약학박사학위논문

Total Syntheses of (-)-Protoemetinol and 6-Desmethyl-*N*-methylfluvirucin A_1 via Aza-Claisen Rearrangement

aza-Claisen 전이를 이용한 생리활성 알칼로이드의 전합성 연구 : protoemetinol 및 6-desmethyl-*N*-methylfluvirucin A_1의 전합성

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Part I. Total Synthesis of (-)-Protoemetinol and Studies on the Synthesis of (-)-Emetine

Abstract

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Benzo[*α*]quinolizidine alkaloids, mainly isolated from the two different families, *Alangium lamarckii* and *Psychotria ipecacuanha*, have received constant attention because of their multiple pharmacological interests. A number of benzo[*α*]quinolizine derivatives have been synthesized in the pharmaceutical industry to evaluate their biological activities in numerous cell lines.

After the completion of the (+)-tetrabenazine synthesis, we directed our synthetic efforts to establish a unified and stereoselective strategy for the synthesis of benzo[α]quinolizidine alkaloids. Subsequently, we realized that protoemetinol could be an excellent intermediate for the synthesis of other benzo[α]quinolizidine alkaloids including emetine, tubulosine because the structure of protoemetinol is identical to that of the core upper part of those alkaloids.

Our approach relies on a sequential diastereoselective aza-Claisen rearrangement of *N*-acyl-*α*-vinyl-tetrahydroisoquinoline, efficiently prepared utilizing cross metathesis, and diastereoselective acid-promoted transannulation for the construction of the benzo[α]quinolizine framework as well as three stereogenic centers. The concise asymmetric synthesis of (-)-protoemetinol has been accomplished through nine steps (17% overall yield) from the known homoallylic amine. Our unique strategy envisages a unified and versatile synthetic strategy for structurally diverse benzo[α]quinolizidine alkaloids.

Keywords : (-)-Protoemetinol, benzo[α]quinolizidine alkaloids, aza-Claisen rearrangement, transannulation, cross metathesis, asymmetric allylation

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Abbreviations

ACR: aza-Claisen rearrangement

Bn: benzyl

Boc: t-butyloxycarbonyl

BQ: 1, 4-benzoquinone

CM: cross metathesis

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DIBAL: diisobutylaluminum hydride

DMF: *N,N*-dimethylformamide

dNs: 2,4-dinitrophenylsulfonyl

ee: enantiomeric excess

FDA: US food and drug administration

H-G2: Hoveyda-Grubbs' 2nd generation catalyst

HPLC: high-performance liquid chromatography

iPrMgCl: isopropyl magnesium chloride

G2: Grubbs' 2nd generation catalyst

LC/MS: liquid chromatography-mass spectrometry

LHMDS: lithium bis(trimethylsilyl)amide

NMO: *N*-methylmorpholine *N*-oxide

NMR: nuclear magnetic resonance

Ns: 4-nitrophenylsulfonyl

PMB: 4-methoxybenzyl ether

PTSA: *p*-toluenesulfonic acid

SM: starting material

TBS: *tert*-butyldimethylsilyl

TES: triethylsilyl

THF: tetrahydrofuran

TMSOTf: trimethylsilyl trifluoromethanesulfonate

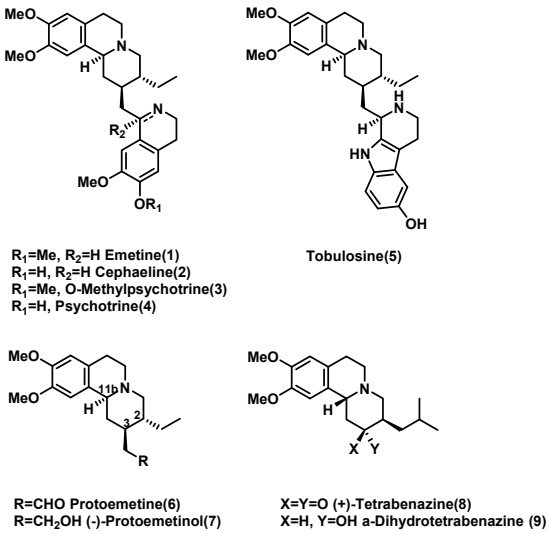
Ts: tosyl, 4-toluenesulfonyl

I. Introduction

1. Benzo[α]quinolizidine alkaloids and Protoemetinol

Benzo[α]quinolizidine alkaloids[1], which are mainly isolated from the two different families, *Alangium lamarckii* and *Psychotria ipecacuanha*, have received constant attention because of their multiple pharmacological interests.[2] Particularly, emetine **1** (Fig. 1), which acts as a protein synthesis inhibitor and DNA interacting agent, has been clinically used for the treatment of a protozoan infection. Recently, additional biological activities including antiviral properties and NF-κB signaling inhibitory effects were reported.[3] Tubulosine **5** also exhibits various biological activities[4] such as broad cytotoxicity in cancer cell lines, antimalarial activity, HIV reverse transcriptase inhibitory activity, and HIF-1 transcriptional inhibitory activity. Accordingly, numerous syntheses of benzo[α]quinolizine alkaloids including emetine and tubulosine have been attempted due to their biological importance and the unique structural features.[5]

Fig 1. The representative benzo[α]quinolizidine alkaloids and derivatives



Benzo[α]quinolizine has been considered as one of the privileged structure from the viewpoint of biological and medicinal chemistry.[6] Therefore, a number of benzo[α]quinolizine derivatives have been synthesized in the pharmaceutical industry to evaluate their biological activities in numerous cell lines. Tetrabenazine **8**,[7] the first and only drug approved by the U. S. FDA as a racemate for the treatment of chorea, represents a major advancement for Huntington's disease patients. The urgent demand for an optically pure drug to reduce or eliminate undesired effects invoked the enantioselective synthesis of (+)-tetrabenazine included in our work.[8]

After the accomplishment of the synthesis of (+)-tetrabenazine, we directed our synthetic efforts to establish an original and unified strategy for the synthesis of benzo[α]quinolizidine alkaloids, because the reported syntheses were limited on utilizing similar procedures such as Michael addition, Bischler-Napierlski or Pictet-Spengler reaction. We chose protoemetinol[9] **7** as our target, which is an excellent intermediate for the syntheses of other benzo[α]quinolizidine alkaloids including emetine **1**, tubulosine **5**, cephaeline **2**, *O*-methylpsychotrine **3**, and psychotrine **4** in that the structure of protoemetinol is identical to that of the core upper part of those alkaloids.

2. Reported Synthetic Studies of (-)-Protoemetinol

Most of the reported protoemetinol synthetic strategies have been limited to racemic approaches.[10] Recently, the several enantioselective syntheses have been reported, but all synthetic approaches, except the first one, based on the same proline-catalyzed Micheal addition as a key reaction (see below) to construct the stereogenic centers. In addition, they had mainly employed the conventional procedure such as Bischler-Napieralski cyclization/reduction or Pictet-Spengler synthesis to elaborate the tetrahydroisoquinoline

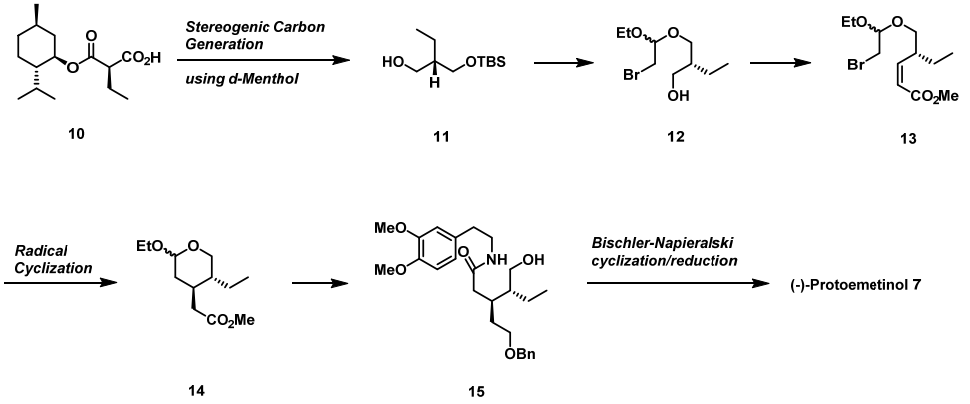
system.[11]

2-1. Asymmetric syntheses

2-1-1. K. Fukumoto's work [10g]

The unsymmetrical silyl-protected propane-1,3-diol **11**, derived from an acid **10** produced by the condensation of ethylmalonic acid with *d*-menthol, was reacted with the 1,2-dibromoethyl ethyl ether and deprotected to afford the alcohol **12**. After its conversion into the corresponding aldehyde, the (*Z*)-*α,β*-unsaturated ester **13** was selectively synthesized by the Still's method. Radical cyclization of **13** under irradiation in the presence of nBu_3SnH produced methyl ester **14**, which was converted into the lactone. Further transformation via amidation and Bischler-Napieralski cyclization/reduction process produced (-)-protoemetinol **7** (Fig 2).

Fig 2. (-)-Protoemetinol synthesis *via* radical cyclization as a key step by Fukumoto.

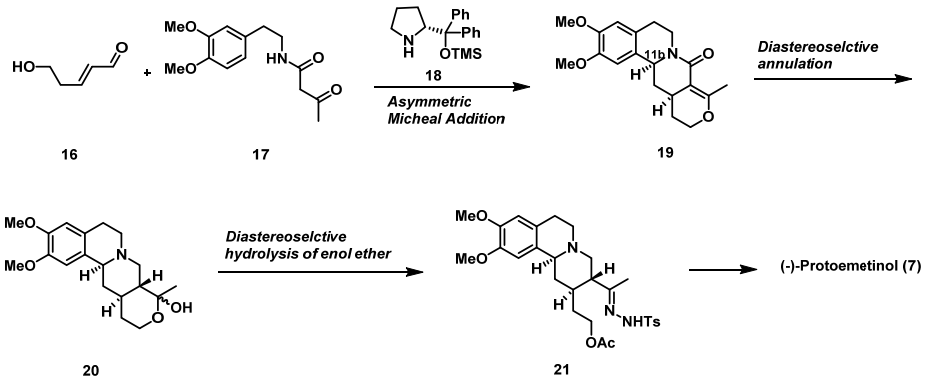


2-1-2. J. Franzén's work [10i]

The *β*-Ketoamide **17** reacted with the *α,β*-unsaturated aldehyde **16** in the presence of catalyst **18** to give a Michael adduct, which was spontaneously converted into

diastereomeric mixture of lactols *in situ*. The crude mixtures of lactol were quenched by addition of $SnCl_4$ to give the desired *β* stereoisomer **19** of C11b (78:22). Hydration of the dihydropyran of **19**, followed by acetylation of resulting lactol, gave the ketone form of **21** which was transformed the hydrazone in the treatment of tosyl hydrazide in AcOH/MeOH. DIBAL reduction of hydrazone with prolonged reaction time at elevated temperature gave the (-)-protoemetinol (Fig 3).

Fig 3. (-)-Protoemetinol synthesis *via* asymmetric Micheal addition as a key step by Franzén.

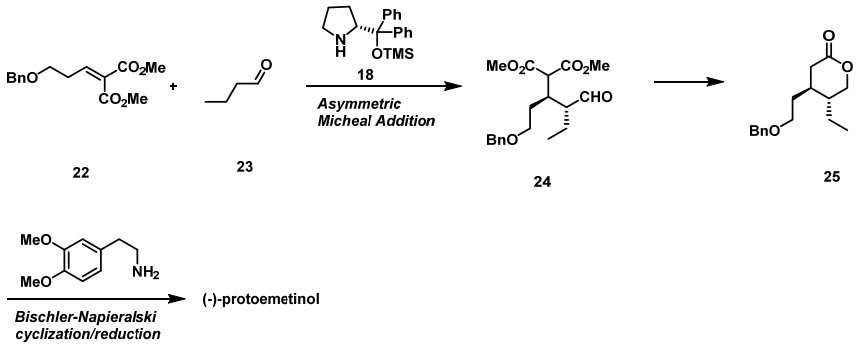


2-1-3 D. Ma's work [10h]

The Córdova group had demonstrated that an OTMS-protected diphenylproline **18** was the best catalyst for promoting the Michael addition of aldehydes to simple arylidene malonates in terms of diastereo- and enantioselectivity. Ma group also explored the Micheal reaction of *n*-butanal **23** with an alkylidene malonate **22** in the presence of catalyst **18** (Fig 4). The stereochemistry of C2 and C3 were established from this early stage. Lactone **25** was assembled from a Michael adduct **24** by a reduction, lactonization and decarboxylation reaction sequence. Following the procedure reported by Fukumoto et al.[10g], lactone **25** was transformed into tricyclic intermediate by the condensation with 3,4-

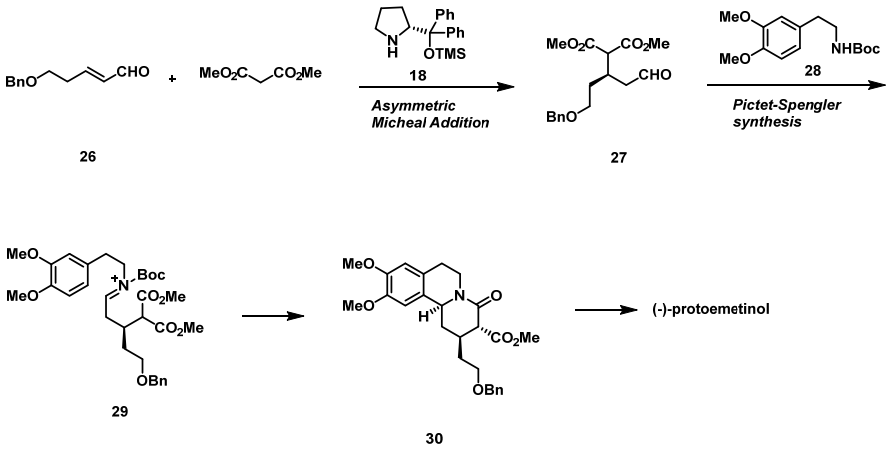
dimethoxyphenethylamine, treatment of the resulting amide with $POCl_3$ and subsequent reduction with $NaBH_4$ to give (-)-protoemetinol **7**.

