高活性アシル化触媒の開発を基盤とした
生物活性天然物の全合成研究

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創薬科学専攻　博士後期課程

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目次

略語表

Ac	Acetyl
aq.	Aqueous solution
Bn	Benzyl
Brsm	Based on recovered starting material
Bt	Benzotriazole
Bu	Butyl
Bz	Benzoyl
CSA	10-camphorsulfonic acid
DCE	1,2-dichloroethane
DFT	Density functional theory
DIBAL	Diisobutylaluminium hydride
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
d.r.	Diastereomer ratio
2,6-DTBP	2,6-di-*tert*-butylpyridine
E	Entgegen
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
ee	Enantiomeric excess
eq.	Equivalent
Et	Ethyl
h	Hour
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	Hexamethylphosphoric triamide
HRMS	High-resolution mass spectrum
Hz	Hertz
IR	Infrared
J	Coupling constant
LDA	Lithium diisopropylamide
LRMS	Low-resolution mass spectrum
*m*CPBA	*m*-chloroperoxybenzoic acid
M	Molar

Me	Methyl
min	Minute
MHz	Megahertz
MOM	Methoxymethyl
MS	Molecular sieve
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetic acid
M. W.	Micro Wave
m/*z*	Mass to charge ratio
NBS	*N*-bromosuccinimide
Nic	Nicotinyl
NIS	*N*-iodosuccinimide
NMR	Nuclear magnetic resonance
Ns	*o*-nitrobenzenesulfonyl
Ph	Phenyl
PMB	*p*-methoxybenzyl
ppm	Parts per million
Pr	Propyl
rt	Room temperature
TBAF	Tetrabutylammonium floride
TBAI	Tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
temp.	Temperature
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
TS	Transition state
Ts	*p*-toluenesulfonyl
Z	Zusammen

序論

生物活性天然物は強力で多様な生物活性を示すものの、複雑な構造のため合成が困難であるものが多い。複雑な構造を有する活性天然物の代表例として、Kansuinine A (**1**)や Kansuiphorin A (**2**)、Kopetdaghinane A (**3**)などが挙げられる（Figure 1）。これらは共通して立体的に混み入ったアシル基を有しており、それらアシル基の存在が合成を困難にしている要因の一つとなっていた。このため、以下に示す天然物の全合成を達成するためには、反応性の低い水酸基に対する高活性アシル化触媒の開発が必要であった。

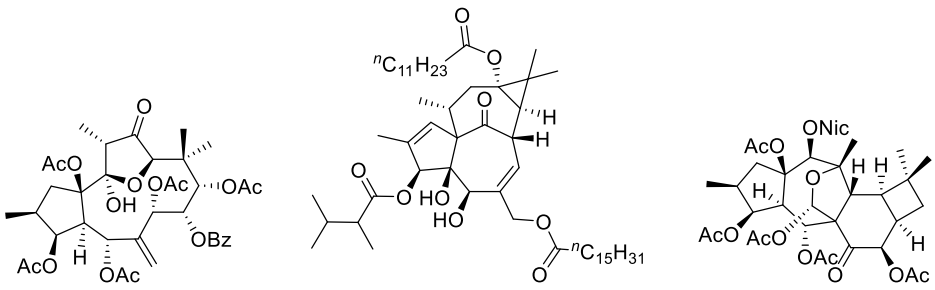


Figure 1

上記の背景を基に、著者はアシル化触媒である *N*,*N*-Dimethyl-4-aminopyridine (DMAP, **4**)[1]に着目した（Figure 2）。2003 年に Steglich らは、**4** の誘導体である 9-Azajulolidine (9-AJ, **5**)が **4** を上回る高いアシル化触媒活性を有することを理論計算によって報告し、実際に **5** を合成しその高い触媒活性を実証した[2]。一方、1,1,7,7-Tetramethyl-9-Azajulolidine (TMAJ, **6**)が **5** を上回るアシル化活性を有する触媒として、2005 年に理論計算によって報告されていたもの[3]、その合成難度の高さから、報告から 15 年もの間合成は達成されていなかった。そこで **6** を合成し実用化することができれば、反応性の低い水酸基に対するアシル化の問題を解決できると考えた。

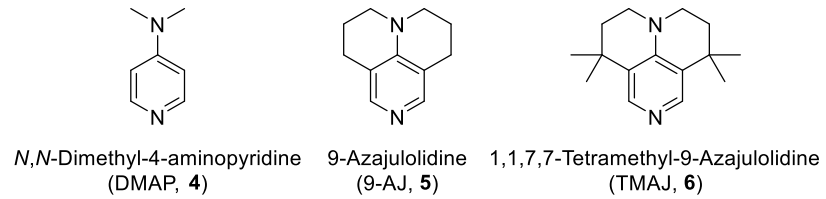
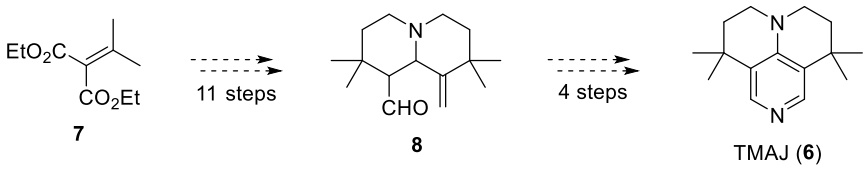


Figure 2

第 1 章では、TMAJ (**6**)の合成を行った（Scheme 1）[4]。これまでに報告されている 9-AJ (**5**)の合成は、ピリジン環を有する化合物を出発原料として用いている。しかしながら、ピリジン環の隣接位に四級炭素を構築することは一般に困難であることが知られており、本合成法を **6** の合成に適用することはできなかった。そこで市販の不飽和エステル **7** からアルデヒド **8** を合成した後、最後にピリジン環を構築する新たな合成経路により **6** の初の合成を達成した。さらに **6** を用いて、触媒活性の評価および基質適用範囲の調査を行った。



Scheme 1

第 2 章では、TMAJ (**6**)の合成時に確立した新規な Octahydro-2*H*-quinolizine (Quinolizidine) 骨格の効率的構築法を天然物の全合成へと応用した。Quinolizidine 骨格を有する天然物としては、(+)-Epilupinine (**9**)や Sparteine (**10**)、Matrine (**11**)が知られている（Figure 3）。特に **9** はマメ科の *Lupinus* 属植物に広く分布しているアルカロイド[5]であり、生物活性として白血病細胞に対する増殖阻害活性を有することが報告されている[6]。このため合成化学者からも高い関心を集めており、これまでに 15 報の不斉全合成[6,7]および 30 報を超えるラセミ体全合成[8]が報告されている。しかしながらグラムスケールを超える不斉全合成は報告されていなかったことから、**9** の迅速かつ大量供給可能な効率的不斉全合成を検討した[9]。

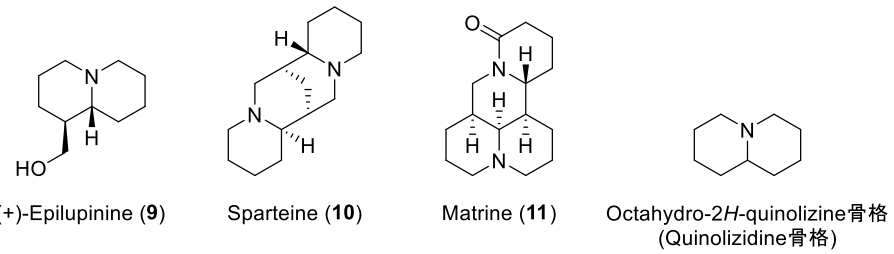
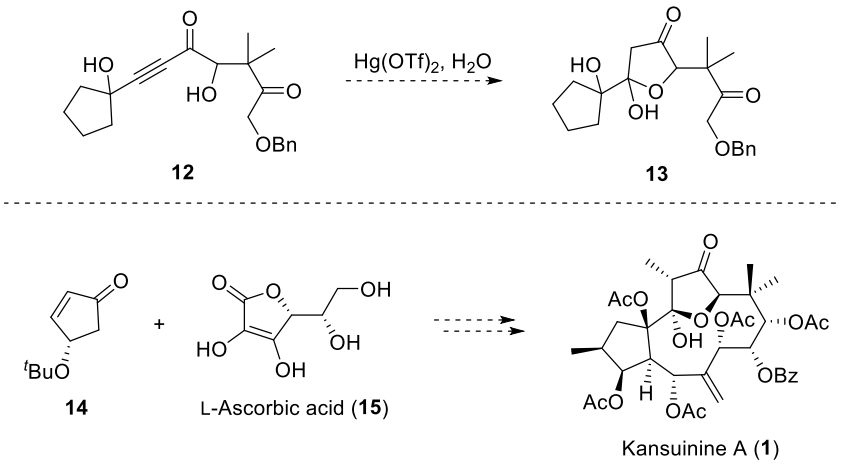


Figure 3

第 3 章では、Kansuinine A (**1**)の全合成研究を行った（Scheme 2）。**1** は、1975 年に上村・平田らによってトウダイグサ科の植物 *Euphorbia Kansui* の根から単離構造決定されたジテルペノイドであり[10]、生物活性として神経成長因子（NGF）に対する産生促進作用を有することが知られている。また構造的特徴として、高度に酸素官能基化された Jatrophane 骨格、五員環上の全てが *cis* に配置された 4 連続不斉中心とそれらを含む 7 個の連続する不斉中心、および不安定なヘミケタール構造を有することが挙げられる。**1** の全合成は報告されておらず、合成研究としてシクロペンタン核部位の合成が 1 例報告されている[11]。合成が困難であると予想される五員環上のヘミケタール部位の構築を最初の課題に設定し、モデル基質であるイノン **12** を用いてヘミケタール構造の構築を検討した。続いて、既知のシクロペンタノン誘導体 **14**[12]および市販の L-Ascorbic acid (**15**)を出発原料として、**1** の不斉全合成研究に着手した。



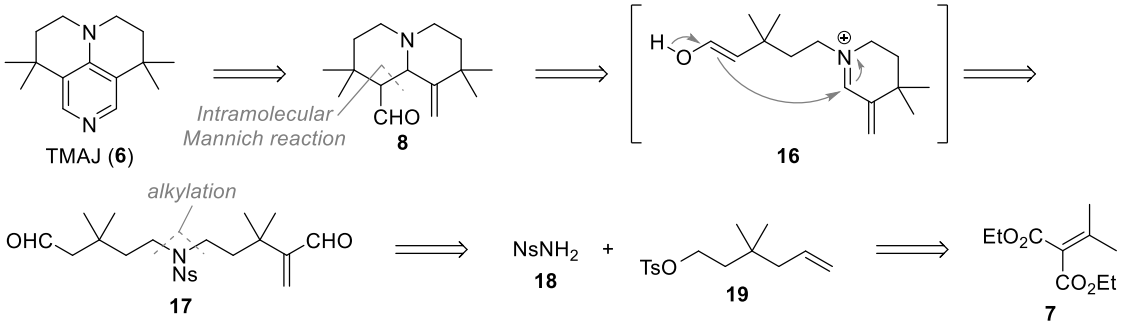
Scheme 2

本論

第 1 章　高触媒活性 DMAP 誘導体の開発

1-1. TMAJ (**6**)の合成計画

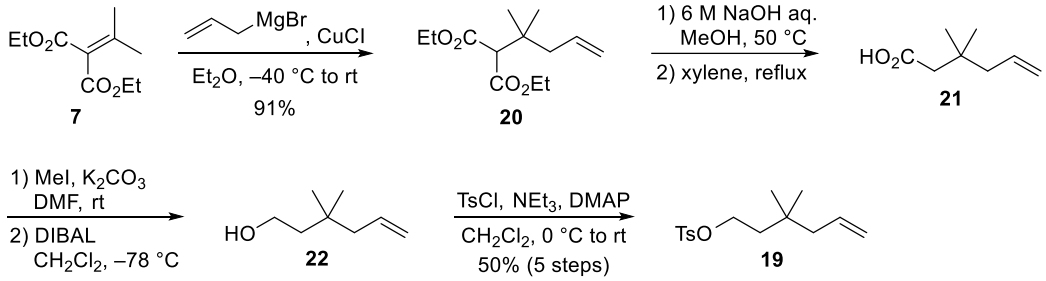
TMAJ (**6**)に関して、以下の合成計画を立案した（Scheme 3）。**6** のピリジン環は、合成終盤にアルデヒドおよびオレフィンを足掛かりとしてアルデヒド **8** から構築することとした。**8** の Quinolizidine 骨格は、イミニウム **16** に対して分子内 Mannich 反応が進行することで得られるものとし、**16** はエナール **17** の Ns 基の除去と分子内脱水縮合により生成するものと考えた。なお本反応は、**17** から **8** の生成までが一挙に進行することを期待した。**17** は、市販の $NsNH_2$ **18** に対する Ts 体 **19** を用いた 2 度のアルキル化と各種官能基変換により合成できるものとし、**19** は市販の不飽和エステル **7** から導くことができると予想した。



Scheme 3

1-2. Ts 体 **19** の合成

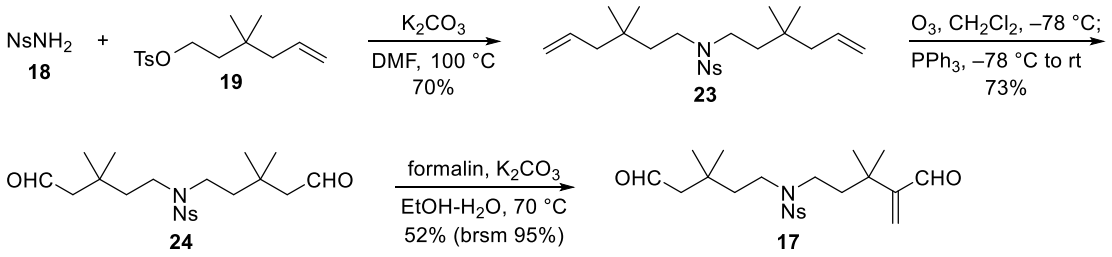
初めに、Ts 体 **19** の合成を行った（Scheme 4）。市販の不飽和エステル **7** を出発原料としてアリル基の導入によりジエステル **20** とした。次いで **20** に対して加水分解によりジカルボン酸とした後、キシレン溶媒中加熱還流を行うことでカルボン酸 **21** へと変換した。得られた **21** をメチルエステルへと導いた後、DIBAL 還元によりアルコール **22** を得た。最後に、生じた水酸基の Ts 化を行うことで目的の **19** を合成した。



Scheme 4

1-3. エナール **17** の合成

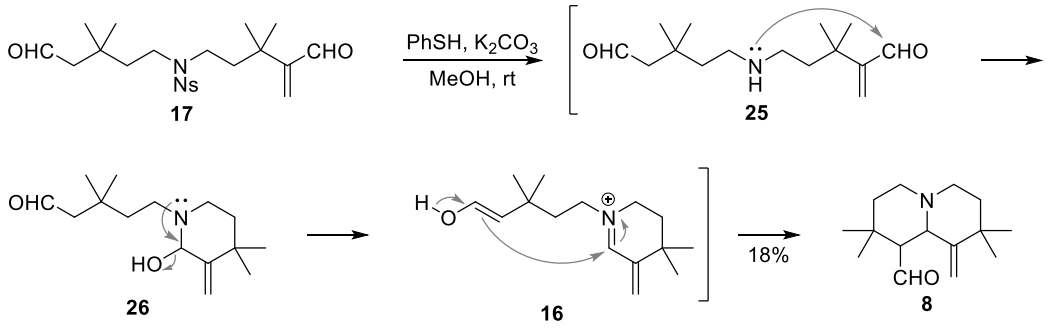
合成した Ts 体 **19** を用いて、エナール **17** の合成を行った（Scheme 5）。$NsNH_2$ **18** および **19** の混合物をアルキル化の条件に付したところ、円滑に反応が進行しジエン **23** が得られた。得られた **23** に対してオゾン酸化を行うことでジアルデヒド **24** へと導いた後、炭酸カリウム存在下ホルマリンを作用させることで目的の **17** を合成した。



Scheme 5

1-4. エナール **17** を用いた Quinolizidine 骨格の構築

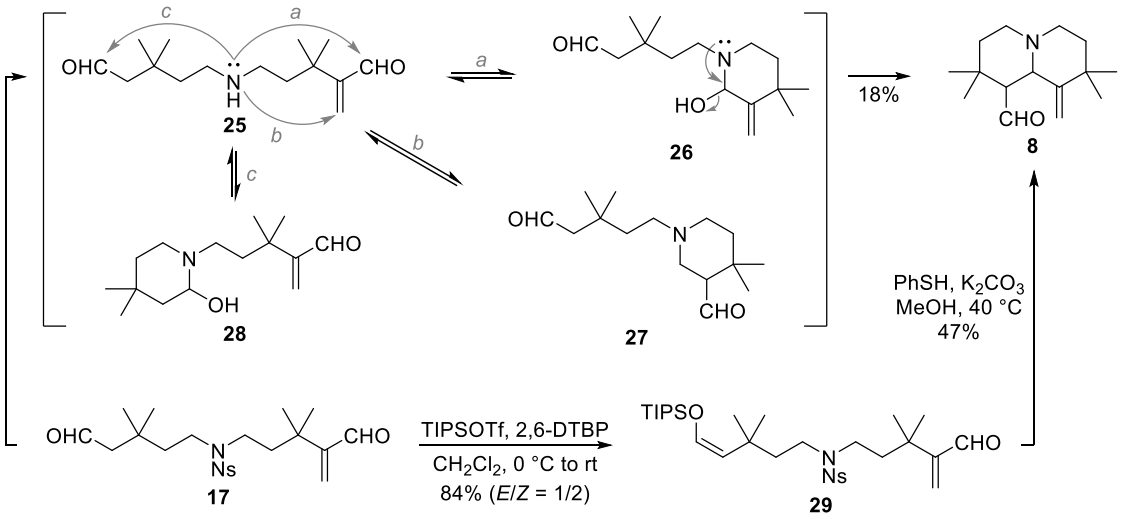
エナール **17** を用いて、連続環化反応による Quinolizidine 骨格の構築を検討した（Scheme 6）。**17** に対して、炭酸カリウム存在下チオフェノールを作用させたところ[13]、Ns 基の除去によりアミン **25** を生じた後、分子内での 1,2-付加反応によりヘミアミナール **26** を生成した。その後脱水によりイミニウム **16** となった後、分子内 Mannich 反応が進行することで低収率ではあるが目的のアルデヒド **8** を単一のジアステレオマーとして得ることに成功した。



Scheme 6

1-5. 連続環化反応が低収率であった原因の考察と改善策

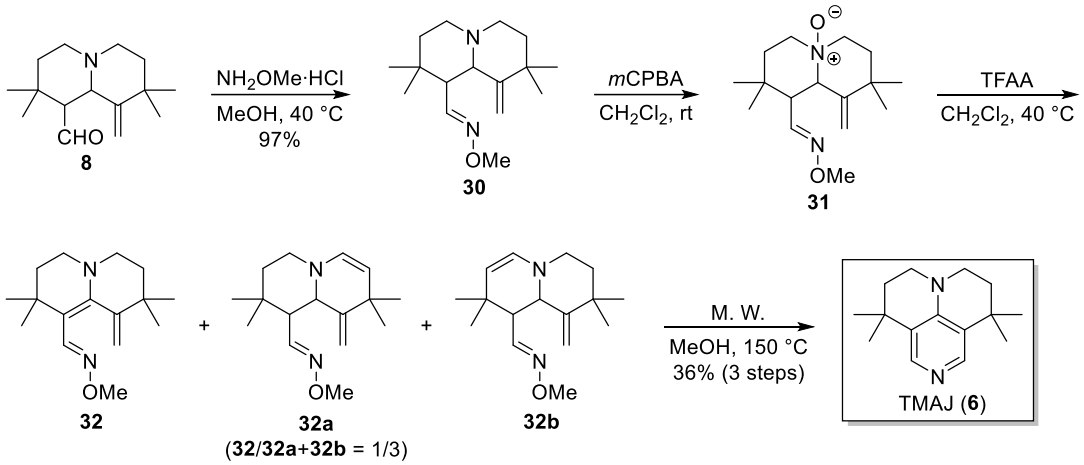
推定される連続環化反応における問題点を、以下に記載する（Scheme 7）。目的のアルデヒド **8** は、エナール **17** の Ns 基の除去後に生成するアミン **25** に対して、1,2-付加反応が進行することでヘミアミナール **26** を生じた後（経路 *a*）、イミニウムの生成と分子内 Mannich 反応が進行することで得ることができる。さらに **25** に対して、1,4-付加反応によりアルデヒド **27** が生成する経路 *b* およびアルデヒドへの付加によりヘミアミナール **28** を形成する経路 *c* が競合し、これが低収率の原因であると推定した。そこで、経路 *b* および *c* を抑制することができれば収率の改善につながると考えたが、オレフィンを変換することによる経路 *b* の抑制は困難であった。そこで、アルデヒドを保護することによる経路 *c* の抑制を検討した。**17** に対して TIPS エノールエーテル化によりエナール **29** とした後、Ns 基の除去に続く連続環化反応を試みたところ、47%と収率を向上させることに成功した。



Scheme 7

1-6. TMAJ (**9**)の合成

アルデヒド **8** を得ることができたので、ピリジン環形成による TMAJ (**6**)の合成を行った（Scheme 8）。**8** に対して NH_2OMe を作用させることでオキシム **30** へと変換した後、三級アミンの酸化を行うことで *N*-オキシド **31** へと導いた。得られた **31** に対して Polonovski 反応[14]の条件に付したところ、所望のエナミン **32** と望まない位置異性体 **32a**, **32b** の混合物が得られた。望まないエナミン **32a**, **32b** が主生成物として得られたものの、これらは反応系中で **32** へと異性化させることが可能であると考え[15]、**32**, **32a**, **32b** の混合物に対してメタノール溶媒中マイクロウェーブを照射したこところ、ペリ環状反応に続く MeO 基の脱離により **6** の合成を達成した。



Scheme 8

1-7. TMAJ (**6**)の活性評価

TMAJ (**6**)の初の合成を達成したので、触媒活性の評価を行った（Figure 4）。すなわち、市販の嵩高いアルコール **33** からアセテート **34** への変換に関して、反応速度を ^{1}H NMR を用いて追跡するというものである。その結果 TMAJ (**6**)は、DMAP (**4**)および 9-AJ (**5**)を上回る高い触媒活性を有しており、本反応の半減期から DMAP (**4**)と比較して 15 倍以上、9-AJ (**5**)と比較して 1.5 倍以上の高い触媒活性を有していることが明らかになった。

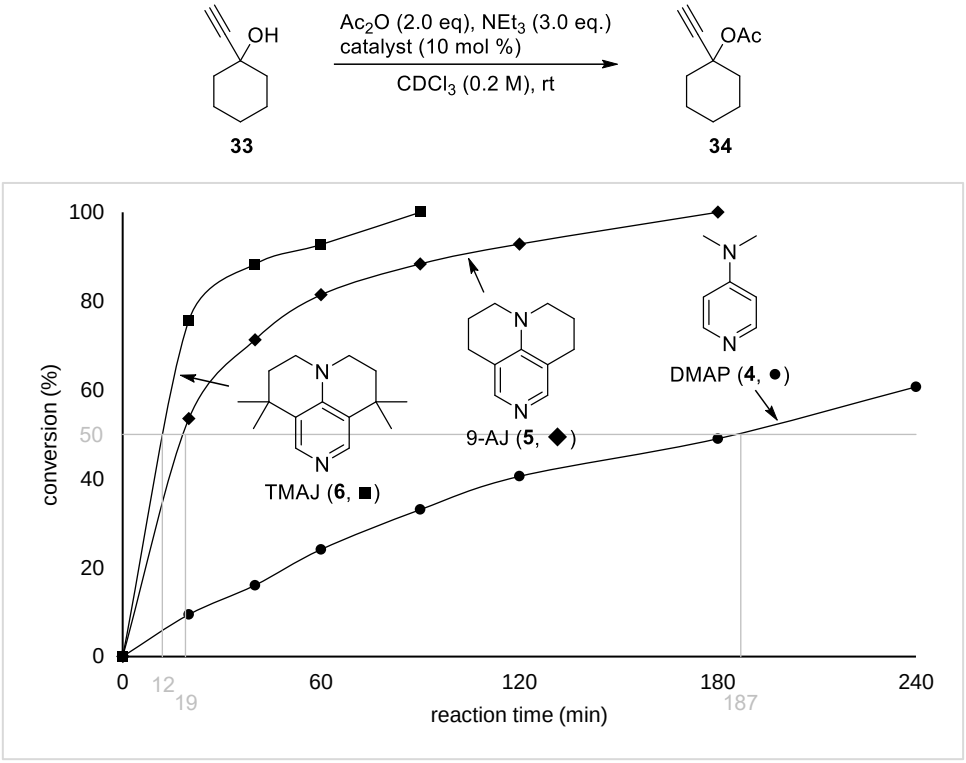
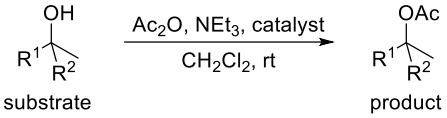


