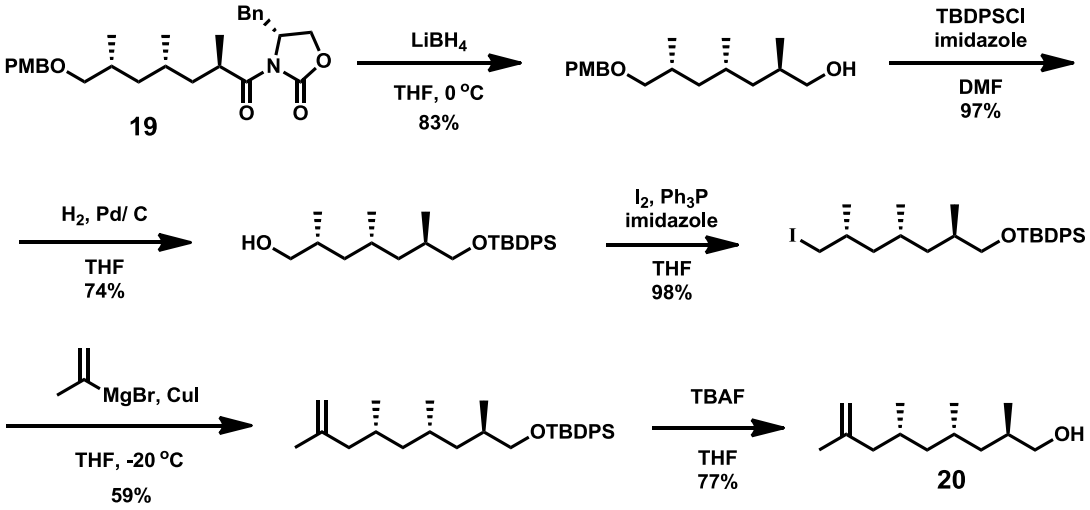
Scheme 10 に示した合成計画に基づいて、segment C1-C10 の合成を開始した(Scheme 12)。既知の手法によって光学純度 98%のアルコール **17**[51-53] を合成し、**17** を IBX 酸化に付すことでアルデヒドとした後、正宗法[61,62] から不飽和アミドへ導いた。続いて、AcOEt 溶媒中 Pd/ C を用いてオレフィン部の接触水素化を行った。PMB 基の脱保護といった副反応は起こらず高収率で還元体アミド **18** が得られた。次に、LHMDS を 3 当量、MeI を 10 当量用いてメチル化[63] を行ったところ、収率 83%で目的とするメチル化体 **19** が得られた。この時、少量生成したジアステレオマーはシリカゲルカラムクロマトグラフィーによって分離できた。



Scheme 12

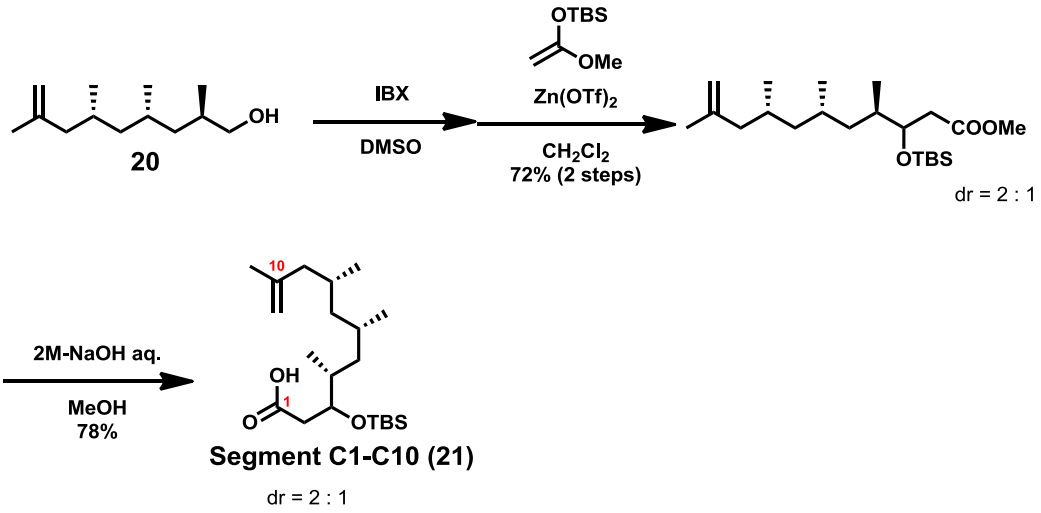
メチル化体 **19** を $LiBH_4$ で還元しアルコールへと導き、生じた水酸基を TBDPS 基によって保護を行った。得られたシリルエーテルに対して水素雰囲気下、THF 溶媒中 Pd/ C を用いて PMB 基の脱保護を行い、アルコールを得た(Scheme 13)。アルコールをヨウ化物へ変換し、イソプロペニルグリニャール試薬 4.5 当量、CuI 1.5 当量、-20℃でヨウ化物に対し反応を行ったところ、望む化合物が収率 59%で得られた。得られた化合物の TBDPS 基を TBAF で脱保護しアルコール **20** へ導いた。アルコール **20** のエナンチオマーが既知物質[64] でありこれらの比旋光度を比較した。著者が合成した **20** の比旋光度は$[\alpha]_D$ = +33.9 (c = 0.87, $CHCl_3$)であり、*ent*-**20** の

比旋光度は$[\alpha]_D$ = -26.4 (c = 0.5, $CHCl_3$)と報告されており鏡像異性の関係であることを確認した。



Scheme 13

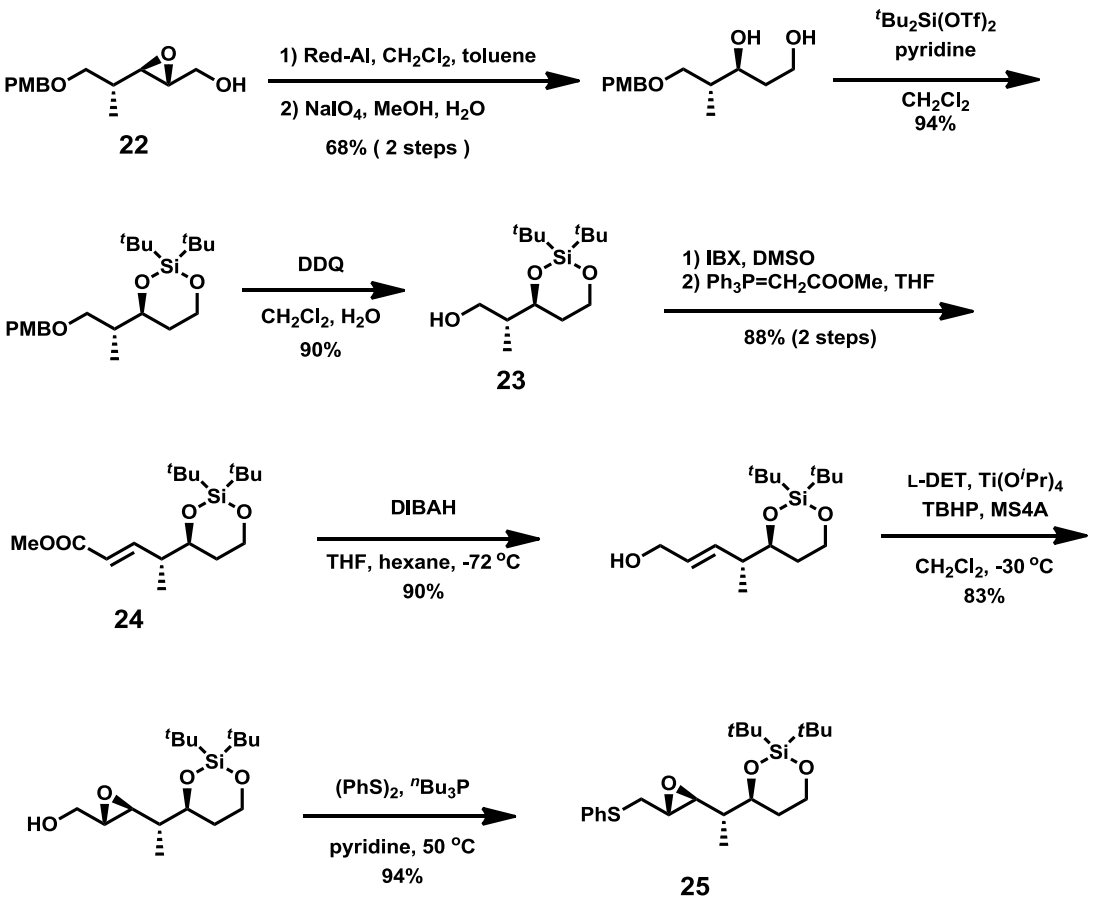
アルコール**20**をIBXで酸化し、得られたアルデヒドを向山アルドール反応の条件により、エステルへ導いた。最後にエステルをアルカリ加水分解することで segment C1-C10 (**21**)がえられた(**Scheme 14**)。



Scheme 14

第五節　第二級エポキシアルコール中間体の合成

Scheme 11 に示した合成計画に基づいて、segment C11-C21 の合成を行った(Scheme 15)。宮下らが報告している方法[55] で合成したエポキシアルコール **22** に対し Red-Al を用いて開環反応[65] を行い、粗生成物を $NaIO_4$ で処理し目的とする 1,3-ジオールを 2 段階収率 68%で得た。ジオールをシリレンで保護[66] した後、DDQ で処理することにより PMB 基を除去しアルコール **23** を得た。**23** の水酸基を IBX で酸化、続いて Wittig 反応に付すことでエステル **24** へ導いた。DIBAH 還元によりアリルアルコールとした後、香月-Sharpless エポキシ化からエポキシアルコールを得、第一級水酸基をフェニルスルフィドへと変換しエポキシスルフィド **25** を合成した。



Scheme 15

次に C15-C16 位の水酸基とメチル基が *syn* 配置の部分の構築には、エポキシスルフィドを基質とする二重立体反転を伴うメチル化[56-58]が適しているものと考えられる。この反応はエポキシドが Me_3Al で活性化され、スルフィドがエポキシドへ求核攻撃する。そしてアンチエピスルホニュウムイオンを経由しアルミニウムからメチル基が導入される(**Figure 19**)。

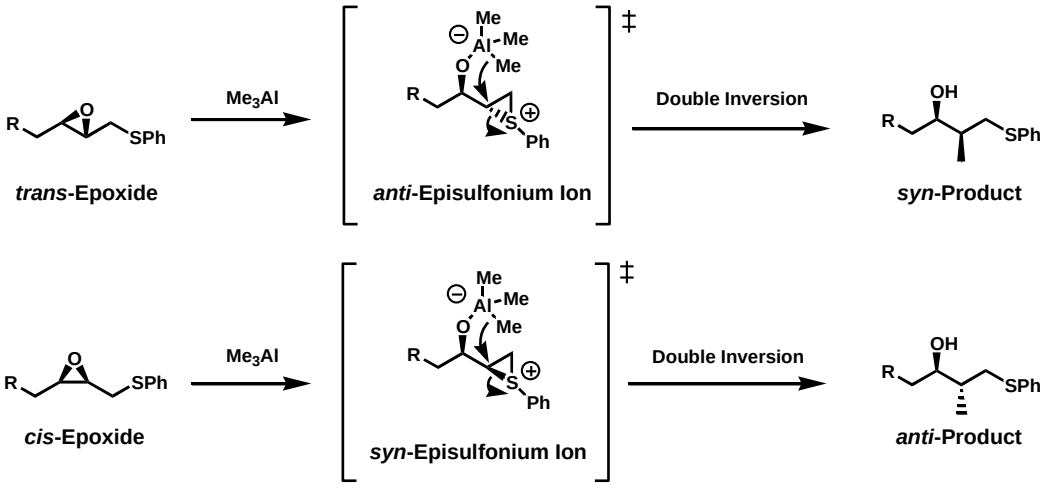
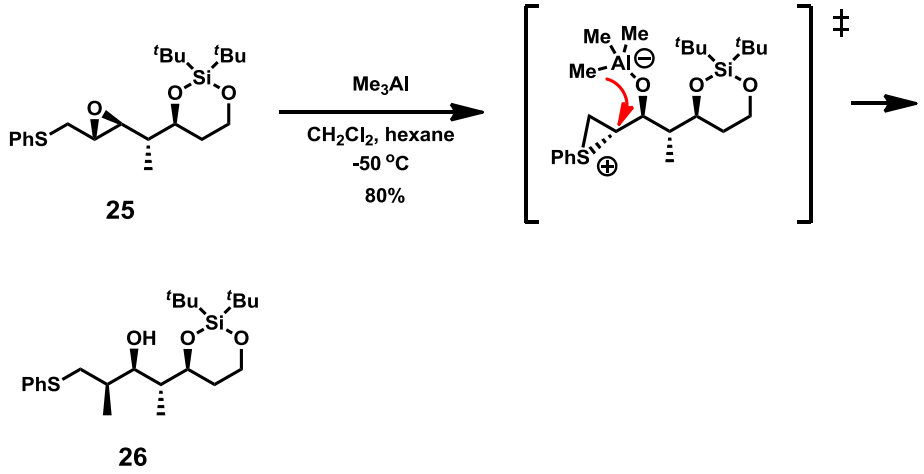


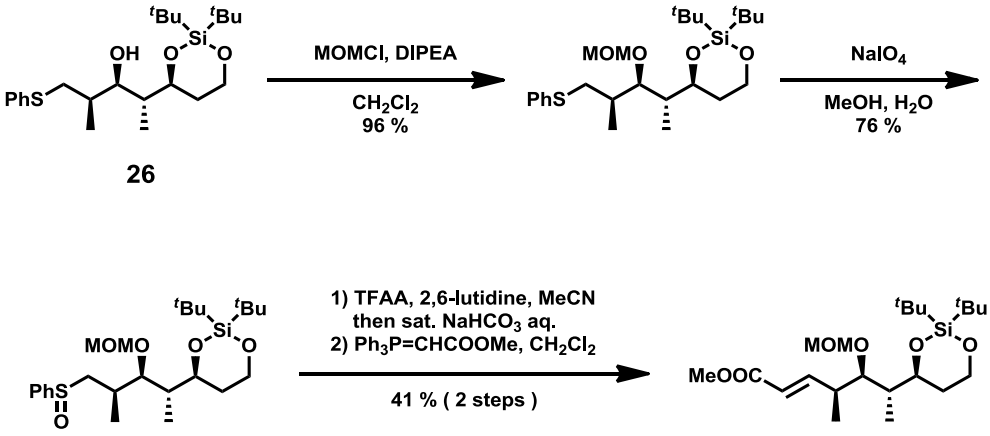
Figure 19. 二重立体反転を伴うメチル化

得られたエポキシスルフィド **25** と Me_3Al によるメチル化を CH_2Cl_2 溶媒中-50℃で行った。その結果、目的とする水酸基とメチル基が *syn* 配置の化合物 **26** を収率 80%で得られた(**Scheme 16**)。



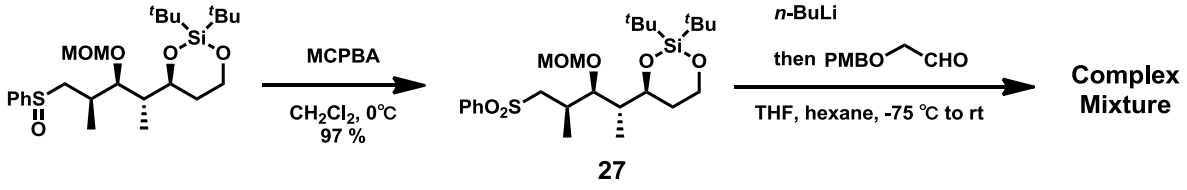
Scheme 16

次に増炭反応を行った。化合物 **26** の第二級水酸基を MOM 基で保護後、$NaIO_4$ で酸化することによりスルホキシドへ導いた。無水トリフルオロ酢酸と 2,6-lutidine を用いて Pummerer 転位、[67,68] 続く加水分解からアルデヒドへ導きこれに Wittig 反応を行った。共役エステルは得られたが 2 段階で最高収率 41%であったためこのルートは断念した(**Scheme 17**)。



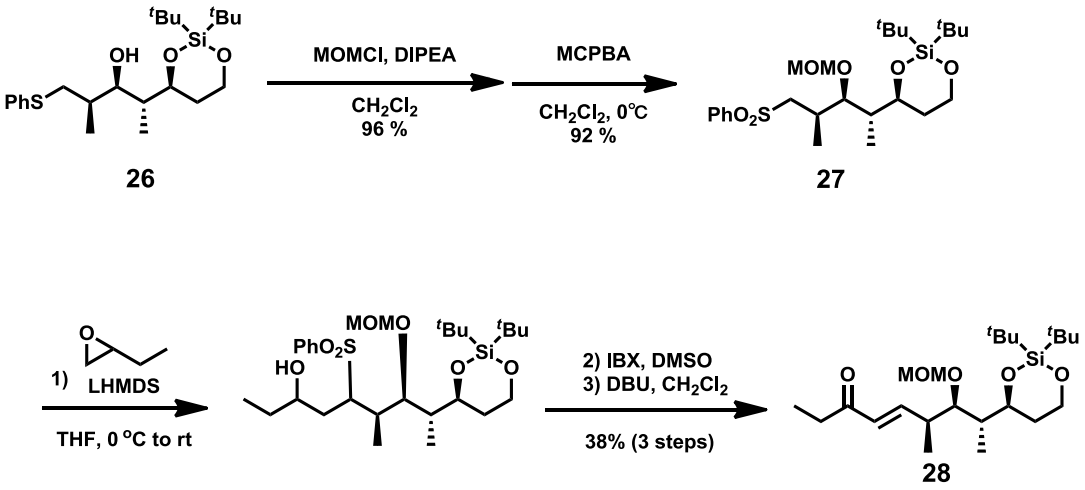
Scheme 17

そこでスルホキシドをスルホン **27** まで酸化し ^{n}BuLi からアニオンを発生させ、別途調製したアルデヒドと Julia カップリング [69,70] を試みた。しかし、複雑な混合物となり目的とするカップリング体を得ることができなかった(**Scheme 18**)。



Scheme 18

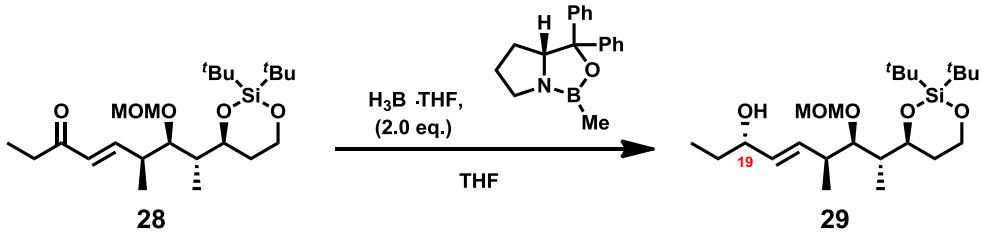
次にスルホン **27** とブチレンオキシドのカップリングを試みた。塩基は LHMDS で反応を行った。原料の **27** は TLC 上で消失し目的とする 4 種のジアステレオマー混合物が得られた。この混合物に IBX 酸化を行い、得られたケトンを DBU で処理するとスルホンが脱離し、エノン **28** が 3 段階収率 38%で生成した(**Scheme 19**)。



Scheme 19

得られたエノン **28** の立体選択的な還元反応を検討した。*R* 体の oxazaborolidine 0.2 当量と H_3B･THF を 2.0 当量用い、反応温度-45℃で還元反応を行った(**Table 9**, **Entry 1**)。反応は速やかに進行し第二級のアリルアルコール **29** が得られた。

Table 9



Entry	Oxazaborolidine (eq.)	Temp. (°C)	dr	Yield (%)
1	0.2	-45	2 : 1	86
2	0.6	-45	6 : 1	97
3	0.2	-70	3 : 1	10
4	1.0	-70	15 : 1	56
5[a]	1.2	-40	15 : 1	97
6[a]	—	-40	1 : 1	21[b]

a: This reaction was used H_3B･THF complex of 1.2 eq., b: Recovered SM (75%)

Entry 1 ではジアステレオ選択比が 2:1 と低かったため、立体選択性を上げるために oxazaborolidine の当量数を増やして反応を行った(**Entry 2**)。Oxazaborolidine を 0.6 当量、

H_3B･THF を 2.0 当量、反応温度-45℃で還元反応を行ったところ、ジアステレオ選択比は 6:1 と向上した。反応温度による変化を観察した。oxazaborolidine を 0.2 当量用い、反応温度を-70℃に下げた(**Entry 3**)。TLC 上では原料の消失が見られクエンチしたが、反応粗生成物を TLC で確認したところ原料がかなり残っていた。これは恐らく、TLC でモニタリングする際の、キャピラリー内で還元反応が進行したためと考えられる。結果としてこの条件では収率わずか 10%であった。また、この時のジアステレオ選択比は 3:1 とさほど向上していなかった。**Entry 4** ではさらに、oxazaborolidine を 1.0 当量、H_3B･THF を 2.0 当量用い、反応温度-70℃で還元反応を行ったところ、選択性は 15:1 と大幅に向上したが、収率は 56%と満足いく結果ではなかった。これまでの検討結果を踏まえ oxazaborolidine を 1.2 当量、H_3B･THF を 1.2 当量で、反応温度-40℃で還元反応を行ったところ、ジアステレオ選択比 15:1、収率 97%とよい結果が得られた(**Entry 5**)。

ところで、一般に CBS 還元を行う際、oxazaborolidine は触媒量用いるだけで十分に立体選択性が発現する。しかし、**28** に対する CBS 還元では 1 当量以上加えないとよい選択性が得られなかった。この原因として反応系内では oxazaborolidine をかえした還元と H_3B･THF 単独での還元反応が競合して進行しているのではないかと考えた。そこで、oxazaborolidine を加えないで反応を試みた(**Entry 6**)。その結果、還元反応は進行し且つ選択性は 1:1 であった。ゆえに還元反応の競合が示唆された。

得られた化合物 **29** の C19 位水酸基の立体化学は、*S* 及び *R* 体の新 Mosher エステル [71] とへと導き、両者の ^{1}H-NMR のケミカルシフトを解析することで決定した(**Figure 20**)。解析結果から望む *S* 配置のアリルアルコール **29** が主として生成していることが確認された。

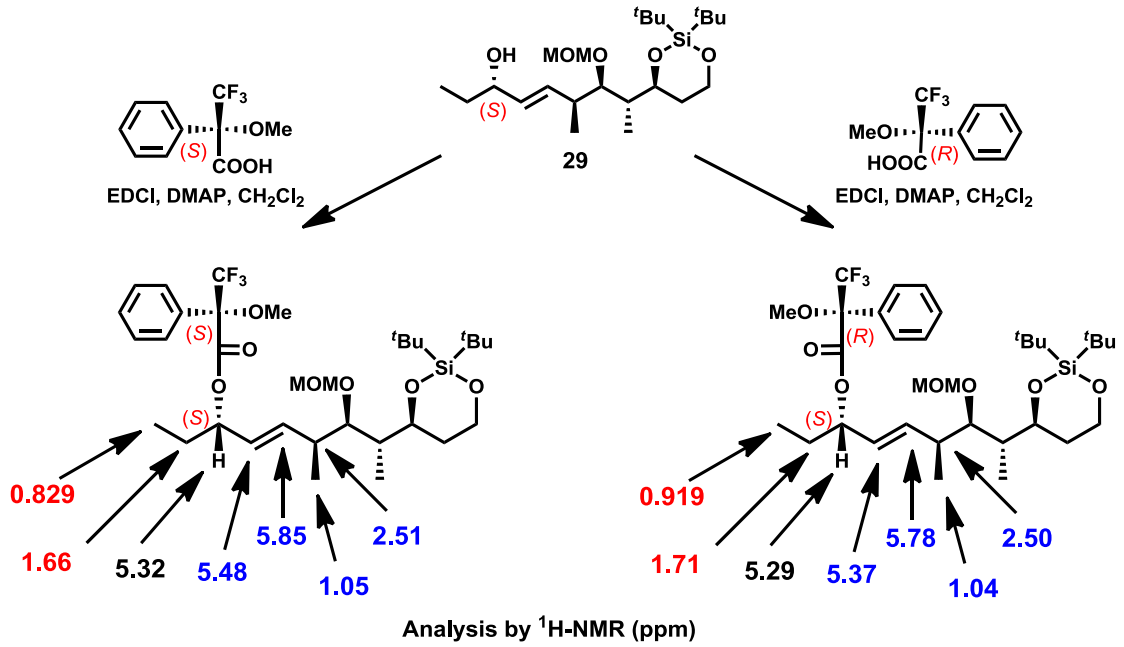
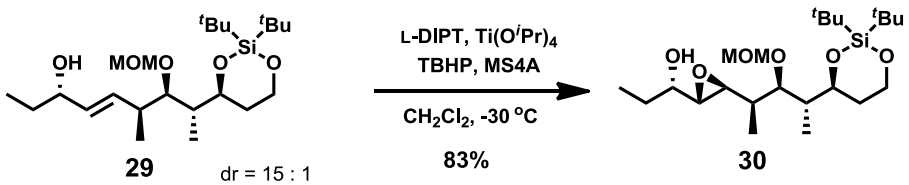


Figure 20　新 Mosher 法による立体化学の決定

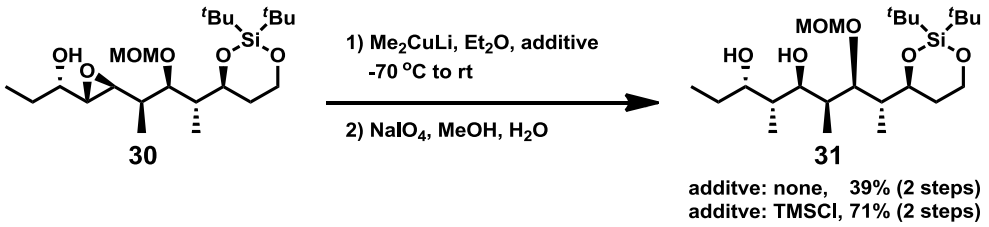
次に、アリルアルコール **29** とそのジアステレオマーの混合物(dr=15:1)に対し香月-Sharpless エポキシ化の条件に付した(**Scheme 20**)。この条件では、第二級水酸基に対する速度論的分割が生じることが知られている。[72] 立体障害の大きいジイソプロピル基酒石酸エステルを用いると特に効果が大きいということから、その条件で反応を行ったところ、*S* 体のアリルアルコール **29** が優先的にエポキシアルコール **30** へ変換された。



Scheme 20

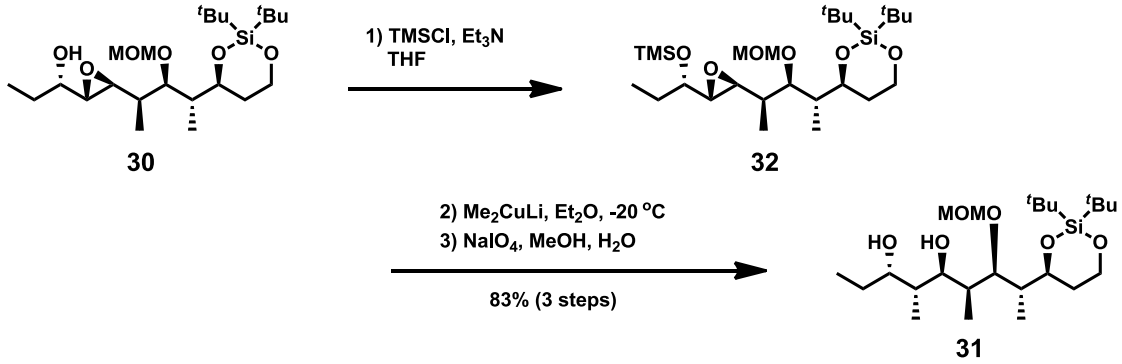
第六節　有機銅試薬による第二級エポキシアルコールの置換反応

第二級エポキシアルコール **30** が合成できたので、第一章で述べた新手法を用いてメチル化を試みた。まず **30** のメチル化を Gilman 試薬(5 当量)のみで行った。粗生成物の ^{1}H-NMR から、1,3-ジオールと 1,2-ジオールの生成比はほぼ 1:1 であることが確認された。1,2-ジオールを除くため粗生成物を $NaIO_4$ で処理したところ 1,3-ジオール **31** が 2 段階収率 39%で得られた。次に TMSCl を添加する条件でして反応を試みた。Gilman 試薬と TMSCl をそれぞれ 5 当量用いメチル化を行ったところ、望む 1,3-ジオール **31** を 2 段階収率 71%で得た(**Scheme 21**)。



Scheme 21

先の検討結果からエポキシアルコール **30** の水酸基を TMS で保護した **32** を合成しこれにメチル化を行った(**Scheme 22**)。Gilman 試薬を 5 当量用い-20℃でメチル化を行ったところ、1,3 ジオール **31** を 3 段階収率 83%で得た。なおメチル化の粗生成物の ^{1}H-NMR から、この反応はほぼ完全な位置選択性で進行していたことがわかった。



Scheme 22

新たに構築した立体化学の確認[73]のために、得られた1,3-ジオール**31**をアセトニドへ変換し^{13}C-NMRスペクトルを測定した。その結果、アセトニドの2つのメチル基のケミカルシフトが23.6、25.1 ppmであり、第四級炭素のケミカルシフトが100.1 ppmであった。このことから、**figure 21**に示した立体化学であることが確認された。