Fig 4. (-)-Protoemetinol synthesis *via* asymmetric Micheal addition as a key step by Ma.



2-1-4. A. Córdova's work [10j]

Fig 5. (-)-Protoemetinol synthesis via asymmetric Micheal addition as a key step by Córdova.



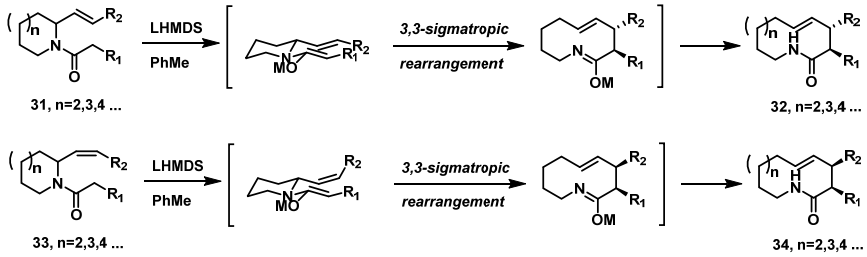
They investigated the one-pot three-component asymmetric Michael reaction sequence between enal **26**, malonate, and Boc-protected 3,4-dimethoxyphenethylamine **28** in the presence of a organocatalyst **18** as similar as the syntheses above. The Pictet-Spengler

reaction occurred smoothly, then a tricyclic compound **30** was synthesized by a lactamization. In the treatment of LAH, the carbonyl group of lactam and methyester of **30** were reduced, and the resulting alcohol intermediate was converted into (-)-protoemetinol by the sequence of Swern oxidation, Wittig olefination, hydrogenation and deprotection of a benzyl group (Fig 5).

3. Aza-Claisen Rearrangement and Acid-Promoted Transannulation Sequence

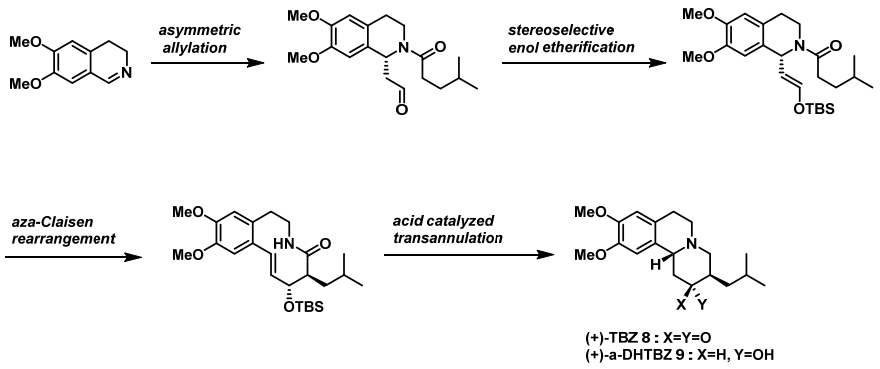
The principle of aza-Claisen rearrangement (ACR) is shown in Fig 6. To the amide **31** or **33** is treated LHMDS at reflux condition, the 3,3-sigmatropic rearrangement occurs to afford the ring-expanded products. The chirality is transferred *via* a chairlike transition state, 1, 2-*anti* for (*E)* enol ether and 1, 2-*syn* for (*Z)* enol ether. Our group had demonstrated that an ACR was proceeded at various ring size systems *via* a chairlike transition state, and the ACR-induced ring expansion could provide an opportunity for the rapid assembly of complex macrolactams or other types of alkaloids.

Fig 6. The principle of Aza-Claisen rearrangement (ACR)



The ring-expanded resultants could be transformed to the fused-ring system in diastereoselective manners *via* succeeding transannulation reaction. The fused ring framework was found in various natural products including benzo[α]quinolizidine alkaloids. We reported the total syntheses of (+)-tetrabenazine **8** and (+)-dihydrotetrabenazine **9** *via* the subsequent *i*PrMgCl-mediated ACR and acid-promoted transannulation as key reactions (Fig 7), which showed not only the ring could be expanded to medium or macro-sized ring but also the diastereoselective fused-ring system could be constructed by an additional transannulation reaction.

Fig 7. Total syntheses of (+)-Tetrabenazine and (+)-α-Dihydrotetrabenazine

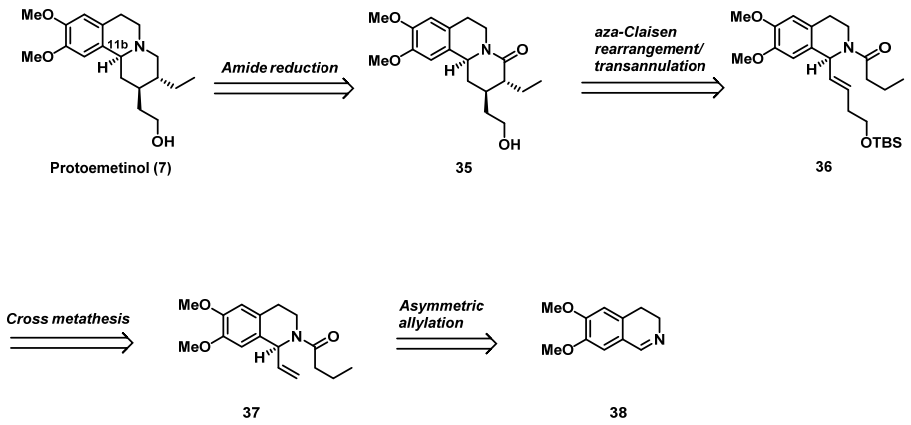


II. Results and Discussion

1. Retrosynthetic Strategy

Our approach relies on a sequential diastereoselective aza-Claisen rearrangement of *N*-acyl-*α*-vinyl-tetrahydroisoquinoline **36**, efficiently prepared utilizing a cross metathesis, and diastereoselective acid-promoted transannulation for the construction of the benzo[α]quinolizine framework as well as three stereogenic centers. Our unique approach provides easy access to structurally diverse benzo[α]quinolizines. The retrosynthetic analysis of (-)-protoemetinol **7** is shown in Fig 8.

Fig 8. Retrosynthetic analysis of (-)-protoemetinol



We planned to pursue a stereoselective sequence of aza-Claisen rearrangement (ACR)[12] and acid-promoted transannulation[13] as the key reactions to readily create the required stereogenic centers via 1, 4 and 1, 5 remote chiral transfers and to diastereoselectively elaborate the benzo[α]quinolizine skeleton. The benzo[α]quinolizine intermediate **35** can be

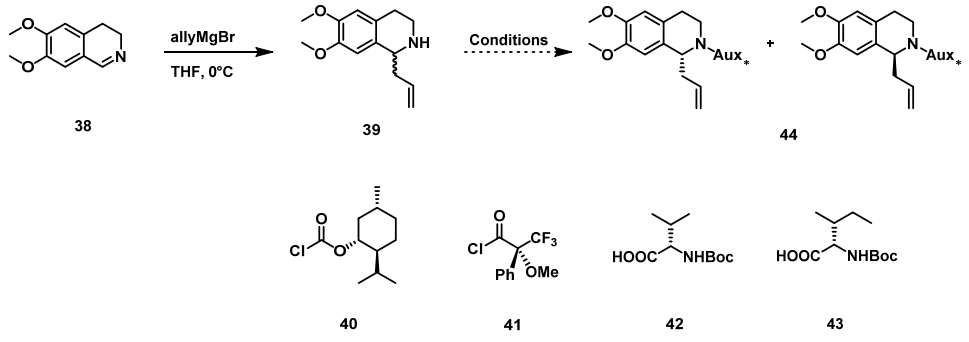
effectively transformed into protoemetinol **7** by the lactam reduction. Intermediate (*E*)-olefin **36** can be conveniently synthesized from amide **37** by a cross metathesis reaction. The initial stereogenic center C11b is introduced by an optimized Nakamura's asymmetric allylation[8b,14] of commercially available dihydroisoquinoline **38**.

2. Preparation of Cross Metathesis Precursors

2-1. Chemical resolution by a chiral auxiliary

Before executing an asymmetric allylation for establishing an initial stereogenic center of C11b[14], we searched more facile way for introducing the allyl group stereoselectively. Racemic allylation was carried out in the treatment of allylMgBr, and then the chemical resolution of allyl tetrahydroisoquinoline **39** was investigated in with chiral auxiliaries or amino acids such as (-)-menthyl chloroformate **40**, Mosher's ester **41**, *N*-Boc-*L*-valine **42** and *N*-Boc-*L*-isoleucine **43**. Unfortunately, none of these auxiliaries could discriminate among enantiomers of **39** (Scheme 1).

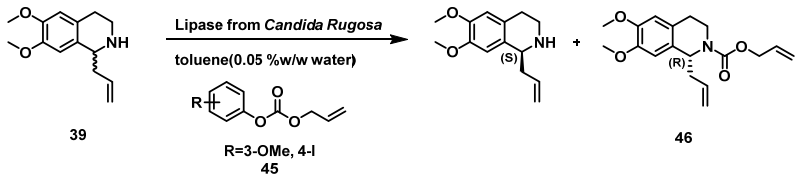
Scheme 1. The trial on Chemical resolution



2-2. Enzymatic resolution

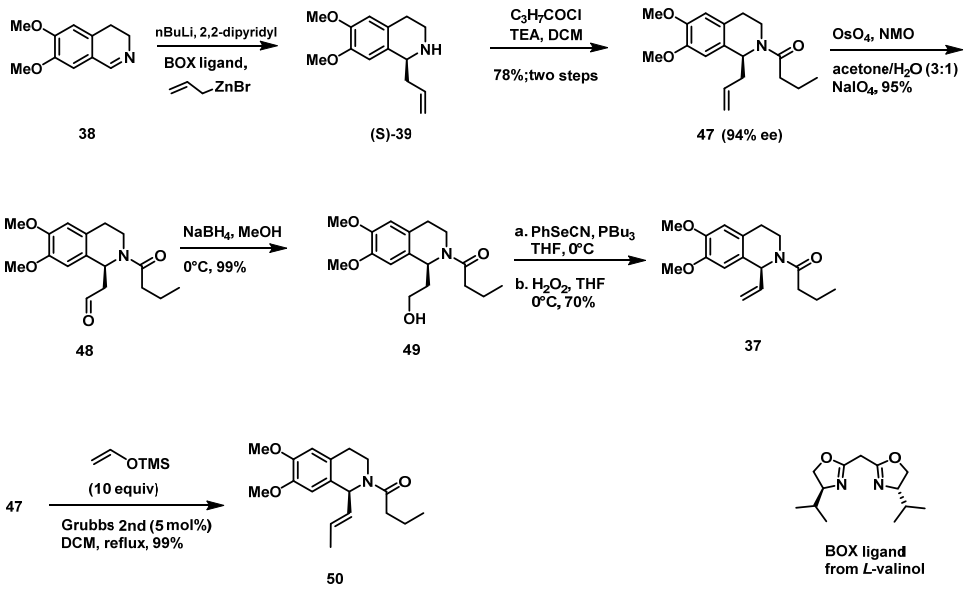
We also conducted a trial on enzymatic resolution (Scheme 2), and chose the lipase from *Candida Rugosa* as the enzyme and the allyl carbonates **45** as an acylating reagent. Although the allyl carbonates was reacted with the (*R*)-allyl tetraisoquinoline of **39** to afford **46** enantioselectively, the conversion yield was too low (9~12 %).

Scheme 2. The trial on enzymatic resolution



2-3. Substrate preparation *via* an asymmetric allylation

Scheme 3. Preparation of cross metathesis substrates



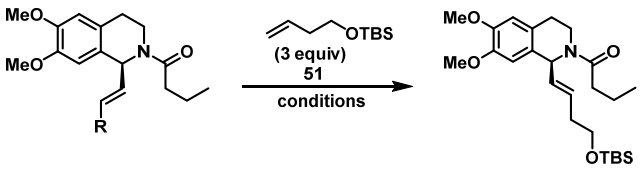
Our synthesis commenced with the preparation of precursors **37** and **50** for cross metathesis as shown in Scheme 3. The known homoallylic amine[15] **39** possessing the stereogenic center C11b was prepared by an asymmetric allylation of the commercially available dihydroisoquinoline **38** in the presence of an enantiomerically enriched bisoxazoline (BOX) ligand and allyl zinc bromide. The amidation of the resulting amine **(*S*)-39** with butyryl chloride followed by an dihydroxylation and the $NaIO_4$ treatment of the resulting diol intermediate provided the aldehyde **48** in an excellent yield. The aldehyde **48** was reduced with sodium borohydride and the resulting alcohol **49** was converted to the vinyl-substituted dihydroisoquinoline **37** utilizing Grieco's protocol.[17] The olefin-isomerized product **50** as another precursor for cross metathesis, was also prepared by the treatment of **47** with excess vinyloxytrimethylsilane in the presence of Grubbs' 2nd generation catalyst[16] in high yield.

3. Cross Metathesis

We conducted the cross metathesis of olefins **37** or **50** with a counterpart **51** to secure an ACR precursor **36** as outlined in Table 1. In case of **50**, the desired product was not detected under both Grubbs' 2nd and Hoveyda-Grubbs' 2nd catalyst presumably due to the insufficient reactivity of the methyl vinyl group of compound **50**. After numerous attempts of cross metathesis with the vinyl tetrahydroisoquinoline **37**, the Hoveyda-Grubbs' 2nd catalyst turned out to be superior over Grubbs' 2nd catalyst in terms of yield, of which the best result was observed with 20 mol%. Addition of 1, 4-benzoquinone (BQ) minimized the isomerization[16] of **51**. Other endeavour such as altering solvent, adding Lewis acid, prolonged reaction time did not improve the outcome. It is noted that the substantially

different results were made depending on the amount of substrates **37**. The yield tended to diminish in the relatively large scale (above 1.0 mmol) (entry 6).