Figure 4

1-8. TMAJ (**6**)の基質適用範囲の調査

TMAJ (**6**)の高い触媒活性を確認することができたので、最後に基質適用範囲の調査を行った（Table 1）。すなわち、種々の三級アルコールに対するアセチル化反応の収率を DMAP (**4**)と比較した。entry 1 では、脂肪族アルキニルアルコール **35** を用いたところ円滑に反応が進行し、TMAJ (**6**)を用いた場合は目的のアセテート **36** が 83%の収率で得られた。一方、**35** に対する DMAP (**4**)を用いたアセチル化は収率の低下が確認された。entry 2, 3 ではアルケニルアルコール **37** およびアルキルアルコール **39** を用いて反応を行ったところ、同様に TMAJ (**6**)を用いた場合に良好な収率でアセテート **38** および **40** が得られた。なお、これら置換基の立体障害を反映し、アルキニル、アルケニル、アルキルの順に反応時間の延長が確認された。entry 4 では、電子求引性基であるケトンを α 位に有するアルコール **41** に対して反応を行ったが、良好な収率でアセテート **42** を与えた。entry 5 の環状トリアルキルアルコール **43** を用いた場合も、同様に DMAP (**4**)と比較して高い収率で目的のアセテート **44** が得られた。

最後に、entry 6 ではジオール **45** に対して、これまでと比較して 2 倍量の無水酢酸を用いてアセチル化反応を行ったところ、ジアセテート **46** が良好な収率で得られた。今回検討した基質において、TMAJ (**6**)は DMAP (**4**)よりもはるかに高い触媒活性を示した。



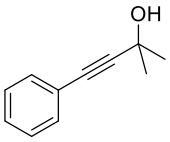
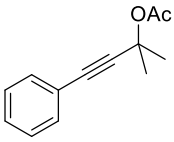
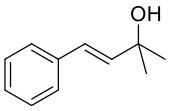
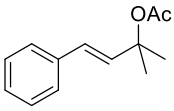
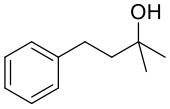
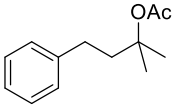
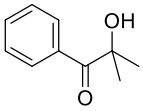
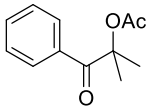
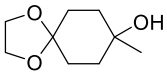
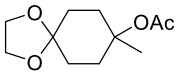
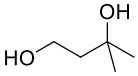
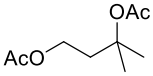
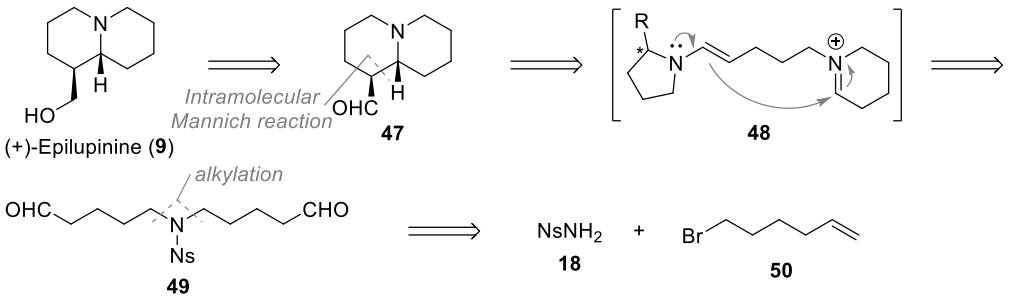
entry	substrate	product	time (h)	yield (%) DMAP (**4**)	yield (%) TMAJ (**6**)
1	 **35**	 **36**	1.3	46	83
2	 **37**	 **38**	7.0	51	84
3	 **39**	 **40**	11	27	82
4	 **41**	 **42**	0.5	42	85
5	 **43**	 **44**	33	54	85
6	 **45**	 **46**	8	26	82

Table 1

第 2 章　(+)-Epilupinine の効率的不斉全合成

2-1. (+)-Epilupinine (**9**)の合成計画

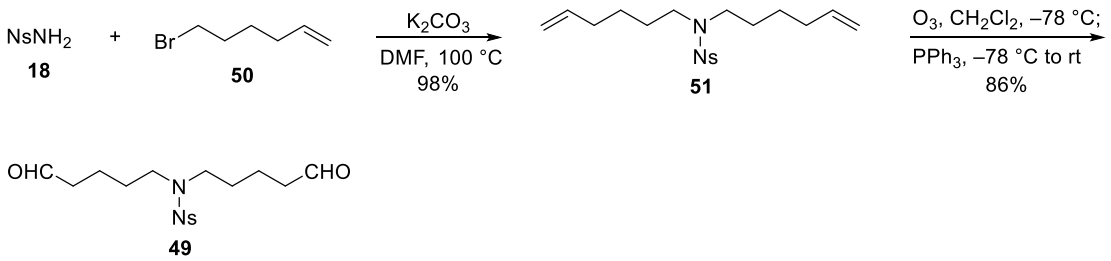
第 1 章で確立した Quinolizidine 骨格の構築法を踏まえ、(+)-Epilupinine (**9**)に関して以下の合成計画を立案した（Scheme 9）。**9** はアルデヒド **47** を還元することで合成できると考えた。**47** の Quinolizidine 骨格は、イミニウム **48** に対して分子内 Mannich 反応が進行することで得られるものとし、**48** はジアルデヒド **49** の Ns 基の除去と分子内脱水縮合により生成するものと考えた。なお本反応は、第 1 章と同様に **49** から **47** の生成までが一挙に進行することを期待した。また本カスケード反応において、分子内 Mannich 反応を触媒的な不斉反応へと展開することで効率的な不斉合成が可能と考えた。最後に **49** は、$NsNH_2$ **18** に対して市販の臭化アルキル **50** を用いた 2 度のアルキル化とオレフィンの酸化開裂により導けると考えた。



Scheme 9

2-2. ジアルデヒド **49** の合成

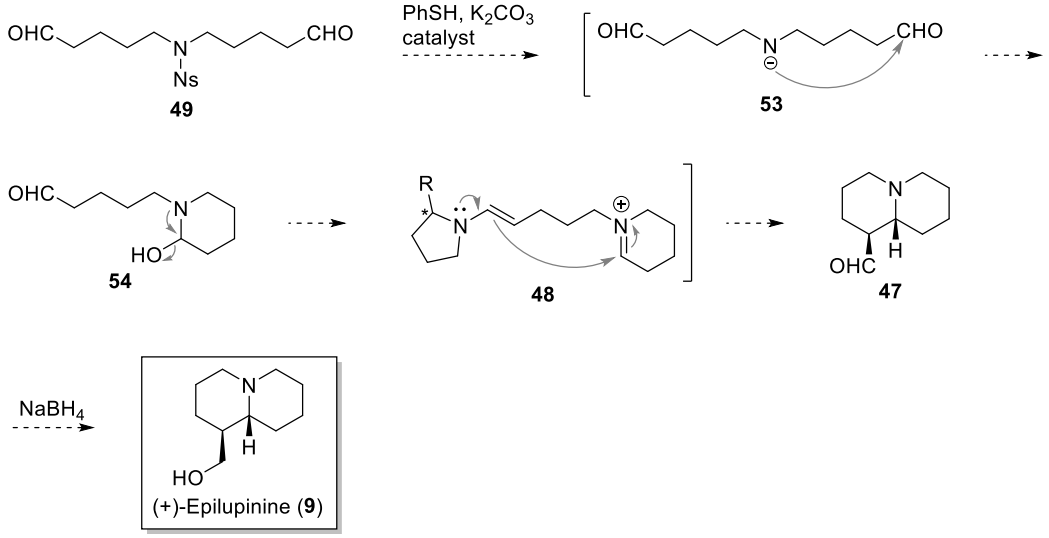
初めに、連続環化反応前駆体であるジアルデヒド **49** の合成を行った（Scheme 10）。市販の $NsNH_2$ **18** および臭化アルキル **50** を出発原料とし、2 度のアルキル化反応によりジエン **51** へと導いた。さらに **51** に対して、オゾン酸化を行うことで目的のジアルデヒド **49** を合成した。



Scheme 10

2-3. 連続環化反応を用いた(+)-Epilupinine (**9**)の合成計画

ジアルデヒド **49** から(+)-Epilupinine (**9**)が得られる反応を以下に示す（Scheme 11）。**49** に対して、炭酸カリウム及び不斉有機触媒存在下チオフェノールを作用させると、Ns 基の除去によりアミン **53** を生じた後、分子内環化反応によりヘミアミナール **54** を生成する。その後、不斉有機触媒とアルデヒド間のエナミン形成および脱水によりイミニウム **48** となった後､不斉分子内 Mannich 反応が進行することでアルデヒド **47** が得られることを期待した。最後に、還元を行うことで **9** へと導くことができると考えた。

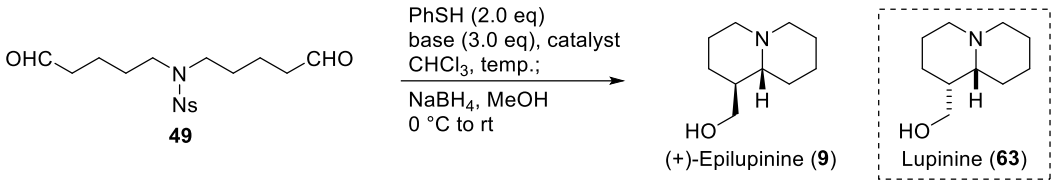


Scheme 11

2-4. 不斉分子内 Mannich 反応に関する検討

ジアルデヒド **49** を用いた(+)-Epilupinine (**9**)の全合成を行った。**49** に対して、炭酸カリウム及び Jørgensen 触媒(**52**)[16]存在下チオフェノールを作用させたところ、目的の連続環化反応が円滑に進行しアルデヒド **47** が得られた。**47** は、不安定かつ揮発性があったため one-pot で $NaBH_4$ を用いた還元を行うことで **9** の全合成を達成した。しかしながら、総収率は良好なものの、光学純度は 5% *ee* 以下であり満足のいくものではなかった。そこで、光学純度を向上させるべく不斉分子内 Mannich 反応の更なる検討を行った（Table 2）。entry 2 では MacMillan 触媒(**55**)[7m,17]を用いて反応を行ったが目的の(+)-Epilupinine (**9**)を得ることはできなかった。一方で、entry 3 では触媒として Hayashi-Jørgensen 触媒(**56**)[18]を使用したところ、61% *ee* と良好なエナンチオ選択性で **9** を与えた。そこで entry 4 では **56** の当量を 50 mol %へと増加させたが、結果の改善は確認されなかった。また、entry 5, 6 では **56** と類似の触媒である **57**[19]，**58**[20]を用いて反応を行ったが、収率および *ee* 共に低下する結果となった。さらに entry 7, 8 では、**59**[21]および D-Prolinamide (**60**)[22]を用いて反応を行ったが、同様に収率の低下が観測された。一方、entry 9 で D-Proline (**61**)[23]を用いて反応を行ったところ、良好な収率かつ 26% *ee* で **9** が得られる結果となった。そこで、entry 10 では **61** の当量を 100 mol %へと増加させたところ、収率およびエナンチオ選択性が向上した。ここで、**61** を用い

て反応を行った場合(–)-Epilupinine (**ent-9**)が得られたため、その後の検討では L-Proline (**ent-61**)を用いることとした。entry 11, 12 では、温度を段階的に低下させたところ 0 °C において 76% *ee* と光学純度の向上が確認されたが、–15 °C においては収率およびエナンチオ選択性が低下する結果となった。entry 13 では塩基を炭酸セシウムに変更したところ、83% *ee* とエナンチオ選択性が向上する結果となった。そこで entry 14 では、あらかじめセシウム塩とした触媒 **62** を用いて反応を行ったところエナンチオ選択性のさらなる向上が確認されたのに対し、収率は低下する結果となった。ここで **ent-61** の不斉誘起は、カルボン酸塩のカウンターカチオンに影響を受けていると考え、entry 15 ではより嵩高いアンモニウム塩である Triton B を用いて反応を行ったが良好な結果は得られなかった。一方で小さいカウンターカチオンを用いた entry 16, 17 では、**9** を得ることはできなかった。以上の結果から収率およびエナンチオ選択性を考慮し、entry 13 を最適条件と決定した。さらに本最適条件では、1.6 g スケールでも再現性良く反応が進行することを確認した。なお、本反応ではジアステレオマーである Lupinine (**63**)は確認されなかった。



entry	catalyst (mol %)	base	temp. (°C)	yield (%)	*ee* (%)
1	**52** (20)	K_2CO_3	rt	71	<5
2	**55** (20)	K_2CO_3	rt	-	-
3	**56** (20)	K_2CO_3	rt	73	61
4	**56** (50)	K_2CO_3	rt	61	59
5	**57** (20)	K_2CO_3	rt	33	<5
6	**58** (20)	K_2CO_3	rt	28	8
7	**59** (20)	K_2CO_3	rt	trace	11
8	**60** (20)	K_2CO_3	rt	-	-
9	**61** (20)	K_2CO_3	rt	57	30*
10	**61** (100)	K_2CO_3	rt	68	69*
11	**ent-61** (100)	K_2CO_3	0	61	76
12	**ent-61** (100)	K_2CO_3	–15	38	28
13	**ent-61** (100)	Cs_2CO_3	0	70	83
14	**62** (100)	Cs_2CO_3	0	35	92
15	**ent-61** (100)	Triton B	0	53	25
16	**ent-61** (100)	Li_2CO_3	0	-	-
17	**ent-61** (100)	Me_4NOH	0	-	-

*(–)-epilupinine (**ent-9**) was obtained.

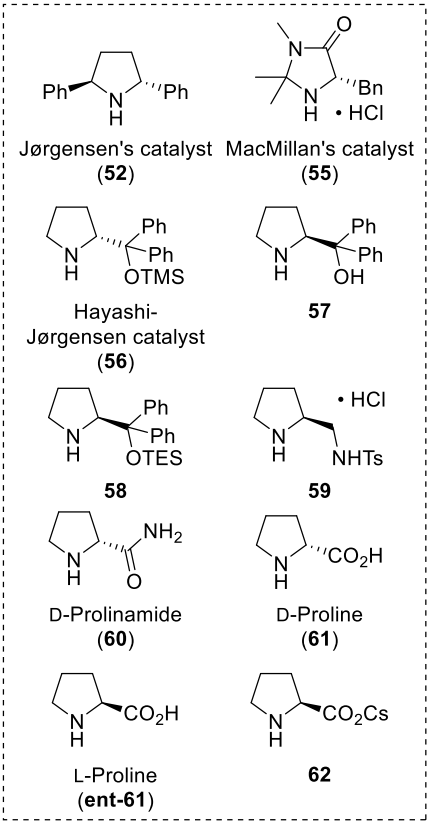


Table 2

2-5. DFT 計算を用いたエナンチオ選択性の考察

不斉分子内 Mannich 反応のエナンチオ選択性に関して、密度汎関数理論（DFT）計算を用いて解明を行った（Figure 5）[24]。すなわち、イミニウム **48a** から不斉分子内 Mannich 反応が進行する場合の遷移状態（TS）を計算するというものである。計算の結果、*Re* 面から反応が進行する場合の遷移状態である TS_{Re} **(64)**は、5.36 kcal/mol の活性化障壁が存在した。一方で、*Si* 面から反応が進行する場合の遷移状態である TS_{Si} **(65)**は、活性化障壁が存在せず有利であることが明らかになった。さらに **65** は、分子内の O-H 間で相互作用が存在するため **64** と比較して安定化されていることも確認された。続いて、炭酸カリウムおよび炭酸セシウムを用いた場合のエナンチオ選択性の違いを調査した。計算の結果、セシウム塩はカリウム塩と比較して、**64** および **65** 間のエネルギー差がより大きいことが明らかになった。また、このエネルギー差の違いは分子内相互作用に起因しており、セシウム塩では O-H 間の距離が 2.88Å であるのに対し、カリウム塩では 3.22Å であった。すなわちセシウム塩の場合、**65** の安定化がより強いためエナンチオ選択性が向上したと考察した。

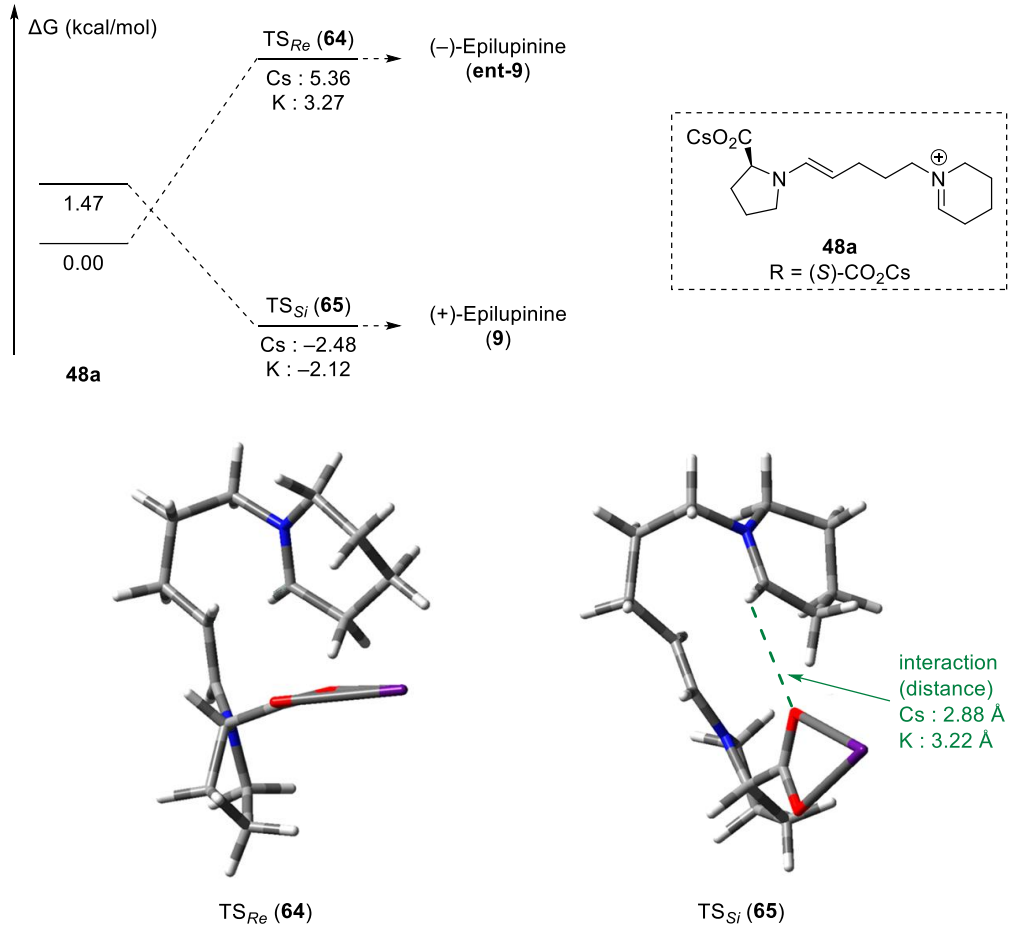
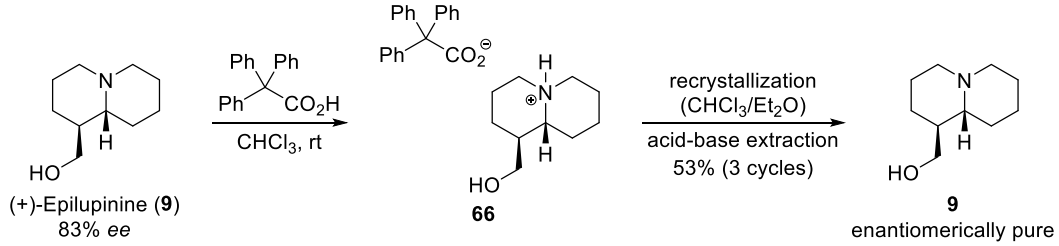


Figure 5

2-6. 再結晶による *ee* の向上

最適な反応条件が明らかになったため、再結晶による *ee* の向上を検討した（Scheme 12）。しかしながら、(+)-Epilupinine (**9**)はアモルファス状化合物であったため塩形成による結晶化を試みた。種々検討の結果、トリフェニル酢酸を用いた場合に固体の塩を形成することが明らかになった。そこで **9** のトリフェニル酢酸塩 **66** を用いて再結晶を行った後、酸塩基分配による脱塩を行ったところ、光学的に純粋な **9** を得ることに成功した。

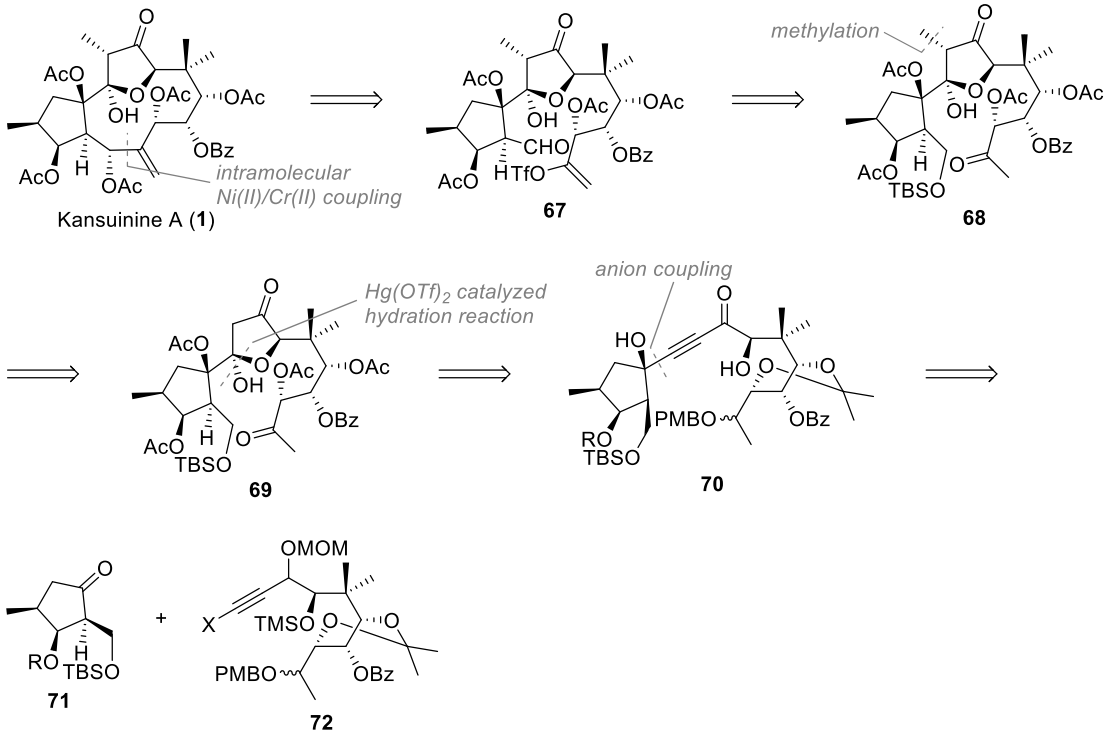


Scheme 12

第 3 章　Kansuinine A の全合成研究

3-1. Kansuinine A (**1**)の合成計画

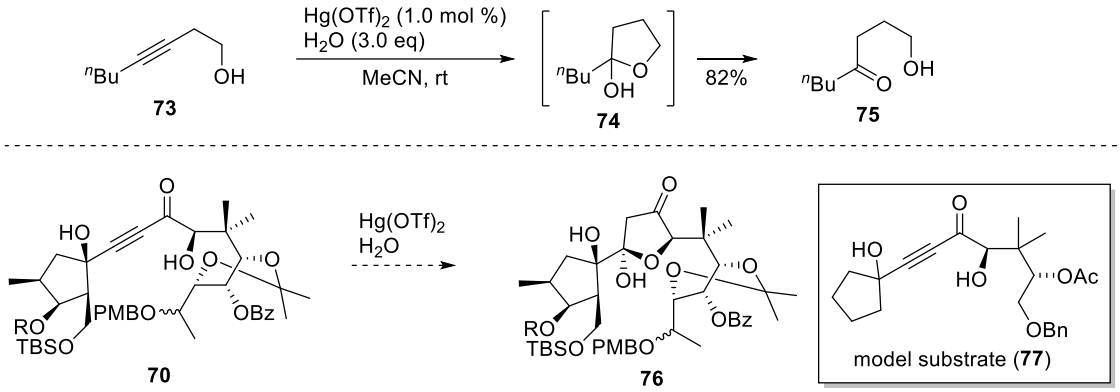
Kansuinine A (**1**)に関して、以下の合成計画を立案した（Scheme 13）。**1** の十二員環に含まれるアリルアルコールは、合成終盤に分子内 Ni(II)/Cr(II)カップリングを用いてビニルトリフラートを有するアルデヒド **67** から構築するものとし、**67** のビニルトリフラートおよびアルデヒド部位はそれぞれ対応するメチルケトンおよび一級アルコールを有する **68** から導くこととした。また **68** の五員環に位置するメチル基は、ヘミケタール **69** のメチル化により得られるものとし、**69** のテトラヒドロフラン環はイノン **70** に対する $Hg(OTf)_2$ を用いたアルキンの水和反応により合成できると考えた。最後に **70** は、ケトン **71** およびハロアルキン **72** をアニオンカップリングにより連結することで得られると考えた。全合成研究に先立ち、この $Hg(OTf)_2$ を用いたアルキンの水和反応が実際に可能であるかについて調査を行うこととした。