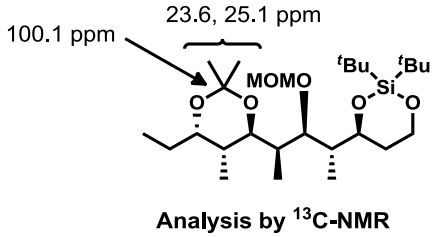
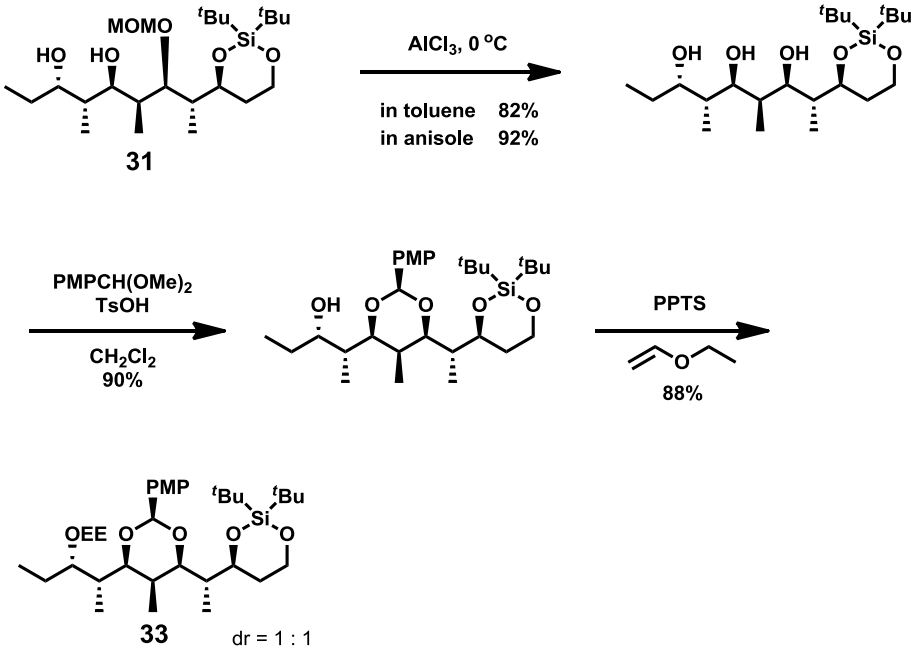


Figure 21. 水酸基の立体化学の決定

第七節　Segment C11-C21 の合成

ここまでの合成検討で、側鎖部の7連続不斉中心を、全て構築できた。残る変換は、segment C1-C10 とのメタセシス反応に必要な末端アルケンの導入である。その前に MOM 基をあらかじめ別の保護基に変換することにした。それは全合成の最終段階での MOM 基の脱保護は困難が予想されるからである。ジオール **31** を toluene 溶媒中 $AlCl_3$ で処理[74,75] したところ、MOM 基が選択的に脱保護され 82%の収率でトリオールを得ることができた(**Scheme 23**)。さらに溶媒として anisole を用いて行うと、収率は 92%まで向上した。得られたトリオールに対し、*p*-メトキシベンジリデンへ保護基の架け替えを行った。残る C19 位の水酸基は EE 基で保護し **33** へ導いた。



Scheme 23

ベンジリデンの立体構造は ^{1}H-NMR のカップリング定数と NOESY から決定した(**Figure 22**)。

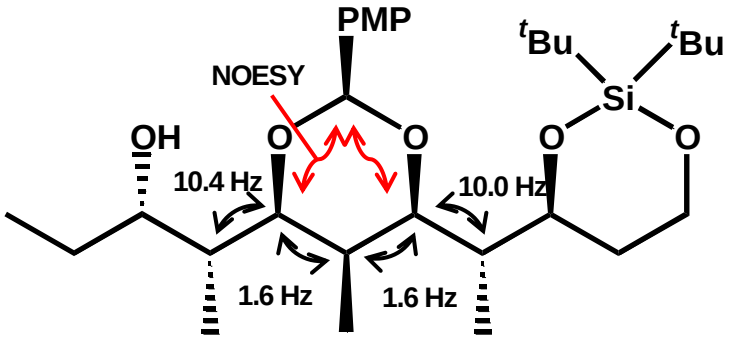
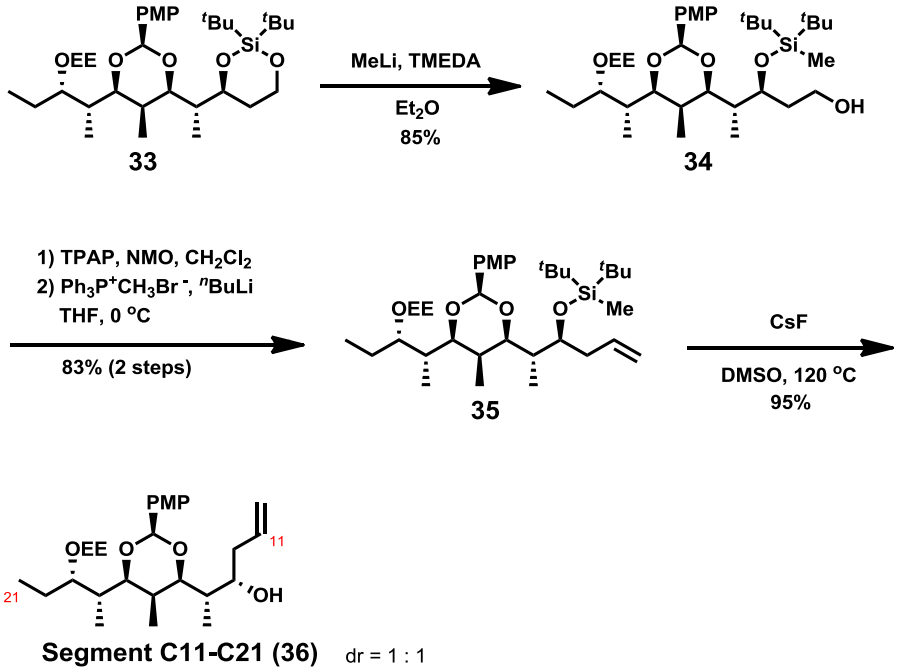


Figure 22.　ベンジリデンの立体構造

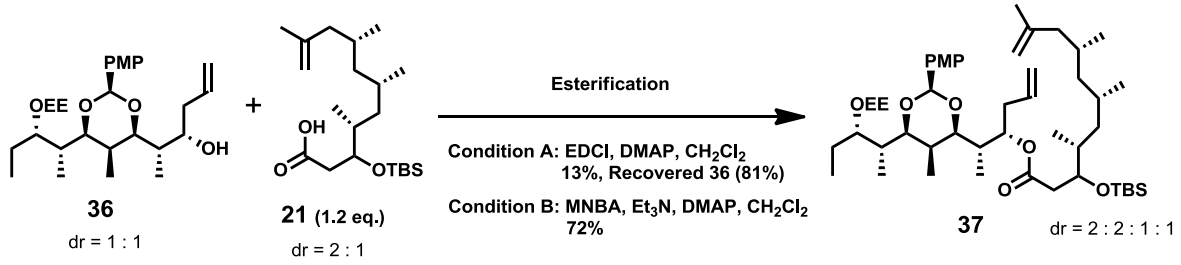
次に予備実験で検討した条件でシリレンの位置選択的開裂反応を行った。化合物 **33** に MeLi とTMEDAをそれぞれ5当量用い室温にて反応を行ったところ、第一級アルコール **34** が高収率で得られた。次に、第一級水酸基をLey酸化[76] に付し、さらに得られたアルデヒドにWittig反応を行うことで末端オレフィン **35** を合成した。最後に **35** の脱シリル化を、DMSO 中 120℃において10当量のCsFを用いて行った。反応は38時間かかったがシリル基が除去され、収率95%でsegment C11-C21 (**36**)を得ることができた(**Scheme 24**)。



Scheme 24

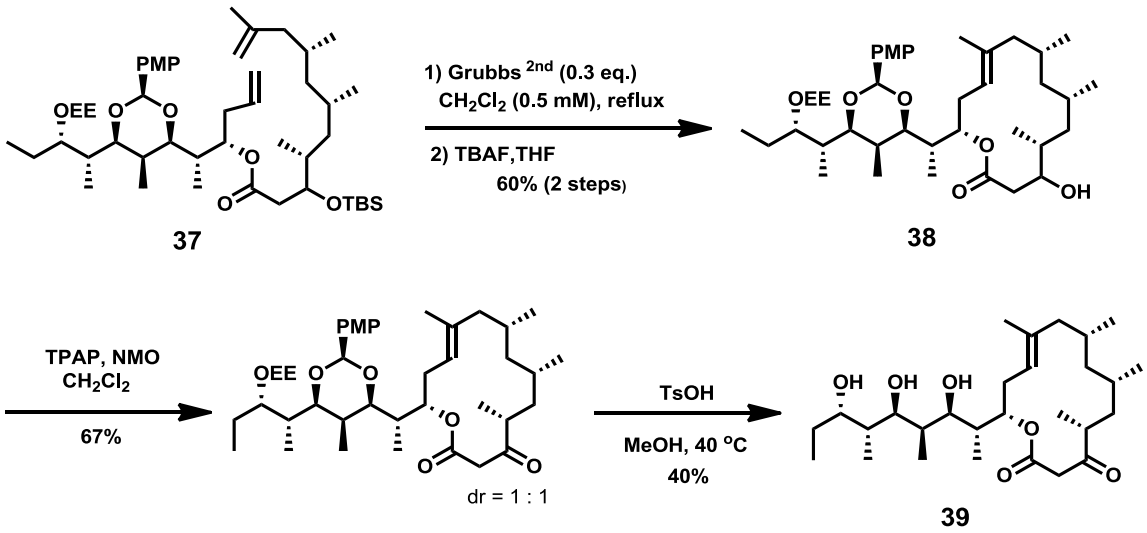
第八節　Sekothrixide の提唱構造体の合成

Segment C1-10 (**21**)と segment C11-C21 (**36**)が合成できたので、これらの連結を以下のように行った。**36** に対して 1.2 当量の **21** を用い EDCI でエステル化を行ったところ、ジエン **37** の収率は 13%であり、**36** が 81%回収された(**Scheme 25**)。そこで、椎名試薬(MNBA)、Et_3N、DMAP を用いてエステル化[77] を行ったところ、72%の収率でジエン **37** が得られた。



Scheme 25

第二世代 Grubbs 触媒を 0.3 当量用い、CH_2Cl_2 溶液中 0.5 mM の濃度で加熱還流しジエン **37** の閉環メタセシス反応を行った。原料の消失を TLC 上にて確認した後、ショートパッドシリカゲルカラムクロマトグラフィーで Grubbs 触媒を除いた。得られた環化体をそのまま TBS 基の脱保護に付して **38** を得た。**38** に Ley 酸化を行いβケトエステルとした後、酸性条件下アセタール類の脱保護から sekothrixide の提唱構造体である **39** を得ることができた(**Scheme 26**)。



Scheme 26

これにより目標とする **39** の合成が完成したので天然物[22,23]と比較した。しかしながら両者は一致しなかった(**Table 10**, **Figure 23**, **24**)。

Table 10. 化合物 **39** の NMR スペクトルデータ

^{1}H-NMR (400 MHz, $CDCl_3$)	**^{13}C-NMR** (100 MHz, $CDCl_3$)
5.19 (m, 1H)	205.1
5.08 (t, *J* = 6.0 Hz, 1H)	166.0
4.03 (brs, 1H)	137.5
3.84 (d, *J* = 9.6 Hz, 1H)	120.4
3.75-3.69 (m, 1H)	79.6
3.67-3.63 (m, 1H)	79.4
3.49 (d, *J* = 12.4 Hz, 1H)	77.3
3.40 (d, *J* = 12.4 Hz, 1H)	76.4
3.33 (brs, 1H)	47.6
2.72 (m, 1H)	47.2
2.46 (d, *J* = 5.6 Hz, 1H)	45.3
2.39 (m, 1H)	43.4
2.26 (m, 1H)	40.1
2.15-2.04 (m, 2H)	39.8
1.93-1.77 (m, 2H)	39.6
1.75-1.65 (m, 3H)	35.2
1.63 (s, 3H)	29.3
1.60-1.30 (m, 4H)	28.7
1.09 (d, *J* = 7.6 Hz, 3H)	26.8
1.06-0.95 (m, 1H)	25.1
1.01 (t, *J* = 7.2 Hz, 3H)	23.5
0.908 (d, *J* = 7.6 Hz, 3H)	21.0
0.900 (d, *J* = 6.4 Hz, 3H)	18.0
0.86 (d, *J* = 6.4 Hz, 6H)	17.6
0.78 (d, *J* = 6.8 Hz, 3H)	12.1
0.72 (m, 1H)	11.2
	11.1
	4.0

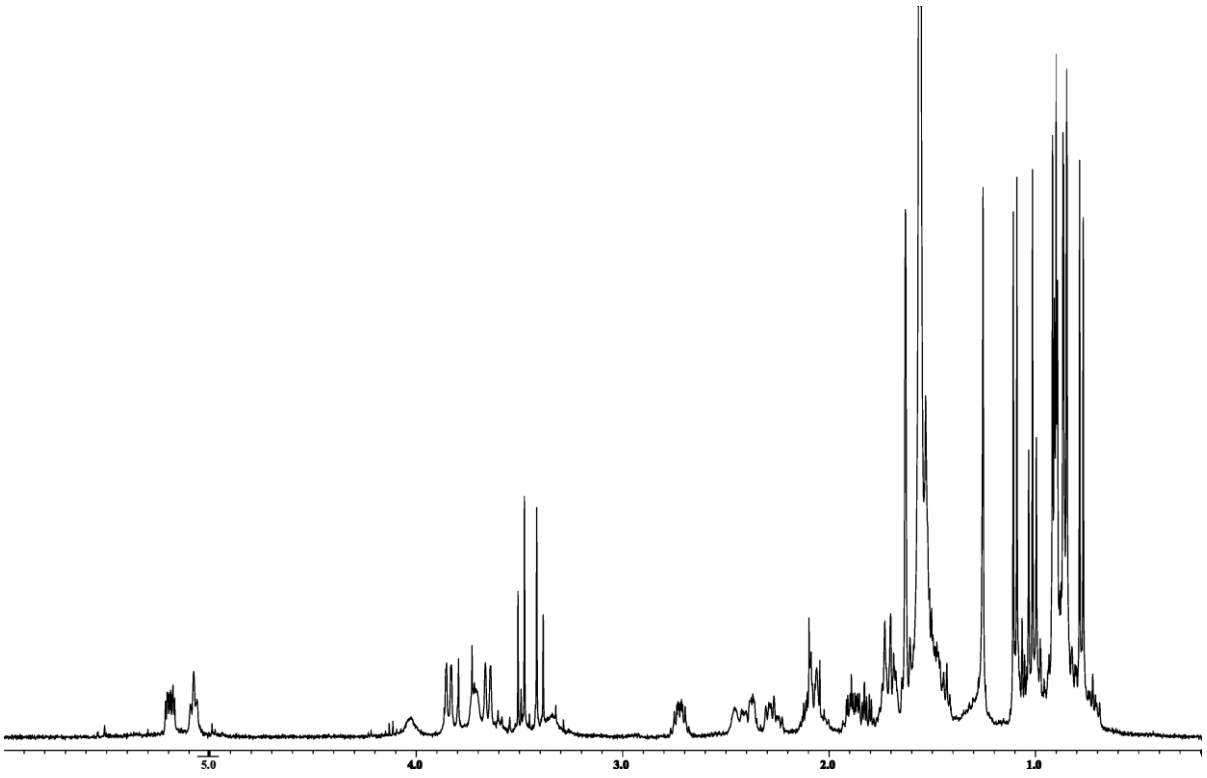


Figure 23. 化合物 **39** の ^{1}H-NMR

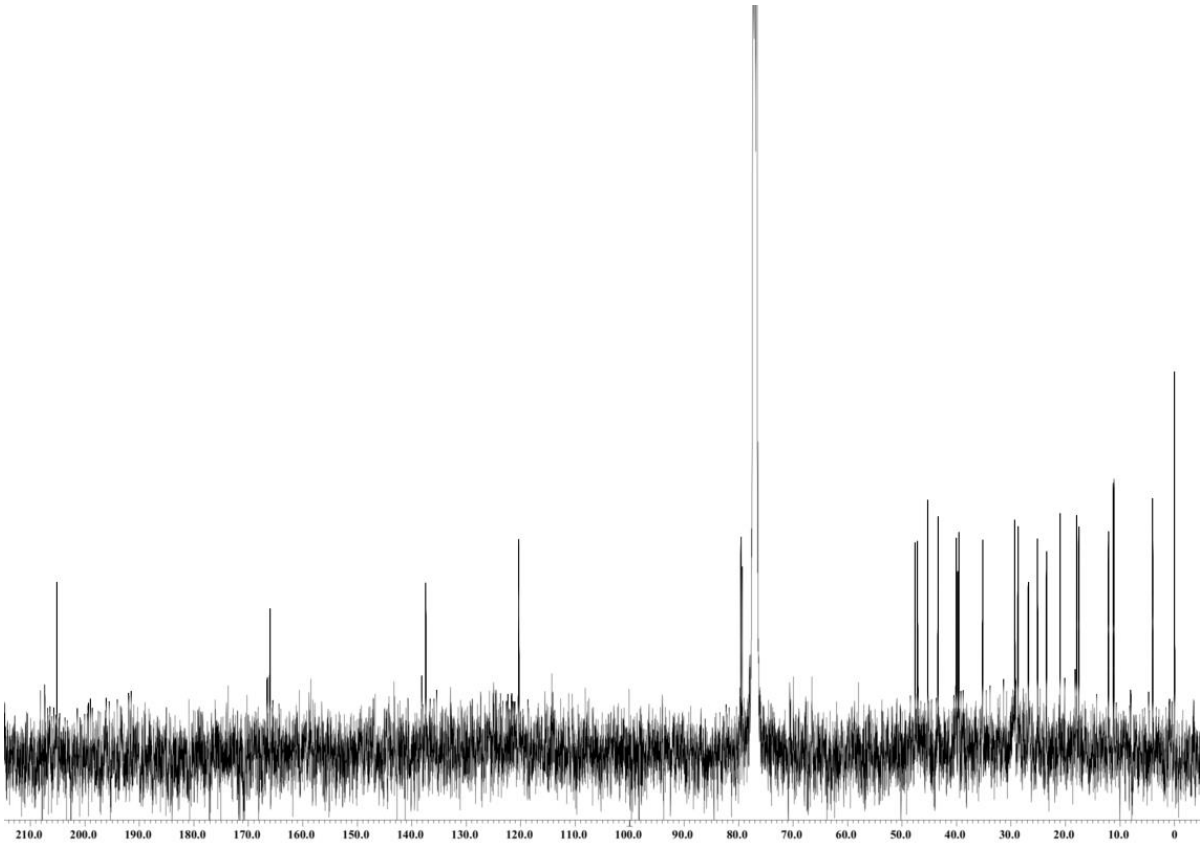
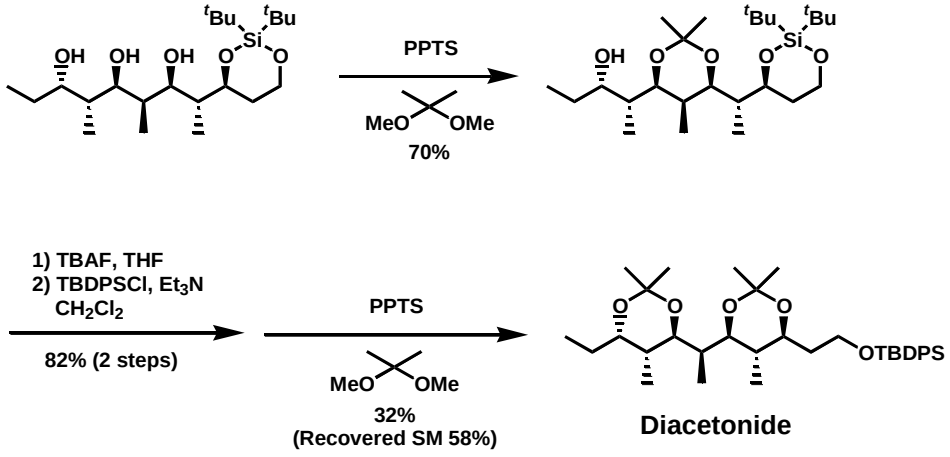


Figure 24. 化合物 **39** の ^{13}C-NMR

著者が行った合成研究において不斉中心を構築するたびに立体化学を確実に決定してきた。ゆえに合成した **39** と天然物の不一致は瀬戸らが提唱した構造に誤りがあることを示唆する。そこで提唱構造の誤っている箇所を絞るため **scheme 23** のトリオール体を **scheme 1** に示したジアセトニド体へ導き両者を比較することにした。

合成したトリオールを位置選択的アセトニド保護した後、三工程でジアセトニド体へ変換した（**Scheme 27**）。そのジアセトニド体と sekothrixide から誘導されたジアセトニド体を比較したところ NMR スペクトルデータは一致した(**Table 11**, **12**, **Figure 25**, **26**)。したがって、提唱構造体の C13 位から C19 位の相対配置は正しく、誤りはラクトン上に存在するメチル基のいずれかにあることがあきらかとなった。



Scheme 27

Table 11. 両ジアセトニド体の比較 (^{1}H-NMR)

^{1}H-NMR (400 MHz, C_6D_6) δ(ppm) Diacetonide from triol	**^{1}H-NMR** (500 MHz, C_6D_6) δ(ppm) Literature data [23]
7.86-7.77 (m, 4H)	7.82 (2H)
	7.82 (2H)
7.28-7.21 (m, 6H)	7.17 (2H)
	7.17 (2H)
	7.16 (2H)
4.06 (td, J= 9.6, 5.2 Hz, 1H)	4.06 (1H)
3.88 (dq, J= 10.0, 4.0 Hz, 1H)	3.89 (1H)
3.81-3.74 (m, 3H)	3.79 (1H)
	3.79 (1H)
	3.79 (1H)
3.50 (t, J= 6.4 Hz, 1H)	3.50 (1H)
2.01-1.85 (m, 3H)	1.97 (1H)
	1.91 (1H)
	1.90 (1H)
1.66-1.51 (m, 3H)	1.58 (1H)
	1.58 (1H)
	1.57 (1H)
1.48 (s, 3H)	1.47 (3H)
1.44 (s, 3H)	1.44 (3H)
1.40 (s, 3H)	1.40 (3H)
1.38 (s, 3H)	1.38 (3H)
1.34-1.23 (m, 1H)	1.32 (1H)
1.21 (d, J= 5.6 Hz, 3H)	1.20 (3H)
1.20 (s, 9H)	1.20 (9H)
0.99 (d, J= 7.2 Hz, 3H)	0.99 (3H)
0.98 (t, J= 7.2 Hz, 1H)	0.98 (1H)
0.62 (d, J= 6.4 Hz, 3H)	0.63 (3H)

Table 12. 両ジアセトニド体の比較 (^{13}C-NMR)

^{13}C-NMR (100 MHz, C_6D_6) δ(ppm) Diacetonide from triol	**^{13}C-NMR** (125 MHz, C_6D_6) δ(ppm) Literature data [23]
136.0 (8C)	135.7 (2C)
	135.7 (2C)
	135.7 (2C)
	135.7 (2C)
134.4 (2C)	134.4 (2C)
130.0 (2C)	129.9 (2C)
100.2	100.3
97.8	97.7
77.0	77.0
73.5	73.5
71.1	71.2
71.0	71.0
60.3	60.3
39.7	39.7
37.3	37.2
36.9	37.0
35.6	35.6
30.5	30.5
27.1 (3C)	27.1 (3C)
26.2	26.1
24.2	24.1
23.9	23.8
19.9	19.8
19.5	19.4
13.1	13.0
12.3	12.3
10.9	10.8
10.2	10.1

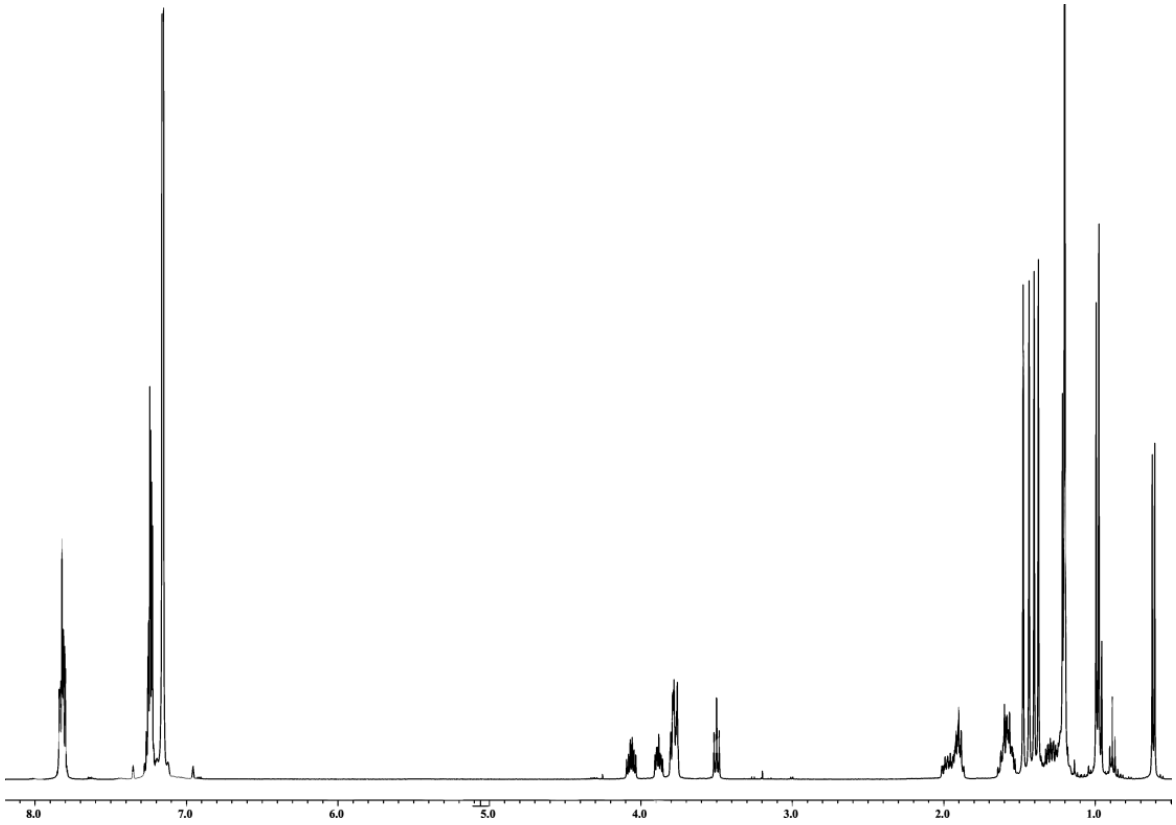


Figure 25. トリオールから導いたジアセトニド体の ^{1}H-NMR

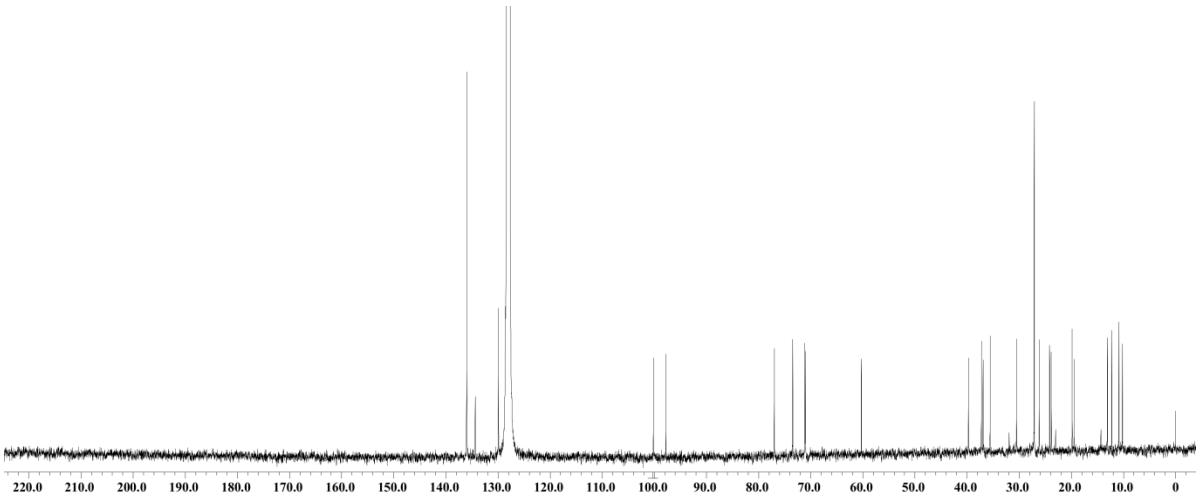
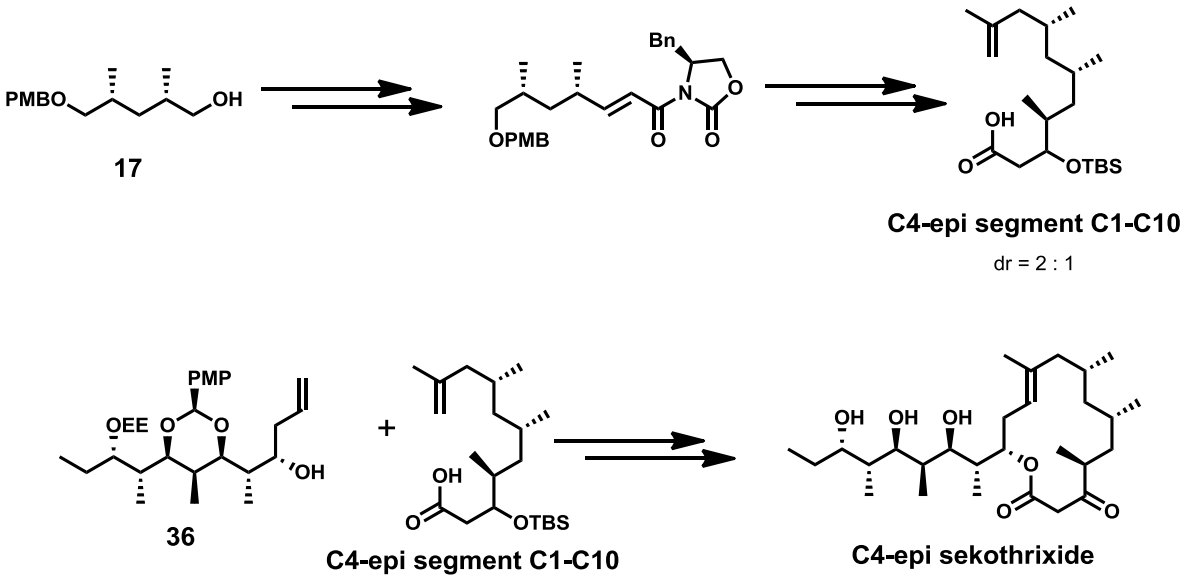