Table 1. Cross metathesis studies



R=H, **37**
R=Me, **50**

36

entry	Substrate(mmol)	Catalyst(mol%)	Additive(eq)	T(hrs)	Result
1	**50**	G2 (20)	-		No reaction
2	**50**	H-G2 (20)	-		No reaction
3	**37** (0.5)	G2 (20)	BQ(3)	48	6% (brsm 14%)
4	**37** (0.5)	H-G2 (10)	BQ(3)	48	15% (brsm 29%)
5	**37** (0.2)	H-G2 (20)	BQ(3)	48	**52% (brsm 73%)**
6	**37** (1.0)	H-G2 (20)	BQ(3)	48	12% (brsm 18%)

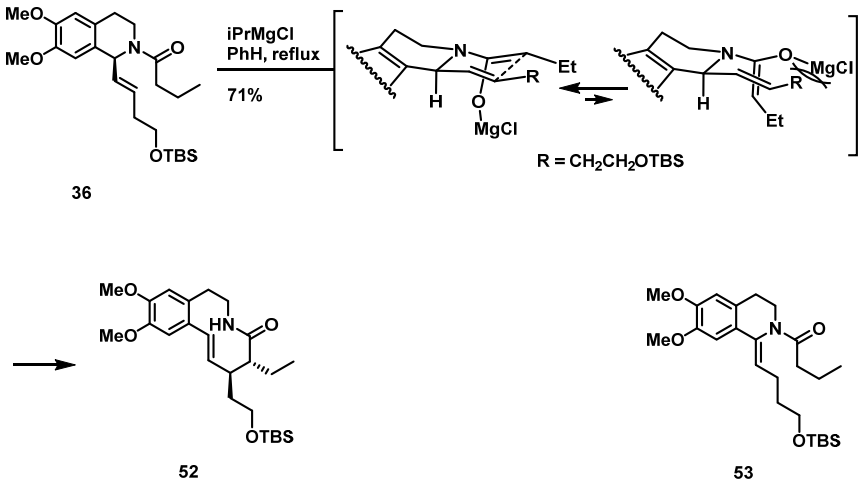
G2: Grubbs' 2nd catalyst
H-G2: Hoveyda-Grubbs' 2nd catalyst
BQ: 1, 4-benzoquinone

4. Aza-Claisen Rearrangement(ACR) and Transannulation Sequence, and Completion of Total Synthesis of (-)-Protoemetinol

We executed the key aza-Claisen rearrangement (ACR) to obtain the lactam intermediate **52** and two stereogenic centers as well as a *trans*-ring olefin (Table 2). The lithium amide enolate, derived from the LHMDS treatment of **36**, afford the isomerized side product[19] **53** exclusively instead of the rearranged product, which resulted from the abstraction of a benzylic proton of C11b. In contrast, the ACR with *i*-PrMgCl proceeded smoothly to give

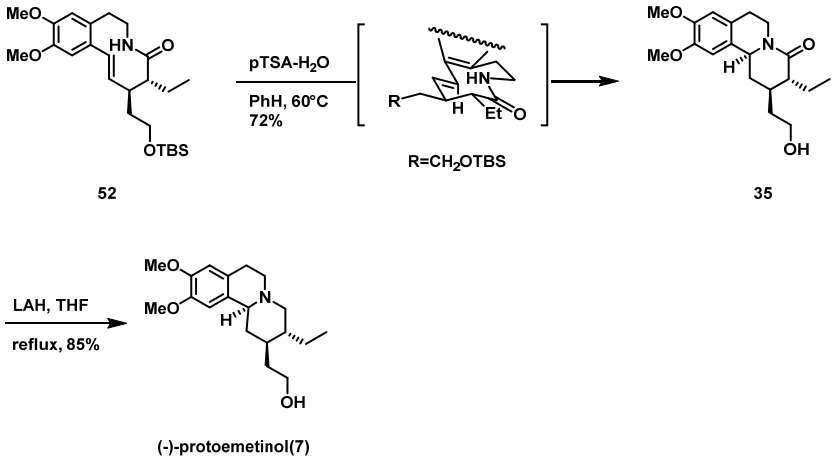
the ring-expansion product[20] **52**. The superiority of *i*-PrMgCl over LHMDS can be explained by the gauche interaction between the bulky MgCl complex and the silyloxyethyl group. This interaction may forces the highly ordered chair-like transition state. The ACR product **52** underwent the facile acid-promoted transannulation to give alcohol **35** as a sole product with the desired diastereoselectivity under the optimized condition (pTSA·H_2O in benzene, 60 °C, 2 hours). The tricyclic lactam **35** was finally reduced with LAH to produce the (-)-protoemetinol **7** (Scheme 4).

Table 2. Aza-Claisen rearrangement studies



entry	Base(eq)	solvent	T(hr)	Result
1	LHMDS (3)	PhMe	2	**53** (21 %)
2	LHMDS (5)	PhMe	2	**53** (51 %)
3	iPrMgCl (3)	PhH	5	**52** (48 %)
4	iPrMgCl (4)	PhH	3	**52** (**71 %**)

Scheme 4. Diastereoselective transannulation and Completion of the synthesis



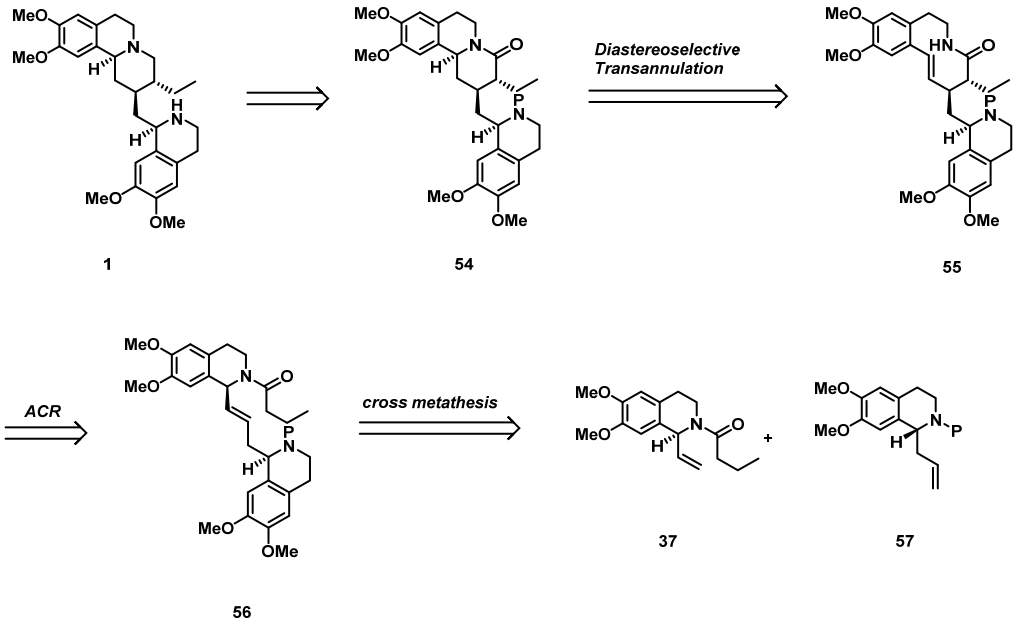
5. Further Studies on the Synthesis of (-)-Emetine

5-1. Retrosynthetic analysis

After the total synthesis of (-)-protoemetinol was accomplished, we further explored the synthesis of (-)-emetine **1**, one of the representative benzo[α]quinolizine alkaloids. Emetine is a well-known alkaloid because of the multiple biological activities as mentioned earlier.

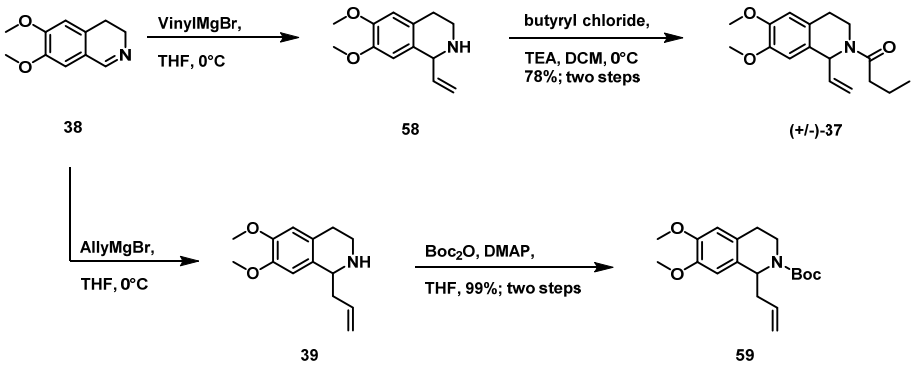
The retrosynthetic analysis is shown in Fig 9. The reported total syntheses of emetine almost started from protoemetinol or its relatives, because it possesses a tetrahydroisoquinoline moiety at lower part. Therefore, we focus on the convergent synthetic approach. Two tetrahydroisoquinoline fragments are prepared and then coupled *via* optimized cross metathesis. With the major building blocks constructed, the key sequence reactions are conducted to build the benzo[α]quinolizine framework. Formation of a proper chairlike transition state will be major concern for the desired stereoselectivity on the ACR and transannulation reactions.

Fig 9. Retrosynthesis of (-)-emetine



5-2. Cross metathesis

Scheme 5. Preparation of cross metathesis precursors

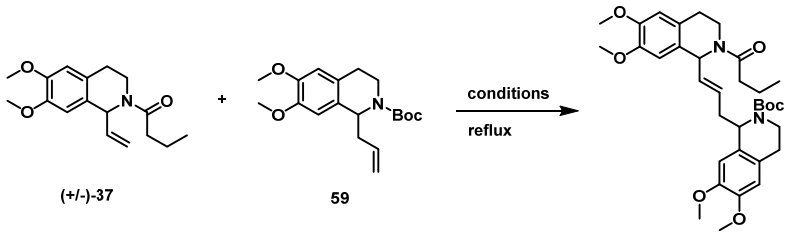


For efficiency, the cross metathesis precursors were prepared as racemates (Scheme 5). The dihydroisoquinoline **38** was converted in the treatment of vinylMgBr, followed by a butyryl amidation to give the vinyl counterpart **37**. A portion of **38** was also reacted with

allylMgBr, followed by Boc protection to obtain allyl counterpart **59**.

We conducted a cross metathesis reaction of **37** and **59** under the various conditions. The isomerized and dimer compounds of **59** were mainly identified in entry 3 because of the sufficient reactivity of allyl tetrahydroisoquinoline, while either isomerization or dimerization of vinyl counter **37** were not observed. We conducted a lot of trials to increase the yield of cross metathesis such as extending the loading amount of catalyst up to 50 mol%, adding Lewis acid like Cy_2BCl, (entry 9 and 10) or changing the solvent such as hexafluorobenzene, 1,2-difluorobenzene or xylene (entry 6, 7 and 8). However, little improvement was shown, and the low reactivity of **37** was likely the main cause (Table 3).

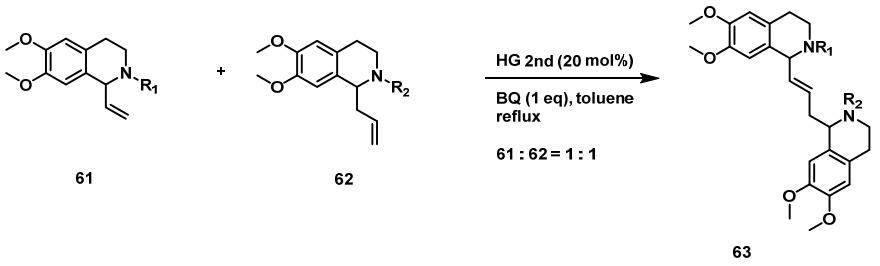
Table 3. Trial on cross metathesis I



(+/-)-37 59 60

entry	Catalyst(mol%)	Additives(eq)	solvent	t	result
1	G2 (30)	-	toluene	74hr	Trace
2	Schrock (30)	-	benzene	30hr	Trace
3	HG2 (20)	-	toluene	2hr	3%
4	HG2 (20)	BQ (2)	toluene	67hr	6%
5	HG2 (30)	BQ (1)	toluene	140hr	14%
6	HG2 (20)	BQ (1)	hexafluorobenzene	69hr	6%
7	HG2 (20)	BQ (1)	1,2-difluorobenzene	72hr	8%
8	HG2 (20)	BQ (1)	xylene	94hr	9%
9	HG2 (20)	BQ (1), Cy_2BCl (20 mol%)	toluene	30hr	10%
10	HG2 (50)	BQ (1), Cy_2BCl (10 mol%)	toluene	72hr	19%

Table 4. Trial on cross metathesis II



61 62 63

No.	R_1	R_2	t	Result
1	butyryl	PMB	72hr	no rxn
2	butyryl	Bn	73hr	no rxn
3	α -bromobutyryl	Boc	87hr	22%
4	α -bromobutyryl	Ts	72hr	Ts dimer 36% (E/Z isomer 2:1)
5	α -bromobutyryl	CO_2Me	69hr	CO_2Me dimer 60%
6	α -bromobutyryl	Bn	64hr	no rxn
7	α -bromobutyryl	Me	53hr	no rxn
8	CO_2Me	Boc	66hr	43%
9	CO_2Me	Bn	60hr	5%
10	CO_2Me	Ts	45hr	30%, Ts dimer 25%
11	$COCF_3$	Boc	66hr	Boc dimer 49%
12	Ts	Boc	56hr	**65%**
13	Ns*	Boc	61hr	**73%**
14	dNs**	Boc	56hr	**75%**

*:4-Nitrophenylsulfonyl
**:2,4-Dinitrophenylsulfonyl

We decided to alter the electronic properties of two substrates, especially the vinyl counterpart, for increasing the yield of cross metathesis. The alkyl chain of a vinyl counterpart **37** and the Boc protecting group of an allyl counterpart **59** were converted to electron withdrawing or donating groups. Substituting the Boc group to more electron donating groups such as benzyl or PMB, the cross metathesis reaction did not occur (entry 1 and 2, Table 4). The cross metathesis is well-known for the preference of electron withdrawing conditions. Adding the Lewis acid like Cy_2BCl, seen above, can be understood in the same context. Therefore, when the Boc group was transformed to the tosyl or CO_2Me,

the dimer of **62** was formed because of the excessively increasing reactivity (entry 4, 5 and 10). When we altered the butyryl group of vinyl substrate **61** to the electron withdrawing groups such as α-bromobutyryl, CO_2Me, $COCF_3$, Ts, Ns(4-nitrophenylsulfonyl) or dNs(2, 4-dinitrophenylsulfonyl), the big improvement was shown. Especially in case of Ts, Ns and dNs, the best yields were obtained (entry 13, 17 and 18). The preparation of Ts and dNs-protected substrate is shown in Scheme 6.