Scheme 13

3-2. $Hg(OTf)_2$ を用いたアルキンの水和反応に関する知見

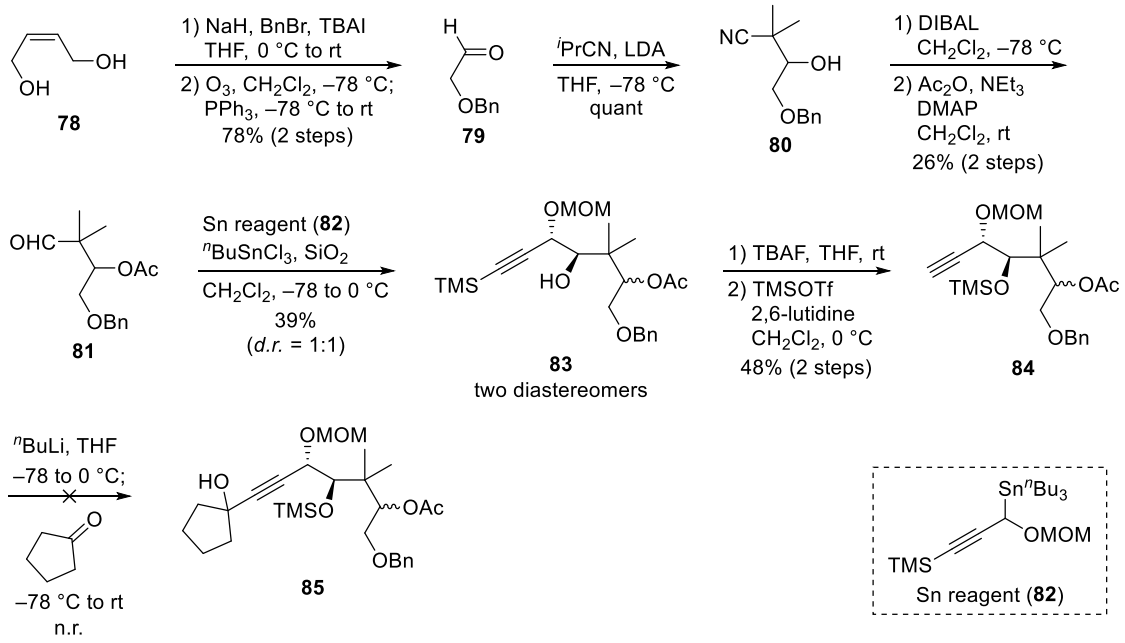
当研究室で報告している $Hg(OTf)_2$ に関する知見を以下に示す（Scheme 14）。すなわち、ホモプロパルギルアルコール **73** に対して H_2O 存在下触媒量の $Hg(OTf)_2$ を作用させると、ヘミケタール **74** を経由して高収率でケトン **75** が得られるというものである[25]。この知見を基に、イノン構造を有するホモプロパルギルアルコール **70** に対して同様の水和反応を行えば、望むヘミケタール **76** が得られると予想した。そこで、まずモデル基質(**77**)を用いて、本水和反応が Kansuinine A (**1**)の全合成に適用可能かについて調査した。



Scheme 14

3-3. モデル基質(**77**)の合成とその問題点

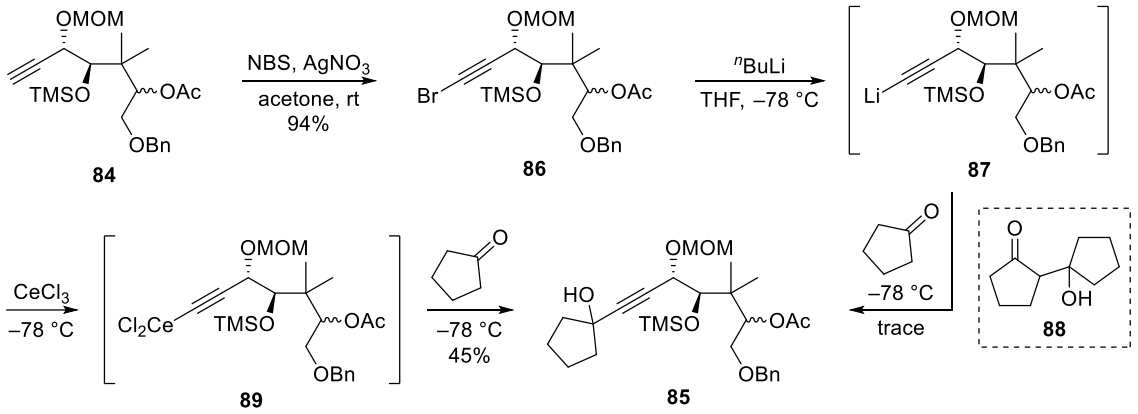
初めに、モデル基質(**77**)の合成を行った（Scheme 15）。市販のジオール **78** を出発原料とし、両水酸基に対するベンジル保護に続くオゾン酸化を行うことでアルデヒド **79** へと導いた。得られた **79** に対して、^{i}PrCN の付加を行いニトリル **80** とした後、ニトリルの DIBAL 還元に続く水酸基のアセチル保護により、アセテート **81** を合成した。続いて、**81** のアルデヒドに対してスズ試薬(**82**)の付加[26]を行うことで、アルコール **83** を 2 種のジアステレオマー混合物として得た。**83** に対してアルキン末端の TMS 基を除去した後、水酸基の TMS 保護を行うことでアルキン **84** へと導いた。最後に **84** に対して、アルキン末端のリチオ化とアニオンカップリングによるシクロペンタン環の導入を試みたが、反応は進行せず目的のカップリング体 **85** を得ることはできなかった。



Scheme 15

3-4. ブロモアルキン **86** を用いたシクロペンタン環の導入

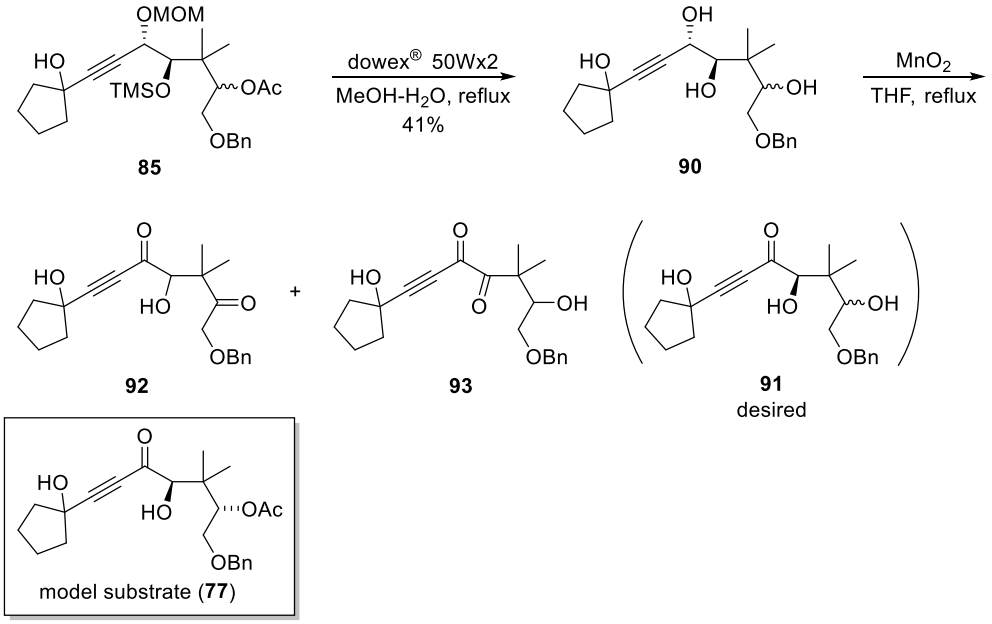
アルキン **84** に対する重水素化実験を行ったところ、アルキン末端の重水素化は進行しなかった。この結果からアルキン末端のリチオ化が問題であると考え、ブロモアルキン **86** を用いたアニオンカップリングを行うこととした（Scheme 16）。アルキン **84** に対してアルキン末端の臭素化[26]を行うことで **86** とした。**86** に対して、ハロゲン-リチウム交換によるリチオ化を行うことでリチウムアセチリド **87** とした後、アニオンカップリングによるシクロペンタン環の導入を試みたところ、痕跡量のカップリング体 **85** が確認されたものの、副生成物であるシクロペンタノンのホモカップリング体 **88** が主生成物として得られる結果となった。ここで **88** が得られる原因は、**87** によるシクロペンタノンの脱プロトン化にあると考え、この副反応を抑制するために付加反応が優先することが知られているセリウムアセチリド **89** を用いることとした。**86** に対してリチオ化を行い **87** とした後、塩化セリウムを加えることで **89** を生成した。最後に、**89** に対してシクロペンタノンを作用させたところ、収率に未だ改善の余地はあるものの、目的の **85** を得ることに成功した。なお本手法では、**88** の生成は確認されなかった。



Scheme 16

3-5. モデル基質(**77**)の合成

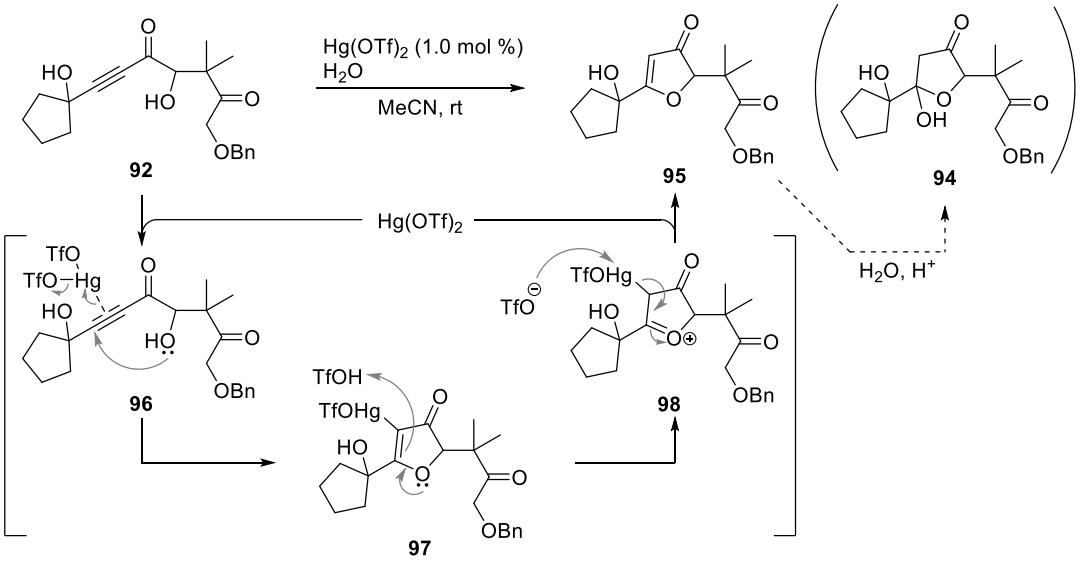
目的のカップリング体 **85** が得られたので、モデル基質(**77**)の合成を行った（Scheme 17）。**85** に対してベンジル基以外の保護基を除去することでテトラオール **90** とした後、二酸化マンガンによるプロパルギルアルコールの酸化を試みた。しかしながら目的物のイノン **91** を得ることはできず、過剰酸化が進行したホモプロパルギルアルコール **92** およびジケトン **93** の混合物が得られた。ここで **92** は、目的のモデル基質(**77**)と同様にホモプロパルギルアルコールユニットを有していることから、**92** を **77** の代わりにモデル基質として用いることとした。



Scheme 17

3-6. $Hg(OTf)_2$ を用いたアルキンの水和反応

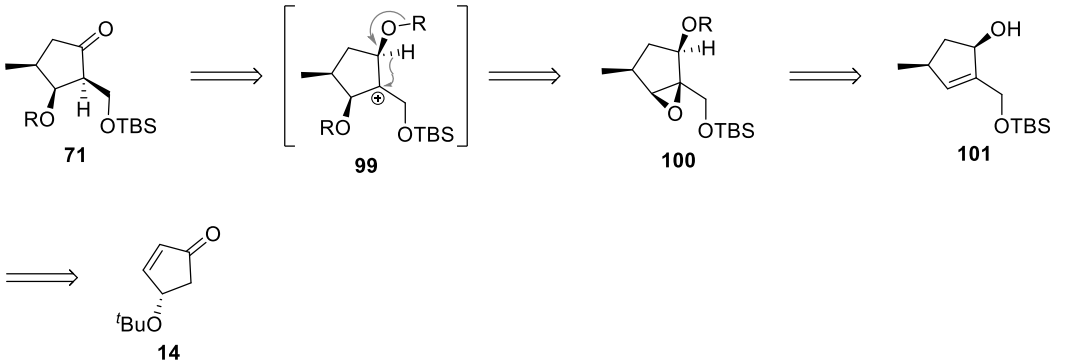
イノン **92** を用いた $Hg(OTf)_2$ によるアルキンの水和反応を以下に示す（Scheme 18）。合成した **92** に対して、H_2O 存在下 1.0 mol %の $Hg(OTf)_2$ を作用させたところ、目的のヘミケタール **94** ではなく脱水体 **95** が得られた。**95** が生成する推定反応機構を以下に示す。初めに **92** に対して $Hg(OTf)_2$ が配位することで中間体 **96** となった後、分子内の水酸基からアルキンへの求核攻撃が進行することでビニル水銀中間体 **97** および TfOH を生成する。続いて、TfOH による **97** のプロトン化によりオキソニウムカチオン **98** となった後、$Hg(OTf)_2$ が脱離することで **95** が得られたと推定した。さらに **95** は、種々の水和反応により目的のヘミケタール **94** に変換可能と予想できたことから、このフラノン誘導体を用いて Kansuinine A (**1**)の全合成を進めることとした。



Scheme 18

3-7. ケトン **71** の合成計画

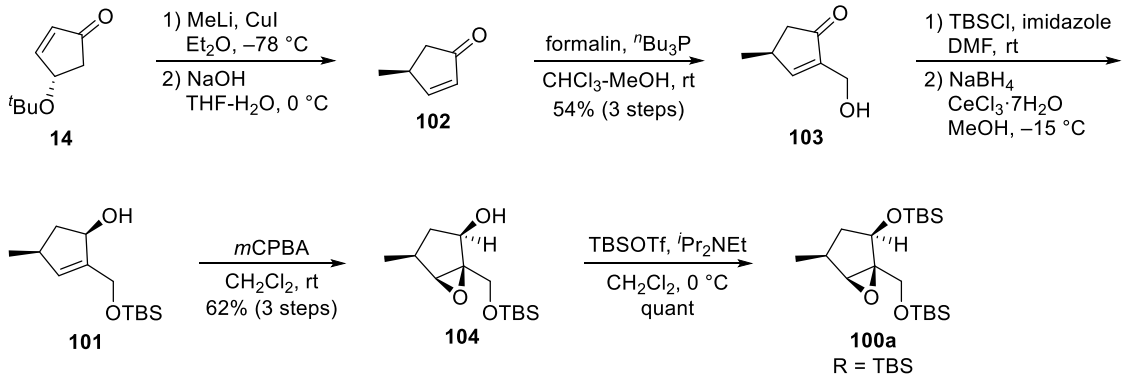
ケトン **71** に関して、以下の合成計画を立案した（Scheme 19）。**71** は、3 個の連続する不斉中心がすべて *cis* に配置されており、合成難度の高いユニットである。そこでこの *cis* に配置された 3 連続不斉中心は、三級カチオン **99** に対してヒドリドが下側から転位してくることで構築できると考えた。また **99** は、エポキシド **100** の酸処理によって形成できると考え、**100** はアリルアルコール **101** のエポキシ化により得られるものとした。なお本エポキシ化は、二級水酸基の配向効果によりジアステレオ選択的に進行することを期待した。最後に **101** は、既知のシクロペンテノン誘導体 **14**[12]から合成できるものとした。



Scheme 19

3-8. TBS 保護エポキシド **100a** の合成

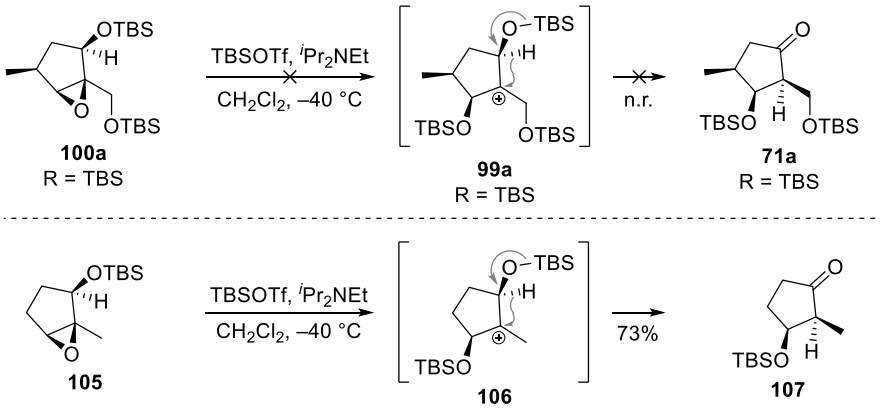
初めに、ヒドリド転位前駆体であるエポキシド **100a** の合成を行った（Scheme 20）。既知の光学活性シクロペンテノン誘導体 **14** を出発原料とし、メチル基のジアステレオ選択的な 1,4-付加と ^{t}BuO 基の脱離によりエノン **102** とした後、Baylis-Hillman 反応によりヒドロキシメチル基を導入することでアルコール **103** へと変換した。次いで **103** の水酸基を TBS 基で保護した後、Luche 還元によりアリルアルコール **101** へと導いた。さらに、**101** に対して *m*CPBA を作用させることで、二級水酸基の配向効果によりジアステレオ選択的に反応が進行し、エポキシアルコール **104** が得られた。最後に、二級水酸基の TBS 保護を行うことで目的の **100a** を合成した。



Scheme 20

3-9. 報告されているヒドリド転位反応とエポキシド **100a** への適用

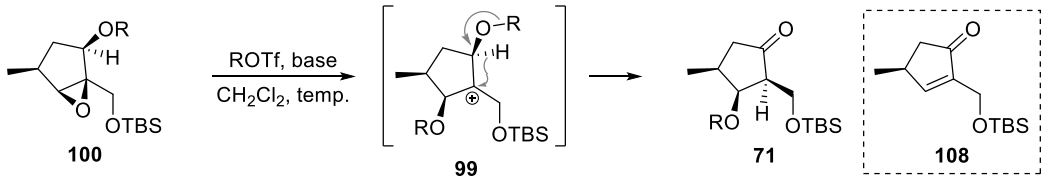
目的のエポキシド **100a** が得られたので、ヒドリド転位の検討を行った（Scheme 21）。ここで文献調査を行ったところ、エポキシド **105** に対して–40 °C で TBSOTf を作用させると三級カチオン **106** の生成とヒドリド転位が進行することで、ケトン **107** が得られると報告されていた[28]。そこでこの文献と同様に、**100a** に対して–40 °C で TBSOTf を作用させたが目的のケトン **71a** は得られず、反応は進行しなかった。



Scheme 21

3-10. エポキシド **100** に対するヒドリド転位反応の検討

エポキシド **100** に対して、ヒドリド転位反応の検討を行った（Table 3）。entry 1 には、**100a** を用いた場合の結果を記載している。entry 2 ではより高温条件で反応を行ったが、反応は進行しなかった。そこで entry 3 ではより高い反応性を期待して TESOTf を用いたところ、目的のケトン **71b** とともに **71b** の TESO 基の脱離が進行したエノン **108** も生成してしまう結果となった。そこで **108** の生成を抑制するため、–78 °C でも反応が進行すると期待される TMSOTf に変更したところ、**108** の生成を抑えることに成功した。さらに塩基を HMDS に変更したところ、**108** の生成が完全に抑制され良好な収率で **71c** を得ることに成功した。



entry	R	base	temp. (°C)	result
1	TBS	$^{i}Pr_2NEt$	–40	n.r.
2	TBS	$^{i}Pr_2NEt$	50*	n.r.
3	TES	$^{i}Pr_2NEt$	–40	<40% (**71b**:**108** = 2:1)
4	TMS	$^{i}Pr_2NEt$	–78	**71c** : 55%, **108** : 11% (NMR yield)
5	TMS	HMDS	–78	**71c** : 70% (NMR yield)

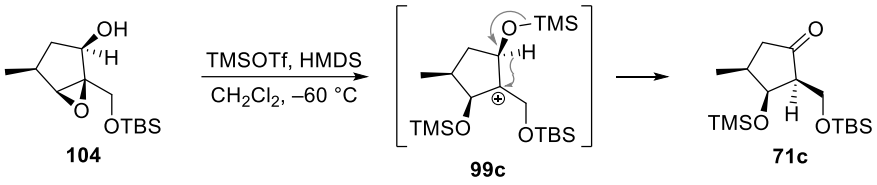
*DCE was used as a solvent.

100a : R = TBS
71b : R = TES
71c : R = TMS

Table 3

3-11. エポキシド **104** に対するヒドリド転位反応

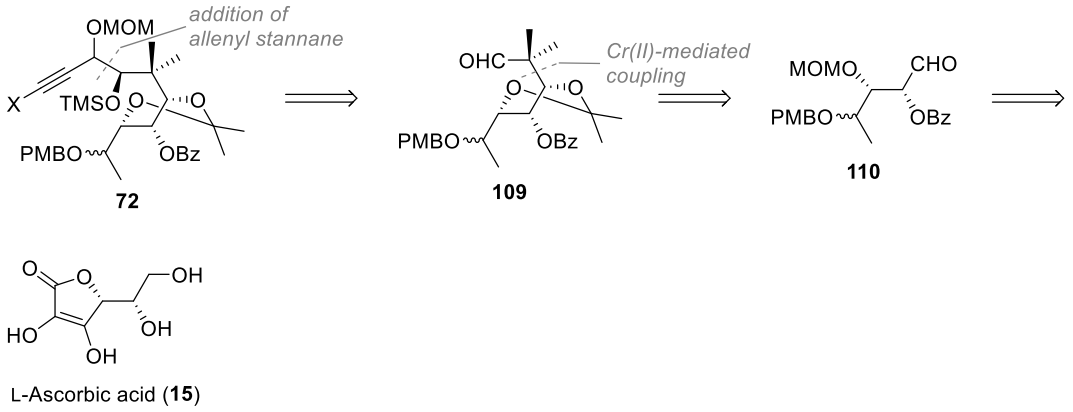
エポキシド **100** を用いたヒドリド転位反応の最適条件を確立できたので、エポキシド **104** に対する one-pot でのケトン **71c** の合成を検討した（Scheme 22）。種々検討の結果、先の条件の反応温度を–60 °C へと変更することで **99c** の形成とヒドリド転位反応が一挙に進行し目的のケトン **71c** を得ることに成功した。



Scheme 22

3-12. ハロアルキン **72** の合成計画

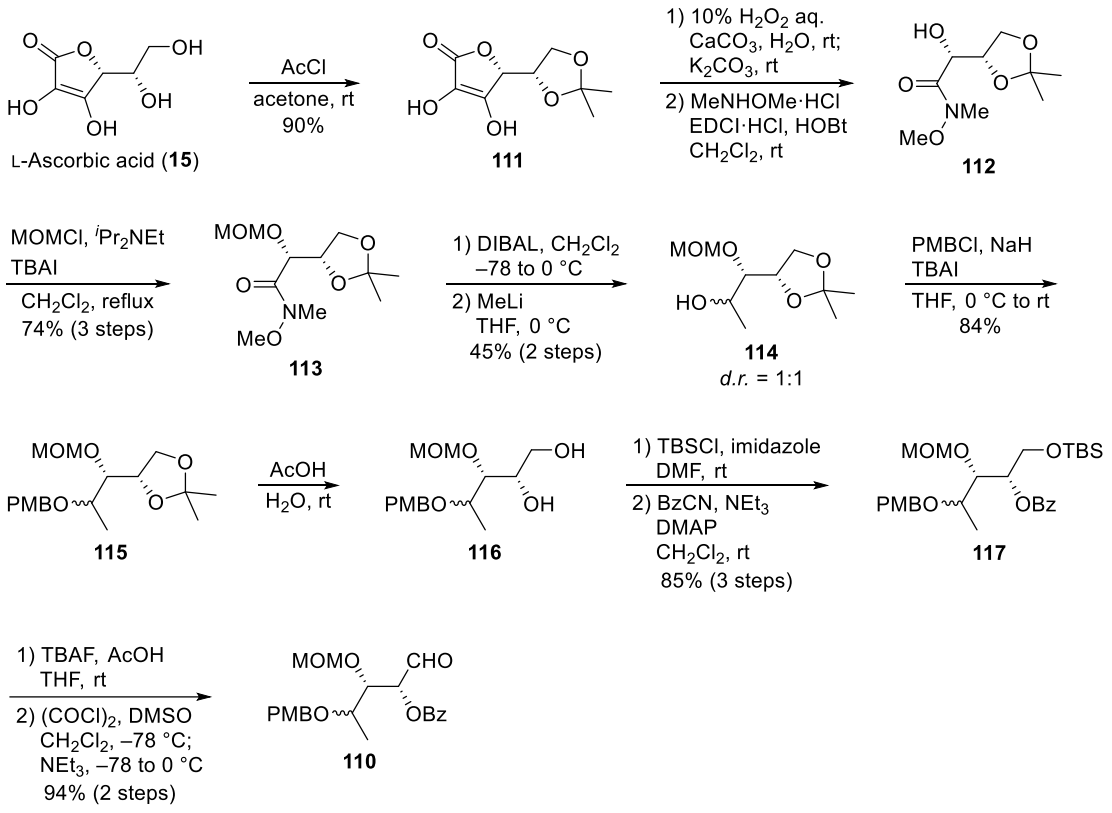
ハロアルキン **72** に関して、以下の合成計画を立案した（Scheme 23）。**72** のプロパルギルアルコールは、アレニルスズの付加によりアルデヒド **109** から得られるものとし、**109** の四級炭素は Cr(II)カップリングにより、アルデヒド **110** から合成できると考えた。最後に **110** は、L-Ascorbic acid (**15**)から導くものとした。