Figure 26. トリオールから導いたジアセトニド体の ^{13}C-NMR

第九節　Sekothrixide の全合成および構造修正

これまでの結果より sekothrixide の提唱構造と天然物の違いは、ラクトン環上の C4,6,8 位の 3 つのメチル基の立体配置によるものであることが示唆された。ところで、C4 位のメチル基はケトンのα位に位置するためエピ化の可能性がある。そこで合成途中でエピ化が起こっていないことを確認するため、C4 位の立体化学を反転させた C4-epi sekothrixide へと導き比較した(**Scheme 28**)。



Scheme 28

C4-epi sekothrixide の NMR スペクトルデータを天然物と比較したが、この場合も両者は一致しなかった(**Figure 27, 28**)。化合物 **39** と C4-epi sekothrixide が異なる NMR スペクトルデータであったことから、合成途中で C4 位のエピ化は起こっていない。

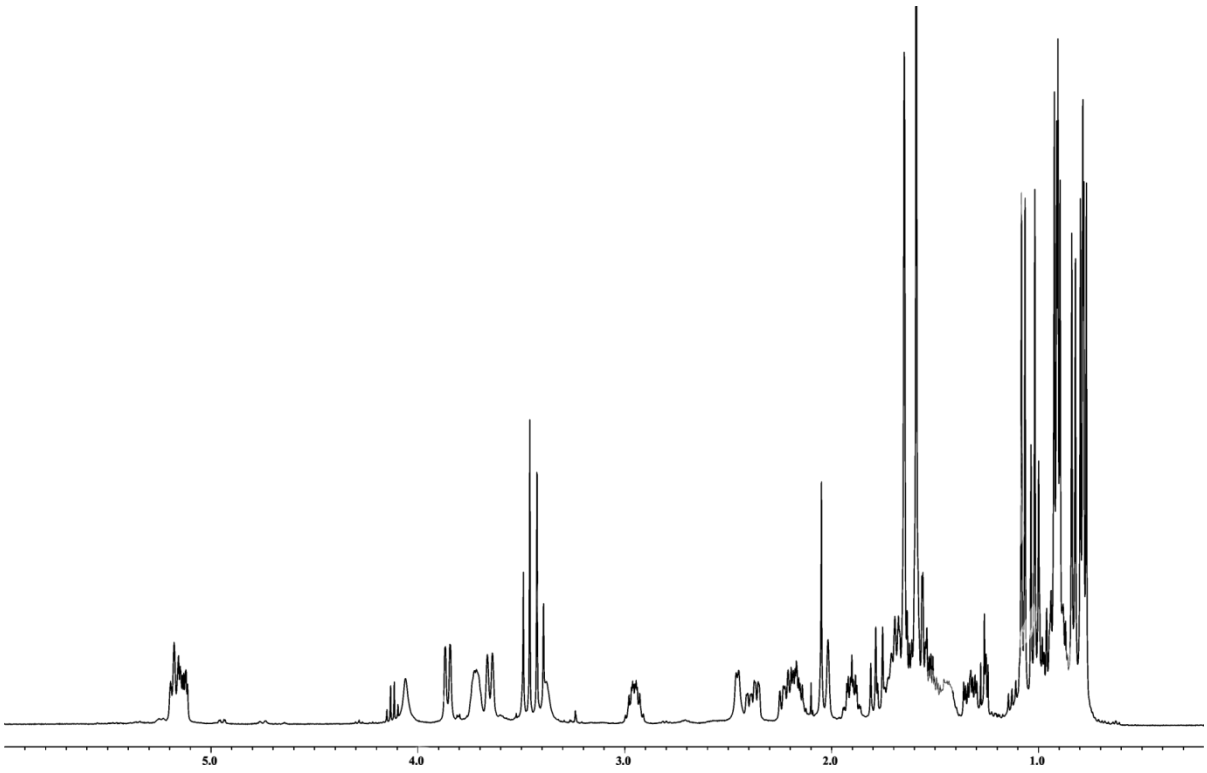


Figure 27. C4-epi sekothrixide の ^{1}H-NMR

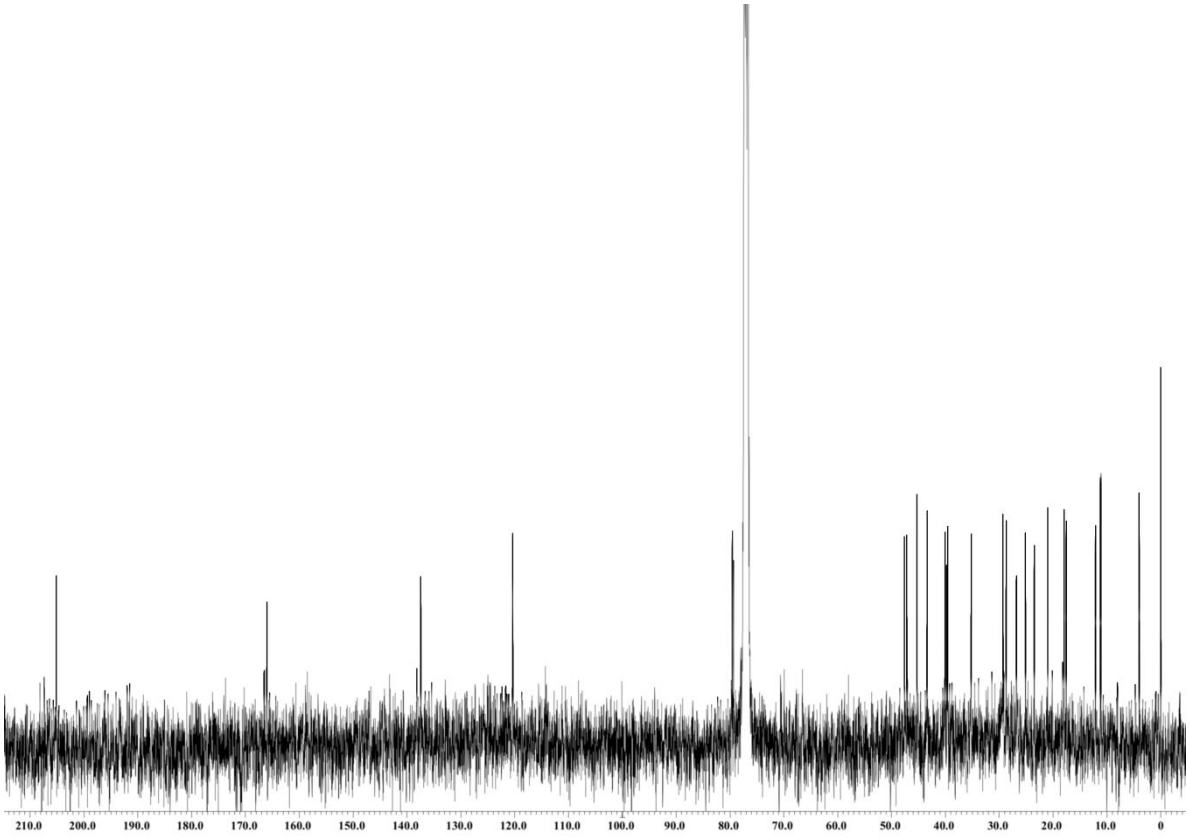
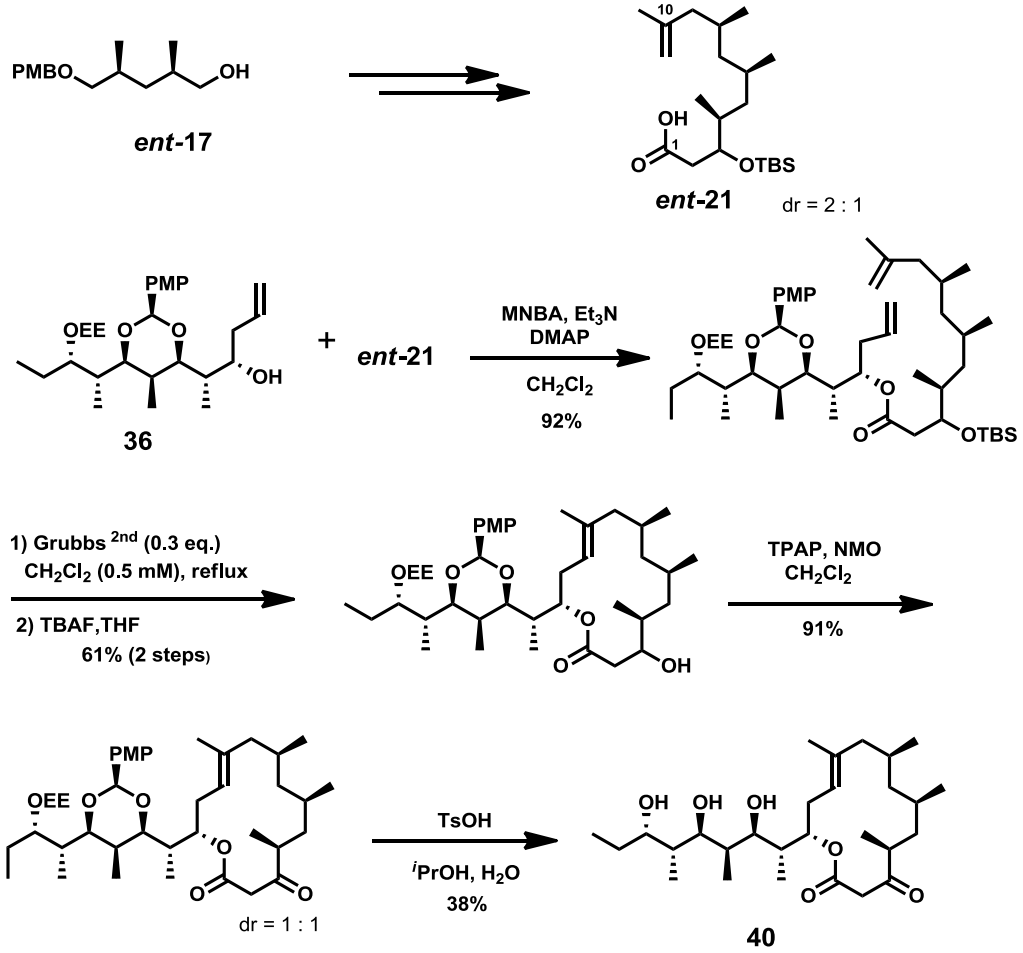


Figure 28. C4-epi sekothrixide の ^{13}C-NMR

ここで著者は天然物の真の構造は、segment C1-C10 のエナンチオマーから誘導された化合物ではないかと推測した。それは、sekothrixide の提唱構造は計算によって導かれたものであるが、天然物の立体化学と大きく異なる結果を出力したとは考えにくい。よって化合物 **40** の合成を試みた(**Scheme 29**)。

その合成はアルコール **17** のエナンチオマーから、これまでの手法を用いて *ent*-**21** を合成し、化合物 **36** とカップリングを行いうものである。得られた化合物 **40** の ^{1}H-NMR および ^{13}C-NMR は天然品のものと非常に良い一致を示した(**Table 13**, **14**, **Figure 29**, **30**)。また **40** の比旋光度は -46.4 (c = 0.18, MeOH)で、天然物($[\alpha]_D$ = -45.1 (c = 1.00, MeOH))と符号も含め良く一致した。以上のことから化合物 **40** が真の sekothrixide の構造であり、その絶対配置も決定できた。



Scheme 29

Table 13. 化合物 **40** と天然物との比較（^{1}H-NMR）

^{1}H-NMR (400 MHz, $CDCl_3$) δ(ppm) Compound **40**	**^{1}H-NMR** (500 MHz, $CDCl_3$) δ(ppm) Natural product [22,23]
5.27 (m, 1H)	5.25 (d, *J*= 11 Hz, 1H)
5.05 (m, 1H)	5.04 (dd, *J*= 7 Hz, 1H m, 1H)
4.04 (brs, 1H, OH)	
3.85 (d, *J*= 9.6 Hz, 1H)	3.84 (d, *J*= 10 Hz, 1H)
3.73 (m, 1H)	3.72 (brs, 1H)
3.63 (d, *J*= 9.6 Hz, 1H)	3.62 (d, *J*= 10 Hz, 1H)
3.54 (d, *J*= 13.6 Hz, 1H)	3.50 (d, *J*= 13 Hz, 1H)
3.45 (brs, 1H, OH)	
3.30 (d, *J*= 13.6 Hz, 1H)	3.29 (d, *J*= 13 Hz, 1H)
2.92 (m, 1H)	2.91 (m, 1H)
2.43 (d, *J*= 5.6 Hz, 1H, OH)	
2.36 (ddd, *J*= 14.4, 10.8, 9.2 Hz, 1H)	2.33 (m, 1H)
2.16 (m, 1H)	2.15 (brd, *J*= 13 Hz, 1H)
2.11-1.98 (m, 2H)	2.03 (m, 1H)
	2.00 (dd, *J*= 13, 6 Hz, 1H)
1.95-1.85 (m, 2H)	1.88 (m, 1H)
	1.88 (m, 1H)
1.74-1.45 (m, 5H)	1.69 (dd, *J*= 13, 6 Hz, 1H)
	1.67 (m, 1H)
	1.61 (m, 1H)
	1.55 (m, 1H)
	1.53 (m, 2H)
1.59 (s, 3H)	1.58 (s, 3H)
1.31 (ddd, *J*= 11.2, 6.4, 4.8 Hz, 1H)	1.30 (ddd, *J*= 7 Hz, 1H)
1.12 (d, *J*= 8.4 Hz, 3H)	1.10 (d, *J*= 7 Hz, 3H)
1.02 (t, *J*= 7.2 Hz, 3H)	1.00 (t, *J*= 7.5 Hz, 3H)
0.96 (m, 1H)	0.94 (m, 1H)
0.91 (d, *J*= 6.8 Hz, 3H)	0.90 (d, *J*= 7.5 Hz, 3H)
0.90 (d, *J*= 6.0 Hz, 3H)	0.89 (d, *J*= 6.0 Hz, 3H)
0.89 (d, *J*= 6.4 Hz, 3H)	0.88 (d, *J*= 7.5 Hz, 3H)
0.85 (d, *J*= 7.6 Hz, 3H)	0.83 (d, *J*= 7.5 Hz, 3H)
0.78 (d, *J*= 7.2 Hz, 3H)	0.77 (d, *J*= 7.5 Hz, 3H)
0.52 (ddd, *J*= 14.8, 8.0, 6.8 Hz, 1H)	0.51 (ddd, *J*= 7 Hz, 1H)

Table 14. 化合物 **40** と天然物との比較（^{13}C-NMR）

^{13}C-NMR (100 MHz, $CDCl_3$) δ(ppm) Compound **40**	**^{13}C-NMR** (125 MHz, $CDCl_3$) δ(ppm) Natural product [22,23]
205.7	205.6
167.0	167.0
137.3	137.3
121.6	121.6
79.6	79.6
79.1	79.1
77.1	77.0
76.5	76.5
49.03	49.0
49.01	49.0
41.6	41.5
41.4	41.4
39.83	39.8
39.78	39.8
39.34	39.3
35.2	35.2
29.8	29.8
28.1	28.2
27.1	27.1
25.1	25.1
23.3	23.3
21.1	21.1
19.3	19.3
16.7	16.6
12.1	12.0
11.1	11.1
10.8	10.8
3.9	3.9

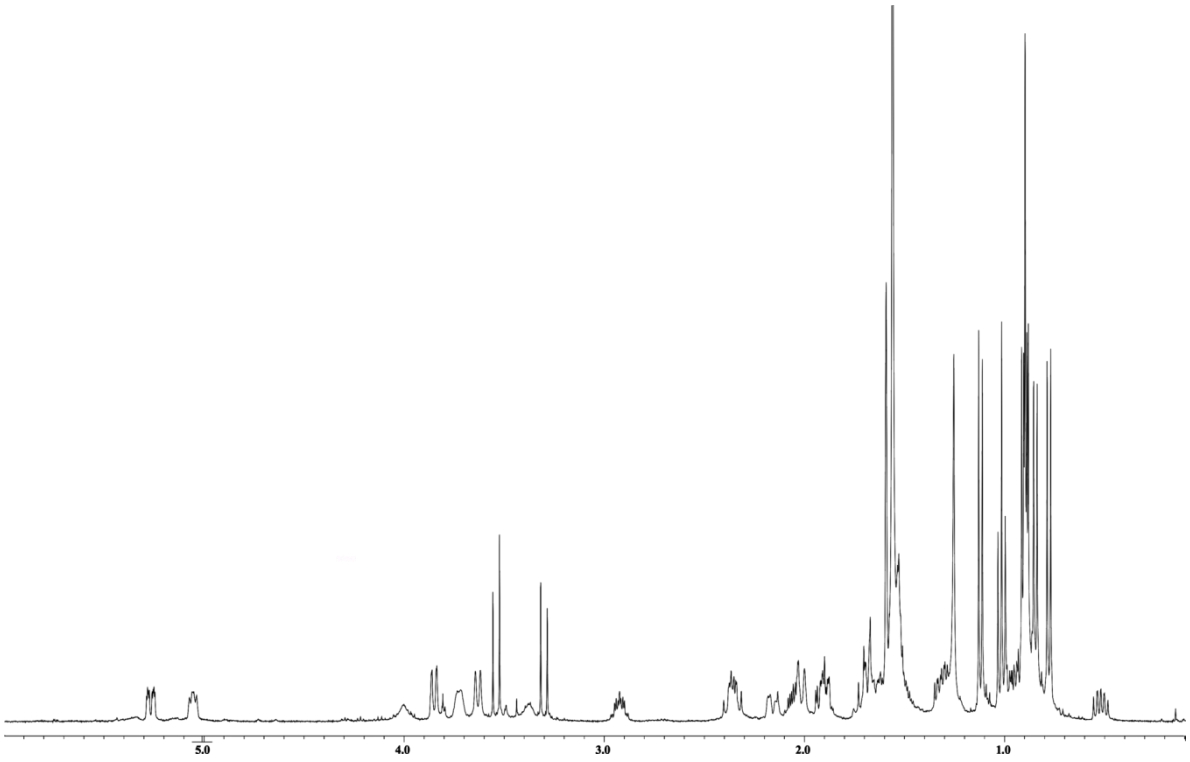


Figure 29. 化合物 **40** の ^{1}H-NMR

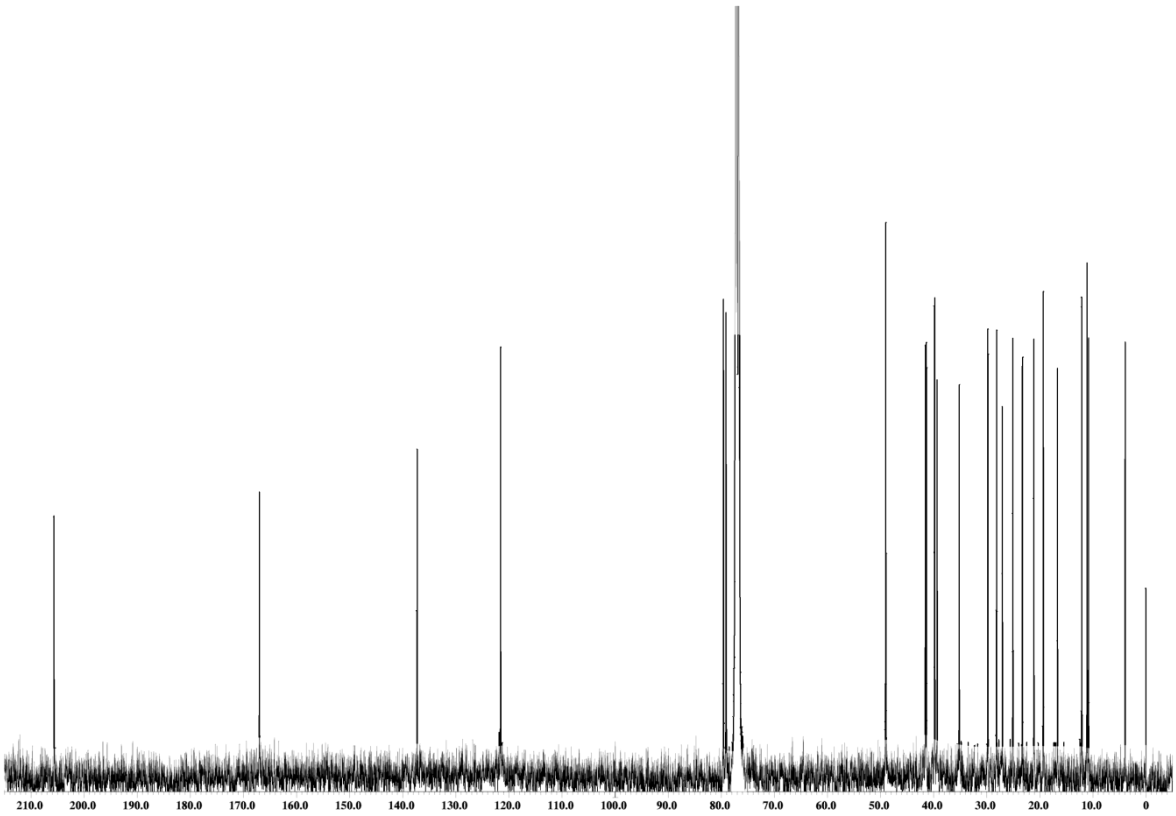


Figure 30. 化合物 **40** の ^{13}C-NMR

結論

今回著者は、第二級エポキシアルコールに対する各種 Gilman 試薬の求核置換反応に関して、主に位置選択性の観点から検討を行った。その結果、エポキシドと水酸基が *anti* 配置の基質では、1,2－ジオールの生成が優先するが、水酸基を TMS 基で保護した後に Gilman 試薬による反応を行うと、位置選択性が逆転し、1,3 ジオール体が主生成物として得られることを見出した。

また本反応および大環状閉環メタセシス反応を鍵反応として、sekothrixide の世界初の全合成を達成しその絶対配置も決定した。

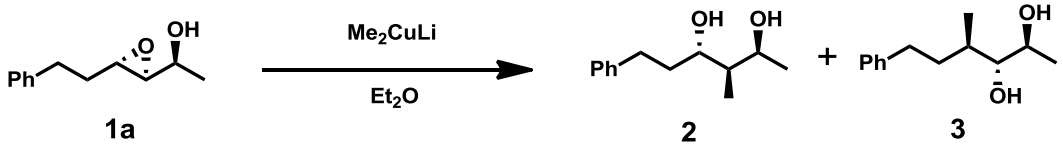
実験項

All reactions were monitored by thin-layer chromatography using MERCK TLC Silica gel 60 F_{254} and were visualized by UV light (254 nm) and/or stained in 12 molybdo (VI) phosphoric acid or H_2SO_4 in MeOH solutions. Column chromatography was performed using Silica Gel 60 N (spherical, neutral, 63-210 μm) or Silica Gel 60 N (spherical, neutral, 40-50 μm, for flash column chromatography) purchased from KANTO CHEMICAL.

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL ECX 400 spectrometer. Chemical shifts were reported in ppm on δ scale. ^{1}H and ^{13}C chemical shifts are referenced to internal solvent resonances ($CHCl_3$ ^{1}H, δ = 7.26 ppm; $CDCl_3$ ^{13}C, δ = 77.0 ppm) and reported relative to Me_4Si (δ = 0.00 ppm). The multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad signal). Coupling constants, *J*, were reported in Hertz. MS spectra were measured on a JEOL JMS-GCmate II or JEOL JMS-700 MStation instruments. Infrared spectra were recorded on a SHIMADZU IRPrestige-21 spectrophotometer. Optical rotations were measured on a Jasco P-2200 polarimeter at a ϕ3.5 mm x 100 mm path-length cell at 589 nm. All concentrations are in g/100 mL.

1. 第二級エポキシアルコール類の求核置換反応開発

Methylation of Epoxy Alcohol **1a** (**Table 2, Entry 1**)

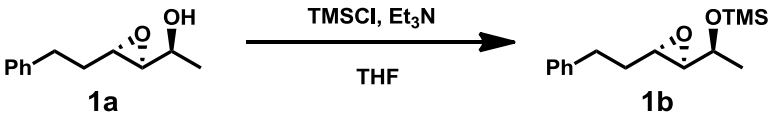


1a **2** **3**

To a suspension of CuI (457 mg, 2.40 mmol) in dry Et_2O (5 mL, dried by distillation from sodium and benzophenone) was added MeLi (4.37 mL, 1.1 M in Et_2O, 4.37 mmol) at -30 °C under Ar atmosphere. The solution was stirred at same temperature for 10 min. The solution of organocopper complex was added the epoxy alcohol **1a** (92.3 mg, 0.480 mmol) in dry Et_2O (5 mL, dried by distillation from sodium and benzophenone) by gastight syringe. The reaction mixture was stirred at 0 °C for 23 h, it was quenched with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The suspension was allowed to stir room temperature under air and then the aqueous phase was turned to bright blue. The reaction mixture was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give mixture of the 1,3-diol **2** and 1,2-diol **3** (75.0 mg, 0.360 mmol, 75%). The ratio of 1,3-diol **2** and 1,2-diol **3** was 1:3.

^{1}H-NMR of 1,3-diol **2** (400 MHz, $CDCl_3$): δ 7.31-7.26 (m, 2H), 7.22-7.17 (m, 3H), 4.17 (dq, J = 6.4, 2.4 Hz, 1H), 3.69 (q, J = 6.4 Hz, 1H), 2.89-2.82 (m, 1H), 2.71-2.64 (m, 1H), 1.88-1.81 (m, 2H), 1.66-1.61 (m, 1H), 1.18 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 7.2 Hz, 3H); **^{13}C-NMR** of 1,3-diol **2** (100 MHz, $CDCl_3$): δ 142.3, 128.60 (2C), 128.57 (2C), 126.0, 75.1, 69.4, 42.7, 37.5, 32.2, 19.8, 11.9; **^{1}H-NMR** of 1,2-diol **3** (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 2H), 7.21-7.15 (m, 3H), 3.91 (dq, J = 6.4, 3.6 Hz, 1H), 3.39 (dd, J = 8.0, 3.6 Hz, 1H), 2.81-2.71 (m, 1H), 2.59-2.49 (m, 1H), 2.11-2.00 (m, 1H), 1.62-1.40 (m, 2H), 1.14 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H); **^{13}C-NMR** of 1,2-diol **3** (100 MHz, $CDCl_3$): δ 142.9, 128.51 (2C), 128.48 (2C), 125.8, 78.8, 68.5, 35.3, 34.8, 33.1, 16.1, 15.5; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3402, 2970, 2931, 987, 756; **HRMS** (EI) *m/z* calculated for $C_{13}H_{20}O_2$ $[M]^{+\cdot}$ 208.1463, found 208.1441.

Synthesis of Epoxy Silyl Ether **1b**

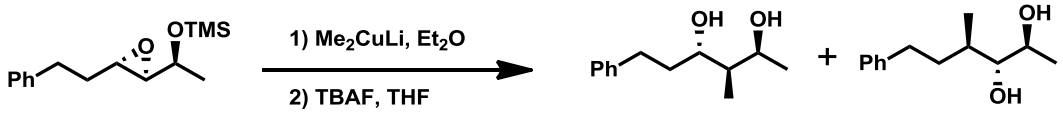


1a **1b**

To a solution of epoxy alcohol **1a** (178 mg, 0.930 mmol) in dry THF (2 mL) was added Et_3N (1.03 mL, 7.18 mmol) and TMSCl (0.78 mL, 4.63 mmol). The solution was stirred at room temperature under Ar atmosphere for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0°C. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 15:1) to give the epoxy silyl ether **1b** (208 mg, 0.790 mmol, 85 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2H), 7.21-7.17 (m, 3H), 3.64-3.58 (m, 1H), 2.89 (ddd, J = 6.4, 5.2, 2.0 Hz, 1H), 2.84-2.69 (m, 2H), 2.66 (dd, J = 5.2, 2.0 Hz, 1H), 1.94-1.80 (m, 2H), 1.20 (d, J = 6.4 Hz, 3H), 0.10 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.4, 128.6 (2C), 128.5 (2C), 126.2, 68.1, 62.2, 56.7, 33.7, 32.4, 21.0, 0.31 (3C); **IR** ν_{max} (thin film/NaCl) cm^{-1}: 2962, 1250, 1095, 903, 840; **HRMS** (EI) *m/z* calculated for $C_{15}H_{24}O_2Si$ $[M]^{+\cdot}$ 264.1546, found 264.1569.

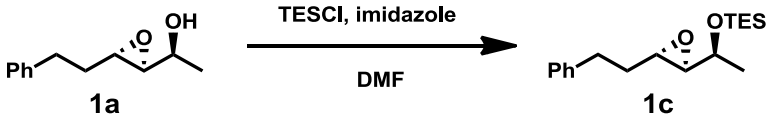
Methylation of Epoxy Silyl Ether **1b (Table 2, Entry 3)**



1b **2** **3**

Methylation of epoxy silyl ether **1b** was the same method as the case of **1a**. The crude residue was treated with TBAF (5 eq.). The deprotected compounds were purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give mixture of the 1,3-diol **2** and 1,2-diol **3** (81% yield, 2 steps). The ratio of 1,3-diol **2** and 1,2-diol **3** was 3:1.

Synthesis of Epoxy Silyl Ether **1c**

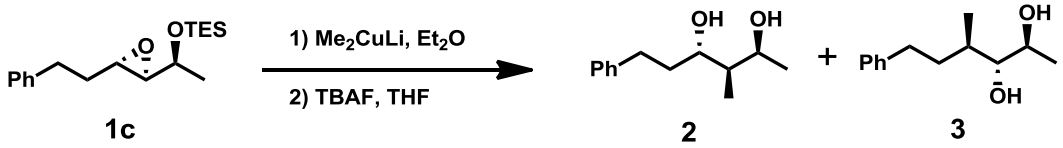


1a **1c**

To a solution of epoxy alcohol **1a** (116 mg, 0.600 mmol) in dry DMF (3 mL) was added imidazole (164 mg, 2.41 mmol) and TESCl (202 μL, 1.20 mmol). The solution was stirred at room temperature under Ar atmosphere for 22 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0°C. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 10:1) to give the epoxy silyl ether **1c** (157 mg, 0.510 mmol, 85 %).