Scheme 6. Preparation of the Ts or dNs-protected substrate

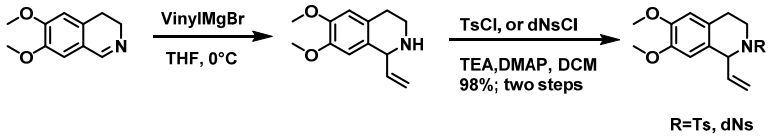
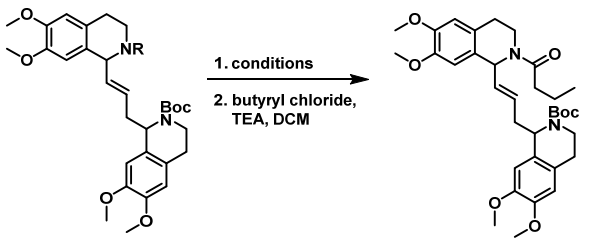


Table 5. Re-introduction of butyryl group: Ts and dNs deprotection



64 60

Entry	R	condition	Solvent	T	result
1	Ts	LiOH	THF/H_2O	rt	no reaction
2	Ts	5% Na-Hg, NaH_2PO_4•$2H_2O$	MeOH	〃	no reaction
3	Ts	Na•Np	DME	-56℃	side reaction
4	Ts	Na, NH_3, 20min	-	-78℃	10%
5	Ts	Na, NH_3, 10min	-	-42℃	**59%**
6	dNs	$HSCH_2CO_2H$, TEA	DCM	rt	no reaction
7	dNs	$HSCH_2CO_2H$, LiOH•H_2O(4eq)	DCM	〃	no reaction
8	dNs	$HSCH_2CO_2H$, LiOH(4eq)	DMF	〃	43%
9	dNs	$HSCH_2CO_2H$, LiOH(excess)	DMF	〃	degradation
10	dNs	$HSCH_2CO_2H$, LiOH•H_2O(4eq)	DMF	〃	**45%**
11	dNs	$HSCH_2CO_2H$(2eq), LiOH•H_2O(4eq)	DMF	60℃	20%

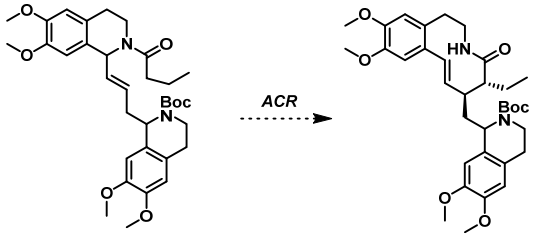
With the cross metathesis product **64** in our hand, we re-introduced the butyryl group on amine group (Table 5). Among the various deprotection conditions, entry 8 turned out to be the best result for the tosyl group and entry 13 for the dNs group.

5-3. Studies on aza-Claisen rearrangement

We executed the key ACR to obtain the 10-membered lactam intermediate **65** with two desired stereogenic centers. Because we observed the superiority of *i*-PrMgCl in the benzylic proton-presence ACR (see Table 2), *i*-PrMgCl was the first choice of an ACR base. When the ACR precursor **60** was treated in the optimized condition (*i*PrMgCl, benzene, reflux), the rearrangement did not occur, but there was the degradation. The TMS trapping was also failed in the use of TMSOTf. We then examined the LHMDS-mediated ACR as well. Although the substrate of ACR **60** was survived in the treatment of LHMDS, neither the rearranged or even isomerized products were detected. Other base screening resulted in failure (Table 6).

Reformatsky-type aza-Claisen rearrangement was attempted as well. However, we could not observe either the silyl trapped or rearranged product in several conditions, but only a de-bromide compound **60** and the degradation eventually (Table 7).

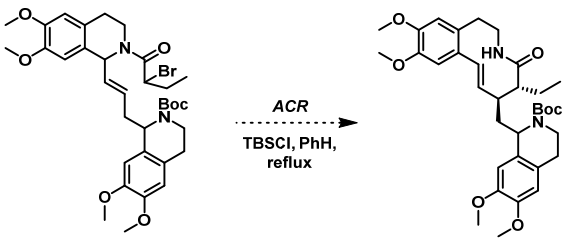
Table 6. Aza-Claisen rearrangement studies



60 **65**

Entry	base	Additive	solvent	temperature	Result
1	iPrMgCl	-	toluene	120℃	Degradation
2	iPrMgCl	-	benzene	90℃	Remained SM, Degradation
3	iPrMgCl	TMSOTf	benzene	-78℃ to reflux	Degradation
4	iPrMgCl	TMSOTf,	THF	-78℃ to reflux	Degradation
5	iPrMgCl	TMSOTf,	toluene	-78℃ to reflux	Degradation
6	LHMDS	-	toluene	120℃	Remained SM
7	LHMDS	TMSOTf,	toluene	-78℃ to reflux	Remained SM
8	LHMDS	TBSOTf	toluene	-78℃ to reflux	Remained SM
9	LHMDS	TBSCl	toluene	-78℃ to reflux	Remained SM
10	nPrMgCl	TMSOTf	toluene	-78℃ to reflux	Remained SM
11	nPrMgCl	TMSOTf,	THF	-78℃ to reflux	Remained SM
12	EtMgBr	-	benzene	90℃	Degradation
13	EtMgBr	LiCl	benzene	90℃	Remained SM
14	MesitylMgBr	-	benzene	90℃	Remained SM
15	PropenylMgBr	LiCl	benzene	90℃	Remained SM
16	nBuLi	TMSOTf	toluene	-78℃ to reflux	Remained SM
17	NaHMDS	-	toluene	120℃	Remained SM
18	KHMDS	-	toluene	120℃	Remained SM

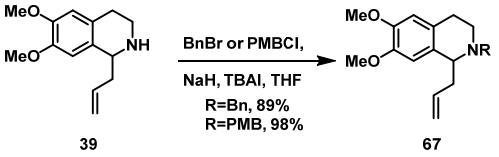
Table 7. Reformatsky-type ACR studies



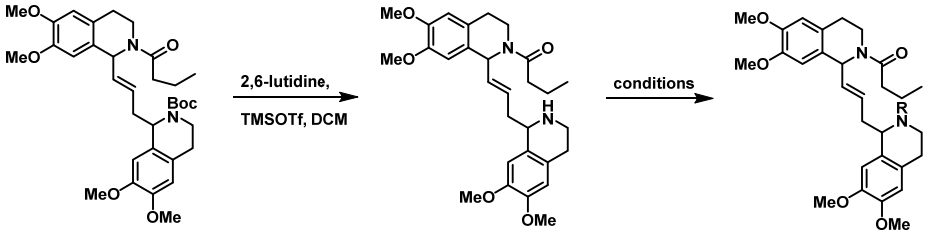
No.	Base (2.4 eq)	Result
1	iPrMgCl	degradation
2	EtMgCl	degradation
3	PhMgCl	degradation
4	CyclopentylMgBr	degradation
5	MesitylMgBr	degradation

We then considered modifying a protecting group of ACR substrate left with the fundamental framework intact. The preparation of the modified precursors was shown in Table 9. We altered the Boc group to the more electron rich groups such as benzyl or PMB. Although the benzylation and PMB protection were carried out smoothly in tetrahydroisoquinoline system (Eq 1), those reactions were struggled in the emetine scaffold. The yield of PMB protection particularly was too low enough to secure the next reaction sequence (entry 5 and 6).

Table 8. Trials on the Bn and PMB protection



39 67 (Eq 1)

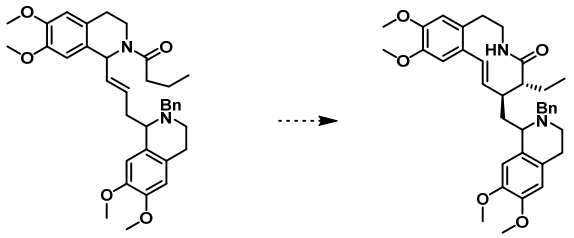


61 68 69 (Eq 2)

No.	R	Base	solvent	Result
1	Bn	K_2CO_3, BnBr, TBAI	EtOH	10%
2	Bn	TEA, BnBr, DMAP	DCM	36%
3	Bn	NaH, BnBr, TBAI	THF	47%
4	Bn	PhCHO, TEA, $NaCNBH_3$	MeOH	**65%**
5	PMB	NaH, PMBCl, TBAI	THF	10%
6	PMB	4-methoxyPhCHO, $Na(OAc)_3BH$	DCM	No reaction

With a small amount of the benzyl substrate **69** available, we conducted the aza-Claisen rearrangement. Although, the stability seemed to be much higher in the *i*-PrMgCl treatment, the reaction did not take place. Isomerized product was detected at a strictly-controlled LHMDS-mediated condition (entry 3, Table 10). The ACR studies for the completion of emetine synthesis are under investigation.

Table 9. ACR study on benzyl substrate



70 71

No.	Base(eq)	Solvent (0.01M)	T	t	Result
1	iPrMgCl (3)	benzene	reflux	2hr	Remained SM
2	LHMDS (2)	toluene	reflux	-	Remained SM
3	LHMDS (3)	toluene	90℃	6hr	Isomerized, 25%*
4	LHMDS (3)	toluene	reflux	2hr	degradation
5	LHMDS (4)	toluene	reflux	3hr	degradation
6	LHMDS (5)	toluene	reflux	1hr	degradation

III. Conclusion

In summary, the concise asymmetric synthesis of (-)-protoemetinol **7** has been accomplished through nine steps (17% overall yield) from the known homoallylic amine **12**. The efficient synthetic procedure employed a sequence of diastereoselective amide enolate-induced ACR of an appropriately substituted dihydroisoquinoline, which is readily prepared via the cross metathesis of *N*-acyl-*a*-vinyl-tetrahydroisoquinoline, and the acid-catalyzed transannulation of the ring-expanded lactam. This unique strategy envisages a unified and versatile synthetic strategy for structurally diverse benzo[α]quinolizidine alkaloids.

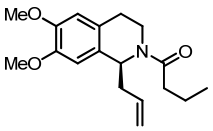
In addition, we further explored the synthesis of one of the representative benzo[α]quinolizine alkaloids, emetine **1**. The reported total syntheses of emetine almost started from protoemetinol or its relatives, because it possesses a tetrahydroisoquinoline moiety at lower part. Therefore, we focus on the convergent synthetic approach. We conducted a cross metathesis reaction of **37** and **59** under the various conditions, but the yield was not satisfactory. We altered the electronic property of the vinyl counterpart, and the big improvement was shown, especially in case of dNs group. Aza-Claisen rearrangement was then conducted in the optimized condition (*i*PrMgCl, benzene, reflux), but the reaction did not occur. The ACR studies for the completion of emetine synthesis are under investigation.

IV. Experimental

General experimental

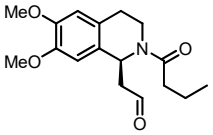
Unless otherwise described, all commercial reagents and solvents were purchased from commercial suppliers and used without further purification, and all anhydrous reactions were carried out under argon gas (1 atm) in flame or oven-dried glassware. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, triethylamine, were freshly distilled with calcium hydride. Flash column chromatography was carried out using silica-gel 60 (230-400 mesh, Merck) and preparative thin layer chromatography was used with glass-backed silica gel plates (1mm, Merck). Thin layer chromatography was performed to monitor reactions. Optical rotations were measured using a JASCO DIP-2000 digital polarimeter at 20 ℃ using 10 or 100 mm cells of 3 mm diameter. Infrared spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. Mass spectra were obtained using a VG Trio-2 GC-MS instrument, and high resolution mass spectra were obtained using a JEOL JMS-AX 505WA unit. ^{1}H and ^{13}C NMR spectra were recorded on either a JEOL JNM-LA 300 (300MHz), JEOL JNM-GCX (400MHz), BRUKERAMX-500 (500MHz) or JEOL (600MHz) spectrometers. Chemical shifts are provided in parts per million (ppm, δ) downfield from tetramethylsilane (internal standard) with coupling constant in hertz (Hz). Multiplicity is indicated by the following abbreviations: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), quintet (quin), quartet of doublet (qd) multiplet (m) and broad (br). The purity of the compounds was determined by normal phase high performance liquid chromatography (HPLC), (Gilson or Waters, CHIRALPAK® AD-H (4.6 × 250 mm) or CHIRALPAK® OD-H (4.6 × 250 mm))

(S)-1-(1-allyl-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)butan-1-one (47)



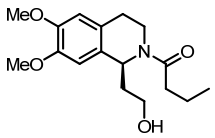
To a solution of the (S)-1-allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (crude, 1.29 mmol) in CH_2Cl_2 (6 mL) was added triethylamine (0.27 ml, 1.93 mmol) followed by an addition of butyryl chloride(1.62 ml, 1.55 mmol) under argon gas at 0℃. The reaction mixture was stirred until complete consumption of the starting material on TLC at ambient temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 1 : 2) afforded 305 mg (78%; two steps) of **47:** $[\alpha]_D^{20}$ +118.6 (*c* 0.93, $CHCl_3$); FT-IR (thin film, neat) *v* max 2960, 1639, 1440 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz, mixture of rotamers) δ 6.41 (d, 1H), 6.64 (d, 1H), 5.97(td, 1H, *J*=5.62, 2.45 Hz), 4.88 (m, 1H), 4.76 (m, 1H), 5.40 (dd, 1H, *J*=6.95, 2.4 Hz), 4.62 (dd, *J*=6.93, 2.55 Hz), 4.46 (dd, *J*=9.28, 5.55 Hz), 3.58 (m, 7H), 3.25 (td, 1H, *J*=12.23, 4.15 Hz), 2.78 (dd, *J*=12.4, 4.15 Hz), 2.64-2.56 (m, 1H), 2.5-2.47 (m, 1H), 2.39-2.24 (m, 2H), 2.21-2.03 (m, 2H), 1.46-1.39 (m, 2H), 0.75-0.67 (m, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.8, 147.0, 146.9, 134.5, 128.5, 124.8, 116.1, 110.7, 109.7, 55.2, 55.1, 50.6, 40.4, 39.1, 34.8, 28.1, 18.0, 13.3; LR-MS (FAB) *m/z* 304 ($M+H^+$); HR-MS (FAB) calcd for $C_{18}H_{26}NO_3$ ($M+H^+$) 304.1913; found 304.1913