Scheme 23

3-13. アルデヒド **110** の合成

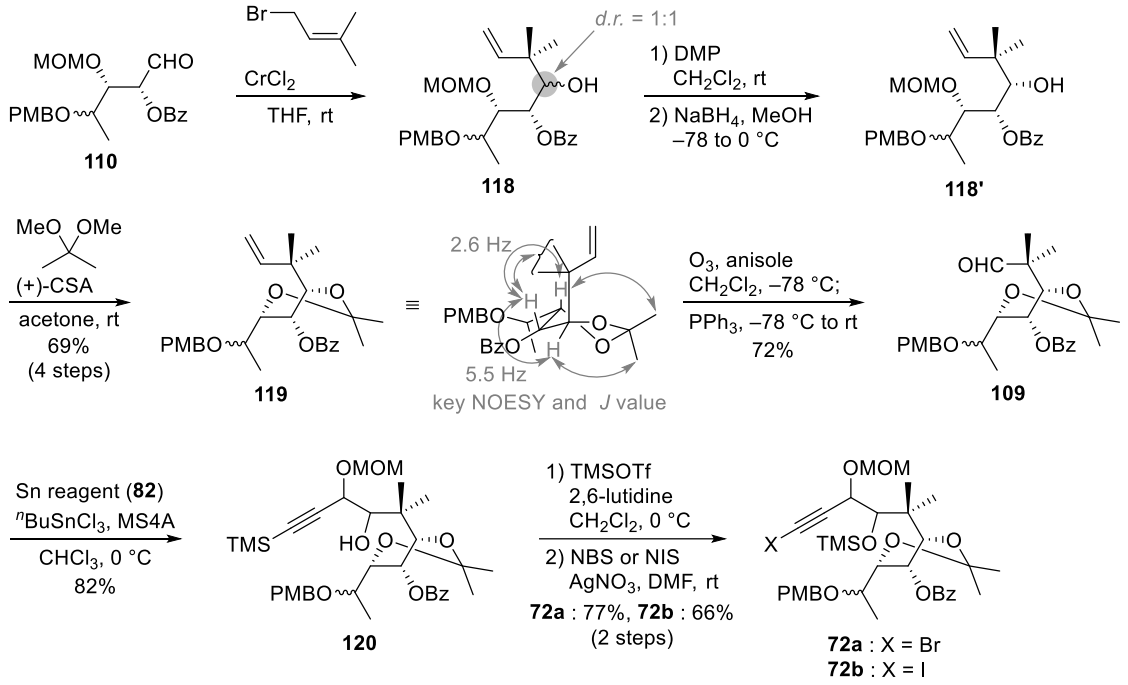
アルデヒド **110** の合成を行った（Scheme 24）。市販の L-Ascorbic acid (**15**)を出発原料として、ジオールのアセトニド保護を行うことで既知のアセトニド保護体 **111** とした[29]。次いで、**111** に対するオレフィンの酸化開裂に続く生じたカルボン酸塩の Weinreb アミド化によりアミド **112** へと導いた後、**112** の水酸基に対する MOM 保護を行うことでアミド **113** を得た。得られた **113** に対して DIBAL 還元を行うことでアルデヒドとした後、生じたアルデヒドへのメチルリチウムの付加により二級アルコール **114** が 1:1 のジアステレオマー混合物として得られた。続いて、生じた水酸基の PMB 保護を行うことで PMB 保護体 **115** とした後、**115** のアセトニド基を除去することでジオール **116** へと導いた。最後に、**116** の一級水酸基に対する TBS 保護と二級水酸基の Bz 保護を行うことでベンゾエート **117** へと変換した後、**117** の TBS 基の除去と生じた一級水酸基の Swern 酸化を行うことで、目的のアルデヒド **110** を合成した。



Scheme 24

3-14. ハロアルキン **72** の合成

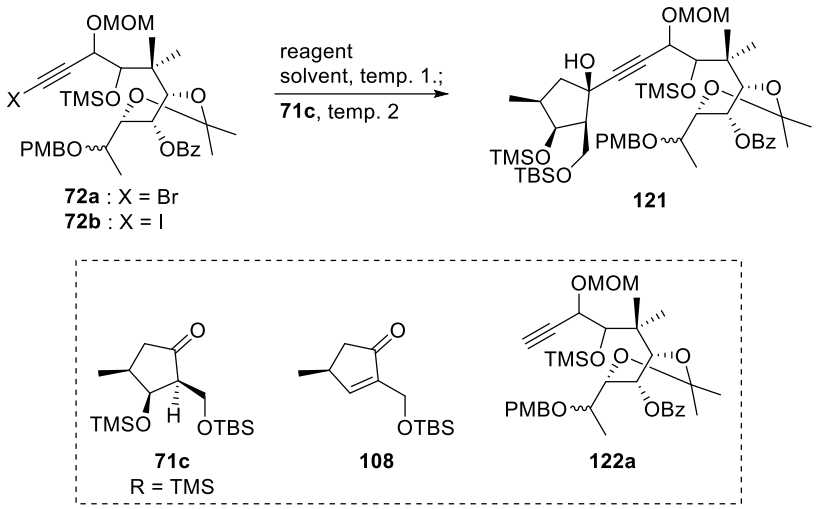
得られたアルデヒド **110** を用いて、ハロアルキン **72** の合成を行った（Scheme 25）。**110** に対して、Cr(II)カップリングによる臭化プレニルの付加[30]を行いアルコール **118** へと導いた。しかしながらプレニル化により生じた二級水酸基は、1:1 のジアステレオマー混合物であったことから、Dess-Martin 酸化に続く $NaBH_4$ を用いた還元によって単一のジアステレオマーであるアルコール **118'**へと収束させた。さらに、**118'**に対して環状構造を有するアセトニド保護体 **119** へと変換した。ここで **119** に対して、^{1}H NMR のカップリング定数および NOESY を確認した結果、二級水酸基は所望の立体化学に収束したことが明らかになった。続いて **119** に対してオゾン酸化を行うことでアルデヒド **109** とした後、アルデヒドへのスズ試薬(**82**)の付加を行うことでアルコール **120** へと変換した。最後に **120** に対して、水酸基の TMS 保護に続くアルキン末端のハロゲン化を行うことで、目的ハロアルキン **72a** および **72b** を得ることに成功した。



Scheme 25

3-15. アニオンカップリングによるカップリング体 **121** の合成

ケトン **71c** およびハロアルキン **72** を得ることができたことから、アニオンカップリングによる連結を検討した（Table 3）。entry 1 では、^{n}BuLi を用いたハロゲン-リチウム交換によるリチウムアセチリドの生成に続く **71c** への付加を試みた。その結果、原料であるブロモアルキン **72a** およびリチウムアセチリドに対するプロトン化が進行したアルキン **122a** が 1:1 の比で生成し、かつ **71c** の TMSO 基が脱離したエノン **108** が生成してしまう結果となった。そこで、entry 2 および 3 ではハロゲン-リチウム交換がより容易に進行することを期待し、^{t}BuLi を用いた条件およびヨードアルキン **72b** を用いた条件を試みたが同様の結果となった。なお、本反応では ^{n}BuLi の **71c** への付加は確認されなかった。続いて entry 4, 5, 6 では、リチウムアセチリドの生成を促進する目的で溶媒の変更を行ったが、良い結果を得ることはできなかった。完全にハロゲン-リチウム交換は進行しなかったものの、リチウムアセチリドが生成していることは示唆されたことから、entry 3 の条件に様々な添加剤を加えてさらなる検討を行ったが目的の **121** を得ることはできなかった。そこで金属を変更することとし、entry 7 では ^{i}PrMgBr を用いて反応を行ったところ、ハロゲン-金属交換は円滑に進行したが **121** は確認できず、$ZnCl_2$ を添加した条件[31]でも同様の結果となった。そこで反応性の向上を期待し entry 8 では、^{i}PrMgCl·LiCl[32]を用いて反応を行ったが目的物を得ることはできなかった。entry 9 ではインジウム[33]、entry 10 ではジエチル亜鉛[34]を用いて反応を行ったが反応は進行しなかった。最後にヨウ化サマリウム[35]を用いて検討を行ったが、**122a** が得られるのみであった。



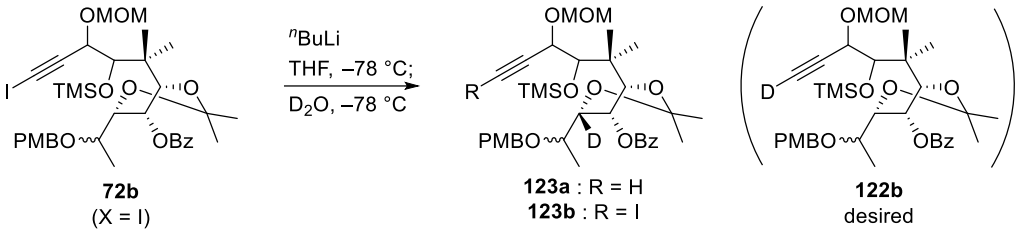
entry	X	reagent	temp. 1 (°C)	temp. 2 (°C)	solvent	result
1	Br	^{n}BuLi	–78 to 0	0	THF	**72a** : **122a** = 1:1, **108**
2	Br	^{t}BuLi	–78 to 0	0	THF	**72a** : **122a** = 1:1, **108**
3[a]	I	^{n}BuLi	0	0	THF	**72b** : **122a** = 2:1, **108**
4	I	^{n}BuLi	0	0	hexane	**72b** : **122a** = 4:1, **108**
5	I	^{n}BuLi	0	0	toluene	**72b** : **122a** = 1:1, **108**
6	I	^{n}BuLi	0	0	Et_2O	**72b** : **122a** = 1:1, **108**
7[b]	Br	^{i}PrMgBr	rt	rt	THF	almost **122a**
8	Br	^{i}PrMgCl·LiCl	0	0	THF	almost **122a**
9	I	In	reflux	reflux	DCE	n.r.
10	I	$ZnEt_2$, PPh_3	rt to reflux	rt to reflux	CH_2Cl_2	n.r.
11	I	SmI_2, HMPA	rt	rt	THF	almost **122a**

[a]Addition of HMPA, LiCl, $CeCl_3$ or TMEDA was failed.
[b]Addition of $ZnCl_2$ was failed.

Table 3

3-16. ヨードアルキン **72b** に対する重水素化実験

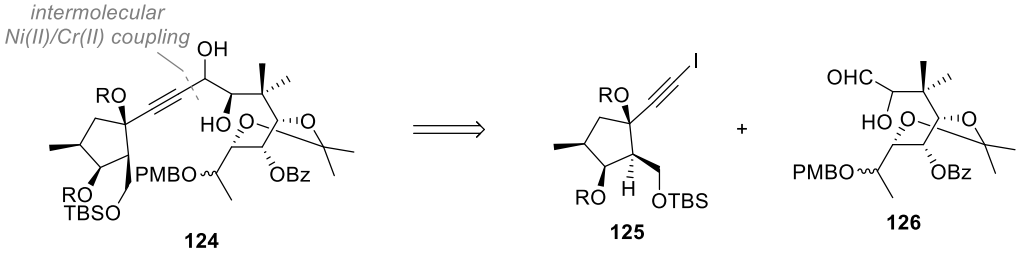
ケトン **71c** およびヨードアルキン **72b** のアニオンカップリングが進行しない原因を精査するため、リチウムアセチリドに対する重水素化実験を行った（Scheme 26）。**72b** に対して、^{n}BuLi を用いたハロゲン-リチウム交換によりリチウムアセチリドとした後、D_2O を添加した。その結果、アルキン末端が重水素化されたアルキン **122b** は確認されず、望まない位置での重水素化が進行したアルキン **123a** および **123b** が 2:1 の比で得られる結果となった。またこの際、アルキン末端のハロゲン-リチウム交換が完全に進行していないことも明らかになった。以上の結果から、ハロゲン-リチウム交換によるリチウムアセチリドの生成よりも塩基による脱プロトン化の方が速いことが示唆された。そこで、アニオンカップリングによる連結は困難であると考え、新たなルートでの合成を行うこととした。



Scheme 26

3-17. 新たなカップリング体 **124** の合成計画

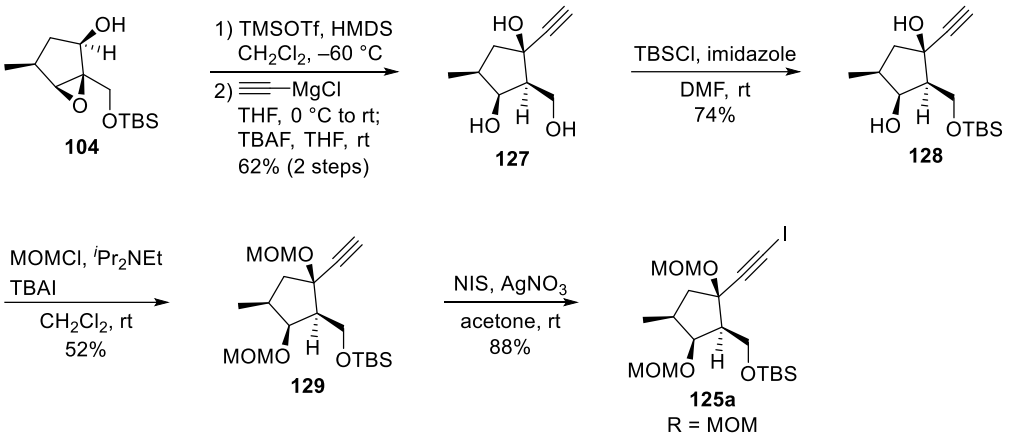
これまでの検討でアニオンカップリングによる連結が困難であったことから、新たな合成計画を立案した（Scheme 27）。カップリング体 **124** は、分子間 Ni(II)/Cr(II)カップリングによりヨードアルキン **125** およびアルデヒド **126** から合成できると考えた。さらに **125** および **126** は、これまでに合成した中間体から導くことができると予想した。



Scheme 27

3-18. ヨードアルキン **125a** の合成

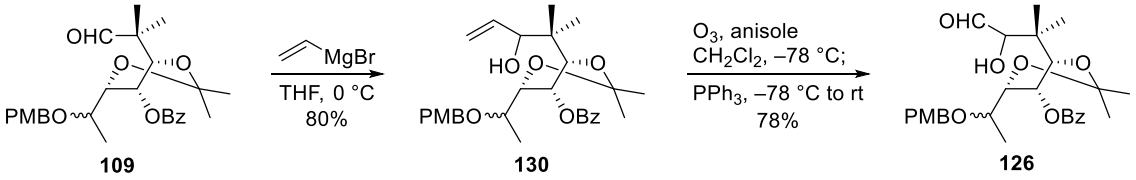
初めに、ヨードアルキン **125a** の合成を行った（Scheme 28）。エポキシド **104** に対して、エポキシドの開環に続くヒドリド転位を行うことでケトンとした後、エチニル基の導入に続くシリル保護基の除去によりトリオール **127** へと導いた。得られた **127** の一級水酸基を TBS 基で保護することでジオール **128** とした後、二つの水酸基の MOM 保護を行うことでアルキン **129** へと変換した。最後に、**129** のアルキン末端をヨウ素化することで目的の **125a** を合成した。



Scheme 28

3-19. アルデヒド **126** の合成

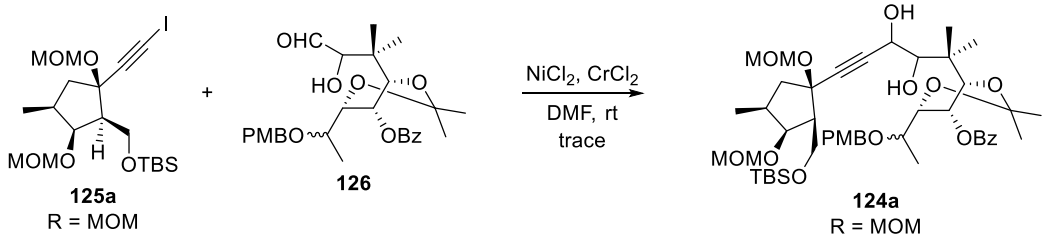
続いてアルデヒド **126** の合成を行った（Scheme 29）。アルデヒド **109** に対して、ビニル基の導入によりアルコール **130** とした後、オゾン酸化を行うことで目的のアルデヒド **126** を合成した。



Scheme 29

3-20. 分子間 Ni(II)/Cr(II)カップリングによるカップリング体 **124a** の合成

ヨードアルキン **125a** およびアルデヒド **126** が得られたため、分子間 Ni(II)/Cr(II)カップリングによる連結を試みた（Scheme 30）。すなわち、**125a** および **126** の混合物に対して $NiCl_2$ 存在下 $CrCl_2$ を作用させたところ、痕跡量ではあるが目的のカップリング体 **124a** が生成していることをマススペクトルにより確認した。これにより、一つの Me 基を除いたすべての炭素原子を有する Kansuinine A (**1**)の基本骨格の不斉合成を達成した。



Scheme 30

総括

本研究では、高活性なアシル化触媒である TMAJ の開発を基盤として、生理活性天然物である(+)-Epilupinine の効率的な不斉全合成および Kansuinine A の全合成研究を行った。

本論第 1 章では TMAJ の合成を初めて達成し、DMAP および 9-AJ と比較して高い触媒活性を有していることを明らかにした。さらに基質適用範囲を確認し、様々な嵩高い三級アルコールに対して適用可能であることを確認した。

本論第 2 章では、TMAJ の合成で見出した連続環化反応による Quinolizidine 骨格の効率的構築法を応用することで、(+)-Epilupinine の不斉全合成をわずか 3 工程で達成した。さらに、不斉触媒を用いた連続環化反応のエナンチオ選択性を DFT 計算により解明した。最後に、再結晶により光学的に純粋な(+)-Epilupinine を得ることに成功した。

本論第 3 章では、Kansuinine A の不斉全合成研究に取り組んだ。初めに、課題であった五員環ヘミケタール部位の構築に関してモデル基質を用いて検討を行うことで、ヘミケタールの等価体であるフラノン誘導体の新規な構築法を確立した。さらに Kansuinine A の不斉全合成に取り組み、一つの Me 基を除くすべての炭素原子を有する Kanuinine A の基本骨格の不斉合成を達成した。

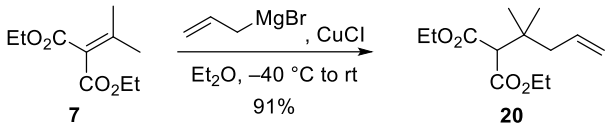
実験の部

General Information

All reactions were carried out under an argon atmosphere. Triethylamine (NEt_3) and *N*,*N*-diisopropylethylamine ($^iPr_2NEt$) was distilled from CaH_2 under argon atmosphere and stored over NaOH. Anhydrous solvents and reagents were commercial grade and used as supplied. NMR spectra were recorded on a JEOL JNM-AL400 (400 MHz), Bruker AVANCE III 500 (500 MHz) or Bruker AVANCE III 400 (400 MHz). Chemical shifts were reported in parts per million (ppm). For ^1H NMR spectra ($CDCl_3$, D_2O), the residual solvent peak was used as the internal reference (7.26, 4.89 ppm), whereas the central solvent peak was used as the reference (77.0 ppm) for ^{13}C NMR spectra. High-resolution Mass spectra (HRMS) were recorded on a Waters/Micromass LCT PREMIER and Low-resolution Mass spectra (LRMS) were recorded on a Waters/Micromass SQ Detector 2. Infrared (IR) spectra were recorded on a JASCO FT/IR-4200 spectrometer using KBr plate. Analytical thin layer chromatography (TLC) was performed with E. Merck pre-coated TLC plates, silica gel 60F-254, layer thickness 0.25 mm. Preparative thin layer chromatography (PTLC) was performed with E. Merck pre-coated TLC plates, silica gel 60F-254, layer thickness 0.5 mm. Reaction components were visualized by ninhydrin in 3% acetic acid in ^{n}BuOH, *p*-anisaldehyde in 10% sulfuric acid in EtOH, phosphomolybdic acid in EtOH or Basic aqueous solution of KMn_2O_7 (using NaOH and K_2CO_3). Flash column chromatography was performed on Kanto Chemical Silica Gel 60 N (spherical, neutral, 0.063-0.210 mm) mesh silica gel, Merch Aluminium oxide 90 active basic (0.063-0.200 mm) or Wako Wakogel 50C18 (0.038-0.063 mm). Optical rotation was recorded on a JASCO P-2200 polarimeter. Micro Wave was used CEM corp. Discover SP. Melting point was measured with AS ONE ATM-01.

Experimental Details in Chapter 1

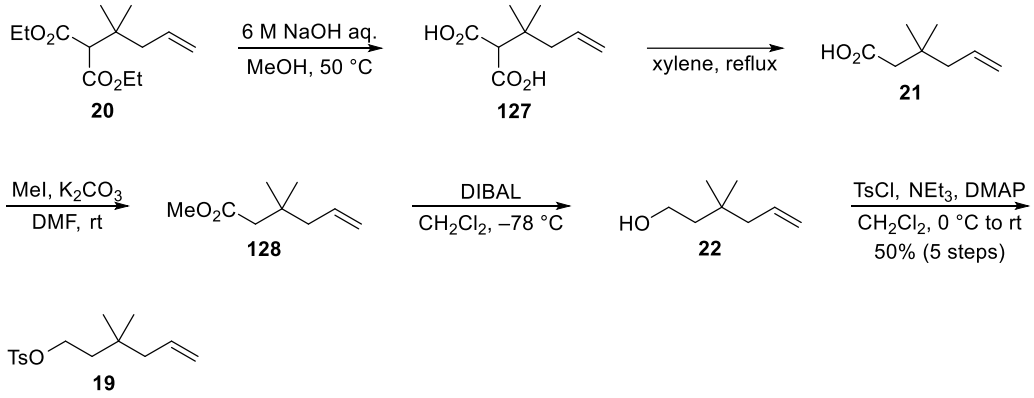
Diethyl 2-(2-methylpent-4-en-2-yl) malonate (20)



7 **20**

To a solution of CuCl (9.00 g, 91.0 mmol) in Et_2O (910 mL) was added 1.0 M Et_2O solution of allyl magnesium bromide (200 mL, 200 mmol) at –40 °C and stirred for 1 hour. To the mixture was added **7** (37.4 mL, 191 mmol) at –40 °C, and the mixture was stirred at room temperature for 30 min. The reaction was quenched with saturated aqueous solution of NH_4Cl, and the mixture was extracted with Et_2O (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 50/1) to give **20** (42.0 g, 173 mmol, 91%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81 (ddt, *J* = 17.1, 10.0, 7.5 Hz, 1H), 5.09 (dd, *J* = 10.1, 2.0 Hz, 1H), 5.05 (dd, *J* = 17.1, 1.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 4H), 3.30 (s, 1H), 2.23 (d, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 6H), 1.11 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 134.1, 118.4, 60.9, 59.2, 45.1, 36.3, 25.0, 14.1; IR (KBr): 3077, 2980, 1750, 1730, 1367, 1227, 1037, 913 cm^{-1}; HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{13}H_{23}O_4$, 243.1596; found, 243.1595.

3,3-dimethylhex-5-en-1-yl 4-methylbenzenesulfonate (19)

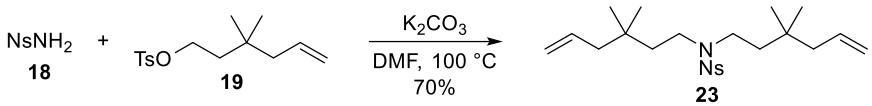


20 **127** **21** **128** **22** **19**

To a solution of **20** (42.0 g, 173 mmol) in MeOH (870 mL) was added 6.0 M aqueous solution of NaOH (870 mL) at room temperature, and the mixture was stirred at 50 °C for 20 hours. The reaction was quenched with 6.0 M aqueous solution of HCl, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used without further purification. The residue was dissolved in xylene (870 mL), and the mixture was heated to reflux for 48 hours. The reaction was quenched with 6.0 M aqueous solution of NaOH, and the mixture was extracted with Et_2O (x3). The aqueous layer was acidified by 6.0 M aqueous solution of HCl until the pH was below 3, and the mixture was

extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude **21**. The crude **21** was used without further purification. To a solution of the crude **21** in DMF (870 mL) was added K_2CO_3 (35.9 g, 260 mmol) and MeI (16.2 mL, 260 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 hour. The reaction was quenched with 1.0 M aqueous solution of HCl and extracted with Hexane (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure (30 °C, >120 Torr) to give the crude **128**. The crude **128** was used without further purification. To a solution of the crude **128** in CH_2Cl_2 (870 mL) was added 1.0 M Hexane solution of DIBAL (347 mL, 347 mmol) at –78 °C, and the mixture was stirred at –78 °C for 30 minutes and diluted with Et_2O. To the mixture was added saturated aqueous solution of NH_4Cl (50 mL) at –78 °C, and the mixture was stirred for 20 min. To the mixture was added $MgSO_4$, and the mixture was stirred at room temperature for 2 hours, filtered, and concentrated under reduced pressure (30 °C, >80 Torr) to give the crude **22**. The crude **22** was used without further purification. To a solution of the crude **22** in CH_2Cl_2 (870 mL) were added NEt_3 (36.2 mL, 260 mmol), TsCl (33.0 g, 173 mmol) and DMAP (4.24 g, 34.7 mmol) at 0 °C, and the mixture was stirred at room temperature for 3 hours. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2 (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 19/1) to give **19** (24.4 g, 86.4 mmol, 50% from **20**) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 5.71 (ddt, *J* = 17.1, 10.1, 7.4 Hz, 1H), 5.03 (ddt, *J* = 10.2, 2.2, 1.0 Hz, 1H), 4.97 (ddt, *J* = 16.9, 2.0, 1.1 Hz, 1H), 4.09 (t, *J* = 7.4 Hz, 2H), 2.45 (s, 3H), 1.90 (d, *J* = 7.3 Hz, 2H), 1.58 (t, *J* = 7.4 Hz, 2H), 0.85 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.6, 134.5, 133.1, 130.0, 127.8, 117.5, 67.9, 46.6, 39.6, 32.4, 26.9, 21.6; IR (KBr): 3073, 2960, 1638, 1598, 1472, 1388, 1362, 1189, 1176, 1097, 997, 921, 815 cm^{-1}; HRMS-ESI (*m*/*z*) [M + Na]$^+$ calcd for $C_{15}H_{22}O_3SNa$ 305.1187; found, 305.1190.