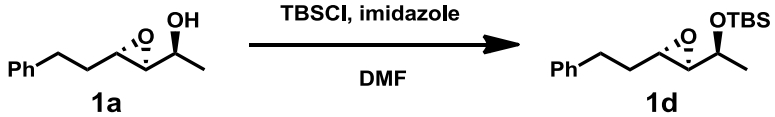
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2H), 7.21-7.16 (m, 3H), 3.62 (dt, J = 11.6, 6.4 Hz, 1H), 2.90 (ddd, J = 6.8, 5.2, 2.4 Hz, 1H), 2.84-2.68 (m, 2H), 2.66 (dd, J = 5.2, 2.4 Hz, 1H), 1.96-1.77 (m, 2H), 1.21 (d, J = 6.4 Hz, 3H), 0.94 (t, J = 8.0 Hz, 9H), 0.57 (q, J = 8.0 Hz, 6H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.4, 128.6 (2C), 128.5 (2C), 126.1, 68.0, 62.3, 56.7, 33.8, 32.4, 21.1, 6.9 (3C), 5.0 (3C); **IR** ν_{max} (thin film/NaCl) cm^{-1}: 2954, 2877, 1584, 1103, 1010, 740; **HRMS** (EI) *m/z* calculated for $C_{16}H_{25}O_2Si$ $[M-C_2H_5]^{+\cdot}$ 277.1624, found 277.1630.

Methylation of Epoxy Silyl Ether **1c** (**Table 3, Entry 1**)



Methylation of epoxy silyl ether **1c** was the same method as the case of **1a**. The crude residue was treated with TBAF (5 eq.). The deprotected compounds were purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give mixture of the 1,3-diol **2** and 1,2-diol **3** (73% yield, 2 steps). The ratio of 1,3-diol **2** and 1,2-diol **3** was 1.6:1.

Synthesis of Epoxy Silyl Ether **1d**

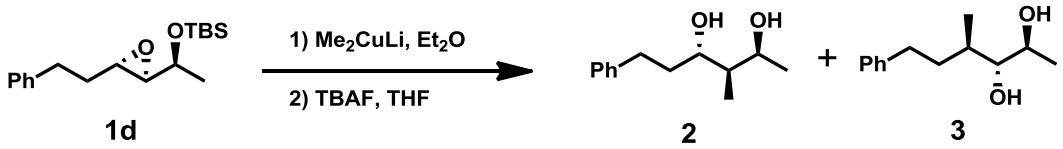


To a solution of epoxy alcohol **1a** (82.9 mg, 0.430 mmol) in dry DMF (3 mL) was added imidazole (148 mg, 2.16 mmol) and TBSCl (191 mg, 1.29 mmol). The solution was

stirred at room temperature under Ar atmosphere for 23 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0°C. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 10:1) to give the epoxy silyl ether **1d** (132 mg, 0.430 mmol, 100 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2H), 7.21-7.17 (m, 3H), 3.67 (m, 1H), 2.91 (dt, J = 6.4, 2.4 Hz, 1H), 2.84-2.68 (m, 2H), 2.65 (dd, J = 4.8, 2.4 Hz, 1H), 1.93-1.79 (m, 2H), 1.18 (d, J = 6.4 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.4, 128.6 (2C), 128.5 (2C), 126.1, 67.9, 62.4, 56.2, 33.8, 32.4, 25.9 (3C), 21.0, 18.3, -4.5, -4.6; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 2931, 2862, 1249, 1103, 833; **HRMS** (EI) *m/z* calculated for $C_{14}H_{21}O_2Si$ $[M-C_4H_9]^{+\cdot}$ 249.1311, found 249.1290.

Methylation of Epoxy Silyl Ether **1d (Table 3, Entry 2)**



Methylation of epoxy silyl ether **1d** was the same method as the case of **1a**. The crude residue was treated with TBAF (5 eq.). The deprotected compounds were purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give mixture of the 1,3-diol **2** and 1,2-diol **3** (66% yield, 2 steps). The ratio of 1,3-diol **2** and 1,2-diol **3** was 1:1.

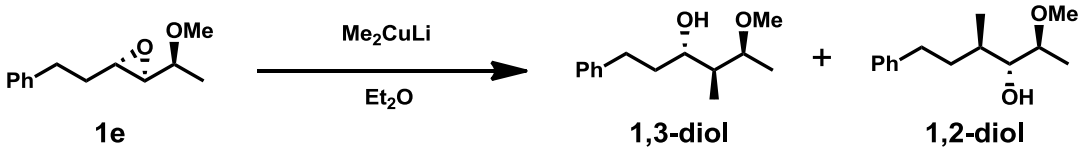
Synthesis of Epoxy Methyl Ether **1e**

To a suspension of epoxy alcohol **1a** (75.0 mg, 0.390 mmol) in dry THF (4 mL) was added NaH (20.3 mg, 60% in oil, 0.470 mmol) at 0 °C under Ar atmosphere. The suspension was stirred at room temperature for 30 min and it was added MeI (128 μL, 1.95 mmol). The reaction mixture was stirred at room temperature for 10 h and it was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with AcOEt.

The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 10:1) to give the epoxy methyl ether **1e** (76.3 mg, 0.370 mmol, 95 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.25 (m, 2H), 7.22-7.17 (m, 3H), 3.34 (s, 3H), 3.15 (dq, *J* = 6.4, 6.0 Hz, 1H), 2.95 (ddd, *J* = 6.8, 4.8, 2.4 Hz, 1H), 2.86-2.71 (m, 2H), 2.66 (dd, *J* = 6.4, 2.4 Hz, 1H), 1.99-1.80 (m, 2H), 1.20 (d, *J* = 6.0 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.3, 128.6 (2C), 128.5 (2C), 126.2, 76.5, 60.7, 57.2, 57.1, 56.9, 33.7, 32.3, 17.2; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 2932, 1450, 1095, 702; **HRMS** (EI) *m/z* calculated for $C_{13}H_{16}O$ $[M-H_2O]^{+\cdot}$ 188.1201, found 188.1214.

Methylation of Epoxy Methyl Ether **1e** (Table 3, Entry 3)



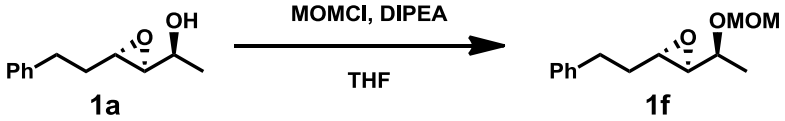
1e **1,3-diol** **1,2-diol**

To a suspension of CuI (332 mg, 1.74 mmol) in dry Et_2O (5 mL, dried by distillation from sodium and benzophenone) was added MeLi (3.1 mL, 1.13 M in Et_2O, 3.47 mmol) at -30 °C under Ar atmosphere. The solution was stirred at same temperature for 10 min. The solution of organocopper complex was added the epoxy methyl ether **1e** (71.6 mg, 0.347 mmol) in dry Et_2O (3 mL, dried by distillation from sodium and benzophenone) by gastight syringe. The reaction mixture was stirred at 0 °C for 4 h, it was quenched with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The suspension was allowed to stir room temperature under air and then the aqueous phase was turned to bright blue. The reaction mixture was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give mixture of the 1,3-diol and 1,2-diol (66.3 mg, 0.298 mmol, 86%). The ratio of 1,3-diol and 1,2-diol was 1:1.

^{1}H-NMR of 1,3-diol (400 MHz, $CDCl_3$): δ 7.31-7.15 (m, 5H), 3.90 (d, *J* = 3.6 Hz, 1H), 3.68-3.56 (m, 2H), 3.36 (s, 3H), 2.89 (ddd, *J* = 13.2, 10.4, 5.2 Hz, 1H), 2.68 (ddd, *J* = 13.6, 10.4, 6.4 Hz, 1H), 1.85-1.66 (m, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 7.2 Hz, 3H);

^{1}H-NMR of 1,2-diol (400 MHz, $CDCl_3$): δ 7.29-7.13 (m, 5H), 3.53-3.48 (m, 1H), 3.43-3.37 (m, 1H), 3.35 (s, 3H), 2.75 (ddd, *J* = 13.2, 11.2, 5.2 Hz, 1H), 2.56 (ddd, *J* = 13.6, 11.2, 6.4 Hz, 1H), 2.14-2.04 (m, 2H), 1.53-1.40 (m, 1H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H); **^{13}C-NMR** of 1,3-diol (100 MHz, $CDCl_3$): δ 143.1, 128.6 (2C), 128.4 (2C), 125.7, 77.8, 76.0, 56.3, 34.9, 34.8, 33.2, 15.4, 12.2; **^{13}C-NMR** of 1,2-diol (100 MHz, $CDCl_3$): δ 143.0, 128.6 (2C), 128.5 (2C), 125.8, 80.4, 73.5, 56.4, 41.1, 37.8, 32.0, 14.5, 12.9; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3487, 2931, 1095, 1033, 756; **HRMS** (EI) *m/z* calculated for $C_{14}H_{20}O$ $[M]^{+\cdot}$ 222.1620, found 222.1610.

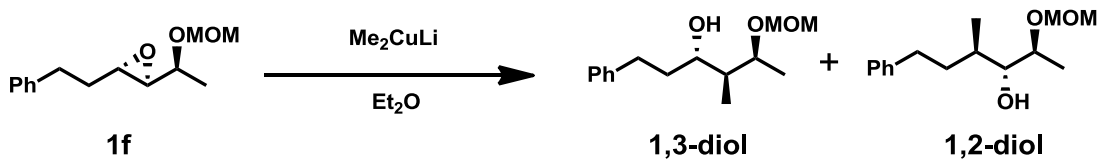
Synthesis of Epoxy MOM ether **1f**



To a solution of epoxy alcohol **1a** (123 mg, 0.640 mmol) in dry CH_2Cl_2 (3 mL) was added DIPEA (0.67 mL, 3.85 mmol) and MOMCl (233 μL, 0.91 mmol). The solution was stirred at room temperature under Ar atmosphere for 18 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0°C. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 7:1) to the give epoxy MOM ether **1f** (136 mg, 0.570 mmol, 90 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31-7.26 (m, 2H), 7.21-7.18 (m, 3H), 4.65 (d, *J* = 6.8 Hz, 2H), 4.61 (d, *J* = 6.8 Hz, 2H), 3.56-3.50 (m, 1H), 3.35 (s, 3H), 2.95 (ddd, *J* = 7.2, 5.2, 2.4 Hz, 1H), 2.84-2.68 (m, 2H), 2.69 (dd, *J* = 5.2, 2.0 Hz, 1H), 1.97-1.80 (m, 2H), 1.23 (d, *J* = 6.4 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.3, 128.6 (2C), 128.5 (2C), 126.2, 95.6, 72.6, 60.9, 57.0, 55.5, 33.7, 32.3, 17.9; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 2932, 1450, 1157, 1103, 1034; **HRMS** (EI) *m/z* calculated for $C_{14}H_{20}O_3$ $[M]^{+\cdot}$ 236.1413, found 236.1418.

Methylation of Epoxy MOM Ether **1f (Table 3, Entry 4)**

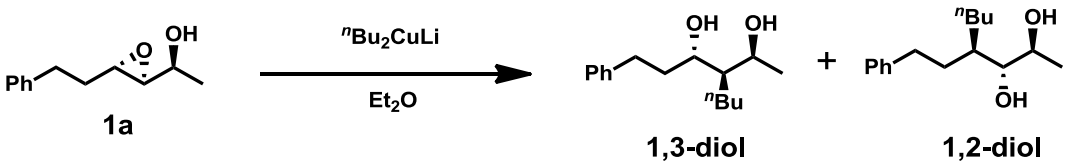


To a suspension of CuI (129 mg, 0.660 mmol) in dry Et_2O (3 mL, dried by distillation from sodium and benzophenone) was added MeLi (1.2 mL, 1.1 M in Et_2O, 1.32 mmol) at -30 °C under Ar atmosphere. The solution was stirred at same temperature for 10 min. The solution of organocopper complex was added the epoxy MOM ether **1f** (31.3 mg, 0.132 mmol) in dry Et_2O (2 mL, dried by distillation from sodium and benzophenone) by gastight syringe. The reaction mixture was stirred at 0 °C for 23 h, it was quenched with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The suspension was allowed to stir room temperature under air and then the aqueous phase was turned to bright blue. The reaction mixture was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 5:1) to give mixture of the 1,3-diol and 1,2-diol (30.6 mg, 0.121 mmol, 92%). The ratio of 1,3-diol and 1,2-diol was 3:1.

^{1}H-NMR of 1,3-diol (400 MHz, $CDCl_3$): δ 7.30-7.14 (m, 5H), 4.68 (d, J = 6.8 Hz, 1H), 4.65 (d, J = 6.8 Hz, 1H), 3.83 (dq, J = 6.4, 3.2 Hz, 1H), 3.50-3.45 (m, 1H), 3.38 (s, 3H), 2.75 (ddd, J = 13.6, 11.6, 5.2 Hz, 1H), 2.56 (ddd, J = 13.2, 10.4, 5.6 Hz, 1H), 2.17 (d, J = 2.4 Hz, 1H), 2.15-2.07 (m, 1H), 1.62-1.40 (m, 2H), 1.14 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); **^{1}H-NMR** of 1,2-diol (400 MHz, $CDCl_3$): δ 7.30-7.15 (m, 5H), 4.70 (d, J = 6.8 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.03 (dq, J = 6.8, 3.6 Hz, 1H), 3.67-3.58 (m, 2H), 3.39 (s, 3H), 2.91 (ddd, J = 13.6, 10.4, 4.8 Hz, 1H), 2.70 (ddd, J = 13.6, 10.4, 6.4 Hz, 1H), 1.91-1.81 (m, 1H), 1.75-1.63 (m, 2H), 1.18 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 7.2 Hz, 3H); **^{13}C-NMR** of 1,3-diol (100 MHz, $CDCl_3$): δ 143.0, 128.5 (2C), 128.4 (2C), 125.7, 94.9, 77.8, 74.2, 55.6, 34.9, 34.8, 33.2, 15.5, 13.0; **^{13}C-NMR** of 1,2-diol (100 MHz, $CDCl_3$): δ 142.9, 128.7 (2C), 128.5 (2C), 125.8, 95.4, 75.7, 72.7, 56.0, 42.9, 37.2, 32.0, 16.2, 12.1; **IR** ν_{max} (thin film/NaCl) cm^{-1}:

3572, 3456, 3017, 2970, 2932, 1604, 1497, 1458, 1219, 1087, 987, 749; **HRMS** (EI) *m/z* calculated for $C_{15}H_{22}O_2$ $[M-H_2O]^{+\cdot}$ 234.1620, found 234.1637.

<u>*n*Buthylation of Epoxy Alcohol **1a** (**Table 4, Entry 1**)</u>

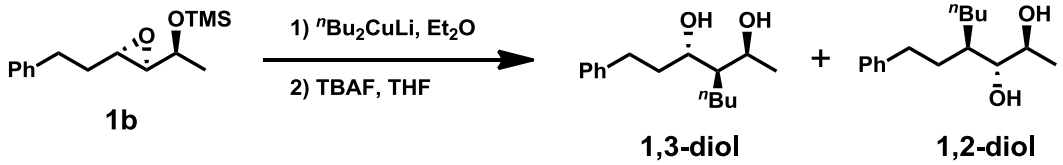


To a suspension of CuI (368 mg, 1.93 mmol) in dry Et_2O (5 mL, dried by distillation from sodium and benzophenone) was added *n*BuLi (2.45 mL, 1.58 M in hexane, 3.87 mmol) at -30 °C under Ar atmosphere. The solution was stirred at same temperature for 10 min. The solution of organocopper complex was added the epoxy alcohol **1a** (74.2 mg, 0.386 mmol) in dry Et_2O (3 mL, dried by distillation from sodium and benzophenone) by gastight syringe. The reaction mixture was stirred at 0 °C for 24 h, it was quenched with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The suspension was allowed to stir room temperature under air and then the aqueous phase was turned to bright blue. The reaction mixture was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give mixture of the 1,3-diol and 1,2-diol (87.0 mg, 0.347 mmol, 90%). The ratio of 1,3-diol and 1,2-diol was 1:4.4.

^{1}H-NMR of 1,3-diol (400 MHz, $CDCl_3$): δ 7.32-7.25 (m, 2H), 7.22-7.17 (m, 3H), 4.31-4.22 (m, 1H), 3.82 (brs, 1H), 2.88-2.79 (m, 1H), 2.73 (br, 1H), 2.70-2.62 (m, 2H), 1.98-1.78 (m, 2H), 1.78-1.22 (m, 6H), 1.19 (d, J = 6.4 Hz, 3H), 0.90 (t, J = 6.8 Hz, 3H); **^{1}H-NMR** of 1,2-diol (400 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2H), 7.22-7.14 (m, 3H), 4.74 (brs, 2H), 3.89-3.82 (m, 1H), 3.51 (dd, J = 6.8, 4.4 Hz, 1H), 2.73 (ddd, J = 13.6, 11.2, 5.6 Hz, 1H), 2.57 (ddd, J = 13.6, 10.8, 6.0 Hz, 1H), 1.95-1.85 (m, 1H), 1.70-1.59 (m, 1H), 1.59-1.50 (m, 1H), 1.42-1.24 (m, 6H), 1.16 (d, J = 6.0 Hz, 3H), 0.92 (t, J = 6.8 Hz, 3H); **^{13}C-NMR** of 1,3-diol (100 MHz, $CDCl_3$): δ 142.2, 128.6 (2C), 128.5 (2C), 126.0, 73.4, 68.2, 47.6, 37.8, 32.6, 30.5, 25.2, 23.1, 20.2, 14.2; **^{13}C-NMR** of 1,2-diol (100 MHz, $CDCl_3$): δ 143.0, 128.54

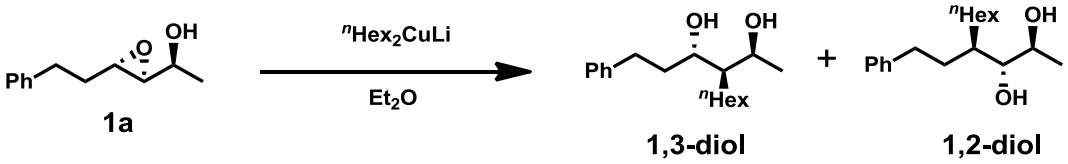
(2C), 128.50 (2C), 125.9, 68.6, 39.1, 33.1, 31.0, 29.4, 28.6, 23.3, 17.2, 14.2; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3426, 3016, 2932, 2870, 1458, 1219, 756; **HRMS** (EI) *m/z* calculated for $C_{16}H_{26}O_2$ $[M]^{+\cdot}$ 250.1933, found 250.1953.

<u>^{n}Buthylation of Epoxy Silyl Ether **1b** (Table 4, Entry 2)</u>



^{n}Buthylation of epoxy silyl ether **1b** was the same method as the case of **1a**. The crude residue was treated with TBAF (5 eq.). The deprotected compounds were purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give mixture of the 1,3-diol and 1,2-diol (60% yield, 2 steps). The ratio of 1,3-diol and 1,2-diol was 2.5:1.

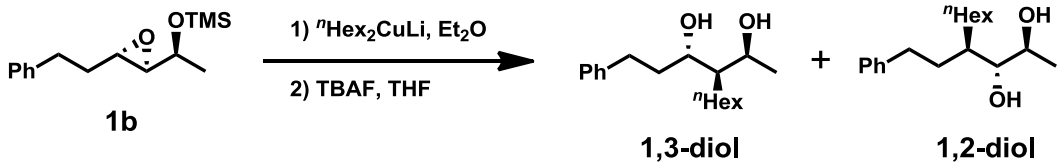
<u>^{n}Hexylation of Epoxy Alcohol **1a** (Table 4, Entry 3)</u>



To a suspension of CuI (330 mg, 1.73 mmol) in dry Et_2O (5 mL, dried by distillation from sodium and benzophenone) was added ^{n}HexLi (4.37 mL, 1.1 M in Et_2O, 4.37 mmol) at -30 °C under Ar atmosphere. The solution was stirred at same temperature for 10 min. The solution of organocopper complex was added the epoxy alcohol **1a** (92.3 mg, 0.480 mmol) in dry Et_2O (5 mL, dried by distillation from sodium and benzophenone) by gastight syringe. The reaction mixture was stirred at 0 °C for 23 h, it was quenched with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The suspension was allowed to stir room temperature under air and then the aqueous phase was turned to bright blue. The reaction mixture was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give mixture of the 1,3-diol and 1,2-diol (116 mg, 0.418 mmol, 87%). The ratio of 1,3-diol and 1,2-diol was 1:4.4.

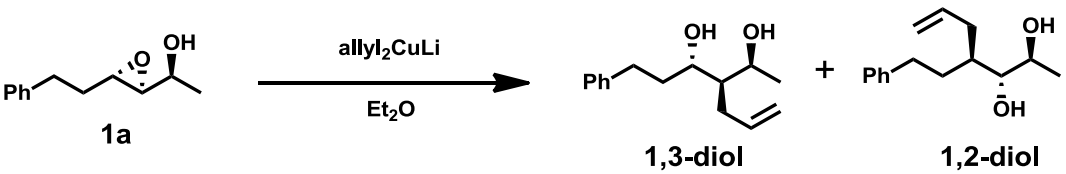
^{1}H-NMR of 1,3-diol (400 MHz, $CDCl_3$): δ 7.31-7.26 (m, 2H), 7.22-7.18 (m, 3H), 4.29-4.23 (m, 1H), 3.84-3.80 (m, 1H), 2.90-2.80 (m, 1H), 2.79-2.61 (m, 3H), 1.99-1.78 (m, 2H), 1.45-1.22 (m, 11H), 1.20 (d, J = 6.4 Hz, 3H) , 0.87 (t, J = 6.4 Hz, 3H); **^{1}H-NMR** of 1,2-diol (400 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2H), 7.23-7.15 (m, 3H), 3.91-3.81 (m, 1H), 3.55-3.48 (m, 1H), 2.72 (ddd, J = 13.6, 10.4, 5.2 Hz, 1H), 2.57 (ddd, J = 13.2, 10.4, 6.0 Hz, 1H), 1.95-1.85 (m, 1H), 1.82 (brs, 1H), 1.70-1.59 (m, 2H), 1.58-1.49 (m, 1H), 1.41-1.22 (m, 10H), 1.16 (d, J = 6.4 Hz 3H) , 0.90 (t, J = 6.4 Hz, 3H); **^{13}C-NMR** of 1,3-diol (100 MHz, $CDCl_3$): δ 142.0, 128.5 (2C), 128.4 (2C), 125.9, 73.2, 68.1, 47.4, 37.6, 32.5, 31.8, 29.6, 28.0, 25.3, 22.6, 20.0, 14.1; **^{13}C-NMR** of 1,2-diol (100 MHz, $CDCl_3$): δ 143.0, 128.54 (2C), 128.50 (2C), 125.9, 76.7, 68.6, 39.1, 33.1, 32.0, 31.0, 29.9, 29.6, 26.3, 22.8, 17.2, 14.3; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3394, 2931, 2862, 1458, 756; **HRMS** (EI) *m/z* calculated for $C_{18}H_{28}O$ $[M-H_2O]^{+\cdot}$ 260.2140, found 260.2158.

<u>^{n}Hexylation of Epoxy Silyl Ether **1b (Table 4, Entry 4)**</u>



^{n}Hexylation of epoxy silyl ether **1b** was the same method as the case of **1a**. The crude residue was treated with TBAF (5 eq.). The deprotected compounds were purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give mixture of the 1,3-diol and 1,2-diol (57% yield, 2 steps). The ratio of 1,3-diol and 1,2-diol was 2.2:1.

<u>Allylation of Epoxy Alcohol **1a (Table 4, Entry 5)**</u>

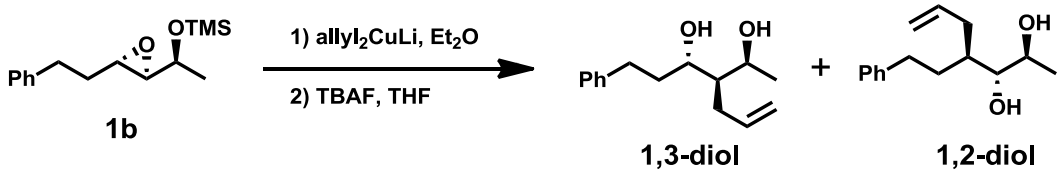


To a suspension of CuI (368 mg, 1.93 mmol) in dry Et_2O (2 mL, dried by distillation from sodium and benzophenone) was added allylLi (7.6 mL, 0.45 M in Et_2O, 3.40 mmol) at -30 °C under Ar atmosphere. The solution was stirred at same temperature for 10

min. The solution of organocopper complex was added the epoxy alcohol **1a** (65.3 mg, 0.340 mmol) in dry Et_2O (4 mL, dried by distillation from sodium and benzophenone) by gastight syringe. The reaction mixture was stirred at 0 °C for 16.5 h, it was quenched with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The suspension was allowed to stir room temperature under air and then the aqueous phase was turned to bright blue. The reaction mixture was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give mixture of the 1,3-diol and 1,2-diol (68.5 mg, 0.292 mmol, 86%). The ratio of 1,3-diol and 1,2-diol was 1:1.5.

^{1}H-NMR of 1,3-diol (400 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2H), 7.21-7.16 (m, 3H), 5.85-5.75 (m, 1H), 5.12-5.05 (m, 1H), 5.05-5.01 (m, 1H), 4.32-4.26 (m, 1H), 3.89-3.82 (m, 1H), 2.95 (brs, 1H), 2.87-2.78 (m, 2H), 2.65 (ddd, J = 13.6, 10.0, 6.4 Hz, 1H), 2.33-2.24 (m, 1H), 2.22-2.14 (m, 1H), 2.00-1.89 (m, 1H), 1.85-1.76 (m, 1H), 1.52-1.45 (m, 1H), 1.20 (d, J = 6.4 Hz, 3H); **^{1}H-NMR** of 1,2-diol (400 MHz, $CDCl_3$): δ 7.31-7.24 (m, 2H), 7.21-7.15 (m, 3H), 5.87-5.75 (m, 1H), 5.15-5.05 (m, 2H), 3.92-3.83 (m, 1H), 3.50 (brs, 1H), 2.81-2.71 (m, 1H), 2.62-2.52 (m, 1H), 2.26-2.11 (m, 2H), 1.99-1.88 (m, 2H), 1.75-1.60 (m, 2H), 1.16 (d, J = 6.4 Hz, 3H); **^{13}C-NMR** of 1,3-diol (100 MHz, $CDCl_3$): δ 142.1, 137.6, 128.6 (2C), 128.5 (2C), 126.1, 116.6, 72.9, 67.8, 47.2, 37.6, 32.6, 30.2, 20.2; **^{13}C-NMR** of 1,2-diol (100 MHz, $CDCl_3$): δ 142.8, 136.3, 128.53 (2C), 128.50 (2C), 125.9, 117.0, 76.6, 68.4, 38.8, 34.5, 33.2, 30.7, 17.5; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3348, 3070, 3024, 2970, 2931, 1450, 756; **HRMS** (EI) *m/z* calculated for $C_{15}H_{20}O$ $[M-H_2O]^{+\cdot}$ 216.1514, found 216.1522.

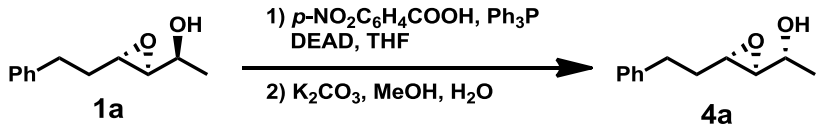
Allylation of Epoxy Silyl Ether **1b (Table 4, Entry 6)**



Allylation of epoxy silyl ether **1b** was the same method as the case of **1a**. The crude residue was treated with TBAF (5 eq.). The deprotected compounds were purified by

column chromatography on silica gel (hexane / AcOEt = 3:1) to give mixture of the 1,3-diol and 1,2-diol (74% yield, 2 steps). The ratio of 1,3-diol and 1,2-diol was 2:1.

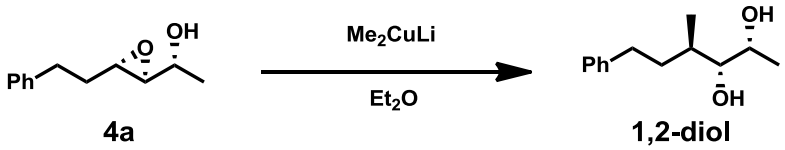
Synthesis of Epoxy Alchohol **4a**



To a solution of epoxy alcohol **1a** (269 mg, 1.40 mmol) in dry THF (5 mL) was added Ph_3P (739 mg, 2.80 mmol), DEAD (0.95 mL, 40 % in toluene, 2.80 mmol) and *p*-nitro benzoic acid (468 mg, 2.80 mmol) at 0 °C under Ar atmosphere. The solution was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 15:1) to give the benzyl ester (478 mg, 1.40 mmol, 100 %).

To a solution of benzyl ester (259 mg, 0.761 mmol) in MeOH (3.7 mL) was added K_2CO_3 (317 mg, 2.28 mmol). The solution was stirred at room temperature for 1.5 h. The reaction was quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 2:1) to give the epoxy alcohol **4a** (138 mg, 0.715 mmol, 94 %). Data for the benzyl ester **4a** were identical to literature values. [78]

Methylation of Epoxy Alcohol **4a** (**Table 5, Entry 1**)

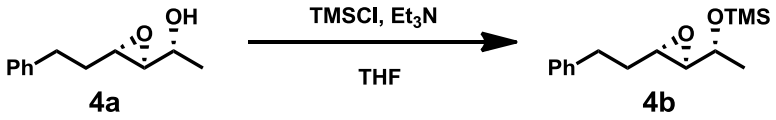


To a suspension of CuI (140 mg, 0.740 mmol) in dry Et_2O (3 mL, dried by distillation from sodium and benzophenone) was added MeLi (1.56 mL, 1.1 M in Et_2O, 1.72 mmol) at -30 °C under Ar atmosphere. The solution was stirred at same temperature for 10 min. The solution of organocopper complex was added the epoxy alcohol **4a** (33.0 mg, 0.172 mmol) in dry Et_2O (2 mL, dried by distillation from sodium and benzophenone) by

gastight syringe. The reaction mixture was stirred at 0 °C for 24 h, it was quenched with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The suspension was allowed to stir room temperature under air and then the aqueous phase was turned to bright blue. The reaction mixture was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 2:1) to give the 1,2-diol (15.4 mg, 0.074 mmol, 43%) and yield of recovered **4a** was 40%. The amount of 1,3-diol was trace.