(S)-2-(2-butyryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)acetaldehyde (43)



To a solution of the terminal olefin **47** (305 mg, 1.01 mmol) in Acetone: H_2O (3 mL: 1 mL) was added N-methylmorpholine N-oxide (355 mg, 3.03 mmol) followed by an addition of OsO4 0.1M in toluene (0.76 ml, 0,076 mmol) dropwise at 0℃. The reaction mixture was stirred overnight at ambient temperature and was added sodium periodate (648 mg, 3.03 mmol). The reaction mixture was further stirred for one hour and was quenched with saturated aqueous $Na_2S_2O_3$ and diluted with EtOAc. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 1 : 2) afforded 293 mg (95%) of **43**: $[\alpha]_D^{20}$ +147.2 (*c* 2.0, $CHCl_3$); FT-IR (thin film, neat) *v* max 2961, 1720, 1636 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 9.70 (s, 1H), 6.58 (s, 1H), 6.51 (s, 1H), 5.93 (t, 1H, *J*=4.4 Hz), 3.74 (m, 7H), 3.40 (m, 1H), 2.78-2.74 (m, 2H), 2.69-2.65 (m, 2H), 2.32-2.17 (m, 2H), 1.57-1.53 (m, 2H), 0.87-0.84 (m, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 199.8, 171.9, 147.8, 147.7, 127.6, 125.4, 111.1, 109.5, 55.8, 55.7, 50.9, 47.5, 39.9, 35.2, 28.4, 18.2, 13.6; LR-MS (FAB) *m/z* 306 ($M+H^+$); HR-MS (FAB) calcd for $C_{17}H_{24}NO_4$ ($M+H^+$) 306.1705; found 306.1708

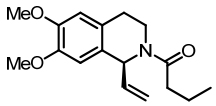
(S)-1-(1-(2-hydroxyethyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)butan-1-one (49)



To a solution of the aldehyde **43** (293 mg, 0.96 mmol) in methanol (5 mL) was added sodium borohydride (18 mg, 0.48 mmol) at room temperature and stirred until complete consumption of the starting material on TLC. The reaction mixture was evaporated and diluted with EtOAc and water. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 2 : 1) afforded 292 mg (99%) of **49**: $[\alpha]_D^{20}$

+81.9 (*c* 1.7, $CHCl_3$); FT-IR (thin film, neat) *v* max 3399, 2958, 1613 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz, mixture of rotamers) δ 6.60 (s, 1H), 6.52 (s, 1H), 5.46 (d, 1H, *J*=11.35 Hz), 3.84 (d, 1H, *J*=12.6 Hz), 3.77 (s, 6H), 3.56 (d, 1H, *J*=10.65 Hz), 3.37-3.27 (m, 2H), 2.88-2.81 (m, 1H), 2.69-2.66 (m,1H), 2.45-2.40 (m, 1H), 2.34-2.28 (m, 1H), 2.08-2.03 (m, 1H), 1.73-1.60 (m, 3H), 0.93(t, 3H, *J*=7.35 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 173.3, 147.8, 147.6, 129.1, 124.8, 111.1, 109.8, 58.0, 55.9, 55.8, 48.9, 39.7, 38.4, 35.2, 28.5, 18.7, 13.8; LR-MS (FAB) *m/z* 308 ($M+H^+$); HR-MS (FAB) calcd for $C_{17}H_{26}NO_4$ ($M+H^+$) 308.1862; found 308.1866.

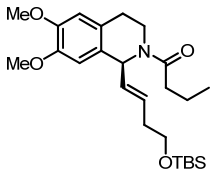
(S)-1-(6,7-dimethoxy-1-vinyl-3,4-dihydroisoquinolin-2(1H)-yl)butan-1-one (37)



To a solution of the alcohol **49** (292 mg, 0.95 mmol) and 1-nitro-2-selenocyanatobenzene (259 mg, 1.14 mmol) in THF (5 mL) was added tributhylphosphine (0.36 ml, 1.43 mmol) slowly at 0℃ under argon gas. The reaction mixture was stirred until complete consumption of the starting material on TLC and was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 2 : 1) afforded (S)-1-(6,7-dimethoxy-1-(2-(2-nitrophenylselanyl)ethyl)-3,4-dihydroisoquinolin-2(1H)-yl)butan-1-one intermediate. Hydrogen peroxide was added dropwise in the solution of the selenide intermediate in THF (5 mL) at 0℃. The reaction mixture was stirred until complete consumption of the starting material on TLC and was quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on

silica gel (EtOAc : Hexane = 1 : 2) afforded 192 mg (70%; two steps) of **37**: $[\alpha]_D^{20}$ +145.7 (*c* 1.99, $CHCl_3$); FT-IR (thin film, neat) *v* max 2960, 1643, 1254 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz, mixture of rotamers) δ 6.57-6.55 (m, 2H), 6.02 (d, 1H, *J*=4.5 Hz), 5.96-8.85 (m, 1H), 5.23-5.22 (m), 5.81 (dd, 1H, *J*=10.2 Hz), 5.01 (dd, 1H, *J*=17.05 Hz), 3.80-3.77 (m, 7H), 3.40 (td, 1H, *J*=12.19, 4.05 Hz), 2.97 (td, *J*=12.05, 3.85 Hz), 2.84-2.75 (m, 1H), 2.68-2.56 (m, 1H), 2.40-2.25 (m, 2H), 1.67-1.61 (m, 2H), 0.94-0.89 (m, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 171.3, 147.7, 147.4, 137.3, 126.6, 125.9, 116.4, 111.0, 110.9, 55.8, 55.7, 53.8, 40.0, 35.4, 28.6, 18.6, 13.9; LR-MS (FAB) *m/z* 290 ($M+H^+$); HR-MS (FAB) calcd for $C_{17}H_{24}NO_3$ ($M+H^+$) 290.1756; found 290.1760.

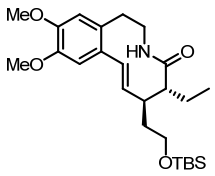
(S,E)-1-(1-(4-(tert-butyldimethylsilyloxy)but-1-enyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)butan-1-one (36)



To a solution of the allylamide **37** (45 mg, 0.16 mmol) and (but-3-enyloxy)(tert-butyl)dimethylsilane (87 mg, 0.47 mmol) in anhydrous toluene (1.5 mL) was added Hoveyda-Grubbs' 2nd generation catalyst (20mg, 0.032 mmol), followed by an addition of 1,4-benzoquinone (51 mg, 0.47 mmol) under argon gas. The reaction mixture was refluxed for 2 days and cooled to room temperature followed by an addition of Dimethyl sulfoxide (0.1 ml, 50 equiv per 1 equiv Hoveyda-Grubbs' cat.). The reaction mixture was stirred open to the air for 12hr and purified by flash column chromatography directly on silica gel (EtOAc : Hexane = 1 : 2) directly afforded 37 mg (52%; brsm 73%) of **36**: $[\alpha]_D^{20}$ +106.9 (*c* 1.5, $CHCl_3$); FT-IR (thin film, neat) *v* max 2956, 1255, 836 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz, mixture of rotamers) δ 6.57 (s, 2H), 6.04 (d, 1H, *J*=5.49 Hz), 5.63-5.36 (m, 2H),

5.23(d, *J*=5.49 Hz), 3.83-3.81 (m, 6H), 3.80-3.76 (m, 1H), 3.62-3.54 (m, 2H), 3.49-3.45 (m, 1H), 3.00 (m), 2.81-2.58 (m, 2H), 2.41-2.31 (m, 2H), 2.28-2.20 (m, 2H), 1.72-1.64 (m, 2H), 0.98-0.92 (m, 3H), 0.88-0.83 (m, 9H), 0.00- -0.02 (m, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 171.4, 147.8, 147.5, 131.2, 129.7, 119.4, 116.1, 111.1, 111.0, 62.6, 55.9, 55.8, 53.3, 39.9, 35.7, 35.5, 28.7, 27.9, 25.8, 25.8, 25.8, 18.7, 13.9, -5.4, -5.4; LR-MS (FAB) *m/z* 448 ($M+H^+$); HR-MS (FAB) calcd for $C_{25}H_{42}NO_4Si$ ($M+H^+$) 448.2883; found 448.2863.

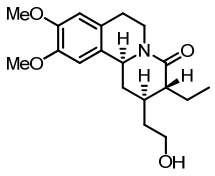
(5R,6S,E)-6-(2-(tert-butyldimethylsilyloxy)ethyl)-5-ethyl-10,11-dimethoxy-2,3,5,6-tetrahydrobenzo[d]azecin-4(1H)-one (54)



To a solution of the (*E*)-olefin **36** (37 mg, 0.083 mmol) in anhydrous benzene (8 mL) was added iPrMgCl (2.0M in THF, 0.17 ml) dropwise at reflux condition under argon gas. The reaction mixture was further refluxed for 6hr and quenched with water. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 1 : 2) afforded 20 mg (55%) of **54**: $[\alpha]_D^{20}$ +144.9 (*c* 0.76, $CHCl_3$); FT-IR (thin film, neat) *v* max 2956, 1509, 837 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.73 (s, 1H), 6.64 (s, 1H), 6.57 (d, 1H, *J*=16.0 Hz), 5.18 (dd, 1H, *J*=16.0, 9.5 Hz), 4.05-4.01 (m, 1H), 3.86 (m, 6H), 3.75-3.70 (m, 1H), 3.67-3.62 (m, 1H), 3.49 (td, 1H, *J*=13.45, 3.35 Hz), 2.78-2.72 (m, 1H), 2.41 (qd, 1H, *J*=10.35, 2.45 Hz), 2.23 (d, 1H, *J*=14.35 Hz), 1.99-1.93 (m, 1H), 1.77-1.70 (m, 1H), 1.62-1.48 (m, 2H), 1.40-1.33 (m, 1H), 0.89-0.81 (m, 12H), 0.06 (s, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 176.1, 147.9, 147.9, 137.7, 133.0, 132.9, 130.4, 113.4, 109.4, 61.9, 56.5, 56.1, 56.1, 44.3, 43.9, 34.8, 30.8, 26.0, 26.0, 26.0, 21.3, 18.3, 12.8, -5.2, -5.2; LR-MS

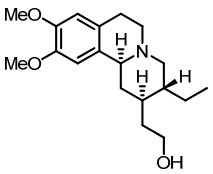
(FAB) *m/z* 448 ($M+H^+$); HR-MS (FAB) calcd for $C_{25}H_{42}NO_4Si$ ($M+H^+$) 448.2883; found 448.2891.

(2R,3R,11bS)-3-ethyl-2-(2-hydroxyethyl)-9,10-dimethoxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one (35)



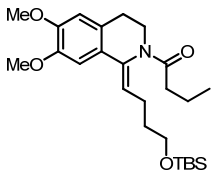
To a solution of the (*E*)-olefin **54** (20 mg, 0.045 mmol) in benzene (4 mL) was added pTSA·H_2O (11 mg, 0.067 mmol). The reaction mixture was stirred stirred at 60℃ until complete consumption of the starting material on TLC and quenched with water. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : MeOH = 10 : 1) afforded 11 mg (72%) of **35**: $[\alpha]_D^{20}$ -55.5 (*c* 0.54, $CHCl_3$); FT-IR (thin film, neat) *v* max 3403, 2925, 1614 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz, mixture of rotamers) *δ* 6.64 (s, 1H), 6.59 (s, 1H), 4.85 (dq, 1H, *J*=11.65, 1.9 Hz), 4.58 (dd, *J*=11.18, 3.35 Hz), 3.85 (s, 3H), 3.84 (s, 3H), 3.83-3.74 (m, 2H), 2.84 (td, 1H, *J*=13.5, 4.7 Hz), 2.75 (td, 1H, *J*=12.1, 2.45 Hz), 2.59 (d, 1H, *J*=15.2 Hz), 2.50 (dt, 1H, *J*=13.2, 3.6 Hz), 2.15-2.09 (m, 2H), 2.09-2.00 (m, 1H), 1.89-1.82 (m, 1H), 1.72-1.63 (m, 1H), 1.46-1.39 (m, 1H), 1.38-1.3 (m, 1H), 1.27-1.19 (m, 1H), 0.91-0.86 (m, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) *δ* 171.4, 147.8, 147.8, 129.1, 127.4, 111.5, 108.6, 60.4, 56.2, 55.9, 55.7, 48.1, 39.6, 37.3, 37.2, 30.9, 28.6, 22.4, 10.0; LR-MS (FAB) *m/z* 334 ($M+H^+$); HR-MS (FAB) calcd for $C_{19}H_{28}NO_4$ ($M+H^+$) 334.2018; found 334.2037.

(-)-Protoemetinol (7)



To a solution of the alcohol **35** (11 mg, 0.033 mmol) in anhydrous THF (1 mL) was added LAH powder (3.75 mg, 0.099 mmol) under argon gas. The reaction mixture was refluxed until complete consumption of the starting material on TLC and cooled to room temperature. The reaction mixture was quenched with saturated aqueous potassium sodium tartrate and diluted with EtOAc. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : MeOH = 10 : 1) afforded 9 mg (85%) of **7**: $[\alpha]_D^{22}$ -44.25 (*c* 0.09, MeOH); FT-IR (thin film, neat) *v* max 2925, 1366, 1257 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.67 (s, 1H), 6.55 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.81-3.71 (m, 2H), 3.13-3.05 (m, 3H), 2.98-2.96 (m, 1H), 2.61 (d, 1H, *J*=15.35 Hz), 2.47 (td, 1H), 2.32 (d, 1H, *J*=12.9 Hz), 2.02-1.98 (m, 1H), 1.97-1.92 (m, 1H), 1.70-1.63 (m, 1H), 1.44-1.43 (m, 3H), 1.28-1.24 (m, 1H), 1.16-1.08 (m, 1H), 0.91 (t, 3H, *J*=7.5 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 147.5, 147.2, 129.4, 126.7, 111.5, 108.3, 62.7, 61.4, 60.7, 56.1, 55.8, 52.5, 41.2, 37.6, 37.3, 35.9, 29.1, 23.5, 11.1; LR-MS (FAB) *m/z* 320 ($M+H^+$); HR-MS (FAB) calcd for $C_{19}H_{30}NO_3$ ($M+H^+$) 320.2226; found 320.2212.