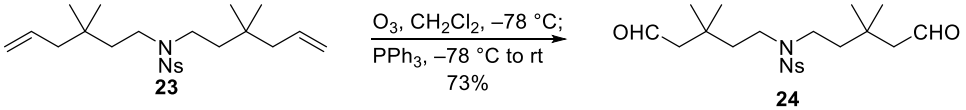
***N*,*N*-bis(3,3-dimethylhex-5-en-1-yl)-2-nitrobenzenesulfonamide (23)**



To a solution of $NsNH_2$ **18** (8.73 g, 43.2 mmol) in DMF (220 mL) was added K_2CO_3 (17.9 g, 130 mmol) at room temperature, and the mixture was heated to 100 °C for 10 minutes. To the mixture was added **19** (24.4 g, 86.4 mmol) at 100 °C, and the mixture was stirred at this temperature for 15 hours. The mixture was diluted with water and extracted with Et_2O (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 19/1) to give **23** (12.6 g, 29.8 mmol, 70%) as a yellow solid. Mp 54-55 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (m,

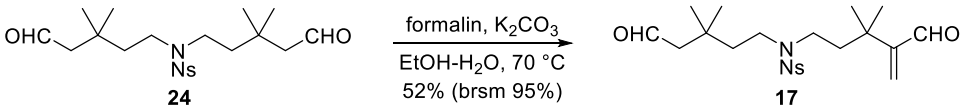
1H), 7.71-7.65 (m, 2H), 7.63 (m, 1H), 5.75 (ddt, *J* = 17.0, 10.1, 7.3 Hz, 2H), 5.03 (dd, *J* = 9.5, 1.5 Hz, 2H), 5.00 (dd, *J* = 17.0, 1.1 Hz, 2H), 3.30-3.25 (m, 4H), 1.93 (d, *J* = 7.4 Hz, 4H), 1.45-1.39 (m, 4H), 0.87 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.0, 134.8, 133.8, 133.3, 131.5, 130.8, 124.2, 117.4, 46.2, 43.2, 39.1, 32.5, 26.9; IR (KBr): 3074, 2958, 1638, 1546, 1472, 1372, 1350, 1160, 1125, 1064, 998, 915, 755 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{22}H_{35}N_2O_4S$, 423.2318; found, 423.2318.

_N_,_N_-bis(3,3-dimethyl-5-oxopentyl)-2-nitrobenzenesulfonamide (24)



Ozone was bubbled through a solution of **23** (4.49 g, 10.6 mmol) in CH_2Cl_2 (50 mL) at –78 °C until the color of the solution changed to blue. After bubbling of argon until the blue color was gone, to the mixture was added PPh_3 (8.36 g, 31.9 mmol) at –78 °C, and the mixture was stirred at room temperature for 2 hours and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 9/1 to 7/3) to give **24** (3.40 g, 7.75 mmol, 73%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.81 (t, *J* = 2.8 Hz, 2H), 8.02 (m, 1H), 7.74-7.68 (m, 2H), 7.63 (m, 1H), 3.34-3.28 (m, 4H), 2.30 (d, *J* = 2.8 Hz, 4H), 1.62-1.56 (m, 4H), 1.08 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.6, 148.0, 133.5, 133.4, 131.7, 130.8, 124.2, 54.1, 43.2, 39.7, 32.7, 27.4; IR (KBr): 2961, 2738, 1716, 1544, 1471, 1372, 1349, 1161, 1124, 1061, 756 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{20}H_{31}N_2O_6S$, 427.1903, found, 427.1905.

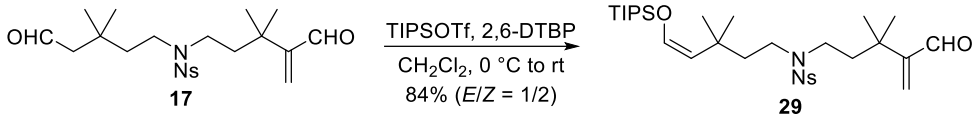
_N_-(3,3-dimethyl-5-oxopentyl)-_N_-(4-formyl-3,3-dimethylpent-4-en-1-yl)-2-nitrobenzenesulfonamide (17)



To a solution of **24** (1.16 g, 2.72 mmol) in EtOH (11 mL) and H_2O (2.7 mL) was added K_2CO_3 (376 mg, 2.72 mmol) at room temperature, and the mixture was warmed to 70 °C. To the mixture was added formalin (221 μL, 2.72 mmol, 37% aqueous solution) with a syringe pump at 70 °C over 30 min. The mixture was diluted with water and extracted with AcOEt (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 17/3) to give **17** (623 mg, 1.42 mmol, 52%) as a pale yellow oil and **24** (503 mg, 1.18 mmol, 43%) as a pale yellow oil. **17**; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.80 (t, *J* = 2.9 Hz, 1H), 9.51 (s, 1H), 7.97 (m, 1H), 7.71-7.67 (m, 2H), 7.61 (m, 1H), 6.35 (s, 1H), 6.05 (s, 1H), 3.30-3.24 (m, 2H), 3.06-3.01 (m, 2H), 2.27 (d, *J* = 2.8 Hz, 2H), 1.94-1.88 (m, 2H), 1.56-1.50 (m, 2H), 1.16 (s, 6H), 1.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.7, 194.8, 155.0, 147.9, 136.5, 133.5, 133.4, 131.6, 130.7, 124.1, 54.3, 43.6, 42.9, 39.7,

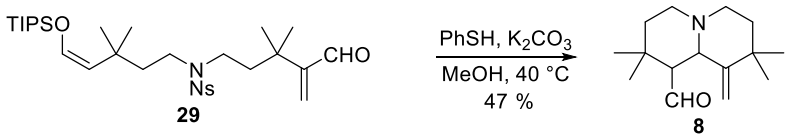
36.7, 36.0, 32.6, 27.3, 27.0; IR (KBr): 3064, 2962, 2928, 2726, 1869, 1747, 1716, 1691, 1543, 1473, 1373, 1350, 1160, 1124, 1082, 851, 761 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{21}H_{31}N_2O_6S$, 439.1903; found, 439.1904.

(*Z*)-*N*-(3,3-dimethyl-5-((triisopropylsilyl)oxy)pent-4-en-1-yl)-*N*-(4-formyl-3,3-dimethylpent-4-en-1-yl)-2-nitrobenzenesulfonamide (29)



To a solution of **17** (675 mg, 1.54 mmol) in CH_2Cl_2 (7.7 mL) were added 2,6-DTBP (745 μL, 3.39 mmol) and TIPSOTf (827 μL, 3.08 mmol) at 0 °C, and the mixture was stirred at room temperature for 14 hours. The reaction was quenched with saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with AcOEt (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 9/1 to 4/1) to give stereoisomeric mixture of **29** (770 mg, 1.29 mmol, 84%, *E*/*Z* = 1/2) as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ *Z* isomer 9.50 (s, 1H), 7.95 (m, 1H), 7.68-7.64 (m, 2H), 7.60 (m, 1H), 6.34 (s, 1H), 6.14 (d, *J* = 6.6 Hz, 1H), 6.03 (s, 1H), 4.03 (d, *J* = 6.6 Hz, 1H), 3.30-3.24 (m, 2H), 3.10-3.04 (m, 2H), 1.93-1.88 (m, 2H), 1.60-1.50 (m, 2H), 1.18-1.09 (m, 3H), 1.17 (s, 6H), 1.07 (s, 18H), 1.05 (s, 6H); *E* isomer 9.51 (s, 1H), 7.95 (m, 1H), 7.68-7.64 (m, 2H), 7.60 (m, 1H), 6.34 (s, 1H), 6.22 (d, *J* = 12.2 Hz, 1H), 6.04 (s, 1H), 4.89 (d, *J* = 12.1 Hz, 1H), 3.21-3.16 (m, 2H), 3.10-3.03 (m, 2H), 1.93-1.88 (m, 2H), 1.43-1.38 (m, 2H), 1.18-1.09 (m, 3H), 1.12 (s, 18H), 1.07 (s, 6H), 0.97 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ *Z* and *E* isomer 194.6, 194.6, 155.1, 155.1, 148.0, 148.0, 139.6, 139.0, 136.2, 136.1, 133.9, 133.7, 133.2, 133.1, 131.5, 131.4, 130.8, 130.7, 124.1, 124.1, 112.0, 115.1, 44.2, 43.8, 43.6, 43.6, 41.2, 40.9, 37.0, 37.0, 36.0, 33.5, 32.7, 28.2, 27.8, 27.0, 27.0, 17.8, 12.0, 11.8; IR (KBr): 3097, 2946, 2893, 2868, 2713, 1871, 1720, 1697, 1656, 1591, 1547, 1440, 1373, 1352, 1162, 1126, 1012, 883, 739, 682 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{30}H_{51}N_2O_6SSi$, 595.3237; found, 595.3240.

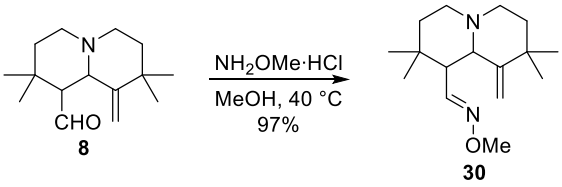
2,2,8,8-tetramethyl-9-methyleneoctahydro-2*H*-quinolizine-1-carbaldehyde (8)



To a solution of **29** (555 mg, 0.933 mmol) in MeOH (23 mL) were added K_2CO_3 (1.16 g, 8.40 mmol) and PhSH (573 μL, 5.60 mmol) at room temperature, and the reaction was stirred at 40 °C for 2 weeks. The reaction was quenched with saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and

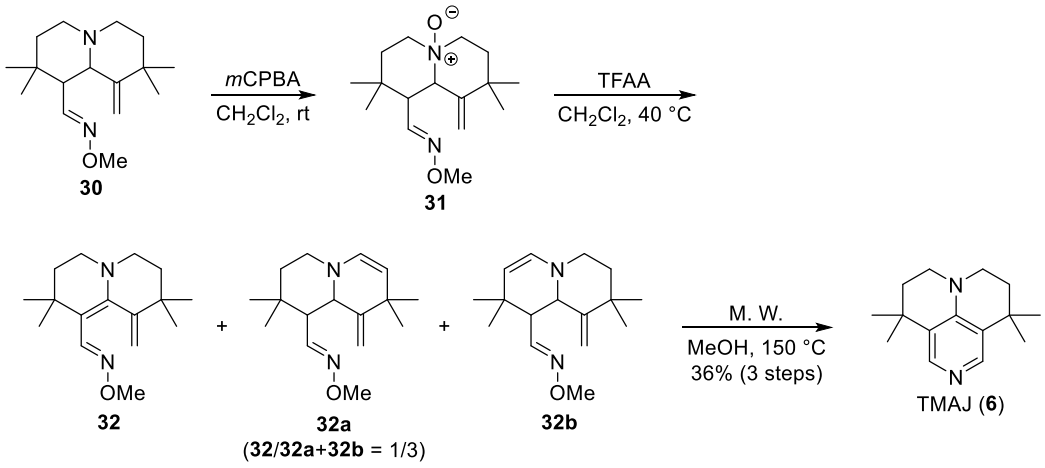
concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (CHCl3/MeOH = 9/1) to give **8** (104 mg, 0.442 mmol, 47%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.47 (d, *J* = 4.2 Hz, 1H), 4.98 (s, 1H), 4.66 (s, 1H), 3.25 (d, *J* = 10.6 Hz, 1H), 2.82 (d, *J* = 9.0 Hz, 1H), 2.75 (d, *J* = 10.0 Hz, 1H), 2.61 (td, *J* = 12.3, 2.7 Hz, 1H), 2.47 (t, *J* = 12.4 Hz, 2H), 1.78-1.56 (m, 2H), 1.50 (dt, *J* = 13.3, 2.8 Hz, 1H), 1.34 (dt, *J* = 13.7, 2.7 Hz, 1H), 1.16 (s, 3H), 1.13 (s, 6H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.7, 153.5, 108.6, 58.3, 56.0, 53.0, 51.7, 40.0, 39.7, 36.2, 33.5, 30.6, 29.6, 25.1, 20.6; IR (KBr): 2953, 2924, 2868, 1722, 1593, 1466, 1180, 670 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{26}NO$, 236.2014; found, 236.2010.

2,2,8,8-tetramethyl-9-methyleneoctahydro-2*H*-quinolizine-1-carbaldehyde *O*-methyl oxime (30)



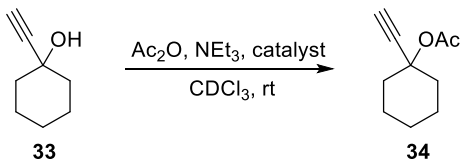
To a solution of **8** (35.9 mg, 0.153 mmol) in MeOH (760 μL) was added $NH_2OMe{\cdot}HCl$ (15.3 mg, 0.183 mmol) at room temperature, and the reaction was stirred at 40 °C for 12 hours. The reaction was quenched with saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography ($CHCl_3$/MeOH = 9/1) to give **30** (39.1 mg, 0.149 mmol, 97%) as a pale orange oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (d, *J* = 8.6 Hz, 1H), 5.02 (s, 1H), 4.97 (s, 1H), 3.83 (s, 3H), 2.88 (d, *J* = 10.9 Hz, 1H), 2.80 (ddd, *J* = 12.0, 4.8, 2.6 Hz, 1H), 2.72 (dt, *J* = 11.7, 3.4 Hz, 1H), 2.54 (td, *J* = 12.4, 3.4 Hz, 1H), 2.50-2.43 (m, 2H), 1.69 (td, *J* = 13.4, 4.0 Hz, 1H), 1.62 (td, *J* = 13.1, 4.9 Hz, 1H), 1.47 (dt, *J* = 13.2, 3.0 Hz, 1H), 1.37 (dt, *J* = 13.6, 2.6 Hz, 1H), 1.10 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.4, 151.6, 109.6, 61.3, 57.8, 52.9, 51.6, 46.6, 40.3, 38.8, 36.1, 32.9, 30.6, 29.5, 24.9, 20.4; IR (KBr): 2952, 2924, 1640, 1602, 1465, 1177, 1047, 911, 676 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{16}H_{28}N_2ONa$ 287.2099; found, 287.2099.

1,1,7,7-Tetramethyl-9-Azajulolidine (TMAJ, 6)



To a solution of **30** (69.3 mg, 0.262 mmol) in CH_2Cl_2 (1.3 mL) was added *m*CPBA (67.9 mg, 0.275 mmol) at room temperature, and the mixture was stirred for 20 minutes. To the mixture was added saturated aqueous solution of $NaHCO_3$ and $CHCl_3$. After stirring for 20 minutes, the mixture was extracted with $CHCl_3$ (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was passed through Basic Alumina to remove *m*-chlorobenzoic acid to give the crude **31**. The crude **31** was used without further purification. To a solution of the crude 31 in CH_2Cl_2 (1.8 mL) was added TFAA (128 μL, 0.906 mmol) at 40 °C, and the mixture was stirred for 10 minutes. The reaction was quenched with saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue including **32**, **32a** and **32b** was used without further purification. The residue was dissolved in MeOH (4.5 mL) at room temperature, and the mixture was heated to 150 °C under microwave irradiation (300W) for 4 hours. The reaction mixture was concentrated under reduced pressure. The residue was purified by Reverse-Phase silica-gel column chromatography (MeCN) followed by silica-gel column chromatography ($CHCl_3$/MeOH = 9/1) to give **6** (21.4 mg, 0.0929 mmol, 36%, 3 steps) as a white powder oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (s, 2H), 3.25 (t, J = 6.0 Hz, 4H), 1.71 (t, J = 6.1 Hz, 4H), 1.29 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 144.1, 124.0, 46.0, 35.9, 30.5, 30.2; IR (KBr): 2924, 1593, 1326, 777, 705 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{15}H_{23}N_2$, 231.1861; found, 231.1858.

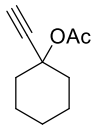
General Procedure of Catalytic Activity Test of DMAP analogues



To a solution of **33** (50.0 μL, 0.389 mmol) in $CDCl_3$ (1.95 mL) were added catalyst (0.0389 mmol),

NEt_3 (162.8 μL, 1.17 mmol) and Ac_2O (73.6 μL, 0.779 mmol) at room temperature. The little amount of reaction mixture was taken out, diluted by $CDCl_3$ and measured by ^1H NMR, and the conversion was determined by the integration ratio of the alkyne or acetyl peaks.

1-ethynylcyclohexyl acetate (34)

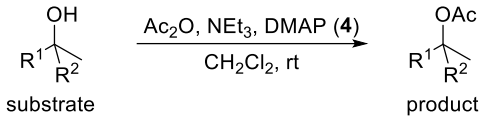


34

colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 2.58 (s, 1H), 2.18-2.04 (m, 2H), 2.02 (s, 3H), 1.81-1.78 (m, 2H), 1.68-1.59 (m, 4H), 1.58-1.46 (m, 1H), 1.37-1.21 (m, 1H).

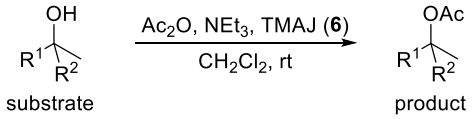
This ^1H NMR data is identical with that of ref 36.

General Procedure for Substrate Scope Using DMAP (4)



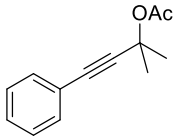
To a solution of substrate (0.409 mmol) in CH_2Cl_2 (2.05 mL) were added DMAP (**4**) (5.0 mg, 0.0409 mmol), NEt_3 (171.1 μL, 1.23 mmol) and Ac_2O (77.4 μL, 0.819 mmol) at room temperature. The reaction was monitored by TLC. When the reaction finished, it was quenched with saturated aqueous solution of NH_4Cl, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was measured by ^1H NMR without further purification, and the yield was determined by the integration ratio compared with pyrazine (8.19 mg, 0.102 mmol) as an internal standard.

General Procedure for Substrate Scope Using TMAJ (6)



To a solution of substrate (43.4 μmol) in CH_2Cl_2 (217.1 μL) were added 1.0 M solution of TMAJ (**6**) in CH_2Cl_2 (4.34 μL, 4.34 μmol), NEt_3 (18.2 μL, 130 μmol) and Ac_2O (8.21 μL, 86.8 μmol) at room temperature. The reaction was monitored by TLC. When the reaction finished, it was quenched with saturated aqueous solution of NH_4Cl, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was measured by ^1H NMR without further purification, and the yield was determined by the integration ratio compared with pyrazine (3.48 mg, 43.4 μmol) as an internal standard.

2-methyl-4-phenylbut-3-yn-2-yl acetate (36)

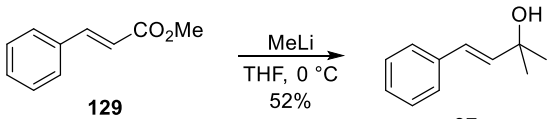


36

colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.43 (m, 2H), 7.30-7.29 (m, 3H), 2.06 (s, 3H), 1.76 (s, 6H).

This ^{1}H NMR data is identical with that of ref 37.

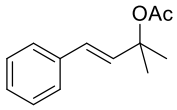
Synthesis of (*E*)-2-methyl-4-phenylbut-3-en-2-ol (37)



129 **37**

To a solution of **129** (850 mg, 5.24 mmol) in THF (26 mL) was added 1.5 M Et_2O solution of MeLi (10.5 mL, 15.7 mmol) at 0 °C, and the mixture was stirred for 10 minutes. The reaction was quenched with saturated aqueous solution of NH_4Cl, and the mixture was extracted with AcOEt (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 4/1) to give **37** (439 mg, 2.71 mmol, 52%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.21 (m, 5H), 6.61-6.57 (d, *J* = 16.0 Hz, 1H), 6.38-6.34 (d, *J* = 16.0 Hz, 1H), 1.54 (s, 1H), 1.43 (s, 6H). This ^{1}H NMR data is identical with that of ref 38.

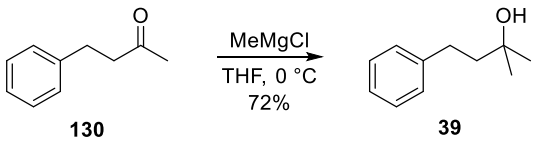
(*E*)-2-methyl-4-phenylbut-3-en-2-yl acetate (38)



38

colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 1H), 6.53 (d, *J* = 16.4 Hz, 1H), 6.49 (d, *J* = 16.4 Hz, 1H), 2.01 (s, 3H), 1.63 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 136.7, 133.9, 128.5, 128.0, 127.6, 126.5, 80.5, 26.8, 22.3; IR (KBr): 2980, 2931, 1732, 1604, 1494, 1246, 1124, 1016, 963, 747, 693 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{13}H_{17}O_2$, 205.1229; found, 205.1225.

Synthesis of 2-methyl-4-phenylbutan-2-ol (39)

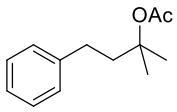


130 **39**

To a solution of **130** (1.00 mL, 6.68 mmol) in THF (33 mL) was added 3.0 M THF solution of MeMgCl (3.34 mL, 10.0 mmol) at 0 °C, and the mixture was stirred for 10 minutes. The reaction was quenched with saturated aqueous solution of NH_4Cl, and the mixture was extracted with AcOEt (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 4/1) to give **39** (786 mg, 4.79 mmol, 72%) as a colorless oil. ^{1}H NMR (500 MHz,

$CDCl_3$): δ 7.34-7.20 (m, 5H), 2.71-2.67 (m, 2H), 1.80 (d, *J* = 17.4 Hz, 1H), 1.78-1.74 (m, 2H), 1.27 (s, 6H). This ^1H NMR data is identical with that of ref 39.

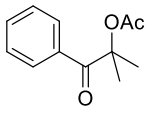
2-methyl-4-phenylbutan-2-yl acetate (40)



40

colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.26-7.20 (m, 2H), 7.17-7.09 (m, 3H), 2.66-2.55 (m, 2H), 2.07-1.98 (m, 2H), 1.92 (s, 3H), 1.47 (s, 6H).
This ^1H NMR data is identical with that of ref 40.

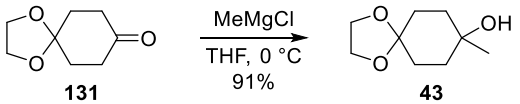
2-methyl-1-oxo-1-phenylpropan-2-yl acetate (42)



42

white solid; ^1H NMR (500 MHz, $CDCl_3$): δ 8.02-8.00 (m, 2H), 7.51-7.48 (m, 1H), 7.42-7.38 (m, 2H), 1.93 (s, 3H), 1.72 (s, 6H).
This ^1H NMR data is identical with that of ref 41.

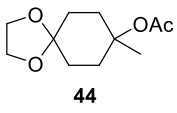
Synthesis of 8-methyl-1,4-dioxaspiro[4.5]decan-8-ol (41)



131 **43**

To a solution of **131** (1.00 g, 6.40 mmol) in THF (32 mL) was added 3.0 M THF solution of MeMgCl (3.20 mL, 9.60 mmol) at 0 °C, and the mixture was stirred for 10 minutes. The reaction was quenched with saturated aqueous solution of NH_4Cl, and the mixture was extracted with AcOEt (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 2/1) to give **43** (1.00 g, 5.81 mmol, 91%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 4.00-3.91 (m, 4H), 1.95-1.80 (m, 3H), 1.77-1.67 (m, 4H), 1.59-1.58 (m, 1H), 1.27 (s, 3H) This ^1H NMR data is identical with that of ref 42.

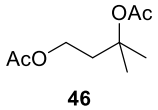
8-methyl-1,4-dioxaspiro[4.5]decan-8-yl acetate (44)



44

colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 3.98-3.91 (m, 4H), 2.30-2.24 (m, 2H), 2.00 (s, 3H) 1.75 (td, *J* = 12.2, 3.9 Hz, 2H), 1.68-1.59 (m, 3H), 1.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 108.0, 80.1, 64.2, 64.1, 33.9, 30.4, 24.8, 22.1; IR (KBr): 2882, 1731, 1445, 1372, 1231, 1149, 1097, 1025, 769 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_{11}H_{18}O_4Na$, 237.1103; found, 237.1098.

3-methylbutane-1,3-diyl diacetate (46)

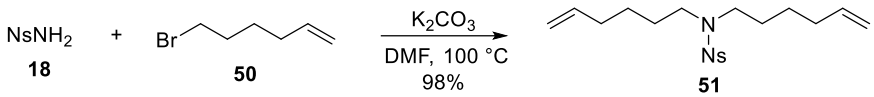


46

colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.16 (t, *J* = 7.1 Hz, 2H), 2.12 (t, *J* = 7.1 Hz, 2H), 2.04 (s, 3H), 1.98 (s, 3H), 1.48 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.9, 170.3, 80.6, 60.6, 38.8, 26.3, 22.3, 20.9; IR (KBr): 2940, 1740, 1475, 1369, 1252, 1152, 1080, 1020, 787 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + Na]^+$ calcd for $C_9H_{16}O_4Na$, 211.0946; found, 211.0951.