^{1}H-NMR of 1,2-diol (400 MHz, $CDCl_3$): δ 7.32-7.25 (m, 2H), 7.22-7.15 (m, 3H), 3.83 (quintet, J = 6.0 Hz, 1H), 3.16 (brs, 1H), 2.78 (ddd, J = 13.6, 10.4, 5.2 Hz, 1H), 2.51 (ddd, J = 13.6, 9.6, 6.8 Hz, 1H), 2.04 (brs, 1H), 1.95 (brs, 1H), 1.88-1.77 (m, 1H), 1.72-1.62 (m, 1H), 1.58-1.47 (m, 1H), 1.13 (d, J = 6.4 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H); **^{13}C-NMR** of 1,2-diol (100 MHz, $CDCl_3$): δ 142.7, 128.50 (2C), 128.48 (2C), 125.9, 80.3, 68.2, 34.8, 33.5, 32.8, 20.1, 16.7; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3387, 2931, 1458, 1381, 987, 756; **HRMS** (EI) *m/z* calculated for $C_{13}H_{18}O$ $[M-H_2O]^{+\cdot}$ 190.1358, found 190.1369.

Synthesis of Epoxy Silyl Ether **4b**

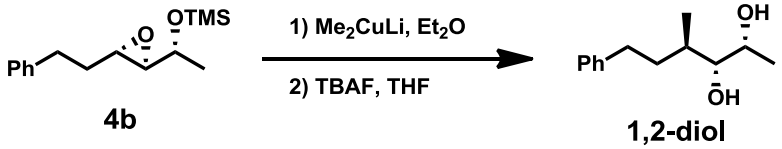


To a solution of epoxy alcohol **4a** (138 mg, 0.720 mmol) in dry THF (2 mL) was added Et_3N (1.03 mL, 7.18 mmol) and TMSCl (0.62 mL, 3.59 mmol). The solution was stirred at room temperature under Ar atmosphere for 13 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0°C. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 15:1) to give the epoxy silyl ether **4b** (190 mg, 0.720 mmol, 100 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.26 (m, 2H), 7.22-7.16 (m, 3H), 3.51 (quintet, J = 6.4 Hz, 1H), 2.85-2.67 (m, 4H), 1.96-1.80 (m, 2H), 1.13 (d, J = 6.4 Hz, 3H), 0.13 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.3, 128.6 (2C), 128.5 (2C), 126.2, 69.5, 63.2, 55.8, 33.6,

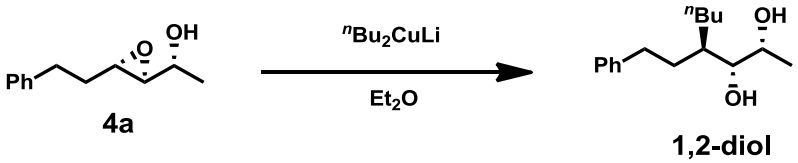
32.3, 20.4, 0.26 (3C); **IR** ν_{max} (thin film/NaCl) cm^{-1}: 2970, 1249, 1103, 849; **HRMS** (EI) *m/z* calculated for $C_{15}H_{24}O_2Si$ $[M]^{+\cdot}$ 264.1546, found 264.1528.

Methylation of Epoxy Silyl Ether **4b (Table 5, Entry 2)**



Methylation of epoxy silyl ether **4b** was the same method as the case of **4a**. The crude residue was treated with TBAF (5 eq.). The deprotected compounds were purified by column chromatography on silica gel (hexane / AcOEt = 2:1) to give the 1,2-diol (88% yield, 2 steps). The amount of 1,3-diol was trace.

^{n}Buthylation of Epoxy Alcohol **4a (Table 5, Entry 3)**

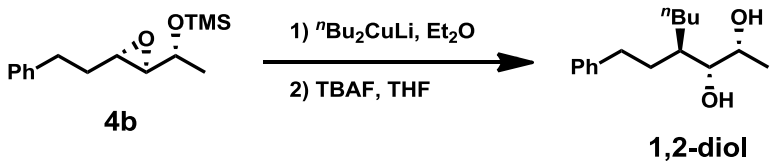


To a suspension of CuI (344 mg, 1.80 mmol) in dry Et_2O (5 mL, dried by distillation from sodium and benzophenone) was added ^{n}BuLi (1.36 mL, 2.65 M in hexane, 3.61 mmol) at -30 °C under Ar atmosphere. The solution was stirred at same temperature for 10 min. The solution of organocopper complex was added the epoxy alcohol **4a** (69.4 mg, 0.361 mmol) in dry Et_2O (3 mL, dried by distillation from sodium and benzophenone) by gastight syringe. The reaction mixture was stirred at 0 °C for 21 h, it was quenched with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The suspension was allowed to stir room temperature under air and then the aqueous phase was turned to bright blue. The reaction mixture was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 2:1) to give the 1,2-diol (83.2 mg, 0.332 mmol, 92%). The amount of 1,3-diol was trace.

^{1}H-NMR of 1,2-diol (400 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2H), 7.20-7.14 (m, 3H), 3.82-3.71 (m, 1H), 3.33 (m, 1H), 2.76 (ddd, *J*= 14.0, 9.8, 4.8 Hz, 1H), 2.52 (ddd, *J*= 13.2, 9.8, 6.8 Hz, 1H), 2.19-2.08 (m, 2H), 1.79-1.65 (m, 1H), 1.64-1.53 (m, 1H), 1.51-1.41 (m, 3H), 1.40-1.20

(m, 4H), 1.05 (d, J = 6.0 Hz, 3H), 0.92 (t, J = 6.8 Hz, 3H); **^{13}C-NMR** of 1,2-diol (100 MHz, $CDCl_3$): δ 142.7, 128.53 (2C), 128.48 (2C), 125.9, 77.8, 68.8, 39.0, 33.7, 30.6, 30.5, 29.5, 23.1, 19.6, 14.3; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3394, 2931, 2862, 1458, 1026, 756; **HRMS** (EI) *m/z* calculated for $C_{16}H_{24}O$ $[M-H_2O]^{+\cdot}$ 232.1827, found 232.1809.

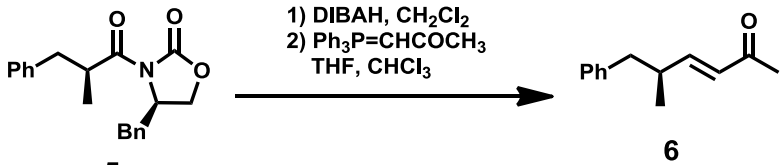
<u>^{n}Butylation of Epoxy Silyl Ether **4b** (**Table 5**, **Entry 4**)</u>



4b **1,2-diol**

^{n}Butylation of epoxy silyl ether **4b** was the same method as the case of **4a**. The crude residue was treated with TBAF (5 eq.). The deprotected compounds were purified by column chromatography on silica gel (hexane / AcOEt = 2:1) to give the1,2-diol (85% yield, 2 steps). The amount of 1,3-diol was trace.

<u>Synthesis of Enone **6**</u>



5 **6**

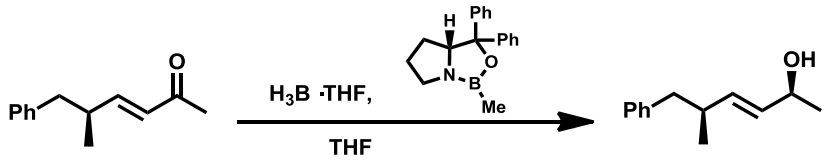
To a solution of amide **5** (2.87 g, 8.86 mmol) in dry CH_2Cl_2 (50 mL) was added DIBAH (17.1 mL, 0.99 M in hexane, 16.9 mmol). The solution was stirred at -78 °C under Ar atmosphere for 40 min. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and it was was vigorously stirred at room temperature. The aqueous phase was extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The aldehyde was used in the next step without purification.

To a solution of aldehyde in THF (9 mL) and $CHCl_3$ (3 mL) was added Ph_3P=CHCOMe (5.64 g, 17.7 mmol). The solution was stirred at room temperature for 1 week and solvent was removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 6:1) to give the enone **6** (1.30 g, 6.91

mmol, 78%, 2 steps).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2H), 7.23-7.17 (m, 1H), 7.15-7.11 (m, 2H), 6.75 (dd, *J* = 16.0, 6.4 Hz, 1H), 5.99 (d, *J* = 16.0 Hz, 1H), 2.8-2.70 (m, 1H), 2.69-2.58 (m, 2H), 2.21 (s, 3H), 1.07 (d, *J* = 6.0 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 199.0, 152.6, 139.6, 129.8, 129.2 (2C), 128.5 (2C), 126.4, 42.7, 38.5, 27.1, 19.0; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3024, 2962, 2924, 1625, 1627, 1450, 1357, 1258, 979, 740, 702; **HRMS** (EI) *m/z* calculated for $C_{13}H_{16}O$ $[M]^{+\cdot}$ 188.1201, found 188.1203.

CBS Reduction of Enone **6**

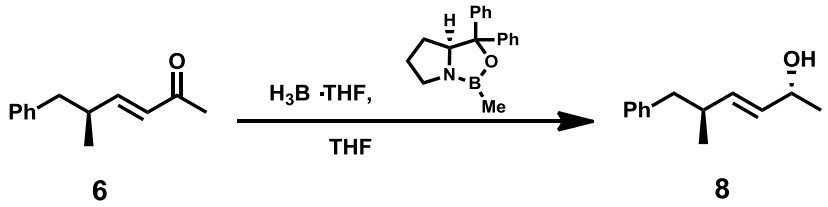


6 **7**

To a solution of enone **6** (148 mg, 0.790 mmol) in dry THF (2 mL) was added (*R*)-Me-CBS (0.79 mL, 1.0 M in toluene, 0.790 mmol) and H_3B · THF (1.0 mL, 0.95 M in THF, 0.950 mmol). The solution was stirred at -30 °C under Ar atmosphere for 1 h. The reaction mixture was quenched with MeOH and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 8:1) to give the allyl alcohol **7** (126 mg, 0.663 mmol, 84 %)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.30-7.23 (m, 2H), 7.20-7.15 (m, 1H), 7.14-7.10 (m, 2H), 5.58 (ddd, *J* = 15.2, 6.8, 0.8 Hz, 1H), 5.40 (ddd, *J* = 15.2, 6.4, 0.8 Hz, 1H), 4.27-4.18 (m, 1H), 2.65 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.53 (dd, *J* = 13.2, 7.6 Hz, 1H), 2.48-2.36 (m, 1H), 1.20 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.4 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 140.7, 136.0, 133.0, 129.4 (2C), 128.2 (2C), 126.0, 69.1, 43.6, 38.1, 23.6, 19.8; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3356, 2970, 2924, 1450, 1373, 1064, 972, 740, 702; **HRMS** (EI) *m/z* calculated for $C_{13}H_{18}O$ $[M]^{+\cdot}$ 190.1358, found 190.1347.

CBS Reduction of Enone **6**

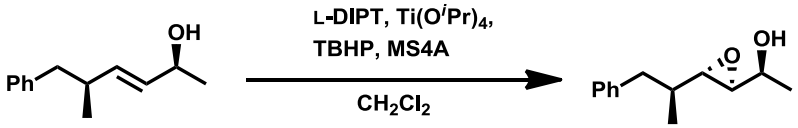


6 **8**

To a solution of enone **6** (581 mg, 3.09 mmol) in dry THF (2 mL) was added (*S*)-Me-CBS (3.1 mL, 1.0M in toluene, 3.10 mmol) and H_3B · THF (6.94 mL, 0.95 M in THF, 6.18 mmol). The solution was stirred at -30 °C under Ar atmosphere for 1 h. The reaction mixture was quenched with MeOH and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (benzene / AcOEt = 4:1) to give the allyl alcohol **8** (515 mg, 2.71mmol, 88 %)

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.29-7.23 (m, 2H), 7.20-7.15 (m, 1H), 7.14-7.10 (m, 2H), 5.58 (ddd, *J* = 15.2, 6.8, 0.8 Hz, 1H), 5.40 (ddd, *J* = 15.2, 6.4, 0.8 Hz, 1H), 4.27-4.16 (m, 1H), 2.65 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.53 (dd, *J* = 13.2, 7.6 Hz, 1H), 2.48-2.36 (m, 1H), 1.21 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 140.8, 136.0, 133.0, 129.4 (2C), 128.2 (2C), 126.0, 69.0, 43.6, 38.1, 23.5, 19.8; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3363, 2970, 2924, 1450, 1373, 1064, 972, 740, 702; **HRMS** (EI) *m/z* calculated for $C_{13}H_{18}O$ $[M]^{+\cdot}$ 190.1358, found 190.1388.

Synthesis of Epoxy Alcohol **9a**



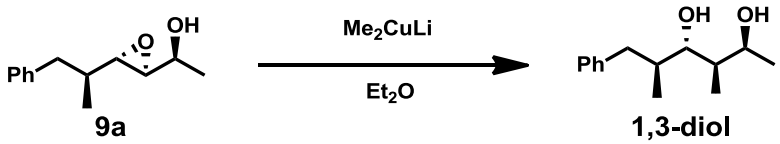
7 **9a**

To a suspension of allyl alcohol **7** (120 mg, 0.631 mmol) and activated MS4A (3 g) in dry CH_2Cl_2 (2 mL, dried by distillation from calcium hydride) was stirred at -30 °C under Ar atmosphere. Other two-necked flask was added dry CH_2Cl_2 (2 mL, dried by distillation from calcium hydride), $Ti(O^iPr)_4$ (190 μL, 0.631 mmol) and L-DIPT (158 μL, 0.757 mmol) at -30 °C under Ar atmosphere. The tithanium complex solution was stirred for 10 min and moved to a suspension via cannula. The suspention was added TBHP (322 μL, 3.0

M in CH_2Cl_2, 0.967 mmol) and resultant mixture was stirred for 27 h. The suspention was quenched with saturated aqueous Na_2SO_3 and saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give the epoxy alcohol **9a** (99.0 mg, 0.480 mmol, 76 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.26 (m, 2H), 7.23-7.15 (m, 3H), 4.01-3.93 (m, 1H), 2.94 (dd, *J*= 13.2, 4.8 Hz, 1H), 2.88 (dd, *J*= 7.6, 2.6 Hz, 1H), 2.83 (t, *J*= 2.6 Hz, 1H), 2.53 (dd, *J*= 13.2, 8.8 Hz, 1H), 1.84 (brs, 1H), 1.77-1.64 (m, 1H), 1.24 (d, *J*= 6.4 Hz, 3H), 0.89 (d, *J*= 6.8 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 139.7, 129.4 (2C), 128.4 (2C), 126.2, 64.7, 61.0, 59.1, 40.5, 37.4, 18.9, 15.5; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3425, 2970, 2924, 1604, 1450, 902, 740, 702; **HRMS** (EI) *m/z* calculated for $C_{13}H_{18}O_2$ $[M]^{+\cdot}$ 206.1307, found 206.1276.

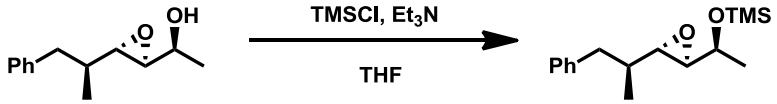
Methylation of Epoxy Alcohol **9a** (**Table 6, Entry 1**)



To a suspension of CuI (223 mg, 1.17 mmol) in dry Et_2O (3 mL, dried by distillation from sodium and benzophenone) was added MeLi (2.07 mL, 1.13 M in Et_2O, 2.34 mmol) at -30 °C under Ar atmosphere. The solution was stirred at same temperature for 10 min. The solution of organocopper complex was added the epoxy alcohol **9a** (48.8 mg, 0.234 mmol) in dry Et_2O (2 mL, dried by distillation from sodium and benzophenone) by gastight syringe. The reaction mixture was stirred at 0 °C for 24 h, it was quenched with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The suspension was allowed to stir room temperature under air and then the aqueous phase was turned to bright blue. The reaction mixture was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 4:1) to give the 1,3-diol (16.5 mg, 0.075 mmol, 32%) and yield of recovered **9a** was 57%.

^{1}H-NMR of 1,3-diol (400 MHz, $CDCl_3$): δ 7.32-7.25 (m, 2H), 7.22-7.15 (m, 3H), 4.25-4.16 (m, 1H), 3.49 (q, *J*= 5.6 Hz, 1H), 3.07 (dd, *J*= 13.2, 3.6 Hz, 1H), 2.80 (d, *J*= 4.8 Hz, 1H), 2.55 (d, *J* = 4.0 Hz, 1H), 2.33 (dd, *J* = 13.2, 10.0 Hz, 1H), 2.04-1.93 (m, 1H), 1.92-1.83 (m, 1H), 1.21 (d, *J*= 6.8 Hz, 3H), 1.01 (d, *J*= 6.8 Hz, 3H), 0.82 (d, *J*= 6.8 Hz, 3H); **^{13}C-NMR** of 1,3-diol (100 MHz, $CDCl_3$): δ 141.4, 129.4 (2C), 128.4 (2C), 126.0, 80.0, 69.1, 39.2, 38.5, 37.9, 20.1, 16.4, 11.7; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3356, 2970, 2924, 1458, 1110, 740, 702; **HRMS** (EI) *m/z* calculated for $C_{14}H_{20}O$ $[M\text{-}H_2O]^{+\cdot}$ 204.1514, found 204.1543.

Synthesis of Epoxy Silyl Ether **9b**

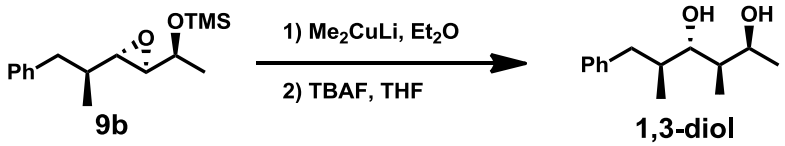


9a **9b**

To a solution of epoxy alcohol **9a** (41.1 mg, 0.197 mmol) in dry THF (1 mL) was added Et_3N (280 μL, 1.97 mmol) and TMSCl (170 μL, 0.987 mmol). The solution was stirred at room temperature under Ar atmosphere for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0°C. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 10:1) to give the epoxy silyl ether **9b** (51.4 mg, 0.185 mmol, 94 %).

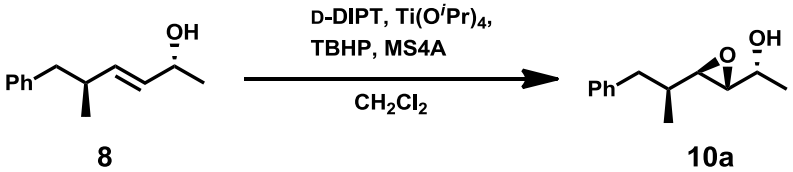
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2H), 7.22-7.15 (m, 3H), 3.67-3.59 (m, 1H), 2.95 (dd, *J* = 13.2, 4.4 Hz, 1H), 2.74-2.69 (m, 2H), 2.48 (dd, *J* = 13.2, 9.2 Hz, 1H), 1.71-1.59 (m, 1H), 1.23 (d, *J*= 6.4 Hz, 3H), 0.88 (d, *J*= 6.8 Hz, 3H), 0.11 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 139.9, 129.4 (2C), 128.4 (2C), 126.1, 68.1, 61.5, 61.4, 40.4, 37.7, 21.2, 15.5, 0.31 (3C); **IR** ν_{max} (thin film/NaCl) cm^{-1}: 2962, 2931, 1450, 1373, 1250, 1095, 902, 849; **HRMS** (EI) *m/z* calculated for $C_{16}H_{26}O_2Si$ $[M]^{+\cdot}$ 278.1702, found 278.1712.

Methylation of Epoxy Silyl Ether **9b (Table 6, Entry 2)**



Methylation of epoxy silyl ether **9b** was the same method as the case of **9a**. The crude residue was treated with TBAF (5 eq.). The deprotected compounds were purified by column chromatography on silica gel (hexane / AcOEt = 4:1) to give the 1,3-diol (77% yield, 2 steps).

Synthesis of Epoxy Alcohol **10a**

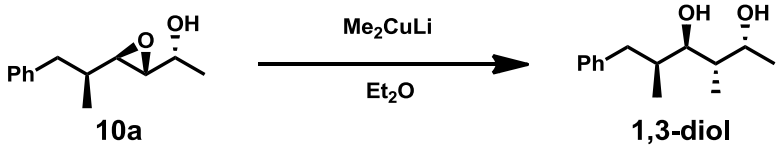


To a suspension of allyl alcohol **8** (515 mg, 2.71 mmol) and activated MS4A (3 g) in dry CH_2Cl_2 (5 mL, dried by distillation from calcium hydride) was stirred at -30 °C under Ar atmosphere. Other two-necked flask was added dry CH_2Cl_2 (3 mL, dried by distillation from calcium hydride), $Ti(O^iPr)_4$ (0.915 mL, 3.09 mmol) and D-DIPT (0.78 mL, 3.71 mmol) at -30 °C under Ar atmosphere. The tithanium complex solution was stirred for 10 min and moved to a suspension via cannula. The suspention was added TBHP (1.16 mL, 4.0 M in CH_2Cl_2, 4.63 mmol) and resultant mixture was stirred for 14 h. The suspention was quenched with saturated aqueous Na_2SO_3 and saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 4:1) to give the epoxy alcohol **10a** (451 mg, 2.16 mmol, 80 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.26 (m, 2H), 7.24-7.14 (m, 3H), 3.78-3.69 (m, 1H), 2.76 (dd, J = 8.0, 2.0 Hz, 1H), 2.69 (dd, J = 13.6, 6.8 Hz, 1H), 2.61 (dd, J = 13.6, 8.0 Hz, 1H), 2.56 (dd, J = 3.6, 2.0 Hz, 1H), 1.78-1.65 (m, 1H), 1.09 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 6.4 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 140.0, 129.2 (2C), 128.6 (2C), 126.4, 65.2, 62.0, 59.9, 40.4, 37.7, 18.5, 17.6; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3448, 2970, 2924, 1458,

902, 887, 740, 702; **HRMS** (EI) *m/z* calculated for $C_{13}H_{18}O_2$ $[M]^{+\cdot}$ 206.1307, found 206.1327.

Methylation of Epoxy Alcohol **10a** (**Table 6, Entry 3**)

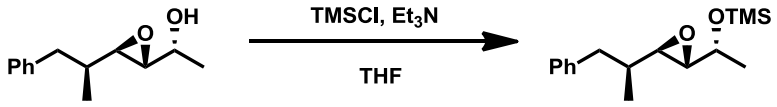


10a **1,3-diol**

To a suspension of CuI (224 mg, 1.18 mmol) in dry Et_2O (3 mL, dried by distillation from sodium and benzophenone) was added MeLi (2.10 mL, 1.13 M in Et_2O, 2.35 mmol) at -30 °C under Ar atmosphere. The solution was stirred at same temperature for 10 min. The solution of organocopper complex was added the epoxy alcohol **10a** (49.0 mg, 0.235 mmol) in dry Et_2O (2 mL, dried by distillation from sodium and benzophenone) by gastight syringe. The reaction mixture was stirred at 0 °C for 24 h, it was quenched with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The suspension was allowed to stir room temperature under air and then the aqueous phase was turned to bright blue. The reaction mixture was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 2:1) to give the 1,3-diol (13.9 mg, 0.063 mmol, 27%) and yield of recovered **10a** was 67%.

^{1}H-NMR of 1,3-diol (400 MHz, $CDCl_3$): δ 7.32-7.25 (m, 2H), 7.22-7.16 (m, 3H), 4.14-4.05 (m, 1H), 3.59 (dd, J = 8.4, 2.8 Hz, 1H), 2.74 (dd, J = 13.2, 6.4 Hz, 1H), 2.65 (brs, 1H), 2.55 (dd, J = 13.2, 8.8 Hz, 1H), 2.42 (brs, 1H), 1.98-1.81 (m, 2H), 1.18 (d, J = 6.4 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H); **^{13}C-NMR** of 1,3-diol (100 MHz, $CDCl_3$): δ 141.1, 129.3 (2C), 128.5 (2C), 126.0, 76.3, 70.8, 40.7, 40.3, 37.5, 18.8, 12.4, 12.3; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3387, 2970, 2931, 1458, 1381, 1111, 1049, 972, 702; **HRMS** (EI) *m/z* calculated for $C_{14}H_{20}O$ $[M\text{-}H_2O]^{+\cdot}$ 204.1514, found 204.1522.

Synthesis of Epoxy Silyl Ether **10b**

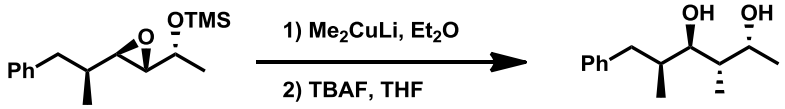


10a **10b**

To a solution of epoxy alcohol **10a** (52.5 mg, 0.273 mmol) in dry THF (1 mL) was added Et_3N (390 μL, 2.73 mmol) and TMSCl (233 μL, 1.37 mmol). The solution was stirred at room temperature under Ar atmosphere for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0°C. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 10:1) to give the epoxy silyl ether **10b** (68.7 mg, 0.247 mmol, 90 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31-7.27 (m, 2H), 7.22-7.13 (m, 3H), 3.65-3.57 (m, 1H), 2.73 (dd, J= 13.2, 6.4 Hz, 1H), 2.70 (dd, J= 7.2, 2.0 Hz, 1H), 2.62 (dd, J= 4.4, 2.0Hz, 1H), 2.51 (dd, J= 13.2, 8.4 Hz, 1H), 1.78-1.66 (m, 1H), 1.10 (d, J= 6.4 Hz, 3H), 0.99 (d, J= 6.8 Hz, 3H), 0.09 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 140.1, 129.2 (2C), 128.5 (2C), 126.2, 67.7, 61.6, 61.0, 40.1, 37.5, 20.5, 16.7, 0.30 (3C); **IR** ν_{max} (thin film/NaCl) cm^{-1}: 2962, 2931, 1450, 1373, 1250, 1096, 895, 840; **HRMS** (EI) *m/z* calculated for $C_{16}H_{26}O_2Si$ $[M]^{+\cdot}$ 278.1702, found 278.1712.

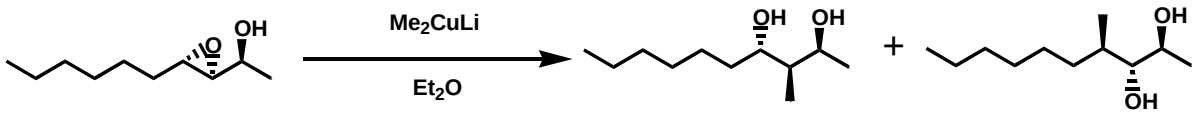
Methylation of Epoxy Silyl Ether **10b (Table 6, Entry 4)**



10b **1,3-diol**

Methylation of epoxy silyl ether **10b** was the same method as the case of **10a**. The crude residue was treated with TBAF (5 eq.). The deprotected compounds were purified by column chromatography on silica gel (hexane / AcOEt = 2:1) to give the 1,3-diol (84% yield, 2 steps).

Methylation of Epoxy Alcohol **11a**

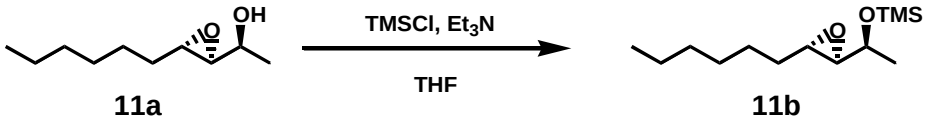


11a **12** **13**

To a suspension of CuI (367 mg, 1.93 mmol) in dry Et_2O (5 mL, dried by distillation from sodium and benzophenone) was added MeLi (3.45 mL, 1.13 M in Et_2O, 3.86 mmol) at -30 °C under Ar atmosphere. The solution was stirred at same temperature for 10 min. The solution of organocopper complex was added the epoxy alcohol **11a** (66.4 mg, 0.386 mmol) in dry Et_2O (2 mL, dried by distillation from sodium and benzophenone) by gastight syringe. The reaction mixture was stirred at 0 °C for 20 h, it was quenched with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The suspension was allowed to stir room temperature under air and then the aqueous phase was turned to bright blue. The reaction mixture was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give mixture of the 1,3-diol **12** and 1,2-diol **13** (68.3mg, 0.363 mmol, 94%). The ratio of 1,3-diol **12** and 1,2-diol **13** was 1:1.5.

^{1}H-NMR of 1,3-diol **12** (400 MHz, $CDCl_3$): δ 4.15 (dq, J= 6.4, 2.0 Hz, 1H), 3.66 (q, J= 6.0 Hz, 1H), 2.73 (brs, 1H), 2.55 (brs, 1H), 1.63-1.57 (m, 1H), 1.57-1.22 (m, 10H), 1.19 (d, J= 6.4 Hz, 3H), 0.93 (d, J= 7.6 Hz, 3H), 0.89 (t, J= 6.8 Hz, 3H); **^{1}H-NMR** of 1,2-diol **13** (400 MHz, $CDCl_3$): δ 3.97-3.86 (m, 1H), 3.37 (dt, J= 8.8, 3.6 Hz, 1H), 1.94 (d, J= 4.4 Hz, 1H), 1.77 (d, J= 6.0 Hz, 1H), 1.74-1.65 (m, 1H), 1.54-1.20 (m, 10H), 1.15 (d, J= 6.4 Hz, 3H) , 0.88 (t, J= 6.4 Hz, 3H), 0.84 (d, J= 6.4 Hz, 3H); **^{13}C-NMR** of 1,3-diol **12** (100 MHz, $CDCl_3$): δ 75.8, 69.2, 42.6, 35.7, 32.0, 29.5, 25.7, 22.8, 19.8, 14.2, 11.9; **^{13}C-NMR** of 1,2-diol **13** (100 MHz, $CDCl_3$): δ 79.0, 68.5, 35.6, 32.9, 32.1, 29.8, 26.7, 22.8, 16.0, 15.3, 14.2; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3402, 2970, 1659, 987, 756; **HRMS** (ESI) *m/z* calculated for $C_{11}H_{24}O_2$ $[M+Na]^{+\cdot}$ 211.1674, found 211.1668.