(Z)-1-(1-(4-(tert-butyldimethylsilyloxy)butylidene)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)butan-1-one (55)



To a solution of the (*E*)-olefin **36** (37 mg, 0.083 mmol) in anhydrous benzene (8 mL) was added LHMDS (1.0M in THF, 0.34 ml) dropwise at reflux condition under argon gas. The reaction mixture was further refluxed for 6hr and quenched with water. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 1 : 2) afforded 19 mg (51%) of **55:** ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.93 (s, 1H), 6.54 (s, 1H), 5.88-5.85 (q, 1H), 4.92-4.89 (q, 1H), 3.89 (s, 3H), 3.87-3.83 (m, 1H), 3.84 (s, 3H), 3.68-3.56 (m, 3H), 3.09-3.02 (td, 1H), 2.97-2.91 (td, 1H), 2.58-2.54 (dd, 1H), 2.33-2.09 (m, 3H), 1.73-1.57 (m, 2H), 0.87 (s, 9H), 0.79-0.76 (t, 3H), 0.03 (s, 6H); LR-MS (FAB) *m/z* 448 ($M+H^+$); HR-MS (FAB) calcd for $C_{25}H_{41}NO_4Si$ ($M+H^+$) 447.28; found 448.2876.

V. References

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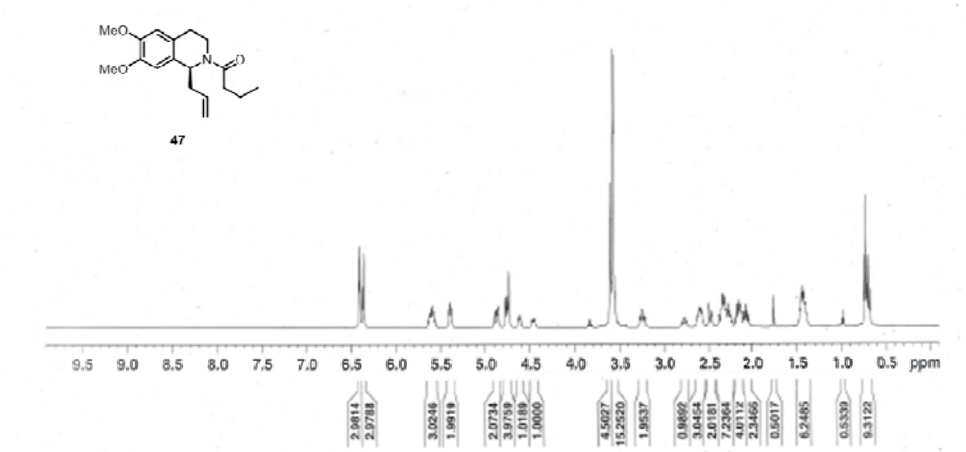
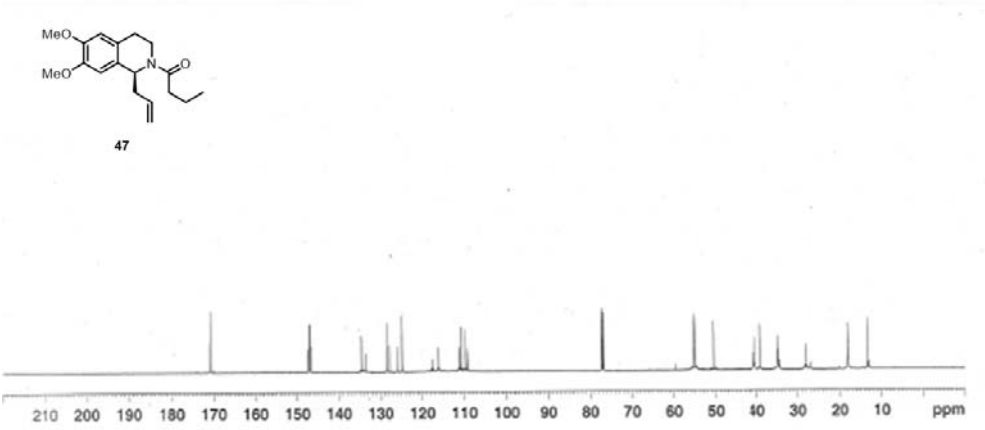
18. All spectral data of the synthetic (-)-protoemetinol were identical to those of the authentic **7.**

VI. Appendix

▼ ^{1}H-NMR ($CDCl_3$, 500 MHz)



▼ ^{13}C-NMR ($CDCl_3$, 125 MHz)



▼ HPLC (chiral AD-H, Hex: ProH= 4: 1)

Thu Aug 25 2011 15:02:37 Results Report Page 1

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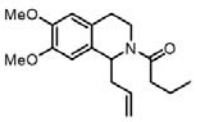

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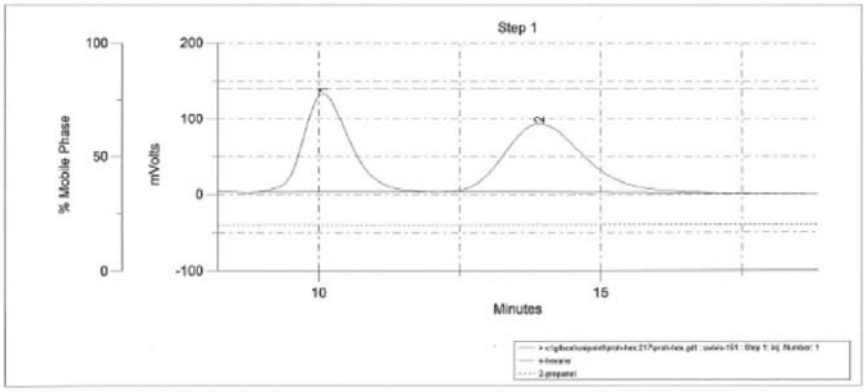

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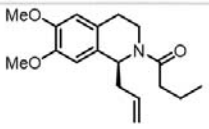

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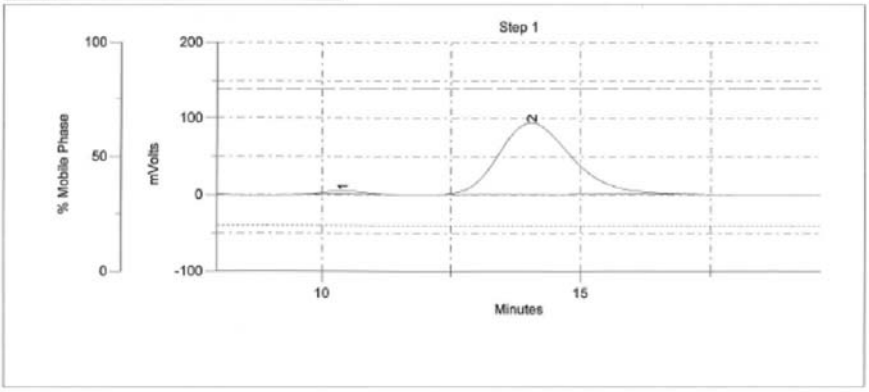

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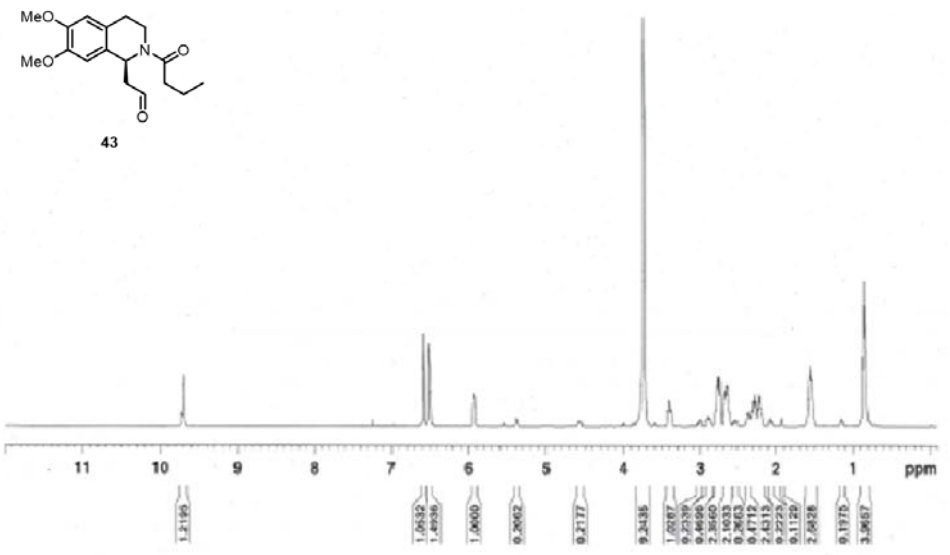

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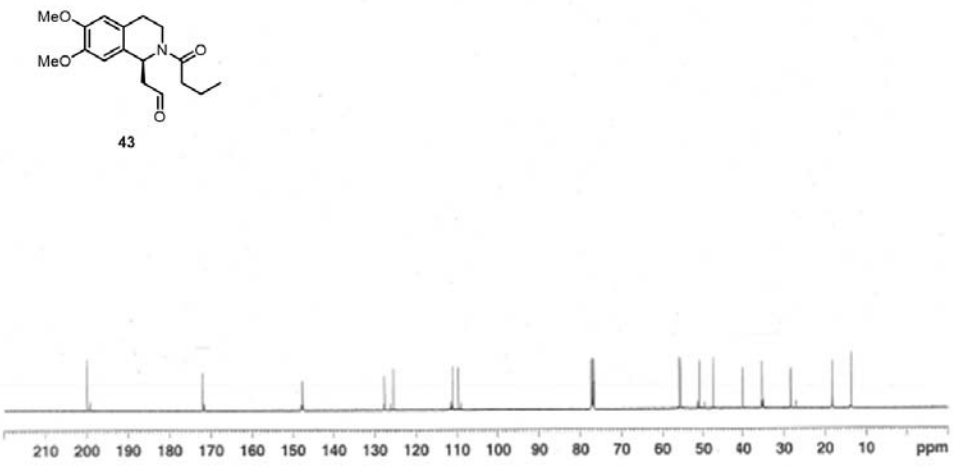

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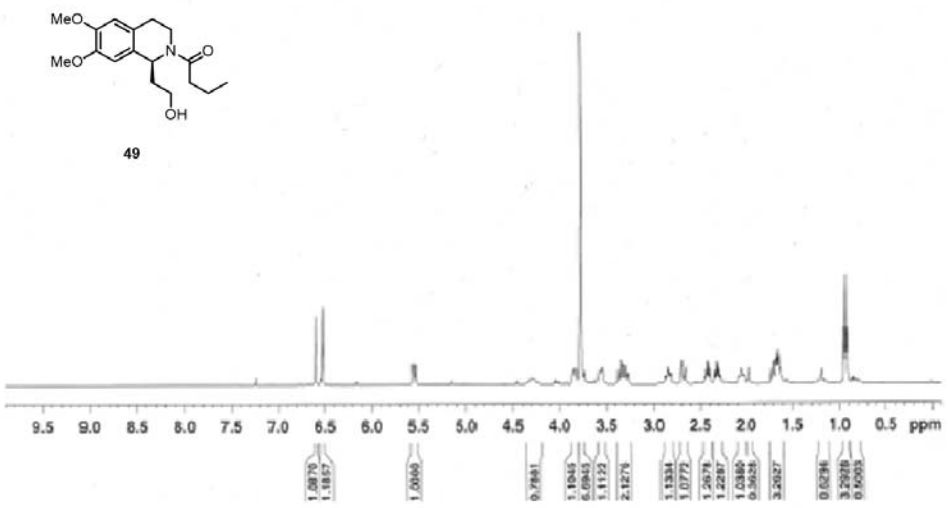

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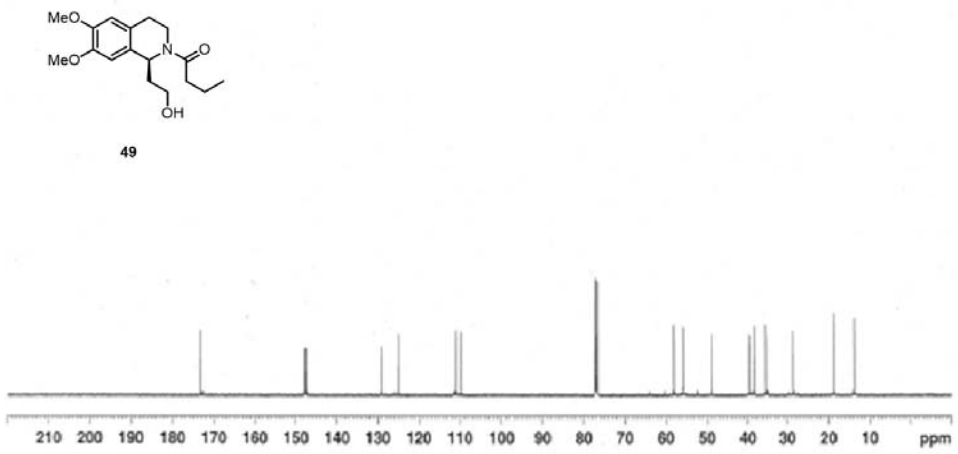

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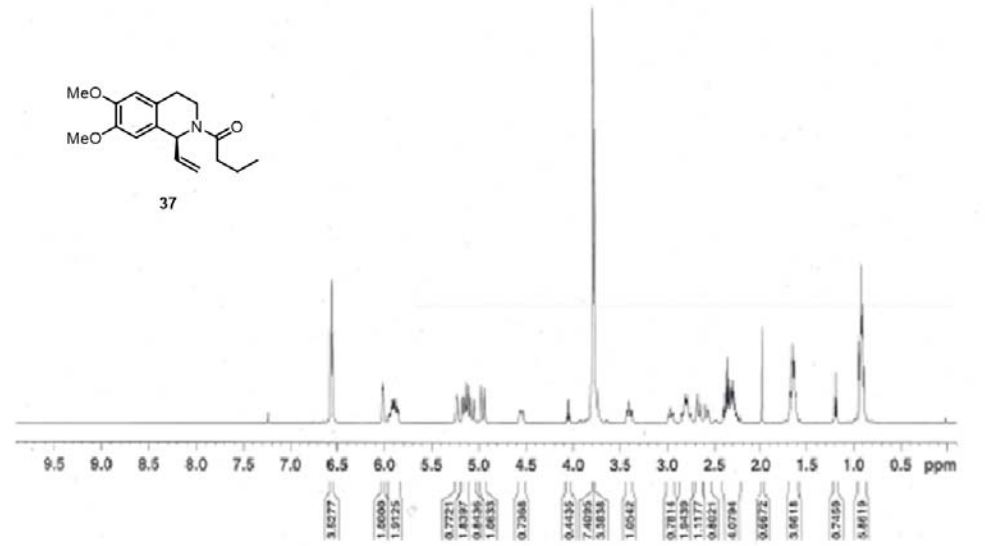