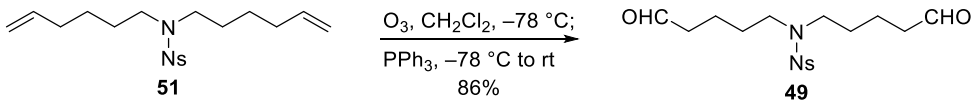
Experimental section in Chapter 2

***N*,*N*-bis(5-hexenyl)-2-nitrobenzenesulfonamide (51)**



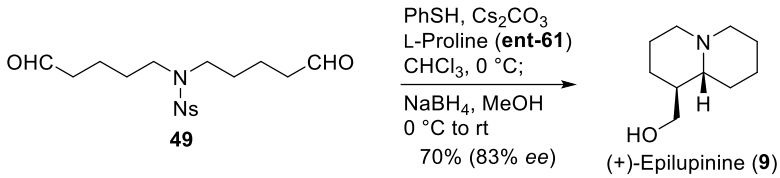
To a solution of $NsNH_2$ **18** (7.56 g, 37.4 mmol) in DMF (375 mL) were added K_2CO_3 (31.0 g, 224 mmol) and **50** (10.0 mL, 74.8 mmol) at room temperature. The reaction mixture was heated to 100 °C for 16 hours. The reaction was quenched with water and the mixture was extracted with Et_2O (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 9/1 to 4/1) to give **51** (13.4 g, 36.6 mmol, 98%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (m, 1H), 7.69-7.65 (m, 2H), 7.61 (m, 1H), 5.73 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 2H), 4.97 (dq, *J* = 17.1, 1.7 Hz, 2H), 4.94 (ddt, *J* = 10.8, 2.1, 1.0 Hz, 2H), 3.28 (t, *J* = 7.6 Hz, 4H), 2.03 (q, *J* = 7.2 Hz, 4H), 1.54 (quint, *J* = 7.7 Hz, 4H), 1.35 (quint, *J* = 7.6 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.1, 138.2, 133.9, 133.2, 131.5, 130.8, 124.1, 114.9, 47.0, 33.2, 27.4, 25.7; IR (KBr): 3076, 2932, 1640, 1545, 1373, 1347, 1160, 1124, 996, 912, 740 cm^{-1}; HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{18}H_{27}N_2O_4S$, 367.1692; found, 367.1689.

***N*,*N*-bis(5-oxopentyl)-2-nitrobenzenesulfonamide (49)**



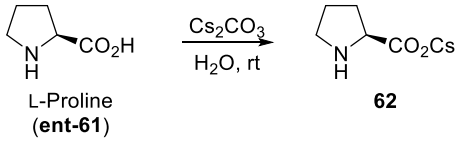
Ozone was bubbled through a solution of **51** (13.4 g, 36.6 mmol) in CH_2Cl_2 (200 mL) at –78 °C until the color of the solution changed to blue. After bubbling of argon until the blue color disappeared, to the mixture was added PPh_3 (28.8 g, 110 mmol) at –78 °C. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (CH_2Cl_2/AcOEt = 1/0 to 19/1) to give **49** (11.7 g, 31.6 mmol, 86%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.74 (t, *J* = 1.4 Hz, 2H), 8.01 (m, 1H), 7.71-7.68 (m, 2H), 7.62 (m, 1H), 3.30 (t, *J* = 7.0 Hz, 4H), 2.46 (td, *J* = 6.7, 1.3 Hz, 4H), 1.62-1.57 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.7, 148.1, 133.5, 133.4, 131.6, 130.7, 124.2, 47.0, 43.1, 27.6, 18.9; IR (KBr): 2929, 2729, 1720, 1542, 1373, 1343, 1160, 1141, 745 cm^{-1}; HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{16}H_{23}N_2O_6S$, 371.1277; found, 371.1278.

(+)-Epilupinine (9)



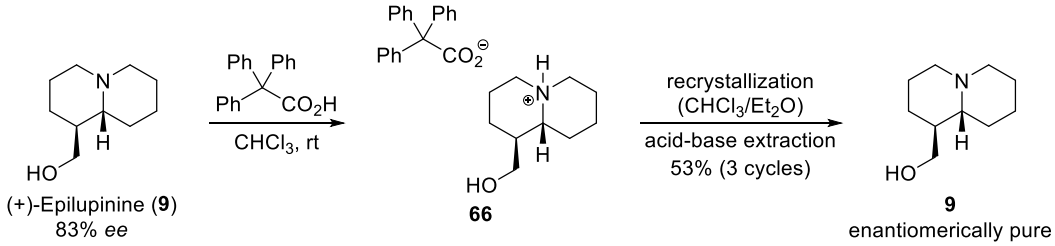
To a solution of **49** (5.00 g, 13.5 mmol) in $CHCl_3$ (335 mL) were added Cs_2CO_3 (13.2 g, 40.5 mmol), L-proline (**ent-61**) (1.55 g, 13.5 mmol) and PhSH (2.76 mL, 27.0 mmol) at 0 °C, and the mixture was stirred at 0 °C for 12 hours. To the mixture were added MeOH (335 mL) and $NaBH_4$ (766 mg, 20.2 mmol), and the mixture was stirred at room temperature for 10 minutes. The reaction was quenched with saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with $CHCl_3$ (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (AcOEt/MeOH = 3/1) to give **9** (1.60 g, 9.45 mmol, 70%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.64 (dd, *J* = 10.9, 3.6 Hz, 1H), 3.55 (dd, *J* = 10.9, 5.8 Hz, 1H), 2.85-2.75 (m, 2H), 2.06-1.98 (m, 2H), 1.89 (m, 1H), 1.83 (m, 1H), 1.76 (m, 1H), 1.72-1.65 (m, 3H), 1.63-1.56 (m, 2H), 1.41 (m, 1H), 1.29-1.14 (m, 3H); ^{13}C NMR (125Hz, $CDCl_3$): δ 64.6, 64.3, 56.9, 56.6, 43.9, 29.7, 28.2, 25.5, 25.0, 24.5; IR (KBr): 3351, 2928, 1443, 1370, 1113, 1092, 1069, 769 cm^{-1}; HRMS-ESI (*m/z*): $[M + H]^+$ calcd for $C_{10}H_{20}NO$, 170.1545; found, 170.1546; $[\alpha]_D^{29}$ +19.2 (c 0.60, EtOH).

Cesium L-prolinate (62)



To a solution of L-Proline (**ent-61**) (5.00 g, 43.4 mmol) in H_2O (45 mL) was added Cs_2CO_3 (7.08 g, 21.7 mmol) at room temperature, and the mixture was stirred at room temperature for 1 hour. The mixture was concentrated under reduced pressure. The residue was used without further purification.

Recrystallization of (+)-Epilupinine (9)



Triphenylacetic acid (1.59 g, 5.52 mmol) was added to a solution of **9** (935 mg, 5.52 mmol) in $CHCl_3$ at room temperature, and the mixture was concentrated under reduced pressure. The residue was recrystallized from $CHCl_3/Et_2O$ at 0 °C in closed vessel. The mixture was filtrated, and the crystals

were collected. The crystals were dissolved in 1M aqueous solution of HCl, and the mixture was extracted with Et_2O (x3). To the aqueous layer was added 3M aqueous solution of NaOH, and the mixture was extracted with ^{n}BuOH (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give 9 (496 mg, 2.93 mmol, 53%, 3 cycles) as a white solid. mp 77-78 °C [lit.[43] 77-79 °C]; $[\alpha]_D^{18}$ +31.5 (c 0.35, EtOH) [lit. $[\alpha]_D^{20}$ +31.8 (c 0.60, EtOH)].

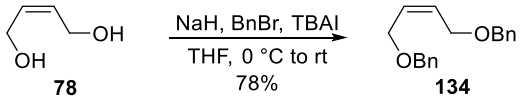
Determination of *ee*

(+)-Epilupinine (**9**) **132** **133**

To a solution of **9** (2.80 mg, 0.0165 mmol) in CH_2Cl_2 (100 μL) were added NEt_3 (3.46 μL, 0.0248 mmol) and (*S*)-MTPACl (3.71 μL, 0.0198 mmol) at 0 °C. The mixture was stirred at room temperature for 12 hours. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was measured by ^{19}F NMR without further purification, and the ee was determined by the integration ratio of the CF_3 peaks.

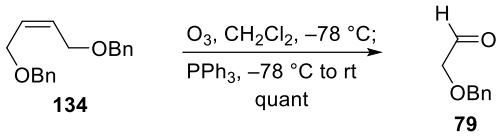
Experimental section in Chapter 3

(*Z*)-1,4-bis(benzyloxy)but-2-ene (134)



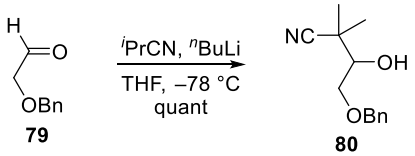
To a solution of **78** (1.00 mL, 12.2 mmol) in THF (60 mL) was added 60% dispersion in paraffin liquid of NaH (1.80 g, 36.6 mmol) at 0 °C and stirred for 30 minutes. To the mixture was added BnBr (3.60 mL, 30.5 mmol) and TBAI (900 mg, 2.44 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 hours. The reaction was quenched with water, and the mixture was extracted with AcOEt (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 19/1 to 4/1) to give **134** (2.50 g, 9.32 mmol, 78%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.27 (m, 5H), 5.79 (ddd, *J* = 4.8, 3.8, 1.0 Hz, 1H), 4.49 (s, 2H), 4.08-4.05 (m, 2H).

2-(benzyloxy)acetaldehyde (79)



Ozone was bubbled through a solution of **134** (2.00 g, 7.45 mmol) in CH_2Cl_2 (40 mL) at –78 °C until the color of the solution changed to blue. After bubbling of argon until the blue color disappeared, to the mixture was added PPh_3 (2.90 g, 110 mmol) at –78 °C. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 4/1) to give **79** (2.27 g, 15.1 mmol, quant) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (t, *J* = 0.7 Hz, 1H), 7.40-7.29 (m, 5H), 4.64 (s, 2H), 4.11 (d, *J* = 0.7 Hz, 2H).

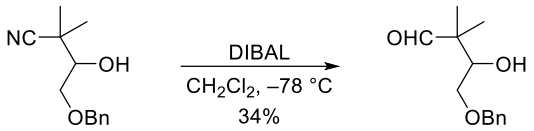
4-(benzyloxy)-3-hydroxy-2,2-dimethylbutanenitrile (80)



To a solution of ^{i}Pr$_2$NH (6.63 mL, 46.9 mmol) in THF (75 mL) was added 2.6 M hexane solution of ^{n}BuLi (18.0 mL, 46.9 mmol) at 0 °C and stirred for 30 minutes. To the mixture was added ^{i}PrCN (4.07 mL, 45.3 mmol) at –78 °C, and the mixture was stirred at 0 °C for 30 minutes. To the mixture was added **79** (2.27 g, 15.1 mmol) at –78 °C, and the mixture was stirred at –78 °C for 20 minutes. The

reaction was quenched with water, and the mixture was extracted with AcOEt (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 4/1) to give **80** (3.30 g, 15.1 mmol, quant) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.29 (m, 5H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 3.74 (dd, *J* = 9.1, 3.0 Hz, 1H), 3.67 (dt, *J* = 7.9, 3.2 Hz, 1H), 3.57 (dd, *J* = 9.1, 8.0 Hz, 1H), 2.80 (d, *J* = 3.4 Hz, 1H), 1.42 (s, 3H), 1.34 (s, 3H).

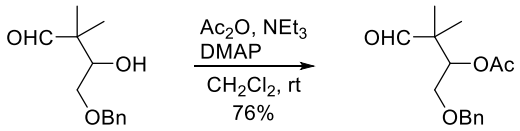
4-(benzyloxy)-3-hydroxy-2,2-dimethylbutanal (135)



80 **135**

To a solution of **80** (522 mg, 2.38 mmol) in CH_2Cl_2 (12.0 mL) was added 1.0 M Hexane solution of DIBAL (7.20 mL, 7.14 mmol) at –78 °C, and the mixture was stirred at –78 °C for 10 minutes. The reaction was quenched with saturated aqueous solution of Rochelle salt, and the mixture was extracted with AcOEt (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 4/1) to give **135** (181 mg, 0.814 mmol, 34%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.60 (s, 1H), 7.41-7.28 (m, 5H), 4.55 (s, 2H), 3.92 (dt, *J* = 7.6, 3. Hz, 1H), 3.58 (dd, *J* = 9.6, 3.1 Hz, 1H), 3.49 (dd, *J* = 9.6, 7.6 Hz, 1H), 2.61 (d, *J* = 3.9 Hz, 1H), 1.10 (s, 3H), 1.09 (s, 3H).

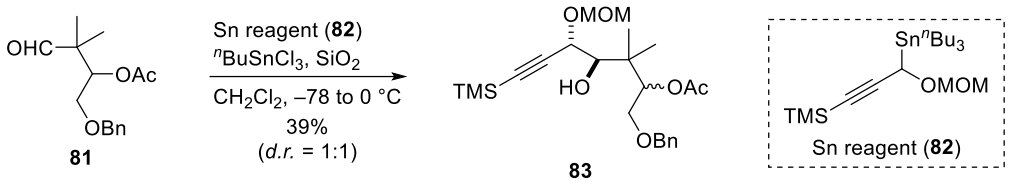
1-(benzyloxy)-3,3-dimethyl-4-oxobutan-2-yl acetate (81)



135 **81**

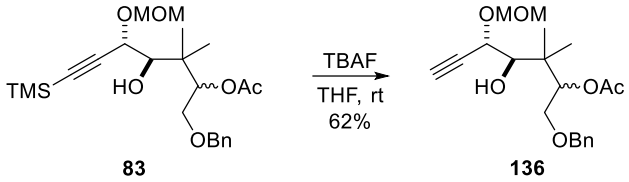
To a solution of **135** (181 mg, 0.814 mmol) in CH_2Cl_2 (4.00 mL) was added DMAP (20.0 mg, 0.163 mmol), NEt_3 (227 µL, 1.63 mmol) and Ac_2O (115 µL, 1.22 mmol) at room temperature, and the mixture was stirred at room temperature for 15 minutes. The reaction was quenched with water, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 4/1) to give **81** (162 mg, 0.613 mmol, 76%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.62 (s, 1H), 7.39-7.26 (m, 5H), 5.21 (dd, *J* = 5.1, 4.5 Hz, 1H), 4.51 (d, *J* = 12.4 Hz, 1H), 4.45 (d, *J* = 12.1 Hz, 1H), 3.58 (dd, *J* = 10.7, 5.2 Hz, 1H), 3.54 (dd, *J* = 10.7, 4.5 Hz, 1H), 2.09 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H).

***trans*-1-(benzyloxy)-4-hydroxy-5-(methoxymethoxy)-3,3-dimethyl-7-(trimethylsilyl)hept-6-yn-2-yl acetate (83)**



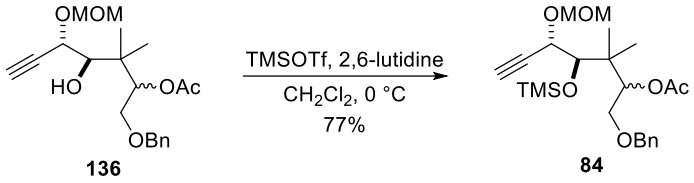
To a solution of **81** (162 mg, 0.613 mmol) and **82** (565 mg, 1.23 mmol) in CH_2Cl_2 (3.00 mL) was added ^{n}BuSnCl$_3$ (210 μL, 1.29 mmol) at –78 °C, and the mixture was stirred at 0 °C for 1 hour. To the mixture was added SiO_2 (160 mg) at 0 °C, and the mixture was stirred at 0 °C for 1 hour. The reaction was quenched with 0.1 M aqueous solution of HCl, and the mixture was extracted with Et_2O (x3). To the combined organic layers were added KF·Celite (850 mg), and the mixture was stirred at room temperature for 2 hours. The mixture was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by 10 w/w % anhydrous K_2CO_3-silica-gel column chromatography (Hexane/AcOEt = 50/1 to 25/1 to 4/1) to give diastereomeric mixture of **83** (103 mg, 0.236 mmol, 39%, *d.r.* = 1:1) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 7.38-7.26 (m, 10H), 5.17 (dd, *J* = 7.1, 3.3 Hz, 1H), 5.04 (dd, *J* = 6.4, 4.0 Hz, 1H), 4.98-4.91 (m, 2H), 4.65-4.39 (m, 8H), 3.79-3.71 (m, 4H), 3.69-3.55 (m, 2H), 3.38 (s, 3H), 3.37 (s, 3H), 2.73 (d, *J* = 5.0 Hz, 1H), 2.70 (d, *J* = 5.5 Hz, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 1.09 (s, 3H), 1.08 (s, 3H), 1.01 (s, 6H), 0.20-0.15 (m, 18H).

***trans*-1-(benzyloxy)-4-hydroxy-5-(methoxymethoxy)-3,3-dimethylhept-6-yn-2-yl acetate (136)**



To a solution of **83** (103 mg, 0.236 mmol) in THF (1.10 mL) was added 1.0 M THF solution of TBAF (350 μL, 0.354 mmol) at room temperature, and the mixture was stirred at room temperature for 10 minutes. The reaction was quenched with water, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 4/1 to 7/3) to give diastereomeric mixture of **136** (52 mg, 0.143 mmol, 62%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 7.40-7.24 (m, 10H), 5.24 (dd, *J* = 7.2, 3.5 Hz, 1H), 5.13 (dd, *J* = 6.9, 3.5 Hz, 1H), 5.00-4.92 (m, 2H), 4.73-4.46 (m, 8H), 3.81-3.71 (m, 4H), 3.69-3.59 (m, 2H), 3.38 (s, 3H), 3.37 (s, 3H), 2.99 (d, *J* = 4.8 Hz, 1H), 2.91 (d, *J* = 4.8 Hz, 1H), 2.56 (d, *J* = 2.2 Hz, 1H), 2.55 (d, *J* = 2.2 Hz, 1H) 2.11 (s, 3H), 2.09 (s, 3H), 1.10 (s, 3H), 1.09 (s, 3H), 1.03 (s, 3H), 1.02 (s, 3H).

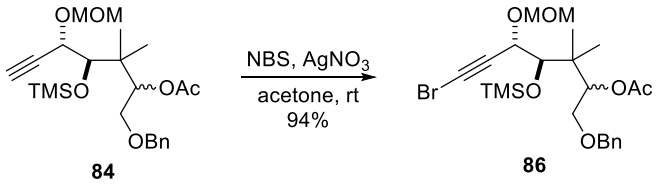
***trans*-1-(benzyloxy)-5-(methoxymethoxy)-3,3-dimethyl-4-((trimethylsilyl)oxy)hept-6-yn-2-yl acetate (84)**



136 **84**

To a solution of **136** (28.6 mg, 0.0785 mmol) in CH_2Cl_2 (400 μL) was added 2,6-lutidinne (58.0 μL, 0.392 mmol) and TMSOTf (35.0 μL, 0.196 mmol) at 0 °C, and the mixture was stirred at room temperature for 15 minutes. The reaction was quenched with saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 19/1) to give diastereomeric mixture of **84** (26.2 mg, 0.0600 mmol, 77%) as a pale yellow oil. ^{1}H NMR (400 MHz, CDCl3): δ diastereomer mixture 7.42-7.26 (m, 10H), 5.25 (dd, *J* = 8.1, 2.7 Hz, 1H), 5.21 (dd, *J* = 7.6, 3.8 Hz, 1H), 4.98 (d, *J* = 6.8 Hz, 1H), 4.95 (d, *J* = 6.8 Hz, 1H), 4.62-4.41 (m, 8H), 3.83 (dd, *J* = 11.0, 2.6 Hz, 1H), 3.75-3.49 (m, 5H), 3.36 (s, 3H), 3.34 (s, 3H), 2.42 (d, *J* = 2.2 Hz, 1H), 2.41 (d, *J* = 2.0 Hz, 1H) 2.09 (s, 6H), 1.02 (s, 6H), 1.01 (s, 3H), 098 (s, 3H), 0.20-0.10 (m, 18H).

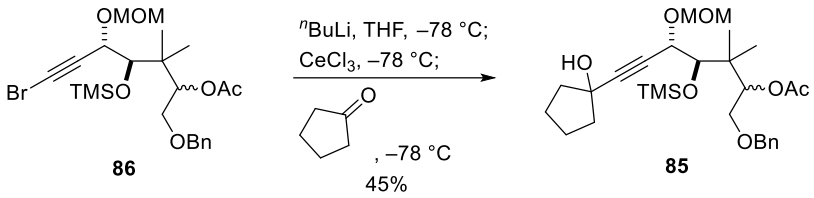
***trans*-1-(benzyloxy)-7-bromo-5-(methoxymethoxy)-3,3-dimethyl-4-((trimethylsilyl)oxy)hept-6-yn-2-yl acetate (86)**



84 **86**

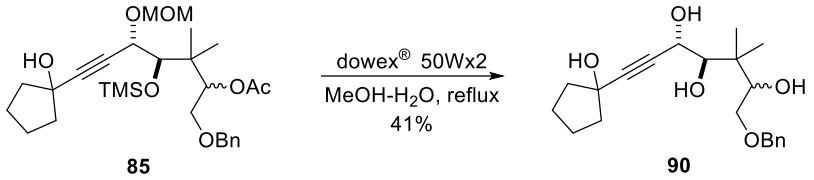
To a solution of **84** (30.6 mg, 0.0701 mmol) in acetone (350 μL) was added NBS (15.0 mg, 0.0841 mmol) and $AgNO_3$ (1.20 mg, 0.00701 mmol) at room temperature, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was cooled to 0 °C, filtered with Celite, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 19/1) to give diastereomeric mixture of **86** (33.9 mg, 0.0658 mmol, 94%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 7.36-7.25 (m, 10H), 5.24 (dd, *J* = 7.9, 2.8 Hz, 2H), 4.94 (d, *J* = 6.8 Hz, 1H), 4.91 (d, *J* = 6.8 Hz, 1H), 4.60-4.40 (m, 8H), 3.80 (dd, J = 10.8, 2.5 Hz, 1H), 3.73-3.50 (m, 5H), 3.36 (s, 3H), 3.34 (s, 3H), 2.08 (s, 6H), 0.99 (s, 6H), 0.98 (s, 3H), 096 (s, 3H), 0.16-0.09 (m, 18H); LRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{23}H_{35}{}^{79}BrO_6SiNa$, 537.1284; found, 537.4110 and calcd for $C_{23}H_{35}{}^{81}BrO_6SiNa$, 539.1264; found, 539.3845.

***trans*-1-(benzyloxy)-7-(1-hydroxycyclopentyl)-5-(methoxymethoxy)-3,3-dimethyl-4-((trimethylsilyl)oxy)hept-6-yn-2-yl acetate (85)**



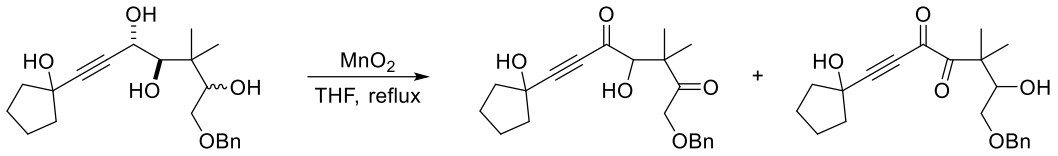
To a solution of **86** (21.4 mg, 0.0415 mmol) in THF (200 μL) was added 2.6 M Hexane solution of ^{n}BuLi (35.0 μL, 0.0914 mmol) at –78 °C, and the mixture was stirred at –78 °C for 10 minutes. To the mixture was added 1.0 M THF solution of anhydrous $CeCl_3$ (62.0 μL, 0.0623 mmol) at –78 °C, and the mixture was stirred at –78 °C for 30 minutes. To the mixture was added cyclopentanone (5.50 μL, 0.0623 mmol) at –78 °C, and the mixture was stirred at –78 °C for 30 minutes. The reaction was quenched with saturated aqueous solution of NH_4Cl, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 19/1 to 1/1) to give diastereomeric mixture of **85** (9.3 mg, 0.0179 mmol, 45%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 7.37-7.24 (m, 10H), 5.59 (dd, J = 8.4, 2.5 Hz, 1H), 5.50 (dd, J = 8.1, 2.4 Hz, 1H), 4.99-4.90 (m, 2H), 4.63-4.42 (m, 8H), 3.92-3.86 (m, 2H), 3.73-3.36 (m, 4H), 3.35 (s, 3H), 3.34 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 1.98-1.44 (m, 16H), 0.99 (s, 3H), 0.98 (s, 3H), 093 (s, 3H), 0.92 (s, 3H), 0.13-0.08 (m, 18H); LRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{28}H_{44}O_7SiNa$, 543.2754; found, 543.4967.

***trans*-1-(benzyloxy)-7-(1-hydroxycyclopentyl)-3,3-dimethylhept-6-yne-2,4,5-triol (90)**



To a solution of **85** (9.30 mg, 0.0179 mmol) in MeOH (150 μL) and H_2O (30.0 μL) was added dowex® 50Wx2 (9.30 mg) at room temperature, and the mixture was stirred at reflux for 13 hours. The reaction mixture was filtered with cotton plug and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 1/1) to give diastereomeric mixture of **90** (2.70 mg, 0.00745 mmol, 41%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 7.39-7.27 (m, 10H), 4.56 (s, 2H), 4.55 (s, 2H), 4.52 (m, 1H), 4.30 (m, 1H), 3.82-3.44 (m, 8H), 1.97-1.66 (m, 16H), 1.10 (s, 3H), 1.07 (s, 3H), 1.01 (s, 3H), 0.97 (s, 3H); LRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{21}H_{30}O_5Na$, 385.1991; found, 385.2669.