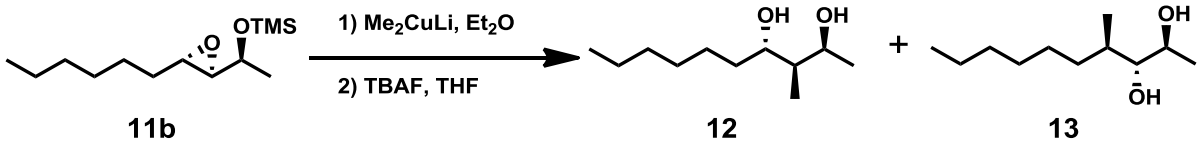
Synthesis of Epoxy Silyl Ether **11b**



To a solution of epoxy alcohol **11a** (101 mg, 0.590 mmol) in dry THF (3 mL) was added Et_3N (0.82 mL, 5.89 mmol) and TMSCl (0.50 mL, 2.94 mmol). The solution was stirred at room temperature under Ar atmosphere for 3 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0°C. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 15:1) to give the epoxy silyl ether **11b** (121 mg, 0.495 mmol, 84 %).

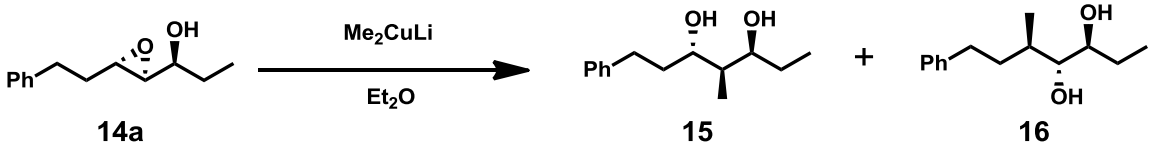
^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.62-3.55 (m, 1H), 2.81 (dt, J= 5.6, 2.4 Hz, 1H), 2.62 (dd, J= 5.2, 2.4 Hz, 1H), 1.60-1.25 (m, 11H), 1.23 (d, J= 6.0 Hz, 3H), 0.89 (t, J= 7.2 Hz, 3H), 0.11 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 68.4, 62.1, 57.7, 31.9, 29.2, 26.1, 22.7, 21.1, 14.2, 0.29 (3C); **IR** ν_{max} (thin film/NaCl) cm^{-1}: 2962, 2931, 2862, 1458, 1249, 1103, 841; **HRMS** (EI) *m/z* calculated for $C_{12}H_{25}O_2Si$ $[M\text{-}CH_3]^{+\cdot}$ 229.1624, found 229.1642.

Methylation of Epoxy Silyl Ether **11b**



Methylation of epoxy silyl ether **11b** was the same method as the case of **11a**. The crude residue was treated with TBAF (5 eq.). The deprotected compounds were purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give mixture of the 1,3-diol **12** and 1,2-diol **13** (95% yield, 2 steps). The ratio of 1,3-diol **12** and 1,2-diol **13** was 1.5:1.

Methylation of Epoxy Alcohol **14a**

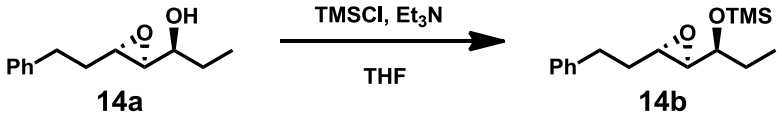


To a suspension of CuI (284 mg, 1.49 mmol) in dry Et_2O (3 mL, dried by distillation

from sodium and benzophenone) was added MeLi (2.65 mL, 1.13 M in Et_2O, 2.98 mmol) at -30 °C under Ar atmosphere. The solution was stirred at same temperature for 10 min. The solution of organocopper complex was added the epoxy alcohol **14a** (61.5 mg, 0.298 mmol) in dry Et_2O (2 mL, dried by distillation from sodium and benzophenone) by gastight syringe. The reaction mixture was stirred at 0 °C for 7 h, it was quenched with saturated aqueous NH_4Cl and saturated aqueous $NaHCO_3$. The suspension was allowed to stir room temperature under air and then the aqueous phase was turned to bright blue. The reaction mixture was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 4:1) to give mixture of the 1,3-diol **15** and 1,2-diol **16** (64.3 mg, 0.289 mmol, 97%). The ratio of 1,3-diol **15** and 1,2-diol **16** was 1:2.5.

^{1}H-NMR of 1,3-diol **15** (400 MHz, $CDCl_3$): δ 7.32-7.25 (m, 2H), 7.22-7.17 (m, 3H) 3.92-3.85 (m, 1H), 3.72-3.64 (m, 1H), 2.90-2.81 (m, 1H), 2.71-2.63 (m, 1H), 2.56 (brs, 1H), 2.36 (brs, 1H), 1.95-1.79 (m, 2H), 1.67-1.57 (m, 2H), 1.48-1.38 (m, 1H), 0.96 (d, J = 6.8 Hz, 3H) , 0.95 (t, J = 7.6 Hz, 3H); **^{1}H-NMR** of 1,2-diol **16** (400 MHz, $CDCl_3$): δ 7.30-7.25 (m, 2H), 7.21-7.15 (m, 3H), 3.61-3.55 (m, 1H), 3.40 (dd, J = 7.6, 4.4 Hz, 1H), 2.76 (ddd, J = 13.6, 10.8, 4.8 Hz, 1H), 2.54 (ddd, J = 13.6, 10.4, 6.4 Hz, 1H), 2.08-1.98 (m, 1H), 1.70-1.60 (m, 1H), 1.60-1.35 (m, 3H), 1.00 (t, J = 7.6 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H); **^{13}C-NMR** of 1,3-diol **15** (100 MHz, $CDCl_3$): δ 142.3, 128.61 (2C), 128.58 (2C), 126.0, 75.7, 74.3, 41.1, 37.7, 32.5, 27.2, 11.3, 10.8; **^{13}C-NMR** of 1,2-diol **16** (100 MHz, $CDCl_3$): δ 142.9, 128.51 (2C), 128.48 (2C), 125.8, 78.9, 74.1, 34.8, 34.4, 33.3, 23.2, 15.8, 10.5; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3410, 2931, 1458, 1219, 972, 756; **HRMS** (EI) *m/z* calculated for $C_{14}H_{20}O$ $[M-H_2O]^{+\cdot}$ 204.1514, found 204.1511.

Synthesis of Epoxy Silyl Ether **14b**



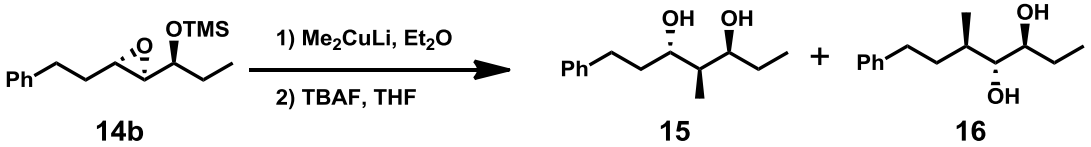
14a **14b**

To a solution of epoxy alcohol **14a** (132 mg, 0.565 mmol) in dry THF (3 mL) was added Et_3N (0.79 mL, 5.65 mmol) and TMSCl (0.49 mL, 2.83 mmol). The solution was stirred

at room temperature under Ar atmosphere for 3 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ at 0°C. The aqueous phase was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 15:1) to give the epoxy silyl ether **14b** (157 mg, 0.565 mmol, 100 %).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31-7.26 (m, 2H), 7.22-7.16 (m, 3H), 3.43 (dt, J = 8.0, 4.4 Hz, 1H), 2.90 (ddd, J = 7.2, 5.2, 2.4 Hz, 1H), 2.84-2.69 (m, 2H), 2.69 (dd, J = 5.2, 2.4 Hz, 1H), 1.96-1.76 (m, 2H), 1.65-1.57 (m, 1H), 1.55-1.41 (m, 1H), 0.94 (t, J = 7.2 Hz, 3H), 0.10 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 141.4, 128.6 (2C), 128.5 (2C), 126.1, 72.9, 61.2, 56.1, 33.8, 32.4, 28.0, 9.8, 0.43 (3C); **IR** ν_{max} (thin film/NaCl) cm^{-1}: 2962, 1458, 1249, 841, 702; **HRMS** (EI) *m/z* calculated for $C_{16}H_{26}O_2Si$ $[M]^{+\cdot}$ 278.1702, found 278.1730.

Methylation of Epoxy Silyl Ether **14b**

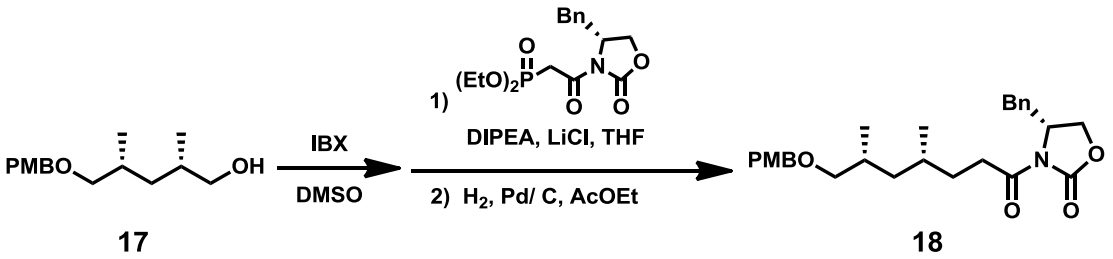


14b **15** **16**

Methylation of epoxy silyl ether **14b** was the same method as the case of **14a**. The crude residue was treated with TBAF (5 eq.). The deprotected compounds were purified by column chromatography on silica gel (hexane / AcOEt = 4:1) to give mixture of the 1,3-diol **15** and 1,2-diol **16** (96% yield, 2 steps). The ratio of 1,3-diol **15** and 1,2-diol **16** was 2.5:1.

2. Sekothrixide の合成研究

Synthesis of Amide **18**



17 **18**

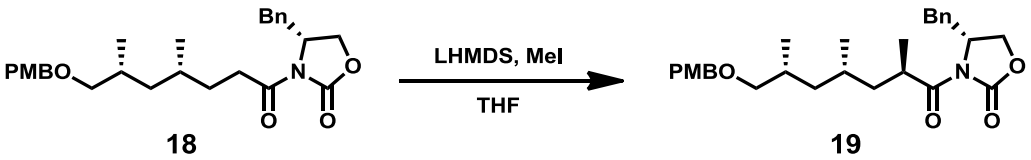
To a solution of optically active alcohol **17** (692 mg, 2.74 mmol) in DMSO (10 mL) was added IBX (1.16 g, 4.13 mmol). The solution was stirred at room temperature under Ar atmosphere for 3 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL) and H_2O (150 mL). The aqueous phase was extracted with AcOEt (3 x 80 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressur. The crude residue was filtered through a short pad of silica gel with mixed solvent (hexane / AcOEt = 2:1) and concentrated *in vacuo*. The filtered aldehyde (667 mg) was used in the next step without further purification.

Next, the phosphate (1.51 g, 4.24 mmol) and LiCl (578 mg, 13.6 mmol) in a flask were dried by high vacuum pump at room temperature for 2 h and purged Ar. The compounds were dissolved by dry THF (10 mL) and added DIPEA (770 μL, 4.42 mmol). The solution was stirred at room temperature for 20 min. The reaction mixture was add aldehyde (667 mg) with dry THF (total amount of used solvent was 10 mL) by Pasteur pipette. The resultant solution was stirred at room temperature for 6 days. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and H_2O (150 mL). The aqueous phase was extracted with AcOEt (3 x 80 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 4:1 > hexane / AcOEt = 1:1) to give the conjugated amide (869 mg, 1.92 mmol, 70%, 2 steps).

To a solution of conjugated amide (455 mg, 1.00 mmol) in AcOEt (20 mL) was added Pd/ C (44.9 mg, 10 wt.%). The suspension was stirred at room temperature under H_2 atmosphere (balloon pressure) for 1.5 h. The reaction mixture was filtered through a short pad of silica gel with AcOEt and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 4:1) to give the amide **18** (413 mg, 0.909 mmol, 90%).

$[\alpha]_D^{27}$ = -35.2° (c = 1.1, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.36-7.31 (m, 2H), 7.30-7.24 (m, 3H), 7.23-7.19 (m, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.65 (m, 1H), 4.45 (d, *J* = 12.0 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.20-4.13 (m, 2H), 3.80 (s, 3H), 3.34-3.27 (m, 2H), 3.19 (dd, *J* = 9.2, 7.6 Hz, 1H), 2.93 (t, *J* = 8.0 Hz, 2H), 2.76 (dd, *J* = 13.6, 10.0 Hz, 1H), 1.88 (m, 1H), 1.77 (m, 1H), 1.61 (m, 1H), 1.47-1.34 (m, 2H), 1.01 (m, 1H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.0 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 173.6, 159.0, 153.4, 135.3, 130.9, 129.4, 129.1, 128.9, 127.3, 113.7, 75.6, 72.6, 66.1, 55.3, 55.2, 41.3, 37.9, 33.2, 30.86, 30.83, 29.7, 20.1, 17.9; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 1782, 1697, 1612, 1249, 825; **HRMS** (FAB matrix NBA) *m/z* calculated for $C_{27}H_{36}O_4N$ $[M+H]^+$ 454.2593, found 454.2584.

Methylation of Amide **18**

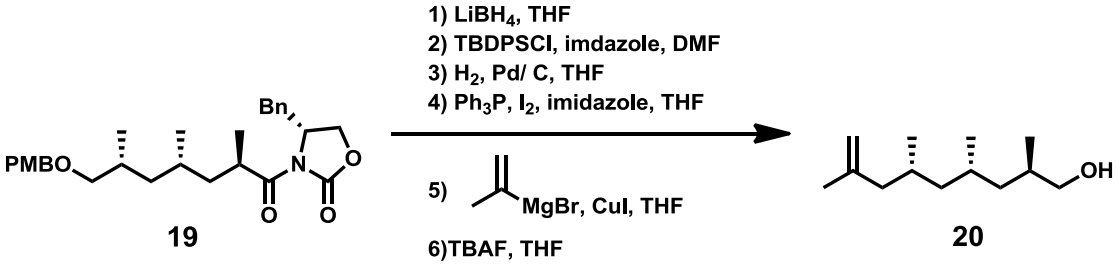


To a solution of amide **18** (408 mg, 0.899 mmol) and MeI (590 μL, 9.00 mmol) in dry THF (10 mL) was added LHMDS (2.7 mL, 1.0 M in THF, 2.7 mmol). The solution was stirred at -70 °C under Ar atmosphere for 30 min. The reaction mixture was slowly warmed to -10 °C for 4 h. The solution was quenched with saturated aqueous NH_4Cl (30 mL) and H_2O (20 mL). The aqueous phase was extracted with AcOEt (3 x 60 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 5:1) to give the trimethyl compound **19** (352 mg, 0.752 mmol, 83%).

$[\alpha]_D^{28}$ = -37.2° (c = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.36-7.31 (m, 2H), 7.31-7.19 (m, 5H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.60 (m, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.39 (d, *J* = 11.2 Hz, 1H), 4.15-4.08 (m, 2H), 3.83 (m, 1H), 3.79 (s, 3H), 3.28-3.23 (m, 2H), 3.18 (dd, *J* = 8.8, 6.8 Hz, 1H), 2.75 (dd, *J* = 13.2, 9.6 Hz, 1H), 1.85 (m, 1H), 1.60 (m, 1H), 1.50-1.39 (m, 2H), 1.33 (m, 1H), 1.19 (d, *J* = 7.2 Hz, 3H), 0.98 (m, 1H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 177.7, 159.0, 153.0, 135.4, 130.8, 129.4,

129.0, 128.9, 127.3, 113.7, 75.8, 72.6, 66.0, 55.4, 55.3, 41.9, 40.1, 37.9, 35.3, 30.7, 27.7, 19.9, 17.8, 16.8; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 1782, 1697, 1612, 1242, 825; **HRMS** (FAB matrix NBA) *m/z* calculated for $C_{28}H_{38}NO_5$ $[M+H]^+$ 468.2750, found 468.2727.

Synthesis of Alcohol **20**



To a solution of trimetyl compound **19** (352 mg, 0.752 mmol) in dry THF (10 mL) was added $LiBH_4$ (55.6 mg, 2.29 mmol). The solution was stirred at room temperature under Ar atmosphere for 6 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and H_2O (90 mL). The aqueous phase was extracted with AcOEt (3 x 80 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 5:1 > hexane / AcOEt = 2:1) to give the alcohol (186 mg, 0.630 mmol, 83%).

To a solution of alcohol (113 mg, 0.382 mmol) and imidazole (81.5 mg, 1.19 mmol) in dry DMF (2 mL) was added TBDPSCl (150 μL, 0.574 mmol). The solution was stirred at room temperature under Ar atmosphere for 6 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and H_2O (20 mL). The aqueous phase was extracted with AcOEt (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 10:1) to give the silyl ether (199 mg, 0.374 mmol, 97%).

To a solution of silyl ether (188 mg, 0.353 mmol) in dry THF (5 mL) was added Pd/ C (20.7 mg, 10 wt.%). The suspension was stirred at room temperature under H_2 atmosphere (balloon pressure) for 56 h. The reaction mixture was filtered through a short pad of silica gel with AcOEt and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 5:1) to give the

alcohol (108 mg, 0.263 mmol, 74%).

To a solution of alcohol (109 mg, 0.263 mmol), imidazole (72.7 mg, 1.06 mmol) and Ph_3P (141 mg, 0.526 mmol) in dry THF (5 mL) was added I_2 (142 mg, 0.559 mmol). The solution was stirred at room temperature under Ar atmosphere for 20 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), saturated aqueous Na_2SO_3 (2 mL) and H_2O (10 mL). The aqueous phase was extracted with AcOEt (3 x 40 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane = 1) to give the iodide (135 mg, 0.258 mmol, 98%).

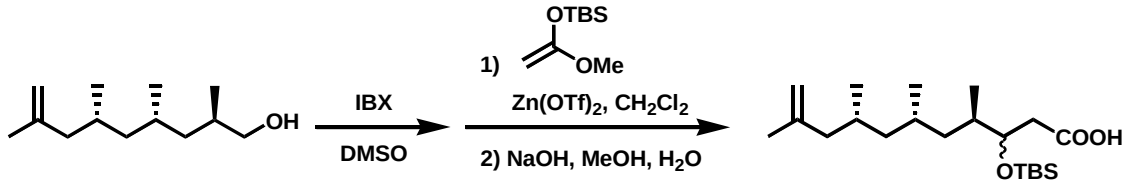
To a suspension of iodide (142 mg, 0.272 mmol) and CuI (77.7 mg, 0.405 mmol) in dry THF (5 mL, dried by distillation from sodium and benzophenone) was added isopropenylmagnesium bromide (2.45 mL, 0.5 M in THF, 1.22 mmol) at -20 °C under Ar atmosphere. After 20 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and saturated aqueous $NaHCO_3$ (5 mL). The suspension was allowed to stir room temperature under air for 2 h and then the aqueous phase was turned to bright blue. The reaction mixture was added H_2O (30 mL) and extracted with AcOEt (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography on silica gel (hexane = 1) to give the alkene (70.6 mg, 0.162 mmol, 59%).

To a solution of alkene (50.8 mg, 0.116 mmol) in dry THF (1 mL) was added TBAF (240 μL, 1.0 M in THF, 0.240 mmol). The solution was stirred at room temperature under Ar atmosphere for 8 h. The reaction mixture was filtered through a short pad of silica gel with AcOEt and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 5:1) to give the alcohol **20** (17.7 mg, 0.0892 mmol, 77%).

$[\alpha]_D^{27}$ = +33.9° (c = 0.87, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 4.73 (s, 1H), 4.65 (s, 1H), 3.47 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.41 (dd, *J* = 10.0, 6.4 Hz, 1H), 2.02 (dd, *J* = 12.4, 4.4 Hz, 1H), 1.79-1.56 (m, 4H), 1.69 (s, 3H), 1.34 (brs, 1H), 1.19 (ddd, *J* = 14.0, 8.0, 6.0 Hz, 1H), 1.10-1.06 (m, 2H), 1.00 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 144.8, 111.4, 69.2, 46.1, 45.9, 40.2,

33.2, 27.8, 27.2, 22.3, 20.1, 19.8, 16.2; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3340 (br), 3078, 1651, 1042, 887; **MS** (EI) *m/z* 198.1.

Synthesis of Segment C1-C10 (**21**)



20 **Segment C1-C10 (21)**

To a solution of alcohol **20** (16.6 mg, 0.0839 mmol) in DMSO (0.5 mL) was added IBX (47.7 mg, 0.170 mmol). The solution was stirred at room temperature under Ar atmosphere for 1.5 h. The reaction mixture was filtered through a short pad of silica gel with Et_2O. The solvent was removed under reduced pressure (300 mmHg, 40 °C). The aldehyde was used in the next step without further purification.

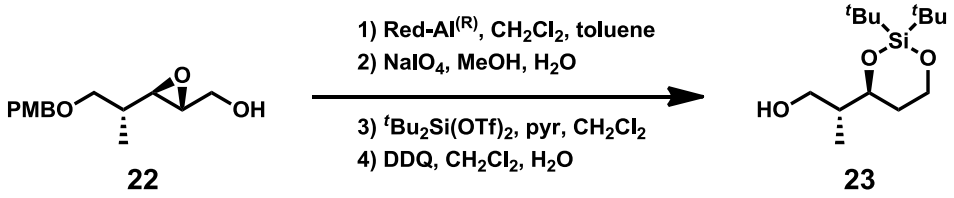
Next, to a solution of aldehyde and 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (38.0 μL, 0.168 mmol) in dry CH_2Cl_2 (1 mL) was added $Zn(OTf)_2$ (15.6 mg, 0.0419 mmol). The reaction mixture was stirred at room temperature under Ar atmosphere for 2 h. The suspension was quenched with saturated aqueous $NHCO_3$ (5 mL) and H_2O (10 mL). The aqueous phase was extracted with AcOEt (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 50:1) to give the aldol compound (23.2 mg, 0.0603 mmol, 72%, 2 steps) as a diastereomeric mixture with a ratio of *ca.* 2:1.

To a solution of aldol compound (21.5 mg, 0.0559 mmol) in MeOH (1 mL) was added 2 M aqueous NaOH (0.5 mL). The solution was stirred at room temperature for 28 h. The reaction mixture was quenched with saturated aqueous $NaHSO_4$ (until exhibit acidic property) and H_2O (20 mL). The aqueous phase was extracted with AcOEt (3 x 30 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 5:1) to give the segment C1-C10 (**21**) (16.3 mg, 0.0439 mmol, 78%) as a diastereomeric mixture with a ratio of *ca.* 2:1.

$[\alpha]_D^{27}$ = +32.2° (c = 0.84, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 4.73 (s, 1H), 4.65 (s,

1H), 4.06-3.98 (m, 1H), 2.49-2.37 (m, 2H), 2.05-1.98 (m, 1H), 1.80-1.64 (m, 3H), 1.68 (s, 3H), 1.60-1.51 (m, 1H), 1.22-0.95 (m, 4H), 0.88 (s, 9H), 0.86-0.79 (m, 9H), 0.08 (s, 3H), 0.05 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 177.4 (C=O), 177.0 (C=O), 144.8 (major), 144.7 (minor), 111.4 (both isomers), 73.7 (minor), 73.5 (major), 46.2 (major), 46.1 (both isomers), 45.9 (minor), 39.6 (minor), 38.9 (major), 38.6 (major), 38.0 (minor), 36.3 (minor), 36.0 (major), 27.8 (both isomers), 27.3 (minor), 27.1 (major), 25.8 (3C for both isomers), 22.2 (both isomers), 20.0 (minor), 19.9 (both isomers), 19.7 (major), 18.0 (both isomers), 14.3 (major), 13.9 (minor), -4.5 (both isomers), -4.7 (major), -4.8 (minor); **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3071, 2708, 1713, 1651, 1250, 1087, 833; **HRMS** (FAB matrix NBA) *m/z* calculated for $C_{21}H_{43}O_3Si$ $[M+H]^+$ 371.2981, found 371.2970.

Synthesis of Alcohol **23**



To a solution of epoxy alcohol **22** (21.1 g, 83.4 mmol) in dry CH_2Cl_2 (100 mL) was added Red-Al(R) (80.0 mL, 65 wt.% in toluene, 262 mmol) at 0 °C. The solution was warmed to ambient temperature and stirred for 22 h under Ar atmosphere. The reaction mixture was stirred at 0 °C for 5 min and quenched with MeOH (20 mL). The resultant mixture was vigorously stirred at room temperature for 2 h and filtered using Büchner funnel with MeOH. The filtrate was concentrated *in vacuo*.

Next, to a solution of the crude diol in MeOH (40 mL) and H_2O (10 mL) was added $NaIO_4$ (9.01 g, 42.1 mmol). The reaction mixture was stirred at room temperature for 1 h and then quenched with saturated aqueous NaCl (500 mL) and H_2O (500 mL). The aqueous phase was extracted with AcOEt (5 x 200 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 1:4) to give the diol (14.4 g, 56.7 mmol, 68%, 2 steps).

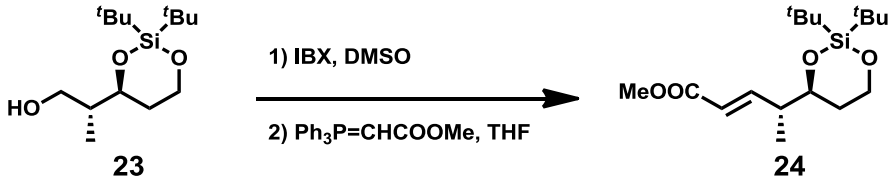
To a solution of diol (13.3 g, 51.9 mmol) in dry CH_2Cl_2 (100 mL) was added pyridine (13.0 mL, 160 mmol) and $^tBu_2Si(OTf)_2$ (20.5 mL, 60.9 mmol) at 0 °C. The solution was

warmed to ambient temperature and stirred for 17 h under Ar atmosphere. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL) and H_2O (100 mL). The aqueous phase was extracted with AcOEt (3 x 200 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane = 1) to give the silylene (19.4 g, 49.1 mmol, 94%).

To a solution of sylylene (108 mg, 0.274 mmol) in CH_2Cl_2 (3 mL) and H_2O (300 μL) was added DDQ (77.7 mg, 0.335 mmol). The solution was stirred at room temperature for 2 h. The dark reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and H_2O (5 mL). The aqueous phase was extracted with AcOEt (3 x 30 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (benzenes / AcOEt = 20:1) to give the alcohol **23** (67.8 mg, 0.247 mmol, 90%).

[α]$_D^{28}$ = +24.1° (c = 1.2, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 4.17-4.07 (m, 2H), 4.01 (ddd, *J*= 10.4, 8.0, 1.6 Hz, 1H), 3.74-3.62 (m, 2H), 3.37 (brd, *J*= 6.4 Hz, 1H), 1.94-1.78 (m, 2H), 1.74 (ddd, *J*= 14.4, 4.0, 2.0 Hz, 1H), 1.05 (s, 9H), 1.01 (s, 9H), 0.84 (d, *J*= 6.8 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 81.2, 68.4, 64.5, 41.7, 34.7, 27.4, 27.1, 22.7, 19.8, 13.4; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3441 (br), 1111, 895; **HRMS** (FAB matrix NBA) *m/z* calculated for $C_{14}H_{31}O_3Si$ $[M+H]^+$ 275.2042, found 275.2068.

Synthesis of Conjugated Ester **24**



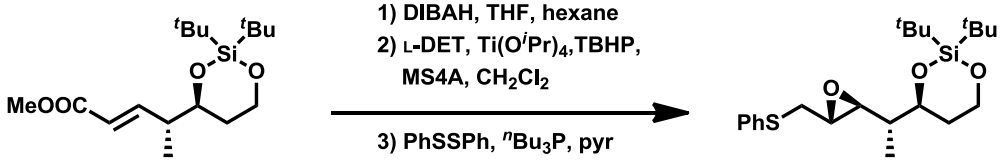
To a solution of alcohol **23** (25.1 mg, 0.0914 mmol) in DMSO (500 μL) was added IBX (54.4 mg, 0.194 mmol). The solution was stirred at room temperature for 2 h under Ar atmosphere. The reaction mixture was filtered through a short pad of silica gel with Et_2O and solvent was removed under reduced pressure.

To a solution of filtered mixture in THF (1 mL) was added Ph_3P=CHCOOMe (83.5 mg,

0.244 mmol). The orange solution was stirred at room temperature for 1 week and solvent was removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 9:1) to give the conjugated ester **24** (25.6 mg, 0.0779 mmol, 85%, 2 steps).

$[\alpha]_D^{28}$ = +22.1° (c = 0.60, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ7.05 (dd, J= 15.6, 8.0 Hz, 1H), 5.86 (dd, J= 15.6, 1.2 Hz, 1H), 4.14-4.07 (m, 2H), 4.03 (ddd, J= 11.2, 4.4, 2.4 Hz, 1H), 3.73 (s, 3H), 2.41 (m, 1H), 1.83 (dtd, J= 14.0, 10.8, 6.0 Hz, 1H), 1.51 (ddd, J= 14.0, 4.8, 2.4 Hz, 1H), 1.12 (d, J= 7.2 Hz, 3H), 1.02 (s, 9H), 0.99 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ167.0, 151.0, 121.1, 77.0, 64.5, 51.4, 43.5, 33.8, 27.5, 27.1, 22.9, 20.0, 15.3; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 1728, 1658, 1111, 895; **HRMS** (EI) *m/z* calculated for $C_{17}H_{32}O_4Si$ $[M]^{+\cdot}$ 328.2070, found 328.2061.