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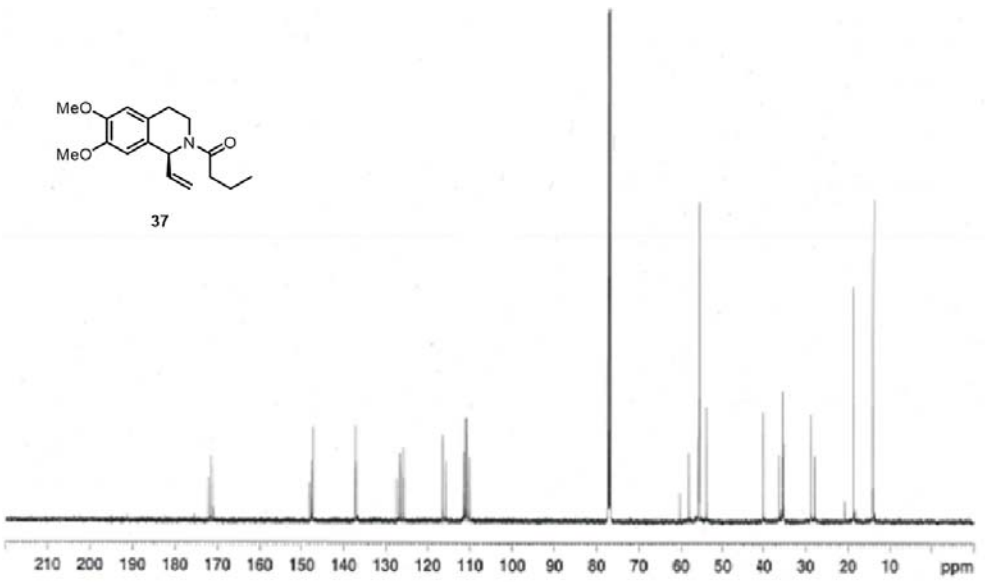

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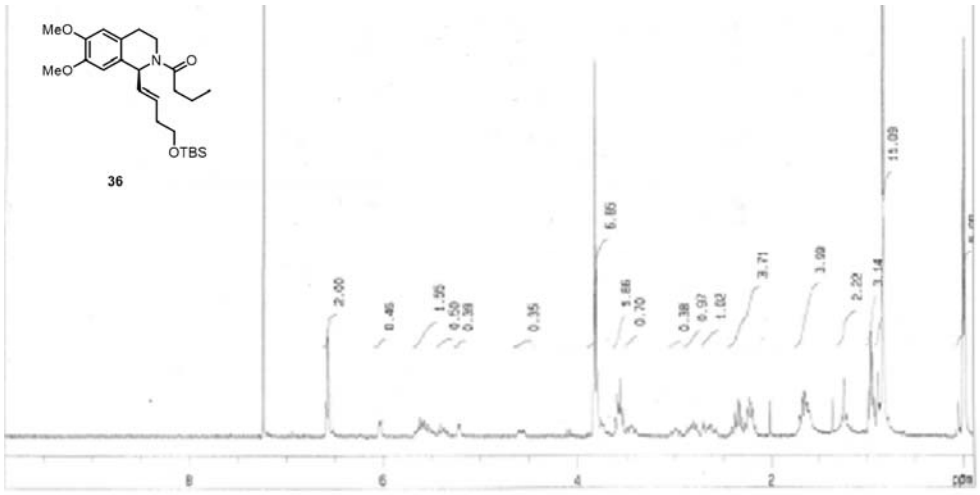

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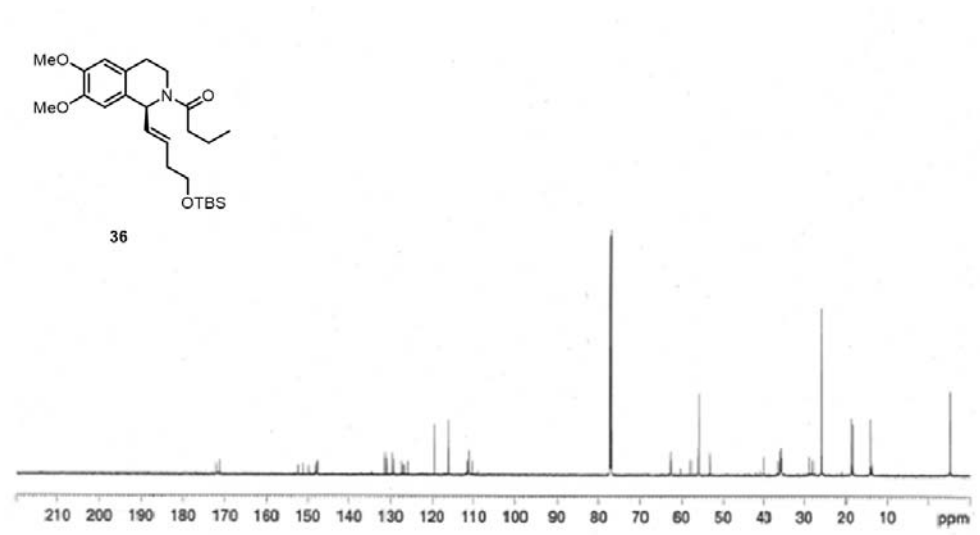

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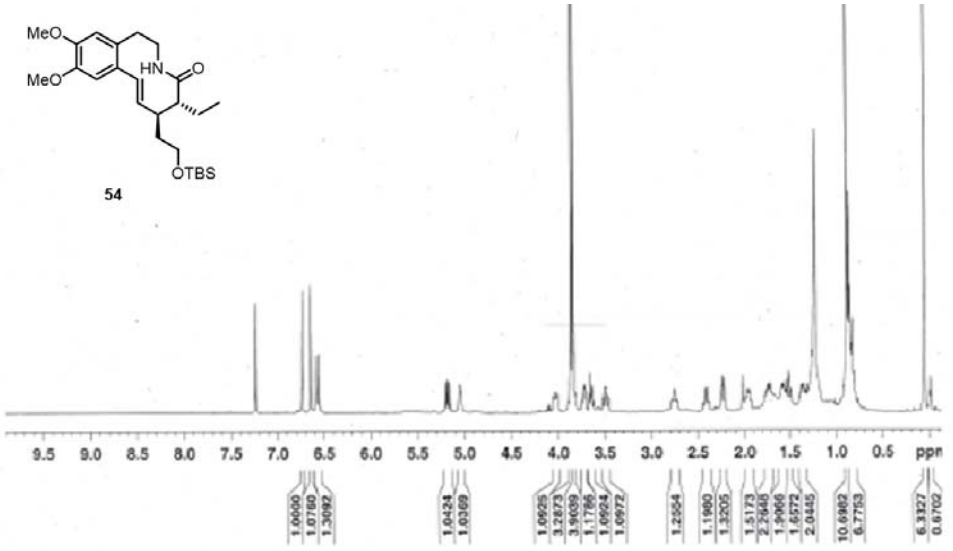

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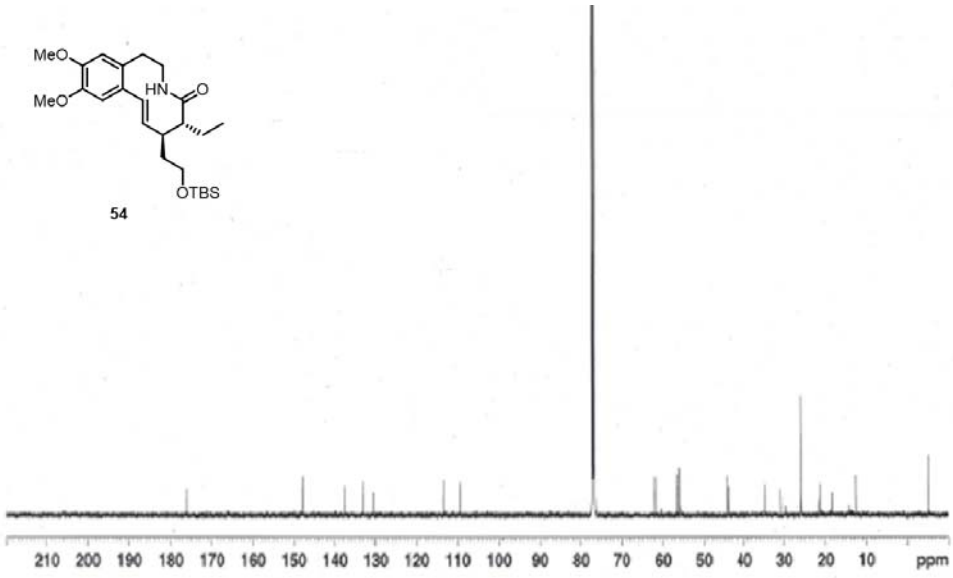

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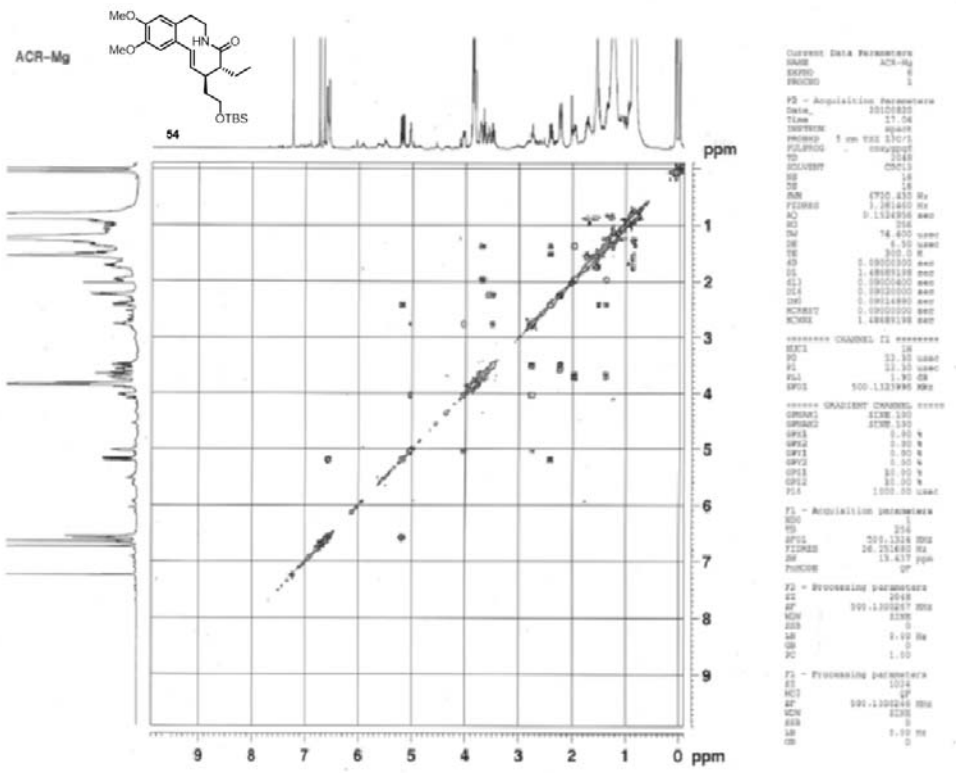

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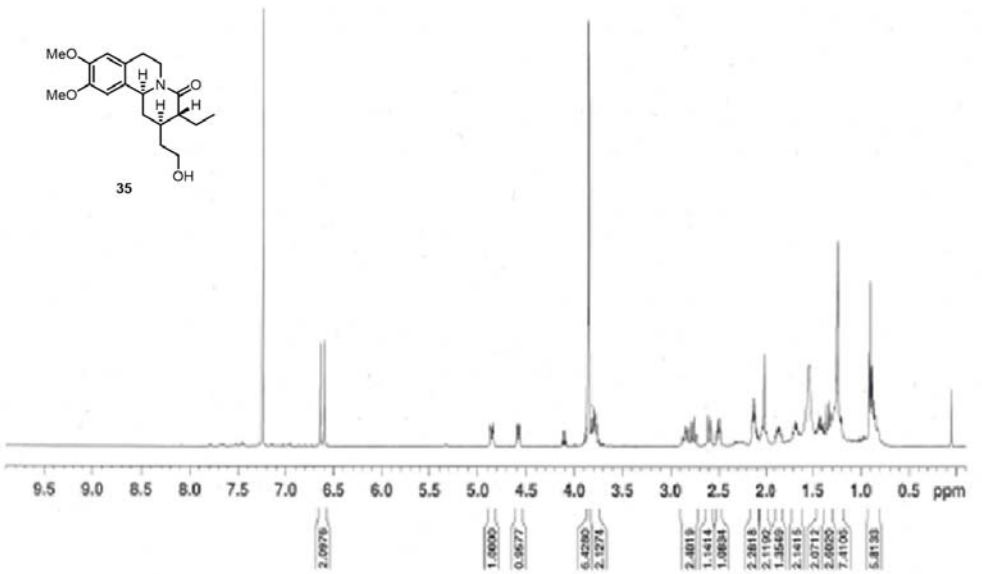