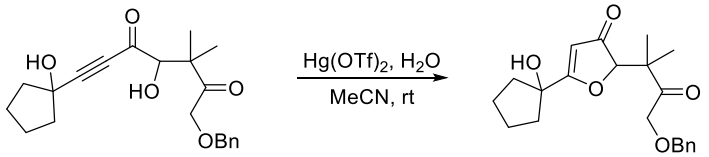
1-(benzyloxy)-4-hydroxy-7-(1-hydroxycyclopentyl)-3,3-dimethylhept-6-yne-2,5-dione (92)



90 **92** **93**

To a solution of **90** (1.50 mg, 0.00414 mmol) in THF (40.0 μL) was added MnO_2 at room temperature, and the mixture was stirred at reflux for 4 hours. The reaction mixture was filtered with Celite and concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (Hexane/AcOEt = 1/1) to give mixture of **92** and **93** (0.500 mg, 0.00139 mmol) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ mixture 7.43-7.22 (m, 10H), 4.95 (s, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.58 (d, *J* = 11.3 Hz, 2H), 4.54 (d, *J* = 11.2 Hz, 1H), 4.23 (dd, *J* = 2.3, 1.7 Hz, 1H), 3.81 (dd, *J* = 10.4, 2.5 Hz, 1H), 3.77-3.66 (m, 2H), 3.55 (dd, *J* = 10.5, 1.5 Hz, 1H), 2.02-1.69 (m, 16H), 1.41 (s, 3H), 1.24 (s, 3H), 1.19 (s, 3H), 1.12 (s, 3H); LRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{21}H_{26}O_5Na$, 381.1678; found, 381.2165.

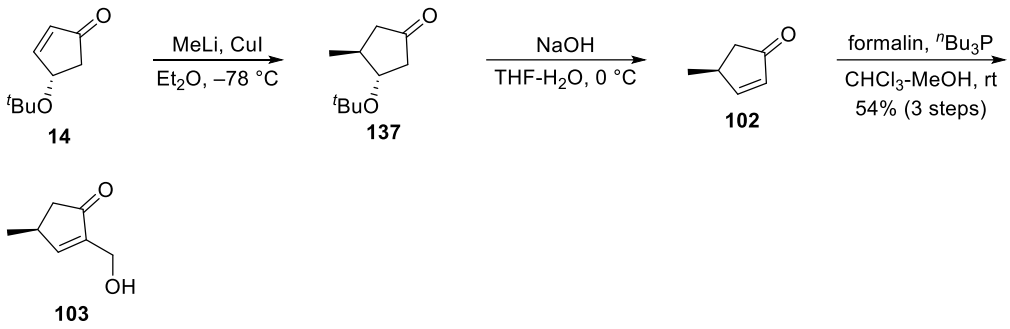
2-(4-(benzyloxy)-2-methyl-3-oxobutan-2-yl)-5-(1-hydroxycyclopentyl)furan-3(2*H*)-one (95)



92 **95**

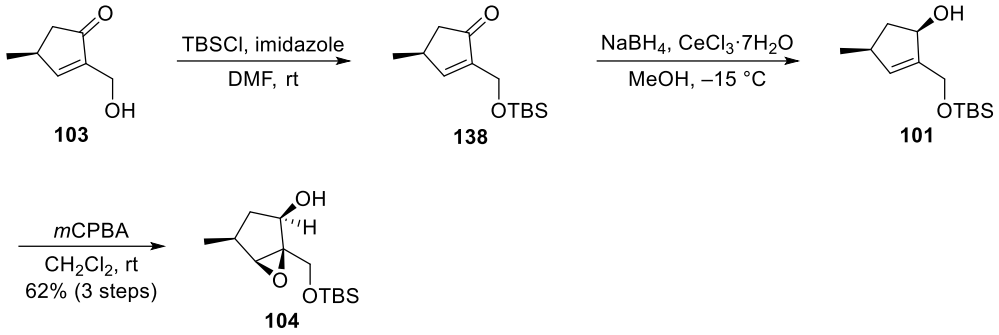
To a solution of mixture of **92** and **93** (0.500 mg, 0.00139 mmol) in MeCN (30.0 μL) was added H_2O (0.100 μL, 0.00418 mmol) and 0.1 M MeCN solution of $Hg(OTf)_2$ (0.150 μL, 0.0139 μmol) at room temperature, and the mixture was stirred at room temperature for 10 minutes. The reaction was quenched with NEt_3, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (Hexane/AcOEt = 3/2) to give mixture of **95** as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.29 (m, 5H), 5.34 (m, 1H), 4.63 (d, *J* = 11.8 Hz, 1H), 4.59 (m, 1H), (d, *J* = 11.8 Hz, 1H), 3.67-3.64 (m, 2H), 1.99-1.67 (m, 8H), 0.95 (s, 6H); LRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{21}H_{26}O_5Na$, 381.1678; found, 381.2365.

(*S*)-2-(hydroxymethyl)-4-methylcyclopent-2-en-1-one (103)



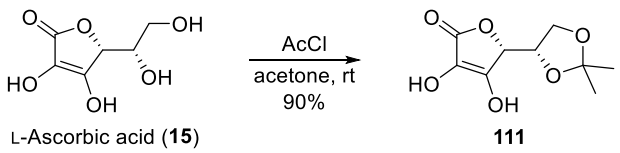
To a solution of CuCl (756 mg, 3.97 mmol) in Et_2O (13.0 mL) was added 1.1 M Et_2O solution of MeLi (7.22 mL, 7.94 mmol) at –40 °C, and the mixture was stirred at 0 °C for 15 minutes. To the mixture was added **14** (408 mg, 2.65 mmol) at –78 °C, and the mixture was stirred at –78 °C for 1 hour. The reaction was quenched with mixture of saturated aqueous solution of NH_4Cl/28% aqueous solution of NH_3 (9/1), and the mixture was extracted with Et_2O (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used without further purification. To a solution of the crude **137** in MeOH (8.80 mL) and H_2O (4.40 mL) was added 6.0 M aqueous solution of NaOH (441 µL, 2.65 mmol) at room temperature, and the mixture was stirred at room temperature for 6 hours. The reaction was quenched with 1.0 M aqueous solution of HCl, and the mixture was extracted with Et_2O (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure (20 °C, >350 Torr). The residue was used without further purification. To a solution of the crude **102** in $CHCl_3$ (3.30 mL) and MeOH (2.20 mL) was added formalin (325 µL, 3.17 mmol) and $^nBu_3P$ (66.0 µL, 0.265 mmol) at room temperature, and the reaction mixture was stirred at room temperature for 30 minutes. The reaction was directly purified by silica-gel column chromatography (Hexane/AcOEt = 4/1 to 2/1) to give **103** (178 mg, 1.42 mmol, 54%, 3 steps) as a pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (dt, J = 2.4, 1.3 Hz, 1H), 4.37 (d, J = 6.0 Hz, 2H), 2.97 (m, 1H), 2.69 (dd, J = 19.0, 6.2 Hz, 1H), 2.23 (t, J = 6.2 Hz, 1H), 2.03 (dd, J = 19.0, 2.1 Hz, 1H), 1.21 (d, J = 7.2 Hz, 3H)

(1R,2R,4S,5S)-1-(((tert-butyldimethylsilyl)oxy)methyl)-4-methyl-6-oxabicyclo[3.1.0]hexan-2-ol (104)



To a solution of **103** (178 mg, 1.42 mmol) in DMF (2.37 mL) was added imidazole (290 mg, 4.27 mmol) and TBSCl (308 mg, 1.71 mmol) at room temperature, and the mixture was stirred at room temperature for 1 hour. The reaction was quenched with H_2O, and the mixture was extracted with Hexane (x3). The combined organic layers were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used without further purification. To a solution of the crude **138** in MeOH (14.2 mL) was added $CeCl_3 \cdot 7H_2O$ (1.59 g, 4.27 mmol) at room temperature, and the mixture was stirred at room temperature while the mixture turned to homogeneous. To the mixture was added $NaBH_4$ (64.6 mg, 1.71 mmol) at –78 °C, and the mixture was stirred at –78 °C for 5 hours. The reaction was quenched with saturated aqueous solution of NH_4Cl, and the mixture was extracted with Hexane (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used without further purification. To a solution of the crude **101** in CH_2Cl_2 (7.20 mL) was added NaHCO3 (598 mg, 7.11 mmol) and *m*CPBA (386 mg, 1.56 mmol) at –15 °C, and the reaction mixture was stirred at –15 °C for 30 minutes. The reaction was quenched with saturated aqueous solution of $Na_2S_2O_3$, and the mixture was extracted with Hexane (x3). The combined organic layers were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 10/1) to give **104** (229 mg, 0.886 mmol, 62%, 3 steps) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33 (td, *J* = 8.0, 6.0 Hz, 1H), 4.03 (d, *J* = 11.7 Hz, 1H), 3.93 (d, *J* = 11.7 Hz, 1H), 3.24 (s, 1H), 2.26 (d, *J* = 5.9 Hz, 1H), 2.121-1.96 (m, 2H), 1.10 (d, *J* = 6.5 Hz, 3H), 1.04 (m, 1H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).

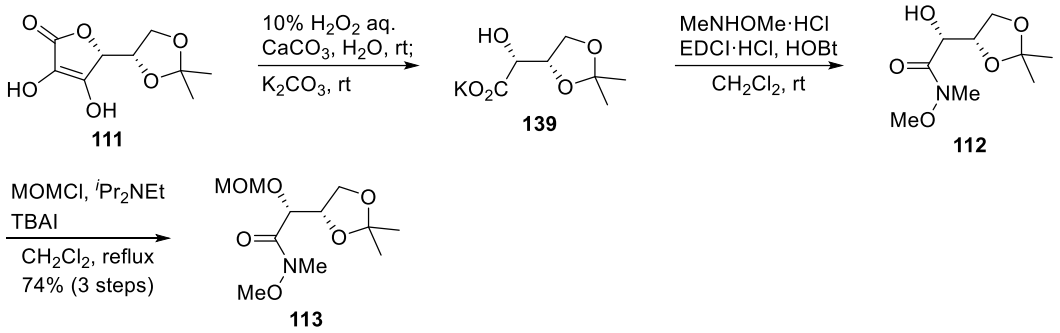
(*R*)-5-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3,4-dihydroxyfuran-2(5*H*)-one (111)



To a solution of L-ascorbic acid (**15**) (30.0 g, 170 mmol) in acetone (170 mL) was added AcCl (2.40 mL, 34.1 mmol) at room temperature, and the mixture was stirred at room temperature for 1 hour. The

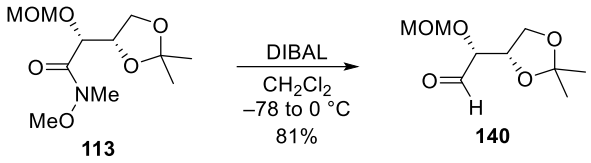
reaction was cooled to –20 °C, and stored at –20 °C for 12 hours. The mixture was filtered with filter paper, and the powders were collected to give **111** (33.2 g, 154 mmol, 90%) as a white powder. ^{1}H NMR (400 MHz, D_2O): δ 4.91 (d, J = 2.4 Hz, 1H), 4.59 (m, 1H), 4.31 (dd, J = 9.3, 7.6 Hz, 1H), 4.19-4.17 (dd, J = 9.3, 5.2 Hz, 1H), 1.37 (s, 6H). This ^{1}H NMR data is identical with that of ref 28.

(*R*)-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-*N*-methoxy-2-(methoxymethoxy)-*N*-methylacetamide (113)



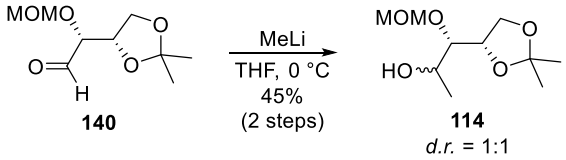
To a solution of **111** (10 g, 46.3 mmol) in H_2O (100 mL) was added $CaCO_3$ (9.30 g, 92.5 mmol) and 10% aqueous solution of H_2O_2 (60.0 mL, 185 mmol) at room temperature divided into three times every 20 minutes, and the mixture was stirred at room temperature for 3 hours. To the mixture was added MnO_2 (300 mg) and K_2CO_3 (3.50 g, 25.4 mmol) at room temperature, and the mixture was stirred at room temperature for 2 days. The mixture was filtered with filter paper, and concentrated under reduced pressure. This reaction was done three times. The combined residue was used without further purification. To a solution of the crude **139** in CH_2Cl_2 (700 mL) was added MeNHOMe·HCl (13.5 g, 139 mmol), HOBt (18.7 g, 139 mmol), and EDCI·HCl (26.6 g, 139 mmol) at room temperature, and the mixture was stirred at room temperature for 2 hours. The reaction was quenched with water, and the mixture was extracted with $CHCl_3$ (x3). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used without further purification. To a solution of the crude **112** in CH_2Cl_2 (7.20 mL) was added ^{i}Pr$_2$NEt (60.0 mL, 347 mmol), TBAI (10.0 g, 27.8 mmol), and MOMCl (15.8 mL, 208 mmol) at room temperature, and the reaction mixture was stirred at reflux for 2 days. The reaction was quenched with water, and the mixture was extracted with $CHCl_3$ (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 3/2) to give **113** (27.0 g, 103 mmol, 74%, 3 steps) as a orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.77 (d, J = 6.9 Hz, 1H), 4.71 (d, J = 6.9 Hz, 1H), 4.66 (d, J = 5.6 Hz, 1H), 4.46 (q, J = 6.5 Hz, 1H), 4.01 (dd, J = 8.4, 6.9 Hz, 1H), 3.93 (dd, J = 8.4, 6.2 Hz, 1H), 3.76 (s, 3H), 3.39 (s, 3H), 3.23 (s, 3H) 1.44 (s, 3H), 1.37 (s, 3H).

(*R*)-2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(methoxymethoxy)acetaldehyde (140)



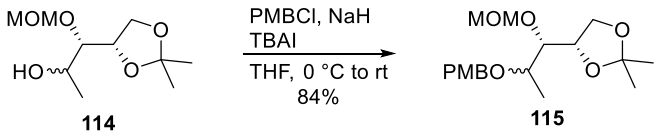
To a solution of **113** (13.5 g, 51.3 mmol) in CH_2Cl_2 (250 mL) was added 1.0 M Hexane solution of DIBAL (60.0 mL, 61.5 mmol) at –78 °C, and the mixture was stirred at 0 °C for 30 minutes. To the mixture was added saturated aqueous solution of NH_4Cl (6.00 mL) and MeOH (12.0 mL) at –78 °C, diluted with Et_2O, and the mixture was stirred at room temperature for 1 hour. To the mixture was added $MgSO_4$ at room temperature, and the mixture was stirred at room temperature for 1 hour, filtered, and concentrated under reduced pressure. This reaction was done two times. The combined residue was purified by silica-gel column chromatography (Hexane/AcOEt = 7/3) to give **140** (16.8 g, 82.3 mmol, 81%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (d, *J* = 1.4 Hz, 1H), 4.79 (s, 2H), 4.39 (q, *J* = 6.1 Hz, 1H), 4.11 (dd, *J* = 8.8, 6.6 Hz, 1H), 4.01 (dd, *J* = 5.7, 1.3 Hz, 1H), 3.95 (dd, *J* = 8.8, 6.1 Hz, 1H), 3.44 (s, 3H), 1.44 (s, 3H), 1.36 (s, 3H).

(1*S*)-1-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-(methoxymethoxy)propan-2-ol (114)



To a solution of **140** (11.3 g, 55.3 mmol) in THF (250 mL) was added 1.5 M Et_2O solution of MeLi (55.0 mL, 83.0 mmol) at 0 °C, and the mixture was stirred at 0 °C for 5 hours. The reaction was quenched with saturated aqueous solution of NH_4Cl, and the mixture was extracted with AcOEt (x3). The combined organic layers were, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 7/3) to give diastereomeric mixture of **114** (6.8 g, 30.9 mmol, 56%, *d.r.* = 1:1) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 4.86 (d, *J* = 6.8 Hz, 1H), 4.79-4.73 (m, 3H), 4.32 (q, *J* = 6.5 Hz, 1H), 4.22 (q, *J* = 6.9 Hz, 1H), 4.15-3.99 (m, 4H), 3.84 (t, *J* = 7.5 Hz, 1H), 3.75 (t, *J* = 7.9 Hz, 1H), 3.55 (dd, *J* = 6.7, 3.7 Hz, 1H), 3.45 (s, 6H), 3.36 (dd, *J* = 5.5, 4.0 Hz, 1H), 1.43 (s, 6H), 1.38 (s, 3H), 1.36 (s, 3H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.21 (d, *J* = 6.5 Hz, 3H).

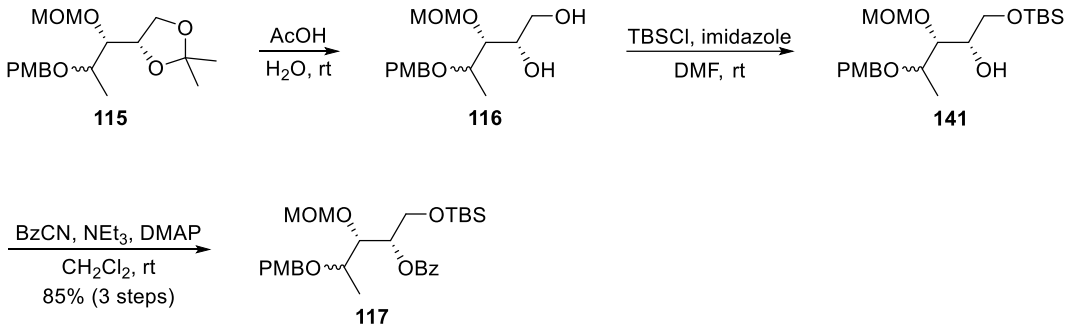
(4*S*)-4-((1*S*)-2-((4-methoxybenzyl)oxy)-1-(methoxymethoxy)propyl)-2,2-dimethyl-1,3-dioxolane (115)



114 **115**

To a solution of **114** (5.00 g, 22.7 mmol) in THF (110 mL) was added PMBCl (4.70 mL, 34.0 mmol), TBAI (1.70 g, 4.54 mmol), and 60% dispersion in paraffin liquid of NaH (1.60 g, 34.0 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 day. The reaction was quenched with water, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 17/3) to give diastereomeric mixture of **115** (6.60 g, 19.4 mmol, 84%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 7.32-7.21 (m, 4H), 6.91-6.84 (m, 4H), 4.89 (d, *J* = 6.9 Hz, 1H), 4.85 (d, *J* = 6.6 Hz, 1H), 4.79 (d, *J* = 6.6 Hz, 1H), 4.73 (d, *J* = 6.6 Hz, 1H), 4.58-4.36 (m , 8H), 4.27 (q, *J* = 7.0 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 1H), 3.96 (dd, *J* = 8.2, 6.5 Hz, 1H), 3.87 (dd, J = 8.4, 6.3 Hz, 1H), 3.80 (s, 6H), 3.71-3.55 (m, 6H), 1.41 (s, 3H), 1.39 (s, 3H), 1.35 (s, 6H), 1.26 (d, *J* = 2.7 Hz, 3H), 1.24 (d, *J* = 2.9 Hz, 3H).

(5*S*,6*S*)-5-(1-((4-methoxybenzyl)oxy)ethyl)-9,9,10,10-tetramethyl-2,4,8-trioxa-9-silaundecan-6-yl benzoate (117)

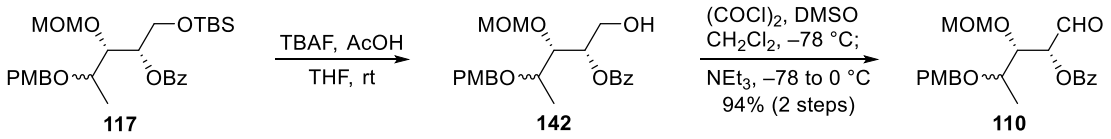


115 **116** **141** **117**

To a solution of **115** (6.60 g, 19.4 mmol) in H_2O (50.0 mL) was added AcOH (50.0 mL) at room temperature, and the mixture was stirred at room temperature for 16 hours. The mixture was directly concentrated under reduced pressure. The residue was used without further purification. To a solution of the crude **116** in DMF (100 mL) was added imidazole (3.30 g, 48.5 mmol), and TBSCl (4.40 g, 29.1 mmol) at room temperature, and the mixture was stirred at room temperature for 1.5 hours. The reaction was quenched with water, and the mixture was extracted with Et_2O (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used without further purification. To a solution of the crude **141** in CH_2Cl_2 (100 mL) was added NEt_3 (5.40 mL, 38.8 mmol), DMAP (470 mg, 3.88 mmol), and BzCN (3.50 mL, 29.1 mmol) at room temperature, and the reaction mixture was stirred at room temperatuire

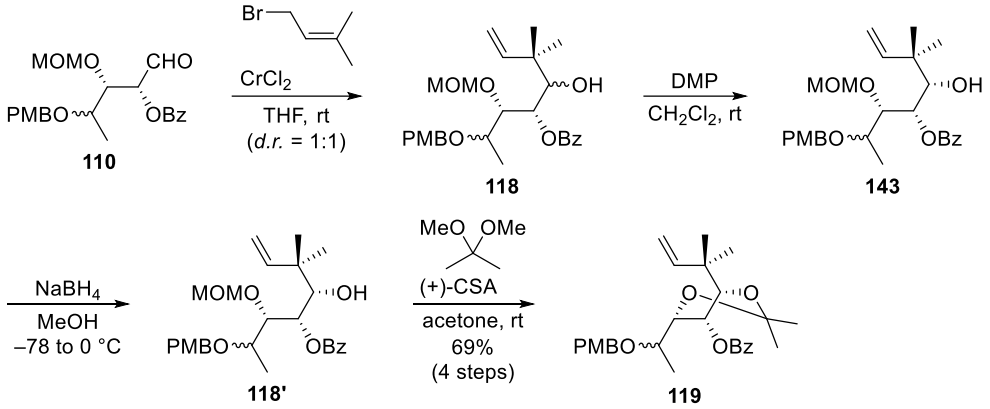
for 7 hours. The reaction was quenched with saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with AcOEt (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 9/1) to give diastereomeric mixture of **117** (8.40 g, 16.2 mmol, 85%, 3 steps) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 8.05 (t, *J* = 6.9 Hz, 4H), 7.56 (t, *J* = 7.0 Hz, 2H), 7.47-7.40 (m, 4H), 7.39-30 (m, 4H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.38 (q, *J* = 5.2 Hz, 1H), 5.31 (q, *J* = 5.2 Hz, 1H), 4.83 (d, *J* = 6.8 Hz, 1H), 4.78 (s, 2H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.67 (s, 2H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.47-4.38 (m , 5H), 3.93-3.68 (m, 6H), 3.81 (s, 3H), 3.80 (s, 3H), 3.40-3.31 (m, 2H), 3.37 (s, 3H), 3.34 (s, 3H), 1.29 (d, *J* = 5.7 Hz, 3H), 1.24 (d, *J* = 6.1 Hz, 3H), 0.96-0.79 (m, 18H), 0.99 (s, 12H).

(2*R*,3*S*)-4-((4-methoxybenzyl)oxy)-3-(methoxymethoxy)-1-oxopentan-2-yl benzoate (110)



To a solution of **117** (750 mg, 1.45 mmol) in THF (7.20 mL) was added AcOH (330 μL, 5.79 mmol) and 1.0 M THF solution of TBAF (2.20 mL, 2.17 mmol) at room temperature, and the mixture was stirred at room temperature for 17 hours. The reaction was diluted with water, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used without further purification. To a solution of DMSO (311 μL, 4.34 mmol) in CH_2Cl_2 (7.20 mL) was added $(COCl)_2$ (250 μL, 2.89 mmol) at –78 °C, and the mixture was stirred at –78 °C for 30 minutes. To the mixture was added the crude **117** at –78 °C, and the mixture was stirred at –78 °C for 30 minutes. To the mixture was added NEt_3 (1.20 mL, 8.68 mmol) at –78 °C, and the mixture was stirred at 0 °C for 1 hour. The reaction was quenched with water, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 4/1) to give diastereomeric mixture of **110** (530 mg, 1.32 mmol, 94%, 2 steps) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 9.74 (s, 1H), 9.61 (s, 1H), 8.06 (d, *J* = 7.3 Hz, 2H), 7.98 (d, *J* = 7.3 Hz, 2H), 7.60 (t, *J* = 6.8 Hz, 2H), 7.45 (t, *J* = 7.7 Hz, 4H), 7.26-7.23 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.72 (d, *J* = 8.6 Hz, 2H), 5.66 (d, *J* = 2.2 Hz, 1H), 5.53 (d, *J* = 4.8 Hz, 1H), 4.87 (d, *J* = 7.0 Hz, 1H), 4.81 (d, *J* = 7.0 Hz, 1H), 4.73 (d, *J* = 6.9 Hz, 1H), 4.69 (d, *J* = 6.9 Hz, 1H), 4.53 (d, *J* = 11.4 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.39 (d, *J* = 11.3 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.39 (d, *J* = 11.3 Hz, 1H), 4.29 (d, *J* = 11.2 Hz, 1H), 4.08 (dd, *J* = 7.6, 2.2 Hz, 1H), 4.05 (dd, *J* = 4.7, 3.6 Hz, 1H) 3.86 (dd, *J* = 6.4, 3.5 Hz, 1H), 3.82-3.76 (m, 3H), 3.78 (s, 3H), 3.68 (s, 3H), 3.44 (s, 3H), 3.32 (s, 3H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.29 (d, *J* = 6.4 Hz, 3H).