Synthesis of Epoxy Sulfide **25**



24 **25**

To a solution of conjugated ester **24** (25.6 mg, 0.0779 mmol) in dry THF (2 mL) was added DIBAH (250 μL, 1.03 M in hexane, 0.257 mmol). The solution was stirred at -72 °C under Ar atmosphere for 1.5 h. The reaction mixture was quenched with MeOH (0.5 mL). The resultant mixture was vigorously stirred at room temperature for 1.5 h. The gel was filtered through a short pad of silica gel with AcOEt and concentrated *in vacuo*. The allyl alcohol was given a 21.1 mg (0.0702 mmol, 90%).

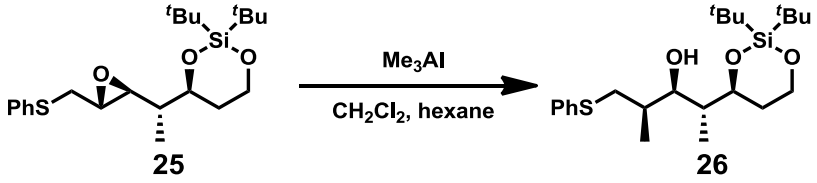
To a suspension of allyl alcohol (21.1 mg, 0.0702 mmol) and activated MS4A (700 mg) in dry CH_2Cl_2 (2 mL, dried by distillation from calcium hydride) was stirred at -30 °C under Ar atmosphere. Other two-necked flask was added dry CH_2Cl_2 (1 mL, dried by distillation from calcium hydride), $Ti(O^iPr)_4$ (20 μL, 0.065 mmol) and L-DET (15 μL, 0.087 mmol) at -30 °C under Ar atmosphere. The solution was stirred for 45 min and moved to a suspension via cannula. The suspention was added TBHP (100 μL, 1.83 M in

CH_2Cl_2, 0.183 mmol) and resultant mixture was stirred for 15 h. The suspention was quenched with saturated aqueous $Na_2S_2O_3$ (200 μL) and stirred at room temperature for 15 min. The reaction mixture was filtered through a short pad of Na_2SO_4 with AcOEt and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 4:1) to give the epoxy alcohol (18.4 mg, 0.0581 mmol, 83%).

To a solution of epoxy alcohol (17.1 mg, 0.0540 mmol) in pyridine (200 μL) was added $^{n}Bu_3P$ (30 μL, 0.11 mmol) and PhSSPh (25.5 mg, 0.114 mmol). The solution was stirred at room temperature under Ar atmosphere for 4 h. The reaction mixture was stirred at 50 °C for 2.5 h and solvent was removed under reduced pressure. The crude residue was purified by column chromatography on silica gel (benzenes = 1) to give the epoxy sulfide **25** (20.8 mg, 0.0508 mmol, 94%).

[α]$_D^{19}$ = +38.7° (c = 1.1, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.40 (m, 2H), 7.29 (m, 2H), 7.21 (m, 1H), 4.14-4.01 (m, 3H), 3.20 (dd, *J* = 12.0, 3.2 Hz, 1H), 2.98-2.89 (m, 3H), 2.06 (dtd, *J* = 14.4, 12.0, 5.2 Hz, 1H), 1.52 (ddd, *J* = 14.4, 4.0, 2.0 Hz, 1H), 1.42 (m, 1H), 1.02 (s, 9H), 1.00 (s, 9H), 0.87 (d, *J* = 6.8 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 135.4, 129.7, 129.0, 126.5, 76.4, 64.9, 60.0, 55.0, 42.3, 36.1, 33.9, 27.5, 27.2, 22.9, 20.0, 12.5; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 1582, 1381, 1250, 1111, 895; **HRMS** (EI) *m/z* calculated for $C_{22}H_{36}O_3SSi$ $[M]^{+\cdot}$ 408.2154, found 408.2143.

Methylation of Epoxy Sulfide **25**

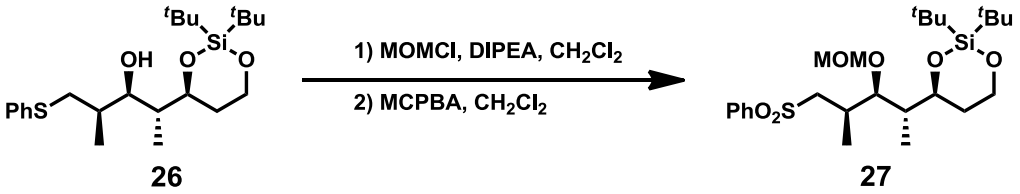


To a solution of epoxy sulfide **25** (29.7 mg, 0.0726 mmol) in dry CH_2Cl_2 (1 mL, dried by distillation from calcium hydride) was added Me_3Al (200 μL, 1.08 M in hexane, 0.216 mmol). The solution was stirred at -50 °C under Ar atmosphere for 19 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL) and stirred at room temperature. The suspension was filtered through a short pad of Na_2SO_4 with CH_2Cl_2

and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 10:1) to give the sulfide **26** (25.0 mg, 0.0588 mmol, 80%).

$[\alpha]_D^{20}$ = +54.8° (c = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.35 (m, 2H), 7.26 (m, 2H), 7.14 (m, 1H), 4.65 (t, *J* = 1.4 Hz, 1H), 4.15-4.07 (m, 3H), 3.81 (ddd, *J* = 9.2, 4.0, 1.6 Hz, 1H), 3.15 (dd, *J* = 12.8, 7.2 Hz, 1H), 2.95 (dd, *J* = 12.8, 6.8 Hz, 1H), 1.92-1.80 (m, 3H), 1.65 (m, 1H), 1.06 (s, 9H), 1.01 (s, 9H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.68 (d, *J* = 6.8 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 137.4, 128.76, 128,74, 125.5, 81.5, 77.2, 64.4, 42.4, 38.2, 35.4, 34.6, 27.4, 27.1, 22.7, 19.8, 12.5, 11.8; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3487, 1582, 1381, 1250, 1111, 895; **HRMS** (EI) *m/z* calculated for $C_{23}H_{40}O_3SSi$ $[M]^{+\cdot}$ 424.2467, found 424.2457.

Synthesis of Sulfone **27** (in **Scheme 19**)



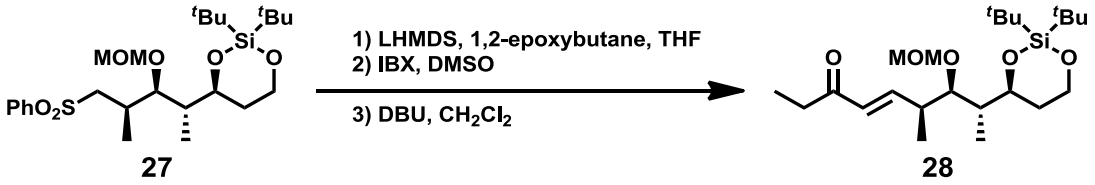
26 **27**

To a solution of sulfide **26** (17.1 mg, 0.0403 mmol) in dry CH_2Cl_2 (1 mL) was added DIPEA (50 μL, 0.28 mmol) and MOMCl (12 μL, 0.12 mmol). The solution was stirred at room temperature under Ar atmosphere for 50 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 10:1) to give the MOM ether (18.2 mg, 0.0388 mmol, 96%).

To a solution of MOM ether (96.7 mg, 0.206 mmol) in CH_2Cl_2 (5 mL) was added MCPBA (102 mg, 77 wt.%, 0.453 mmol). The solution was stirred at 0 °C for 45 min. The suspension was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL), 2 M aqueous NaOH (1 mL) and H_2O (10 mL). The aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 2:1) to give the sulfone **27** (95.6 mg, 0.190 mmol, 92%).

$[\alpha]_D^{26}$ = +26.5° (c = 1.1, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ7.92 (m, 2H), 7.65 (m, 1H), 7.56 (m, 2H), 4.59 (d, J= 6.8 Hz, 1H), 4.51 (d, J= 6.8 Hz, 1H), 4.20 (ddd, J= 11.0, 5.2, 1.6 Hz, 1H), 4.13 (ddd, J= 11.0, 4.8, 2.4 Hz, 1H), 4.05 (td, J= 12.0, 2.4 Hz, 1H), 3.57 (dd, J= 8.0, 2.4 Hz, 1H), 3.43 (dd, J= 14.4, 5.6 Hz, 1H), 3.34 (s, 3H), 3.00 (dd, J= 13.6, 6.8 Hz, 1H), 2.50 (m, 1H), 1.96 (m, 1H), 1.76 (m, 1H), 1.54 (ddd, J= 14.0, 4.0, 2.0 Hz, 1H), 1.10 (d, J= 6.8 Hz, 3H), 1.02 (s, 9H), 0.99 (s, 9H), 0.87 (d, J= 6.8 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ140.4, 133.6, 129.3, 127.8, 97.9, 82.8, 74.4, 64.6, 60.5, 56.0, 43.2, 31.7, 30.2, 27.5, 27.3, 22.8, 20.0 14.6, 10.9; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 1389, 1304, 1150, 1103, 894; **HRMS** (ESI) *m/z* calculated for $C_{25}H_{44}NaO_6Si$ $[M+Na]^+$ 523.2526, found 523.2542.

Synthesis of Enone **28**



To a solution of sulfone **27** (321 mg, 0.640 mmol) in dry THF (3 mL) was added 1,2-epoxybutane (280 μL, 3.22 mmol) and LHMDS (3.2 mL, 1.0 M in THF, 3.2 mmol) at 0 °C. The solution was stirred at room temperature under Ar atmosphere for 6 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and H_2O (60 mL). The aqueous phase was extracted with AcOEt (3 x 60 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude alcohol (364 mg) was used in the next step without purification.

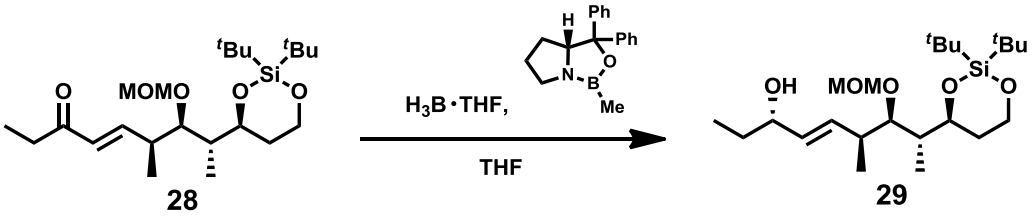
To a solution of crude alcohol (364 mg) in DMSO (5 mL) was added IBX (537 mg, 1.92 mmol). The solution was stirred at room temperature for 18 h. The reaction mixture was quenched with H_2O (80 mL).The suspension was filtered using Kiriyama funnel with AcOEt, excess AcOEt was removed under reduced pressure. The aqueous phase was extracted with AcOEt (3 x 70 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude ketone (348 mg) was used in the next step without purification.

To a solution of crude ketone (348 mg) in CH_2Cl_2 (10 mL) was added DBU (150 μL,

0.982 mmol). The solution was stirred at room temperature for 2 h. The reaction mixture was filtered through a short pad of silica gel with AcOEt and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 9:1) to give the enone **28** (106 mg, 0.248 mmol, 38%, 3 steps).

$[\alpha]_D^{25}$ = +8.0° (c = 1.5, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 6.88 (dd, *J* = 16.0, 8.0 Hz, 1H), 6.12 (dd, *J* = 16.0, 1.2 Hz, 1H), 4.61 (d, *J* = 6.8 Hz, 1H), 4.57 (d, *J* = 6.8 Hz, 1H), 4.14-4.02 (m, 3H), 3.69 (t, *J* = 5.2 Hz, 1H), 3.37 (s, 3H), 2.69 (m, 1H), 2.56 (q, *J* = 7.2 Hz, 2H), 1.99 (m, 1H), 1.80-1.66 (m, 2H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H), 1.03 (s, 9H), 1.01 (s, 9H), 0.91 (d, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 201.0, 150.1, 129.0, 97.5, 82.0, 74.8, 64.5, 56.1, 43.8, 38.9, 33.4, 33.1, 27.4, 27.2, 22.7, 19.9, 15.1, 11.1, 8.1; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 1674, 1628, 1366, 1103, 895; **HRMS** (ESI) *m/z* calculated for $C_{23}H_{44}NaO_5Si$ $[M+Na]^+$ 451.2856, found 451.2868.

Synthesis of Allyl Alcohol **29** (**Table 9, Entry 5**)

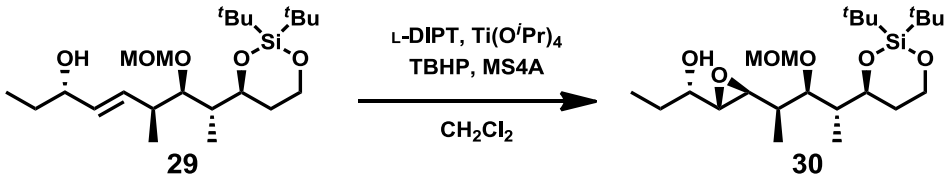


To a solution of enone **28** (176.2 mg, 0.4110 mmol) in dry THF (5 mL) was added (*R*)-Me-CBS (490 μL, 1 M in toluene, 0.490 mmol) and BH_3·THF (520 μL, 0.95 M in THF, 0.494 mmol). The solution was stirred at -40 °C under Ar atmosphere for 70 min. The reaction mixture was quenched with MeOH (3 mL) and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give the allyl alcohol **29** (165 mg, 0.383 mmol, 93%, dr 15:1). Allyl alcohol **29** was obtained as inseparable mixture of C19 diastereomer.

$[\alpha]_D^{29}$ = +7.2° (c = 0.98, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.68 (dd, *J* = 15.6, 8.4 Hz, 1H), 5.48 (dd, *J* =15.6, 6.8 Hz, 1H), 4.60 (s, 2H), 4.22 (ddd, *J* = 10.4, 6.8, 3.2 Hz, 1H), 4.14-4.03 (m, 2H), 3.99 (brq, *J* = 6.4 Hz, 1H), 3.57 (t, *J* = 6.0 Hz, 1H), 3.37 (s, 3H), 2.51 (m, 1H), 1.98 (m, 1H), 1.80-1.66 (m, 2H), 1.61-1.48 (m, 2H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 9H), 1.01 (s, 9H), 0.92 (d, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (100 MHz,

$CDCl_3$): δ 135.8, 132.1, 97.7, 83.1, 74.8, 74.3, 64.7, 56.0, 43.7, 38.6, 32.9, 30.2, 27.5, 27.2, 22.8, 19.9, 16.2, 10.9, 9.7; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3448 (br), 1651, 1381, 1103, 895; **HRMS** (FAB matrix NBA) *m/z* calculated for $C_{23}H_{47}O_5Si$ $[M+H]^+$ 431.3193, found 431.3207.

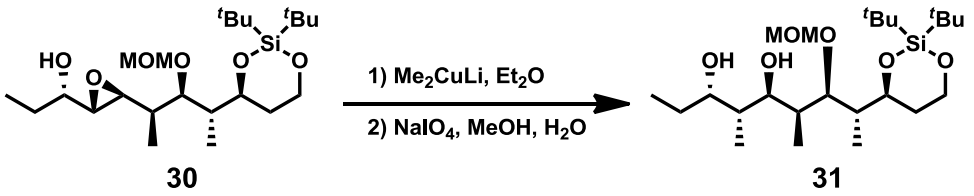
Synthesis of Epoxy Alcohol **30**



To a suspension of allyl alcohol **29** (166.7 mg, 0.3870 mmol) and activated MS4A (2 g) in dry CH_2Cl_2 (5 mL) was added TBHP (180 μL, 3.2 M in CH_2Cl_2, 0.576 mmol) at -30 °C under Ar atmosphere. Other two-necked flask was added L-DIPT (120 μL, 0.572 mmol) and dry CH_2Cl_2 (3 mL) under Ar atmosphere. The solution was allowed to cool to -30 °C before the addition of $Ti(O^iPr)_4$ (137 μL, 0.462 mmol). The reaction mixture was stirred for 10 min and moved to a suspension via cannula. The suspentsion was stirred at same temperature for 18 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and then stirred at room temperature for 3 h. The suspension was filtered and added H_2O (40 mL). The aqueous phase was extracted with AcOEt (4 x 80 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (benzenes / AcOEt = 5:1) to give the epoxy alcohol **30** (145 mg, 0.324 mmol, 83%).

$[\alpha]_D^{28}$ = +45.1° (c = 1.1, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 4.66 (d, *J* = 7.2 Hz, 1H), 4.63 (d, *J* = 7.2 Hz, 1H), 4.16-4.03 (m, 3H), 3.69 (dd, *J* = 7.2, 2.4 Hz, 1H), 3.42 (s, 3H), 3.31 (m, 1H), 2.96 (d, *J* = 1.6 Hz, 1H), 2.86 (dd, *J* = 8.0, 2.0 Hz, 1H), 2.77 (dd, *J* = 6.4, 2.4 Hz, 1H), 2.00 (m, 1H), 1.84-1.45 (m, 5H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.03 (s, 9H), 1.02 (t, *J* = 8.0 Hz, 3H), 1.00 (s, 9H), 0.87 (d, *J* = 7.6 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 97.9, 82.6, 74.9, 72.9, 64.5, 61.5, 60.6, 56.1, 43.5, 38.0, 32.6, 27.5, 27.22, 27.16, 22.8, 19.9, 11.9, 11.0, 9.6; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3472 (br), 1381, 1111, 825; **HRMS** (FAB matrix NBA) *m/z* calculated for $C_{23}H_{47}O_6Si$ $[M+H]^+$ 447.3142, found 447.3138.

Synthesis of Diol **31** from **30**



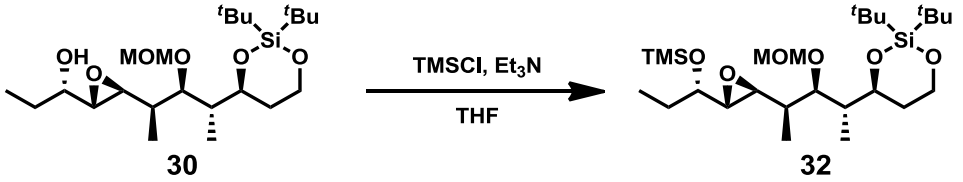
30 **31**

To a suspension of epoxy alcohol **30** (32.9 mg, 0.0703 mmol) and CuI (70.7 mg, 0.371 mmol) in dry Et_2O (1 mL, dried by distillation from sodium and benzophenone) was added MeLi (740 μL, 1.1 M in Et_2O, 0.814 mmol) -70 °C under Ar atmosphere. The raction mixture was slowly warmed to ambient temperature and stirred for 23 h. The solution was quenched with saturated aqueous NH_4Cl (1 mL) and 29 % aqueous NH_4OH (0.1 mL). The suspension was stirred under air, the aqueous phase was turned to bright blue. The reaction mixture was added H_2O (5mL) and extracted with AcOEt (3 x 20 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*.

Next, to a solution of crude residue (35.8 mg) in MeOH (0.5 mL) and H_2O (0.5 mL) was added $NaIO_4$ (76.0 mg, 0.355 mmol). The reaction mixture was stirred at room temperature for 4 h. The suspension was added Na_2SO_4, filtered through a short pad of silica gel with AcOEt and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give the diol **31** (12.8 mg, 0.0276 mmol, 39%).

[α]$_D^{23}$ = +27.0° (c = 0.99, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 4.69 (d, *J* = 6.0 Hz, 1H), 4.67 (d, *J* = 6.0 Hz, 1H), 4.15-4.04 (m, 3H), 3.92 (m, 1H), 3.82 (dt, *J* = 9.6, 2.0 Hz, 1H), 3.74 (d, *J* = 2.0 Hz, 1H, OH), 3.62 (m, 1H), 3.41 (s, 3H), 3.08 (d, *J* = 8.0 Hz, 1H, OH), 2.04-1.86 (m, 3H), 1.82-1.70 (m, 2H), 1.56-1.39 (m, 2H), 1.04-0.98 (m, 6H), 1.02 (s, 9H), 1.00 (s, 9H), 0.89 (d, *J* = 7.6 Hz, 3H), 0.79 (d, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 96.9, 82.5, 79.1, 76.3, 75.8, 64.1, 56.1, 44.6, 39.5, 34.7, 34.3, 27.3, 27.2, 25.4, 22.6, 19.9, 12.5, 11.3, 10.8, 7.5; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3441 (br), 1381, 1111, 895; **HRMS** (ESI) *m/z* calculated for $C_{24}H_{50}NaO_6Si$ $[M+Na]^+$ 485.3274, found 485.3264.

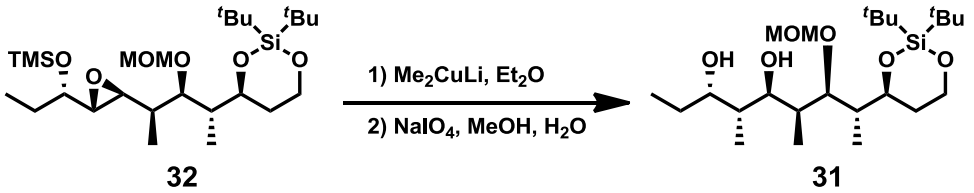
Synthesis of Epoxy Silyl Ether **32**



To a solution of epoxy alcohol **30** (98.8 mg, 0.221 mmol) in dry THF (2 mL) was added Et_3N (310 μL, 2.21 mmol) and TMSCl (145 μL, 1.11 mmol). The solution was stirred at room temperature under Ar atmosphere for 3 h. The reaction mixture was stirred at 0 °C, it was quenched with saturated aqueous $NaHCO_3$ (5 mL) and H_2O (20 mL). The aqueous phase was extracted with AcOEt (3 x 40 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude epoxy silyl ether **32** (115 mg) was used in the next step without purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.67 (d, J = 6.8 Hz, 1H), 4.63 (d, J = 6.8 Hz, 1H), 4.21-4.05 (m, 3H), 3.66 (dd, J= 6.0, 3.2 Hz, 1H), 3.54 (dt, J= 7.2, 4.8 Hz, 1H), 3.39 (s, 3H), 2.88 (dd, J= 6.8, 2.4 Hz, 1H), 2.79 (dd, J= 4.4, 2.4 Hz, 1H), 2.07 (m, 1H), 1.83-1.67 (m, 3H), 1.64-1.47 (m, 2H), 1.04 (d, J= 6.8 Hz, 3H), 1.03 (s, 9H), 1.00 (s, 9H), 0.95 (t, J= 7.2 Hz, 3H), 0.91 (d, J= 7.2 Hz, 3H), 0.09 (s, 9H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 97.7, 81.6, 74.9, 72.4, 64.6, 60.5, 59.5, 56.2, 43.1, 37.6, 32.7, 27.9, 27.6, 27.3, 22.8, 19.9, 11.7, 11.6, 9.7, 0.3; **HRMS** (EI) *m/z* calculated for $C_{22}H_{45}O_6Si_2$ $[M\text{-}^tBu]^{+\cdot}$ 461.2755, found 461.2759.

Synthesis of Diol **31** from **32**

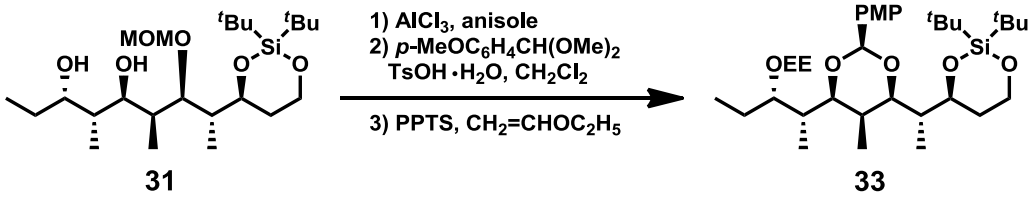


To a suspension of CuI (213 mg, 1.12 mmol) in dry Et_2O (5 mL, dried by distillation from sodium and benzophenone) was added MeLi (1.95 mL, 1.13 M in Et_2O, 2.20 mmol) at -20 °C under Ar atmosphere. The solution was added the crude epoxy silyl ether **32** (115 mg) in dry Et_2O (3 mL, dried by distillation from sodium and benzophenone) by gastight syringe. The reaction mixture was stirred for 7.5 h, it was quenched with saturated aqueous NH_4Cl (10 mL) and saturated aqueous $NaHCO_3$ (5 mL). The suspension was allowed to stir room temperature under air and then the aqueous phase

was turned to bright blue. The reaction mixture was added H_2O (30 mL) and extracted with AcOEt (3 x 40 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*.

Next, to a solution of crude residue (119 mg) in MeOH (4 mL) and H_2O (2 mL) was added $NaIO_4$ (99.9 mg, 0.467 mmol). The reaction mixture was stirred at room temperature for 3.5 h (resulted in selective deprotection of TMS group and oxidative cleavage of 1,2-diol). The suspension was quenched with saturated aqueous Na_2SO_3 (10 mL), saturated aqueous $NaHCO_3$ (5 mL) and H_2O (50 mL). The aqueous phase was extracted with AcOEt (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give the diol **31** (85.9 mg, 0.185 mmol, 83%).

Synthesis of Ethylvinyl Ether **33**



31 **33**

To a solution of diol **31** (25.7 mg, 0.0555 mmol) in anisole (3 mL) was added $AlCl_3$ (37.8 mg, 0.277 mmol). The solution was stirred at 0 °C under Ar atmosphere for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL) and H_2O (10 mL). The aqueous phase was extracted with AcOEt (3 x 50 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 2:1) to give the triol (21.4 mg, 0.0511 mmol, 92%).

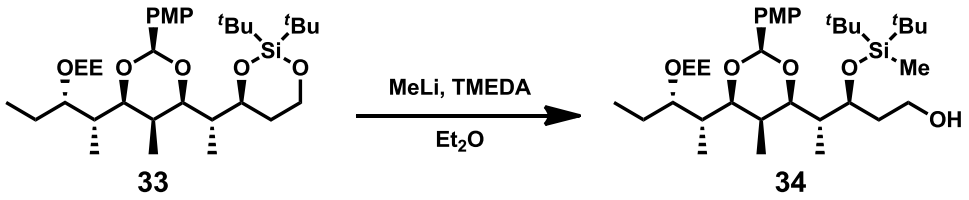
To a solution of triol (72.7 mg, 0.173 mmol) in dry CH_2Cl_2 (2 mL) was added *p*-$MeOC_6H_4CH(OMe)_2$ (62 μL, 0.34 mmol) and TsOH・H_2O (3.2 mg, 0.016 mmol). The solution was stirred at room temperature under Ar atmosphere for 2 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (3 mL) and H_2O (5 mL). The aqueous phase was extracted with AcOEt (3 x 30 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was

purified by column chromatography on silica gel (benzenes = 1 > hexane / AcOEt = 5:1) to give the benzylidene acetal (86.0 mg, 0.160 mmol, 92%).

To a solution of benzylidene acetal (86.0 mg, 0.160 mmol) in CH_2=$CHOC_2H_5$ (3 mL) was added PPTS (4.0 mg, 0.016 mmol). The solution was stirred at room temperature under Ar atmosphere for 20 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL) and H_2O (5 mL). The aqueous phase was extracted with AcOEt (3 x 30 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 10:1) to give the ethylvinyl ether **33** (86.8 mg, 0.142 mmol, 88%) as a diastereomeric mixture with a ratio of *ca.* 1:1.

[α]$_D^{28}$ = +24.4° (c = 1.2, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.36 (d, *J*= 8.8 Hz, 0.5 x 2H x 2), 6.88 (d, *J*= 9.2 Hz, 0.5 x 2H), 6.87 (d, *J*= 8.8 Hz, 0.5 x 2H), 5.42 (s, 0.5H), 5.36 (s, 0.5H), 4.69 (q, *J*= 5.0 Hz, 0.5H), 4.66 (q, *J*= 5.0 Hz, 0.5H), 4.43 (brd, *J*= 12.8 Hz, 0.5H x 2), 4.17-4.02 (m, 0.5 x 2H x 2), 3.93 (ddd, *J*= 7.6, 5.2, 0.8 Hz, 0.5H), 3.89 (dd, *J*= 10.4, 2.0 Hz, 0.5H), 3.82 (m, 0.5H), 3.81 (s, 0.5 x 3H x 2), 3.74-3.58 (m, 0.5 x 2H x 2 + 0.5H), 3.50-3.39 (m, 0.5H x 2), 2.14-1.97 (m, 0.5 x 2H x 2), 1.85-1.40 (m, 0.5 x 5H x 2), 1.29 (d, *J* = 5.2 Hz, 0.5 x 3H), 1.28 (d, *J*= 4.8 Hz, 0.5 x 3H), 1.17 (t, *J*= 6.8 Hz, 0.5 x 3H), 1.11 (t, *J*= 6.8 Hz, 0.5 x 3H), 1.03-1.02 (m, 0.5 x 18H x 2), 0.96-0.91 (m, 0.5 x 6H x 2), 0.88 (d, *J*= 7.2 Hz, 0.5 x 3H), 0.86 (d, *J*= 8.0 Hz, 0.5 x 3H), 0.83 (d, *J*= 7.6 Hz, 0.5 x 3H), 0.81 (d, *J*= 6.8 Hz, 0.5 x 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 159.7, 159.6, 131.9, 131.7, 127.07 (x 2), 127.01 (x 2), 113.53 (x 2), 113.47 (x 2), 100.7, 100.47, 100.42, 99.5, 81.7, 81.5, 81.4, 80.9, 76.5, 76.0, 75.6, 75.4, 65.5, 65.4, 61.5, 60.8, 55.3 (x 2), 40.2 (x 2), 37.0, 36.5, 31.9, 31.6, 30.6 (x 2), 27.6 (x 2), 27.3 (x 2), 25.5, 25.3, 22.9 (x 2), 21.3, 20.6, 20.0 (x 2), 15.5, 15.4, 10.54, 10.52, 10.4, 10.3, 7.4, 7.1, 5.6, 5.5; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 1620, 1381, 1111, 895, 825, 756; **HRMS** (FAB matrix NBA) *m/z* calculated for $C_{34}H_{61}O_7Si$ $[M+H]^+$ 609.4187, found 609.4169.

Synthesis of Alcohol **34**

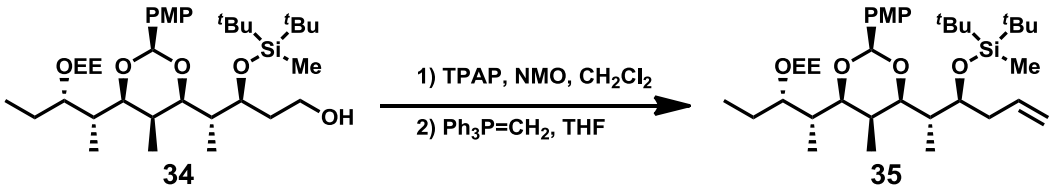


33 **34**

To a solution of ethylvinyl ether **33** (75.7 mg, 0.124 mmol) in dry Et_2O (2 mL) was added TMEDA (95 μL, 0.61 mmol) and MeLi (560 μL, 1.1 M in Et_2O, 0.61 mmol). The solution was stirred at room temperature under Ar atmosphere for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (3 mL) and H_2O (15 mL). The aqueous phase was extracted with AcOEt (3 x 40 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give the alcohol **34** (66.3 mg, 0.106 mmol, 85%) as a diastereomeric mixture with a ratio of *ca.* 1:1.

$[\alpha]_D^{28}$ = +2.3° (c = 1.0, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.360 (d, *J*= 8.8 Hz, 0.5 x 2H), 7.357 (d, *J*= 8.8 Hz, 0.5 x 2H), 6.88 (d, *J*= 9.2 Hz, 0.5 x 2H), 6.87 (d, *J*= 8.8 Hz, 0.5 x 2H), 5.40 (s, 0.5H), 5.34 (s, 0.5H), 4.71 (q, *J*= 5.2 Hz, 0.5H), 4.67 (q, *J*= 5.2 Hz, 0.5H), 4.50 (m, 0.5H x 2), 3.93 (ddd, *J*= 8.4, 6.0, 1.2 Hz, 0.5H), 3.88-3.78 (m, 0.5 x 2H x 2), 3.81 (s, 0.5 x 3H x 2), 3.75-3.59 (m, 0.5 x 3H x 2), 3.57-3.41 (m, 0.5 x 2H x 2 + 0.5H), 2.27-2.17 (m, 0.5 x 2H), 1.83-1.60 (m, 0.5 x 5H x 2), 1.55-1.39 (m, 0.5H x 2), 1.32 (d, *J*= 5.6 Hz, 0.5 x 3H), 1.30 (d, *J*= 4.8 Hz, 0.5 x 3H), 1.18 (t, *J*= 7.2 Hz, 0.5 x 3H), 1.15 (t, *J*= 6.8 Hz, 0.5 x 3H), 1.009 (s, 0.5 x 9H), 1.006 (s, 0.5 x 9H), 0.995 (s, 0.5 x 9H x 2), 0.92 (d, *J*= 6.4 Hz, 0.5 x 3H), 0.91 (d, *J*= 6.8 Hz, 0.5 x 3H), 0.89-0.78 (m, 0.5 x 9H x 2), 0.11 (s, 0.5 x 3H x 2); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 159.7, 159.6, 131.8, 131.6, 127.10, 127.01, 113.5, 113.4, 100.7, 100.53, 100.46, 99.3, 82.6, 82.4, 81.3, 80.8, 76.5, 75.7, 71.2, 71.1, 61.5, 61.3 (x 2), 60.8, 55.3 (x 2), 39.81, 39.75, 37.0, 36.5, 33.9 (x 2), 30.45, 30.41, 28.1 (x 2), 28.0 (x 2), 25.3 (x 2), 25.3 (x 2), 21.3, 21.0, 20.7, 20.6, 15.6, 15.4, 10.5, 10.4, 8.6, 8.5, 7.4, 7.1, 5.42, 5.36, -7.5 (x 2); **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3456 (br), 1620, 1381, 1250, 826, 756; **HRMS** (FAB matrix NBA) *m/z* calculated for $C_{35}H_{65}O_7Si$ $[M+H]^+$ 625.4500, found 625.4514.

Synthesis of Alkene **35**



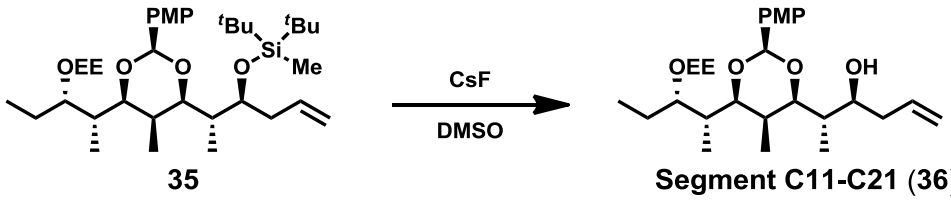
The alcohol **34** (37.0 mg, 0.0592 mmol), TPAP (11.5 mg, 0.0327 mmol) and NMO (10.7 mg, 0.885 mmol) in a flask were dried by high vacuum pump at room temperature for 20 min and purged Ar. The compounds were dissolved by dry CH_2Cl_2 (1 mL) and the solution was stirred at room temperature for 2 h. The reaction mixture was filtered through a short pad of silica gel with AcOEt and concentrated *in vacuo*. The filtered aldehyde (40.1 mg) was used in the next step without purification.

The filtered aldehyde (40.1 mg) was dissolved by dry THF (2 mL) and stirred at 0 °C under Ar atmosphere. The methyltriphenylphosphonium bromide (216.6 mg, 0.594 mmol) was added dry THF (3 mL) in other two-necked flask. The suspension was added ^{n}BuLi (360 μL, 1.64 M in hexane, 0.590 mmol) and stirred at 0 °C under Ar atmosphere for 5 min. The reaction mixture was moved to aldehyde solution by gastight syringe. The solution was stirred for 10 min, quenched with saturated aqueous NH_4Cl (10 mL) and H_2O (20 mL). The aqueous phase was extracted with AcOEt (3 x 40 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give the alkene **35** (31.3 mg, 0.0504 mmol, 85%, 2 steps) as a diastereomeric mixture with a ratio of *ca.* 1:1.

$[\alpha]_D^{28}$ = -5.0° (c = 0.92, $CHCl_3$); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.38 (d, *J*= 8.8 Hz, 0.5 x 2H x 2), 6.881 (d, *J*= 8.4 Hz, 0.5 x 2H), 6.876 (d, *J*= 8.8 Hz, 0.5 x 2H), 5.94-5.82 (m, 0.5H x 2), 5.39 (s, 0.5H), 5.33 (s, 0.5H), 5.03 (dt, *J*= 16.8, 2.0 Hz, 0.5H x 2), 4.98-4.93 (m, 0.5H x 2), 4.71 (q, *J*= 5.2 Hz, 0.5H), 4.69 (q, *J*= 5.2 Hz, 0.5H), 4.39-4.33 (m, 0.5H x 2), 3.94 (t, *J* = 6.8 Hz, 0.5H), 3.88-3.77 (m, 0.5H x 2), 3.81 (s, 0.5 x 3H x 2), 3.73-3.58 (m, 0.5 x 2H x 2 + 0.5H), 3.52-3.42 (m, 0.5H x 2), 2.38-2.28 (m, 0.5H x 2), 2.24-2.13 (m, 0.5 x 2H x 2), 1.84-1.59 (m, 0.5 x 3H x 2), 1.55-1.39 (m, 0.5H x 2), 1.32 (d, *J*= 4.8 Hz, 0.5 x 3H), 1.31 (d, *J*= 5.2 Hz, 0.5 x 3H), 1.19 (t, *J*= 6.8 Hz, 0.5 x 3H), 1.16 (t, *J*= 7.6 Hz, 0.5 x 3H), 0.984 (s, 0.5 x 9H x2), 0.979 (s, 0.5 x 9H x2), 0.91-0.78 (m, 0.5 x 12H x 2), 0.071 (s, 0.5 x 3H), 0.066

(s, 0.5 x 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 159.6, 159.5, 137.23, 137.21, 132.1, 131.9, 127.07, 126.99, 115.9, 115.8, 113.43, 113.36, 100.5 (x 2), 100.2, 99.6, 82.4, 82.2, 81.3, 80.8, 76.5, 76.1, 72.02, 71.98, 61.5, 60.8, 55.3 (x 2), 40.3 (x 2), 37.3, 37.2, 37.1, 36.5, 30.50, 30.45, 28.1 (x 2), 28.0 (x 2), 25.5 (x 2), 25.3 (x 2), 21.3, 20.81, 20.78, 20.7, 15.5, 15.4, 10.6, 10.4, 8.6 (x 2), 7.4, 7.1, 5.3, 5.2, -7.97, -8.02; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3071, 1620, 1519, 1381, 1250, 825; **HRMS** (FAB matrix NBA) *m/z* calculated for $C_{36}H_{65}O_6Si$ $[M+H]^+$ 621.4550, found 621.4526.

Synthesis of Segment C11-C21 (**36**)



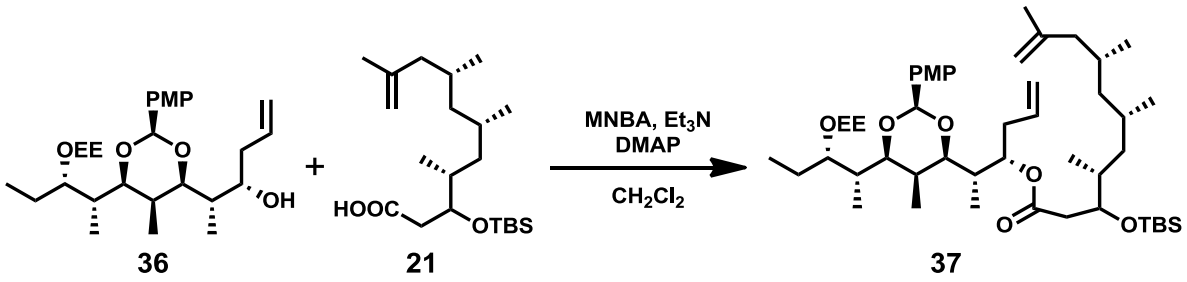
35 **Segment C11-C21 (36)**

To a solution of alkene **35** (28.8 mg, 0.0464 mmol) in DMSO (1 mL) was added CsF (75.3 mg, 0.480 mmol). The solution was stirred at 120 °C under Ar atmosphere for 38 h. The reaction mixture was filtered through a short pad of silica gel with Et_2O and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 5:1 > hexane / AcOEt = 2:1) to give the segment C11-C21 (**36**) (20.7 mg, 0.0445 mmol, 95%) as a diastereomeric mixture with a ratio of *ca.* 1:1.

$[\alpha]_D^{18}$ = +6.6° (c = 0.78, AcOEt); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.8 Hz, 0.5 x 2H x 2), 6.87 (d, *J* = 9.2 Hz, 0.5 x 2H), 6.86 (d, *J* = 8.8 Hz, 0.5 x 2H), 5.99-5.86 (m, 0.5H x 2), 5.51 (s, 0.5H), 5.44 (s, 0.5H), 5.15-5.06 (m, 0.5 x 2H x 2), 4.65 (q, *J* = 5.2 Hz, 0.5H), 4.61 (q, *J* = 5.2 Hz, 0.5H), 3.94-3.87 (m, 0.5H x 2), 3.85-3.71 (m, 0.5 x 4H x 2), 3.80 (s, 0.5 x 3H), 3.79 (s, 0.5 x 3H), 3.66-3.57 (m, 0.5H x 2), 3.48-3.37 (m, 0.5H x 2), 2.43-2.35 (m, 0.5H x 2), 2.17 (dt, *J* = 14.0, 8.0 Hz, 0.5H x 2), 2.01-1.88 (m, 0.5H x 2), 1.86-1.59 (m, 0.5 x 4H x 2), 1.57-1.39 (m, 0.5H x 2), 1.28 (d, *J* = 5.2 Hz, 0.5 x 3H x 2), 1.16 (t, *J* = 6.8 Hz, 0.5 x 3H), 1.11 (t, *J* = 6.8 Hz, 0.5 x 3H), 0.97 (d, *J* = 6.8 Hz, 0.5 x 3H), 0.96 (d, *J* = 6.8 Hz, 0.5 x 3H), 0.87-0.79 (m, 0.5 x 9H x 2); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 160.0, 159.9, 135.4 (x 2), 131.1, 130.9, 127.3, 127.2, 117.0, 116.9, 113.7, 113.6, 101.4, 101.1, 100.3, 99.4, 86.75, 86.70, 81.3, 80.9, 76.1, 75.8, 74.8, 74.7, 61.6, 61.0, 55.3 (x 2), 39.0 (x 2), 38.5 (x 2), 36.8,

36.4, 30.6 (x 2), 25.3, 25.1, 21.3, 20.6, 15.5, 15.3, 10.9 (x 2), 10.5, 10.3, 7.4, 7.1, 5.53, 5.46; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3495 (br), 3071, 1620, 1520, 1250, 833; **HRMS** (FAB matrix NBA) *m/z* calculated for $C_{27}H_{45}O_6$ $[M+H]^+$ 465.3216, found 465.3207.

Coupling of Both Segments



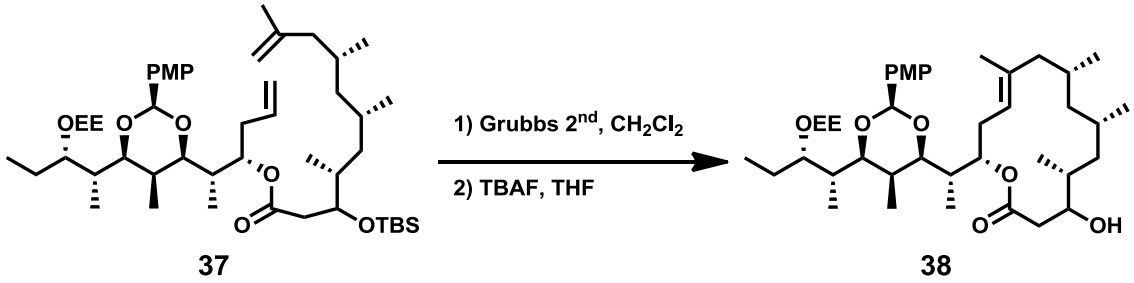
36 **21** **37**

To a solution of segment C11-C21 (**36**) (21.4 mg, 0.0461 mmol) and segment C1-C10 (**21**) (20.4 mg, 0.0551 mmol) in dry CH_2Cl_2 (1 mL, dried by distillation from calcium hydride) was added Et_3N (30.0 μL, 0.214 mmol), MNBA (23.8 mg, 0.0691 mmol) and DMAP (1.66 mg, 0.0135 mmol). The solution was stirred at room temperature under Ar atmosphere for 3 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL) and H_2O (20 mL). The aqueous phase was extracted with AcOEt (3 x 30 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 10:1 > hexane / AcOEt = 5:1) to give the ester **37** (27.3 mg, 0.0334 mmol, 72%, based on segment C11-C21 (**36**)). The ester **37** was a four diastereomixture.

$[\alpha]_D^{25}$ = +30.8° (c = 0.97, AcOEt); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.90-6.86 (m, 2H), 5.84-5.70 (m, 1H), 5.44-5.28 (m, 2H), 5.05 (d, *J* = 16.8 Hz, 1H), 4.99 (d, *J* = 10.0 Hz, 1H), 4.75-4.60 (m, 3H), 4.09-3.58 (m, 5H), 3.81 and 3.80 (s for each peak, 3H), 3.50-3.40 (m, 1H), 2.47-2.26 (m, 4H), 2.26-2.16 (m, 1H), 2.05-1.97 (m, 1H), 1.86-1.40 (m, 8H), 1.68 (s, 3H), 1.33-1.29 (m, 3H), 1.27-1.11 (m, 5H), 1.07-0.94 (m, 2H), 0.92-0.78 (m, 20H), 0.87 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): *δ* 171.4, 171.3, 159.7, 159.6, 144.86, 144.83, 135.25, 135.20, 135.15, 135.11, 131.7, 131.5, 127.2, 127.1, 116.9, 116.8, 113.53, 113.45, 111.3, 100.7, 100.48, 100.42, 99.4, 82.20, 82.17, 82.0, 81.2, 80.7, 76.36, 76.31, 76.01, 75.96, 73.8, 73.6, 73.46, 73.40, 61.6, 60.93, 60.87, 55.3, 46.21,

46.16, 46.05, 46.00, 39.9, 39.4, 39.17, 39.13, 38.7, 37.25, 37.20, 36.9, 36.5, 36.0, 35.5, 34.27, 34.25, 34.06, 34.04, 30.4, 27.79, 27.74, 27.2, 27.1, 25.9, 25.4, 25.2, 22.2, 21.3, 20.7, 20.0, 19.9, 19.8, 19.6, 18.1, 15.5, 15.4, 14.81, 14.75, 13.3, 10.5, 10.4, 10.0, 9.87, 9.80, 7.3, 7.1, 5.37, 5.29, -4.5, -4.62, -4.68; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3071, 1735, 1520, 1250, 1172, 833; **HRMS** (EI) *m/z* calculated for $C_{44}H_{75}O_8Si$ $[M-^tBu]^{+\cdot}$ 759.5231, found 759.5235.

Synthesis of Alcohol **38**



37 **38**

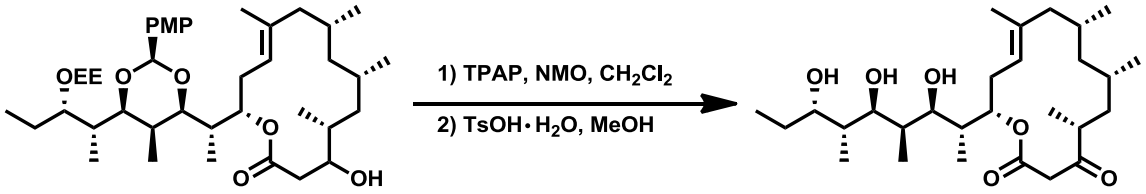
To a solution of ester **37** (19.4 mg, 0.0238 mmol) and Grubbs 2nd (6.09 mg, 7.17 μmol) in ultrasonic degassed dry CH_2Cl_2 (48 mL, 0.5 mM) was stirred under Ar atmosphere and heated reflux for 47 h. The reaction mixture was filtered through a short pad of silica gel with mixed solvent (hexane / AcOEt = 10 / 1) and concentrated *in vacuo*. The filtered macrolactone (16.1 mg) was used in the next step without purification.

To a solution of macrolactone (16.1 mg) in dry THF (300 μL) was added TBAF (55 μL, 1.0 M in THF, 0.055 mmol).The solution was stirred at room temperature under Ar atmosphere for 50 h. The reaction mixture was concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 3:1) to give the secondary alcohol **38** (9.74 mg, 0.0144 mmol, 60%, 2 steps). The secondary alcohol **38** was a four diastereomixture.

$[\alpha]_D^{26}$ = +24.2° (c = 0.49, AcOEt); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 7.45-7.39 (m, 2H), 6.91-6.86 (m, 2H), 5.55-5.32 (m, 2H), 5.17 and 5.05 (m for each peak, 1H), 4.72-4.60 (m, 1H), 3.98-3.58 (m, 5H), 3.803 and 3.801 (s for each peak, 3H), 3.51-3.39 (m, 1H), 2.59-2.48 (m, 1H), 2.46-2.01 (m, 5H), 1.82-1.34 (m, 9H), 1.58 (s, 3H), 1.32-1.28 (m, 3H), 1.20-1.10 (m, 4H), 1.08-0.71 (m, 24H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 172.3, 171.78, 171.75, 159.7, 159.6, 137.2, 137.1, 136.2, 136.1, 131.7, 131.6, 131.5, 131.4, 127.3, 127.2,

121.34, 121.27, 120.5, 113.5, 113.4, 100.9, 100.6, 100.4, 99.4, 82.7, 82.5, 81.1, 80.7, 76.3, 75.9, 75.40, 75.35, 74.7, 73.3, 72.02, 71.99, 62.3, 61.7, 60.9, 60.4, 55.3, 46.71, 46.68, 45.56, 43.3, 43.1, 42.5, 39.33, 39.26, 38.8, 38.3, 38.12, 38.09, 37.7, 36.9, 36.43, 36.37, 36.34, 35.2, 30.5, 30.1, 30.0, 28.9, 28.20, 28.16, 28.0, 25.3, 25.2, 22.8, 21.8, 21.3, 21.22, 21.19, 20.7, 19.68, 19.62, 18.8, 16.51, 16.47, 15.5, 15.4, 15.1, 10.5, 10.4, 10.0, 9.9, 7.3, 7.1, 5.44, 5.37; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3456 (br), 1721, 1250, 1165, 826, 756; **HRMS** (EI) *m/z* calculated for $C_{38}H_{60}O_7$ $[M\text{-}EtOH]^{+\cdot}$ 628.4339, found 628.4363.

Synthesis of Proposed Structure **39**



38 **39**

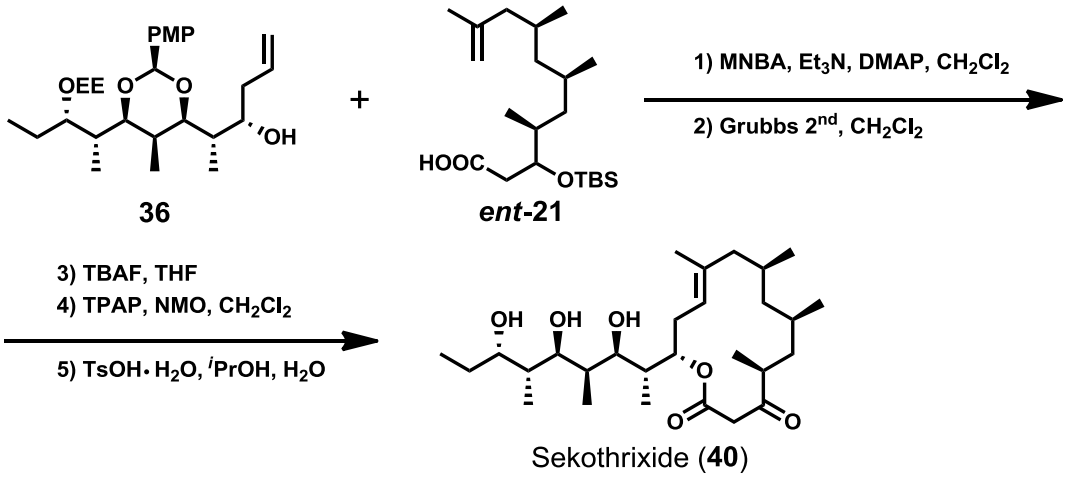
The secondary alcohol **38** (9.74 mg, 0.0144 mmol) and NMO (2.8 mg, 0.020 mmol) in a flask were dried by high vacuum pump at room temperature for 5 min and purged Ar. The compounds were dissolved by dry CH_2Cl_2 (0.5 mL). The reaction mixture was added TPAP (5.5 mg, 0.015 mmol). The solution was stirred at room temperature for 1.5 h. The reaction mixture was filtered through a short pad of silica gel with AcOEt and concentrated *in vacuo*. The ketolide was given a 6.59 mg (9.79 μmol, 67%) as a diastereomeric mixture with a ratio of *ca.* 1:1.

To a solution of ketolide (2.23 mg, 3.31 μmol) in MeOH (100 μL) was added TsOH・H_2O (trace). The solution was stirred at room temperature for 10 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 μL). The suspension was filtered through a short pad of Na_2SO_4 with AcOEt and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 4:1 > hexane / AcOEt = 3:2) to give the proposed structure **39** (0.65 mg, 1.34 μmol, 40%).

$[\alpha]_D^{20}$ = +9.3° (c = 0.035, MeOH); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.19 (m, 1H), 5.08 (t, *J* = 6.0 Hz, 1H), 4.03 (brs, 1H), 3.84 (d, *J* = 9.6 Hz, 1H), 3.75-3.69 (m, 1H), 3.67-3.63 (m, 1H), 3.49 (d, *J* = 12.4 Hz, 1H), 3.40 (d, *J* = 12.4 Hz, 1H), 3.33 (brs, 1H), 2.72 (m, 1H), 2.46

(d, J = 5.6 Hz, 1H), 2.39 (m, 1H), 2.26 (m, 1H), 2.15-2.04 (m, 2H), 1.93-1.77 (m, 2H), 1.75-1.65 (m, 3H), 1.63 (s, 3H), 1.60-1.30 (m, 4H), 1.09 (d, J = 7.6 Hz, 3H), 1.06-0.95 (m, 1H), 1.01 (t, J = 7.2 Hz, 3H), 0.908 (d, J = 7.6 Hz, 3H), 0.900 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.4 Hz, 6H), 0.78 (d, J = 6.8 Hz, 3H), 0.72 (m, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 205.1, 166.0, 137.5, 120.4, 79.6, 79.4, 77.3, 76.4, 47.6, 47.2, 45.3, 43.4, 40.1, 39.8, 39.6, 35.2, 29.3, 28.7, 26.8, 25.1, 23.5, 21.0, 18.0, 17.6, 12.1, 11.2, 11.1, 4.0; **IR** ν_{max} (thin film/NaCl) cm^{-1}:3410 (br), 1736, 1713, 1258, 972, 756; **HRMS** (EI) *m/z* calculated for $C_{28}H_{50}O_6$ $[M]^{+\cdot}$ 482.3607, found 482.3617.

Synthesis of Sekothrixide (**40**)



Sekothrixide (**40**)

To a solution of segment C11-C21 (**36**) (28.8 mg, 0.0621 mmol) and *ent*-**21** (28.9 mg, 0.0779 mmol) in dry CH_2Cl_2 (2 mL) was added Et_3N (44.0 μL, 0.314 mmol), MNBA (43.2 mg, 0.125 mmol) and DMAP (1.01 mg, 8.2 μmol). The solution was stirred at room temperature under Ar atmosphere for 5.5 h. Additionally, the reaction mixture was added Et_3N (22.0 μL, 0.157 mmol) and MNBA (21.0 mg, 0.0610 mmol). After 13 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and H_2O (20 mL). The aqueous phase was extracted with AcOEt (3 x 40 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 10:1) to give the ester (47.1 mg, 0.0577 mmol, 92%, based on **36**). The ester was a four diastereomixture.

To a solution of ester (9.81 mg, 0.0120 mmol) and Grubbs 2nd (3.12 mg, 3.67 μmol) in

ultrasonic degassed dry CH_2Cl_2 (24 mL, 0.5 mM) was stirred under Ar atmosphere and heated reflux for 56 h. The solvent was removed under reduced pressure. The reaction mixture was filtered through a short pad of silica gel with AcOEt and concentrated *in vacuo*. The macrolactone (15.3 mg) was used in the next step without further purification.

To a solution of macrolactone (15.3 mg) in dry THF (300 μL) was added TBAF (120 μL, 1.0 M in THF, 0.120 mmol).The solution was stirred at room temperature under Ar atmosphere for 27 h. The reaction mixture was filtered through a short pad of silica gel with AcOEt and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 10:1 > hexane / AcOEt = 4:1 > hexane / AcOEt = 1:1) to give the secondary alcohol (4.97 mg, 7.38 μmol, 61%, 2 steps). The ester was a four diastereomixture.

The secondary alcohol (13.8 mg, 0.0204 mmol) and NMO (4.7 mg, 0.039 mmol) in a flask were dried by high vacuum pump at room temperature for 5 min and purged Ar. The compounds were dissolved by dry CH_2Cl_2 (1 mL). The reaction mixture was added TPAP (7.9 mg, 0.022 mmol). The solution was stirred at room temperature for 2 h. The reaction mixture was filtered through a short pad of silica gel with AcOEt and concentrated *in vacuo*. The ketolide was given a 12.6 mg (0.0187 μmol, 91%) as a diastereomeric mixture with a ratio of *ca*. 1:1.

To a solution of ketolide (12.6 mg, 0.0187 mmol) in ^{i}PrOH (3 mL) and H_2O (0.3 mL) was added TsOH・H_2O (11.1 mg, 0.0585 mmol). The solution was stirred at 40 ^{o}C for 51 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL) and H_2O (20 mL). The aqueous phase was extracted with AcOEt. The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane / AcOEt = 3:1 > hexane / AcOEt = 1:1) to give the sekothrixide (**40**) (3.50 mg, 7.25 μmol, 38%).

[α]$_D^{27}$ = -46.4^{o} (c = 0.18, MeOH); **^{1}H-NMR** (400 MHz, $CDCl_3$): δ 5.27 (m, 1H), 5.05 (m, 1H), 4.04 (brs, 1H), 3.85 (d, *J*= 9.6 Hz, 1H), 3.73 (m, 1H), 3.63 (d, *J*= 9.6 Hz, 1H), 3.54 (d, *J*= 13.6 Hz, 1H), 3.45 (brs, 1H), 3.30 (d, *J*= 13.6 Hz, 1H), 2.92 (m, 1H), 2.43 (d, *J*= 5.6

Hz, 1H), 2.36 (ddd, J = 14.4, 10.8, 9.2 Hz, 1H), 2.16 (m, 1H), 2.11-1.98 (m, 2H), 1.95-1.85 (m, 2H), 1.74-1.45 (m, 5H), 1.59 (s, 3H), 1.31 (ddd, J = 11.2, 6.4, 4.8 Hz, 1H), 1.12 (d, J = 8.4 Hz, 3H), 1.02 (t, J = 7.2 Hz, 3H), 0.96 (m, 1H), 0.91 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.0 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 7.6 Hz, 3H), 0.78 (d, J = 7.2 Hz, 3H), 0.52 (ddd, J = 14.8, 8.0, 6.8 Hz, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 205.7, 167.0, 137.3, 121.6, 79.6, 79.1, 77.1, 76.5, 49.03, 49.01, 41.6, 41.4, 39.83, 39.78, 39.34, 35.2, 29.8, 28.1, 27.1, 25.1, 23.3, 21.1, 19.3, 16.7, 12.1, 11.1, 10.8, 3.9; **IR** ν_{max} (thin film/NaCl) cm^{-1}: 3418 (br), 1705, 1258, 972, 802, 756; **HRMS** (EI) *m/z* calculated for $C_{28}H_{50}O_6$ $[M]^{+\cdot}$ 482.3607, found 482.3612.

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