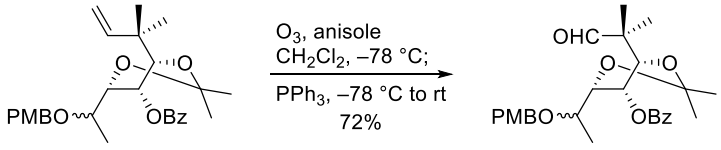
(5*S*,6*R*)-4-(1-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-6-(2-methylbut-3-en-2-yl)-1,3-dioxan-5-yl benzoate (119)



To a solution of **110** (530 mg, 1.32 mmol) in THF (6.50 mL) was added prenyl bromide (230 μL, 1.98 mmol), and degassed with Freeze Pump Thaw cycles. To the mixture was added anhydrous $CrCl_2$ at room temperature under Argon atmosphere with plastic bag, and the mixture was stirred at room temperature for 1 hour in plastic bag. The reaction was diluted with water, and the mixture was extracted with AcOEt (x3). The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used without further purification. To a solution of the crude **118** in CH_2Cl_2 (6.50 mL) was added DMP (840 mg, 1.98 mmol) at room temperature, and the mixture was stirred at room temperature for 40 minutes. The reaction was quenched with saturated aqueous solution of $Na_2S_2O_4$, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used without further purification. To a solution of the crude **143** in MeOH (6.50 mL) was added $NaBH_4$ (120 mg, 3.29 mmol) at –78 °C, and the mixture was stirred at 0 °C for 15 minutes. The reaction was quenched with water, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used without further purification. To a solution of the crude **118'** in acetone (3.00 mL) and 2,2-dimethoxypropane (3.00 mL) was added (+)-CSA (300 mg, 1.31 mmol) at room temperature, and the mixture was stirred at room temperature for 20 hours. The reaction was quenched with saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 19/1) to give diastereomeric mixture of **119** (420 mg, 0.896 mmol, 69%, 4 steps) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 8.15-7.99 (m, 4H), 7.61-7.53 (m, 2H), 7.50-7.41 (m, 4H), 7.26-7.20 (m, 2H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 5.7 Hz, 2H), 5.91 (dd, *J* = 10.8, 1.3 Hz, 1H), 5.86 (dd, *J* = 10.8, 1.6 Hz, 1H), 5.66 (dd, *J* = 6.2, 2.9 Hz, 1H), 5.58 (dd, *J* = 5.4, 2.4 Hz, 1H), 5.09-4.91 (m, 4H), 4.57 (d, *J* = 11.2 Hz,

1H), 4.44 (d, *J* = 11.2 Hz, 1H), 4.26 (d, *J* = 10.2 Hz, 1H), 4.02 (d, *J* = 10.1 Hz, 1H), 3.84-3.46 (m, 6H), 3.81 (s, 3H), 3.76 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H), 1.26 (d, *J* = 4.9 Hz, 3H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.05 (s, 6H), 1.03 (s, 3H), 1.01 (s, 3H).

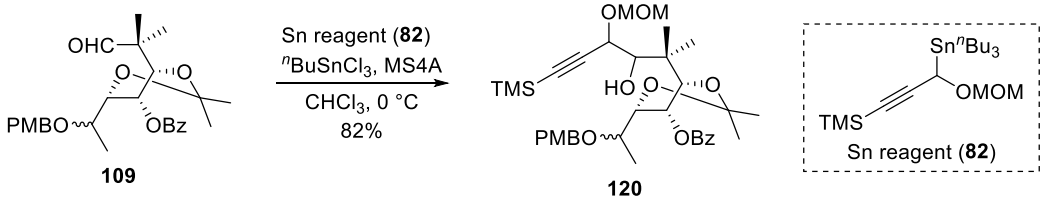
(5*S*,6*R*)-4-(1-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-6-(2-methyl-1-oxopropan-2-yl)-1,3-dioxan-5-yl benzoate (109)



119 **109**

Ozone was bubbled through a solution of **119** (420 mg, 0.896 mmol) and anisole (100 μL, 0.896 mmol) in CH_2Cl_2 (10.0 mL) at –78 °C until the color of the solution changed to black. After bubbling of argon until the black color disappeared, to the mixture was added PPh_3 (350 mg, 1.34 mmol) at –78 °C. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 19/1 to 9/1) to give diastereomeric mixture of **109** (300 mg, 0.638 mmol, 72%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 9.49 (s, 2H), 8.09 (d, *J* = 7.3 Hz, 2H), 8.06 (d, *J* = 7.1 Hz, 2H), 7.64-7.55 (m, 2H), 7.51-7.43 (m, 4H), 7.20 (d, *J* = 5.7 Hz, 2H), 7.18 (d, *J* = 5.9 Hz, 2H), 6.80 (d, *J* = 9.5 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 5.78 (dd, *J* = 6.2, 3.1 Hz, 1H), 5.53 (dd, *J* = 5.4, 2.7 Hz, 1H), 4.61 (d, *J* = 12.3 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 11.2 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 3.79-3.55 (m, 6H), 3.77 (s, 3H), 3.75 (s, 3H), 1.52 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H), 1.35 (d, *J* = 7.4 Hz, 3H), 1.32 (s, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H).

(4*R*,5*S*)-4-(3-hydroxy-4-(methoxymethoxy)-2-methyl-6-(trimethylsilyl)hex-5-yn-2-yl)-6-(1-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-5-yl benzoate (120)

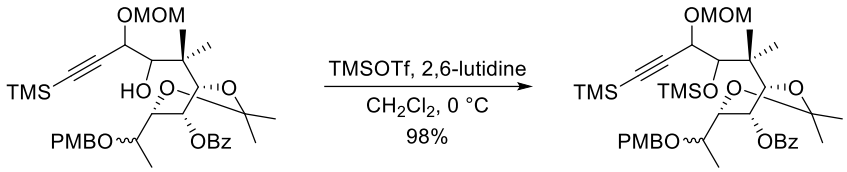


109 **120**

To a solution of **109** (300 mg, 0.638 mmol) and **82** (1.18 g, 2.55 mmol) in $CHCl_3$ (7.00 mL) was added MS4A (300 mg) and ^{n}BuSnCl$_3$ (440 μL, 2.68 mmol) at 0 °C, and the mixture was stirred at 0 °C for 3 hours. To the mixture was added Et_2O and KF·Celite (900 mg), and the mixture was stirred at room temperature for 12 hours. The mixture was filtered with Celite, and concentrated under reduced pressure. The residue was purified by 10 w/w % anhydrous K_2CO_3-silica-gel column chromatography (Hexane/AcOEt = 19/1 to 9/1) to give diastereomeric mixture of **120** (363 mg, 0.565 mmol, 82%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 8.19-8.00 (m, 4H), 7.62-7.52

(m, 2H), 7.50-7.40 (m, 4H), 7.35-7.14 (m, 4H), 6.91-6.83 (m, 2H), 6.83-6.73 (m, 2H), 5.86 (dd, *J* = 5.4, 2.5 Hz, 1H), 5.68 (dd, *J* = 4.6, 2.0 Hz, 1H), 5.01-4.89 (m, 2H), 4.74-4.37 (m, 8H), 3.88-3.46 (m, 8H), 3.77 (s, 3H), 3.76 (s, 3H), 3.37 (s, 3H), 3.36 (s, 3H), 1.51 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.24 (s, 3H), 1.22 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H) 1.01 (d, *J* = 7.5 Hz, 3H), 0.18 (s, 9H), 0.09 (s, 9H) ; LRMS-ESI (*m*/*z*): $[M + Na]^+$ calcd for $C_{35}H_{50}O_9SiNa$, 665.3122; found, 665.5025.

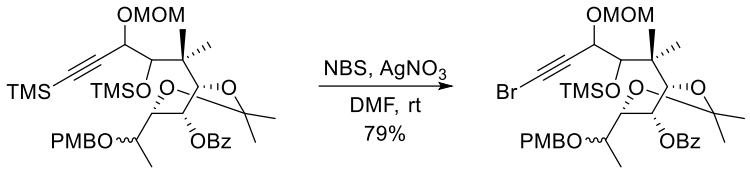
(5*S*,6*R*)-4-(1-((4-methoxybenzyl)oxy)ethyl)-6-(4-(methoxymethoxy)-2-methyl-6-(trimethylsilyl)-3-((trimethylsilyl)oxy)hex-5-yn-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl benzoate (144)



120 **144**

To a solution of **120** (360 mg, 0.560 mmol) in CH_2Cl_2 (3.00 mL) was added 2,6-lutidine (200 μL, 1.40 mmol) and TMSOTf (150 μL, 0.840 mmol) at 0 °C, and the mixture was stirred at 0 °C for 2 hours. The reaction was quenched with saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 19/1) to give diastereomeric mixture of **144** (393 mg, 0.550 mmol, 98%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 8.18-8.02 (m, 4H), 7.61-7.53 (m, 2H), 7.51-7.40 (m, 4H), 7.33-7.26 (m, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.90-6.76 (m, 4H), 5.83 (dd, *J* = 4.9, 2.3 Hz, 1H), 5.59 (dd, *J* = 4.5, 1.7 Hz, 1H), 4.99-4.90 (m, 2H), 4.68-4.23 (m, 8H), 3.91-3.39 (m, 8H), 3.77 (s, 3H), 3.76 (s, 3H), 3.39 (s, 6H), 1.50 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.19 (d, *J* = 6.6 Hz, 3H), 0.99 (s, 3H), 0.98 (s, 6H), 0.95 (s, 3H), 0.20-0.00 (m, 36H).

(4*R*,5*S*)-4-(6-bromo-4-(methoxymethoxy)-2-methyl-3-((trimethylsilyl)oxy)hex-5-yn-2-yl)-6-(1-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-5-yl benzoate (72a)

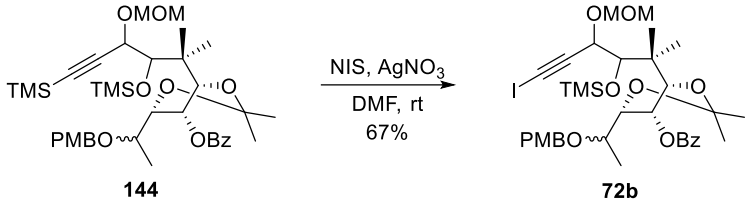


144 **72a**

To a solution of **144** (26 mg, 0.0364 mmol) in DMF (180 μL) was added NBS (7.80 mg, 0.0436 mmol) and $AgNO_3$ (3.00 mg, 0.0181 mmol) at room temperature, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was filtered with Celite, washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was

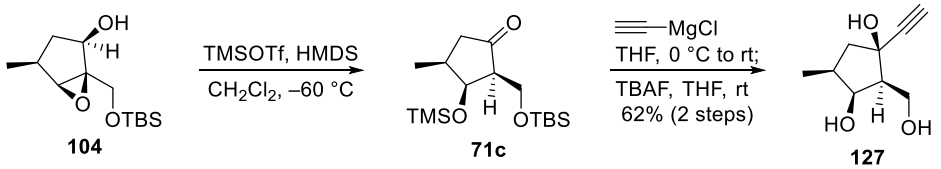
purified by silica-gel column chromatography (Hexane/AcOEt = 9/1) to give diastereomeric mixture of **72a** (20.6 mg, 0.0285 mmol, 79%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ diastereomer mixture 8.10-8.04 (m, 4H), 7.60-7.55 (m, 2H), 7.47-7.42 (m, 4H), 7.27-7.23 (m, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 5.63 (dd, *J* = 4.7, 1.6 Hz, 1H), 5.59 (dd, *J* = 4.9, 2.0 Hz, 1H), 4.92-4.88 (m, 2H), 4.65 (d. *J* = 6.7 Hz, 1H), 4.61-4.50 (m, 6H), 4.45 (d, *J* = 11.1 Hz, 1H), 3.85-3.75 (m, 6H), 3.77 (s, 3H), 3.76 (s, 3H), 3.63-3.55 (m, 2H), 3.35 (s, 3H), 3.34 (s, 3H), 1.53 (s, 3H), 1.43 (s, 3H), 1.42 (s, 6H), 1.21 (d, *J* = 5.8 Hz, 3H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.99 (s, 3H), 0.97 (s, 3H), 0.95 (s, 6H), 0.16-0.12 (m, 18H); LRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{35}H_{49}{}^{79}BrO_9SiNa$, 743.2227; found, 743.4713 and calcd for $C_{35}H_{49}{}^{81}BrO_9SiNa$, 745.2206; found, 745.4761.

(4*R*,5*S*)-4-(6-iodo-4-(methoxymethoxy)-2-methyl-3-((trimethylsilyl)oxy)hex-5-yn-2-yl)-6-(1-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-5-yl benzoate (72b)



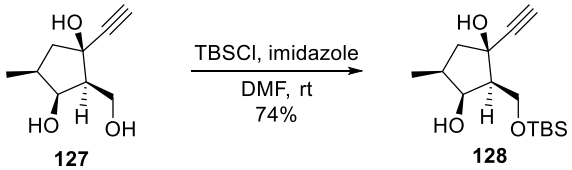
To a solution of **144** (393 mg, 0.550 mmol) in DMF (3.00 mL) was added NIS (110 mg, 0.660 mmol) and $AgNO_3$ (60.0 mg, 0.275 mmol) at room temperature, and the mixture was stirred at room temperature for 2 hours. The reaction mixture was filtered with Celite, washed with water and saturated aqueous solution of $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 19/1 to 9/1) to give diastereomeric mixture of **72b** (285 mg, 0.371 mmol, 67%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 8.17-8.01 (m, 4H), 7.62-7.54 (m, 2H), 7.51-7.41 (m, 4H), 7.33-7.26 (m, 2H), 7.19 (d, *J* = 8.2 Hz, 2H), 6.80 (d, *J* = 8.2 Hz, 2H), 6.79 (d, *J* = 8.2 Hz, 2H), 5.82 (dd, *J* = 5.1, 2.1 Hz, 1H), 5.58 (dd, *J* = 4.5, 1.8 Hz, 1H), 4.94-4.85 (m, 2H), 4.70-4.42 (m, 8H), 3915-3.45 (m, 8H), 3.76 (s, 6H), 3.34 (s, 3H), 3.32 (s, 3H), 1.49 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.99 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.94 (s, 3H), 0.17-0.04 (m, 18H); LRMS-ESI (*m*/*z*): [M + Na]$^+$ calcd for $C_{35}H_{49}IO_9SiNa$, 791.2088; found, 791.4802.

(1*R*,2*S*,3*S*,4*S*)-1-ethynyl-2-(hydroxymethyl)-4-methylcyclopentane-1,3-diol (127)



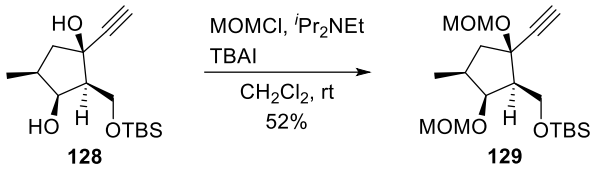
To a solution of **104** (176 mg, 0.681 mmol) in CH_2Cl_2 (3.40 mL) was added HMDS (460 μL, 2.18 mmol) and TMSOTf (370 μL, 2.04 mmol) at –60 °C, and the mixture was stirred at –60 °C for 1 hour. The reaction was quenched with saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with Et_2O (x3). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ well, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was used without further purification. To a solution of the crude **71c** in THF (3.40 mL) was added 0.5 M THF solution of ethynyl magnesium chloride (4.00 mL, 2.04 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 minutes. To the mixture was added 1.0 M THF solution of TBAF (2.7 mL, 2.72 mmol) at room temperature, and the mixture was stirred at room temperature for 1 hour. The reaction was quenched with saturated aqueous solution of NH_4Cl, and the mixture was extracted with AcOEt (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 1/1) to give **127** (72.0 mg, 0.423 mmol, 62%, 2 steps) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.31-4.18 (m, 3H), 2.55 (dd, *J* = 14.1, 9.9 Hz, 1H), 2.54 (s, 1H), 2.21 (m, 1H), 2.10 (q, *J* = 4.5 Hz, 1H), 1.90 (dd, *J* = 14.2, 8.7 Hz, 1H), 1.11 (d, *J* = 7.0 Hz, 3H).

(1*R*,2*S*,3*S*,4*S*)-2-(((tert-butyldimethylsilyl)oxy)methyl)-1-ethynyl-4-methylcyclopentane-1,3-diol (128)



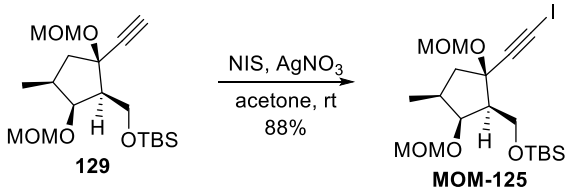
To a solution of **127** (25 mg, 0.147 mmol) in DMF (700 μL) was added imidazole (25.0 mg, 0.367 mmol), and TBSCl (33.0 mg, 0.220 mmol) at room temperature, and the mixture was stirred at room temperature for 1 hour. The reaction was quenched with water, and the mixture was extracted with Et_2O (x3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 19/1) to give **128** (29.3 mg, 0.103 mmol, 74%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20-4.09 (m, 3H), 2.55 (dd, *J* = 14.2, 9.9 Hz, 1H), 2.48 (s, 1H), 2.21-2.10 (m, 2H), 1.87 (dd, J = 14.3, 9.0 Hz, 1H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H).

***tert*-butyl(((1S,2R,4S,5S)-2-ethynyl-2,5-bis(methoxymethoxy)-4-methylcyclopentyl)methoxy)-dimethylsilane (129)**



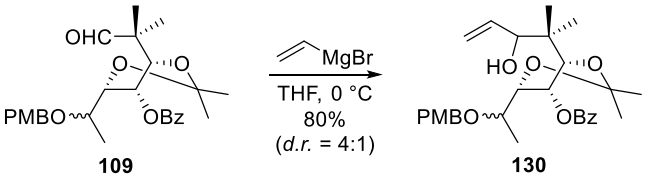
To a solution of **128** (4.50 mg, 0.0158 mmol) in CH_2Cl_2 (80.0 μL) was added $^{i}Pr_2NEt$ (5.50 μL, 0.0316 mmol), and MOMCl (1.80 μL, 0.0237 mmol) at room temperature, and the reaction mixture was stirred at reflux for 12 hours. To the mixture was added TBAI (1.10 mg, 0.00316 mmol) at room temperature, and the mixture was stirred at reflux for 4 hours. To the mixture was added $^{i}Pr_2NEt$ (5.50 μL, 0.0316 mmol), and MOMCl (1.80 μL, 0.0237 mmol) at room temperature for three times every 2 hours, and the mixture was stirred at reflux for 2 hours. The reaction was quenched with water, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 19/1) to give **129** (3.1 mg, 0.00832 mmol, 54%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.03 (d, *J* = 6.6 Hz, 1H), 4.79 (d, *J* = 6.6 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.01 (m, 1H) 3.87-3.76 (m, 2H), 3.41 (s, 3H), 3.39 (s, 3H), 2.54 (s, 1H), 2.36-2.27 (m, 2H), 2.18-1.96 (m, 2H), 1.09 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

tert-butyl(((1S,2R,4S,5S)-2-(iodoethynyl)-2,5-bis(methoxymethoxy)-4-methylcyclopentyl)-methoxy)dimethylsilane (MOM-125)



To a solution of 129 (3.10 mg, 0.00832 mmol) in acetone (40.0 μL) was added NIS (2.20 mg, 0.0100 mmol) and $AgNO_3$ (0.800 mg, 0.00416 mmol) at room temperature, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was filtered with Celite, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 19/1) to give **MOM-125** (3.0 mg, 0.00602 mmol, 88%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.01 (d, *J* = 6.7 Hz, 1H), 4.76 (d, *J* = 6.6 Hz, 1H), 4.72-4.59 (m, 2H), 3.91-3.79 (m, 3H), 3.40 (s, 3H), 3.37 (s, 3H), 2.44-2.24 (m, 2H), 2.19-1.89 (m, 2H), 1.07 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

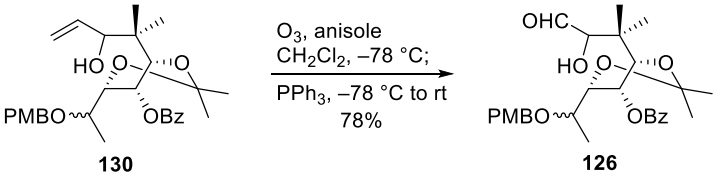
(4*R*,5*S*)-4-(3-hydroxy-2-methylpent-4-en-2-yl)-6-(1-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-5-yl benzoate (130)



109 **130**

To a solution of **109** (33.5 mg, 0.0712 mmol) in THF (360 μL) was added 1.0 M THF solution of vinyl magnesium bromide (100 μL, 0.107 mmol) at 0 °C, and the mixture was stirred at 0 °C for 10 minutes. The reaction was quenched with water, and the mixture was extracted with AcOEt (x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 9/1) to give diastereomeric mixture of **130** (27.9 mg, 0.0560 mmol, 80%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 8.17-7.99 (m, 4H), 7.64-7.51 (m, 2H), 7.51-7.40 (m, 4H), 7.26-7.23 (m, 2H), 7.22-7.15 (m, 2H), 6.92-6.75 (m, 4H), 5.99-5.79 (m, 2H), 5.64-5.53 (m, 2H), 5.38-5.14 (m, 4H), 4.67-3.38 (m, 8H), 3.80 (s, 3H), 3.77 (s, 3H), 1.45 (s, 3H), 1.37 (s, 3H), 1.26 (s, 3H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.06 (d, *J* = 4.9 Hz, 3H), 1.00 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H), 0.83 (s, 3H).

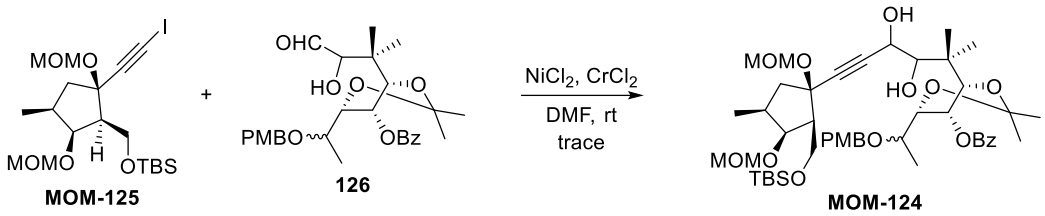
(4*R*,5*S*)-4-(3-hydroxy-2-methyl-4-oxobutan-2-yl)-6-(1-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-5-yl benzoate (126)



130 **126**

Ozone was bubbled through a solution of 130 (10.5 mg, 0.0211 mmol) and anisole (2.30 μL, 0.0211 mmol) in CH_2Cl_2 (200 μL) at –78 °C until the color of the solution changed to black. After bubbling of argon until the black color disappeared, to the mixture was added PPh_3 (8.30 mg, 0.0316 mmol) at –78 °C. The mixture was stirred at room temperature for 2 hour and concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (Hexane/AcOEt = 9/1 to 4/1) to give diastereomeric mixture of **126** (7.80 mg, 0.0156 mmol, 78%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ diastereomer mixture 9.86 (s, 2H), 8.12-8.01 (m, 4H), 7.63-7.53 (m, 2H), 7.51-7.36 (m, 4H), 7.26-7.16 (m, 4H), 6.83-6.76 (m, 4H), 5.82 (dd, *J* = 5.3, 2.2 Hz, 1H), 5.77 (dd, *J* = 6.2, 3.0 Hz, 1H), 4.67-4.17 (m, 6H), 4.13-3.45 (m, 6H), 3.77 (s, 6H), 1.53 (s, 3H), 1.48 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.11 (s, 3H), 1.08 (s, 3H), 1.04 (s, 3H) 0.98 (s, 3H). LRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{28}H_{36}O_8Na$, 523.2308; found, 523.5131

(4S,5S,6S)-4-(6-((1R,2S,3S,4S)-2-(((tert-butyldimethylsilyl)oxy)methyl)-1,3-bis(methoxymethoxy)-4-methylcyclopentyl)-3,4-dihydroxy-2-methylhex-5-yn-2-yl)-6-(1-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyl-1,3-dioxan-5-yl benzoate (MOM-124)



To a solution of **MOM-125** (3.00 mg, 0.00602 mmol) and **126** (5.1 mg, 0.0102 mmol) in MeCN (60.0 μL) was added anhydrous $NiCl_2$ (0.0200 mg, 0.000120 mmol), and degassed with Freeze Pump Thaw cycles. To the mixture was added anhydrous $CrCl_2$ at room temperature under Argon atmosphere with plastic bag, and the mixture was stirred at room temperature for 1 hour in plastic bag. The reaction was diluted with Et_2O, added florisil, filtered with Celite, and concentrated under reduced pressure. LRMS-ESI (*m*/*z*): $[M - MOM - PMB + H]^+$ calcd for $C_{37}H_{61}O_{11}Si$, 709.3983; found, 709.6316 and $[M - 2MOM - PMB + H]^+$ calcd for $C_{35}H_{57}O_{10}Si$, 665.3721; found, 665.6224.

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