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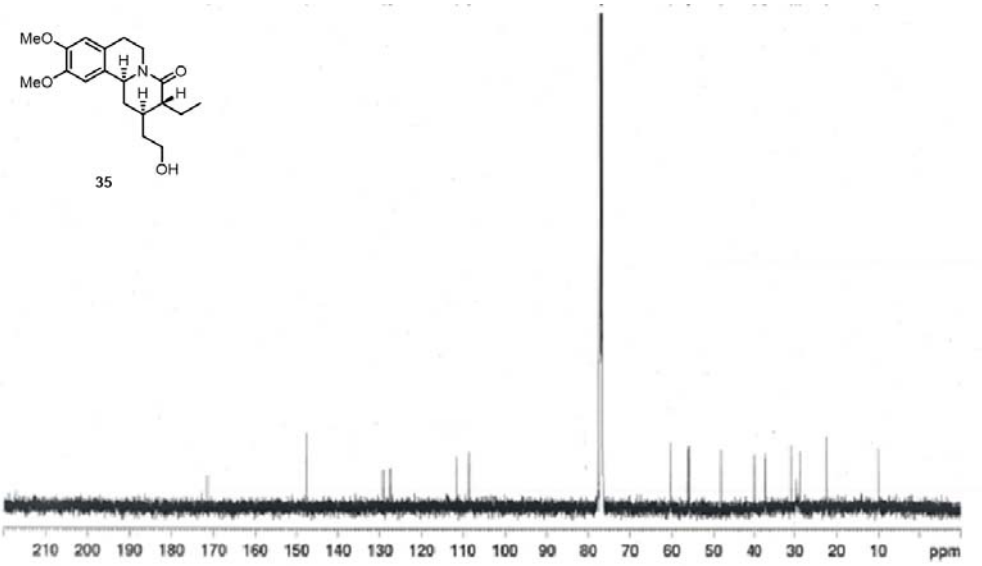

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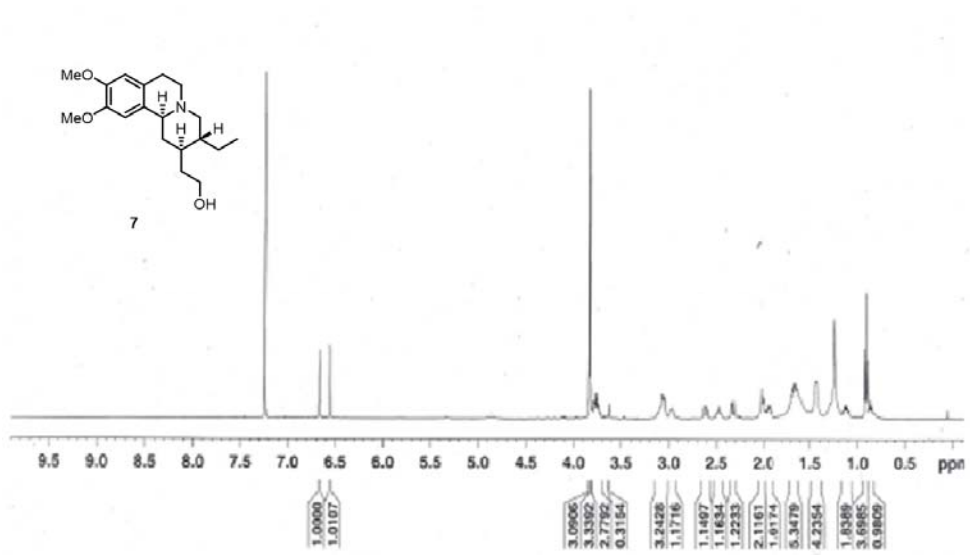

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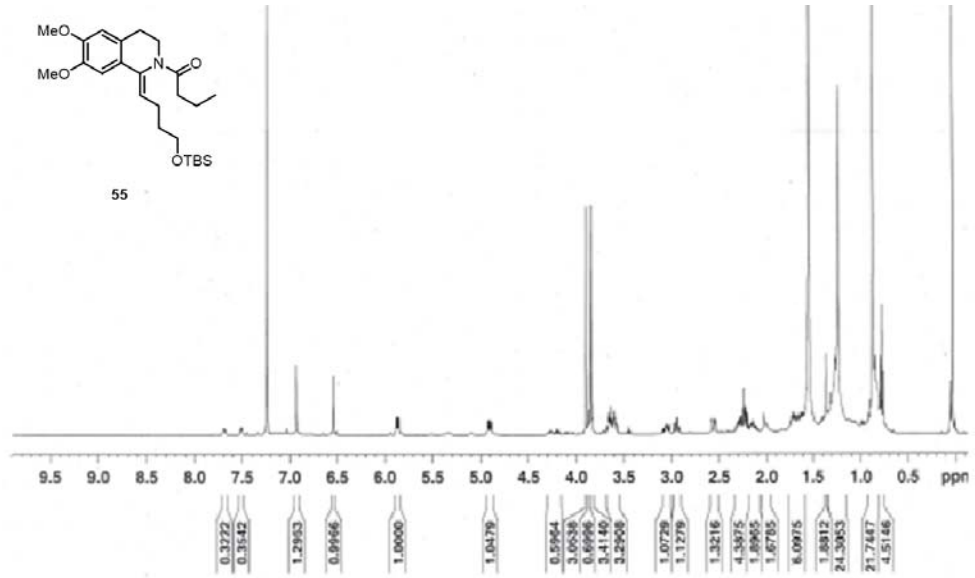

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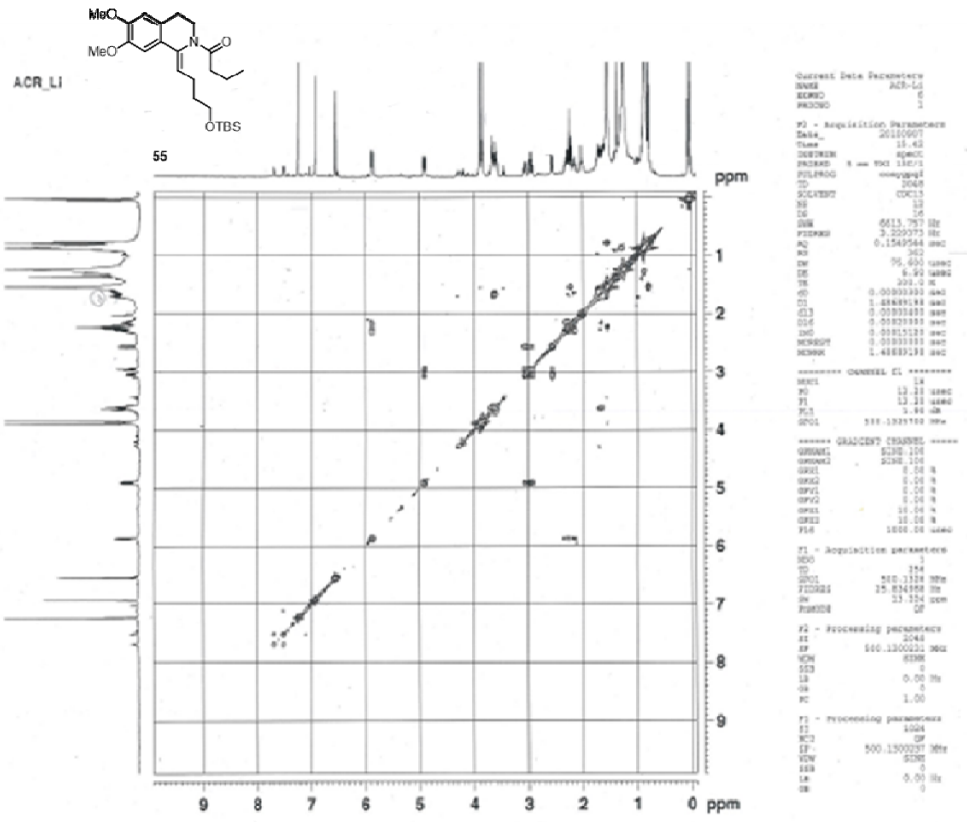

VII. 국문초록

Benzo[α]quinolizidine 계 알칼로이드는 *alangium lamarckii*와 *psychotria ipecacuanha*에서 주로 분리되는 천연물로써, Emetine, Tobulosine, Cephaeline, Psychotrine 등이 보고되었고, 이들의 다양한 약리효과로 인해 오랜 기간 학계로부터 지속적인 주목을 끌어왔다. 이들의 생물학적 중요성과 구조적 특징으로 인해 효과적인 합성법 개발을 위한 많은 시도가 있었고, 본 연구실은 헌팅톤 병에 의한 무도증 치료제로 2008년 FDA승인된 바 있는 benzo[α]quinolizidine 계 알칼로이드 유도체인 Tetrabenazine의 입체선택적 합성법을 개발 보고하였다.

현재까지 보고된 tetrahydroisoquinoline 골격의 입체선택적 합성은 Bischler-Napierlaski cyclization과 Pictet-Spengler synthesis을 이용하는데 국한되어 있다. 이에 본 연구자는 선행 연구를 통해 확립된 ACR(aza-Claisen rearrangement)-transannulation cascade을 응용하여, 2번, 3번 그리고 11b번 탄소에 원하는 입체선택성을 지닌 (-)-Protoemetinol의 합성을 완료하였고, 이를 중간체로 하는 2,3-disubstituted benzo[α]quinolizidine계 알칼로이드의 활발한 합성 연구를 기대한다. 핵심반응을 위한 기질은 Hoveyda-Grubbs' 2nd 촉매를 사용한 cross metathesis 을 통해 *(E)*-selective하게 합성하였고, 처음의 11b 탄소의 입체 중심은 최적화된 Nakamura's asymmetric allylation을 통해 확립하였다.

한편 benzo[α]quinolizidine계 알칼로이드의 대표적 천연물인 emetine의 합성 연구도 진행하였다. 대부분의 보고된 전합성이 protoemetinol 혹은 이의 관련 화합물로부터 linear한 합성을 통해 완결된 점에 착안하여, 본 연구자는 최적화된 선행 연구를 응용하여 두 tetrahydroisoquinoline fragments을 먼저 합성하고 이를 연결한 뒤 benzo[α]quinolizidine 골격을 완성하는 convergent한 접근법을 통해 합성 가능하리라 기대하였다. electron deficient한 기질로부터 성공적인 cross metathesis를 진행하였고 현재 aza-Claisen 전이에 대한 연구를

진행 중이다.

주요어 : (-)-Protoemetinol, (-)-emetine, benzo[α]quinolizidine 알칼로이드, aza-Claisen 전이, transannulation, cross metathesis, convergent synthesis

학번 : 2007-21810

Part II. First Total Synthesis of 6-Desmethyl-*N*-methylfluvirucin A_1

Abstract

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College of Pharmacy

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Fluvirucins, a class of macrolactam antibiotics, were isolated from fermentation broths of actinomycete isolates in 1991 and reported seven species including fluvirucin $A_{1\text{-}2}$, $B_{1\text{-}5}$. Recently, a drug-resistant hurdle have emerged in the livestock market. Three new macrolactams, 6-desmethyl-*N*-methylfluvirucin A_1, *N*-methylfluvirucin A_1 and fluvirucin B_0, and two known macrolactams, fluvirucin B_1, B_3, were isolated by bioassay-guided fractionation as part of the search for new anthelmintics in 2007 and 2008.

6-Desmethyl-*N*-methylfluvirucin A_1 exhibited *in vitro* activity (EC_{90} 15 ± 5 μg/mL) against *Haemonchus contortus* larvae, and fluvirucin B_0 showed very potent activity (EC_{90} <1.0 μg/mL) along with fluvirucin B_1, B_3 (EC_{90} 1.5, 1.7 μg/mL, respectively). But these natural compounds were restricted as new anthelmintics because of their modest *in vivo* activity against *Heligmosomoides polygyrus* in mice. This limitation may be overcome *via* the process of chemical optimization for improving *in vivo* activity. The syntheses of derivatives *via* a pre-established synthetic route can enable the discovery of more powerful compounds as drug candidates.

For this demand, we actively directed our efforts to the synthesis of 6-desmethyl-*N*-methylfluvirucin A_1. Our approach relies on the stereoselective amidoalkylation on the 10-membered lactam *via N*-acyl iminium intermediate taking advantage of the intrinsic ring strain, and *i*PrMgCl-mediated aza-Claisen rearrangemnet to give the ring-expanded *anti* product in high stereoselectivity.

The synthesis of a carbohydrate of 6-desmethyl-*N*-methylfluvirucin A_1 has posed a challenge due to its congested structure in that all substituents are positioned the same

direction, on the β face and a methylamine group was attached at carbon 3'. We installed the *N*-methyl group from the beginning to avoid the difficulty of *N*-methylation and posed the protecting group of amine to a pre-existed phenylethyl group for the double acetylation.

Glycosylation was attempted with the Cbz-protected aglycone and fluoroglycoside. Optimization of glycosylation is under investigation. After the glycosylation and deprotection steps, we hope that the total synthesis of 6-desmethyl-*N*-methylfluvirucin A_1 could be accomplished at an early date.

Keyword: 6-desmethyl-*N*-methylfluvirucin A_1, *N*-methylfluvirucin A_1, 3,6-dideoxy-3-methylamino-*L*-talose, glycosylation, aza-Claisen rearrangement, amidoalkylation, solubility

Student Number : 2007-21801

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Abbreviations

Ac: acetyl

Bn: benzyl

Boc: t-butyloxycarbonyl

Cbz: benzyloxy carbamate

CM: cross metathesis

(-)-CSO: (2*S*, 8*aR*)-(-)-(camphorylsulfonyl)-oxaziridine

DAST: diethylaminosulfur trifluoride

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCM: dichloromethane, methylene chloride, MC

DIBAL: diisobutylaluminum hydride

DMAP: *N,N*-dimethylaminopyridine

DMF: *N,N*-dimethylformamide

EtOAc: ethyl acetate

ee: Enantiomeric Excess

FDA: US Food and Drug Administration

Fmoc: fluorenylmethyloxycarbonyl

iPrMgCl: isopropyl magnesium chloride

LHMDS: lithium bis(trimethylsilyl)amide

MeOH: methanol

MOM: methyloxy methyl

Ms: methansulfonyl

NaHMDS: sodium bis(trimethylsilyl)amide

NBS: *N*-bromosuccinimide

NMO: *N*-methylmorpholine *N*-oxide

NMR: nuclear magnetic resonance

Pd/C: palladium/carbon

RCM: ring closing metathesis

TBAF: tetra-*n*-butylammonium fluoride

TBS: *tert*-butyldimethylsilyl

TEA: triethylamine

TES: triethylsilyl

TFA: trifluoroacetic acid

THF: tetrahydrofuran

Troc: 2,2,2-trichloroethoxycarbonyl

TS: transition state

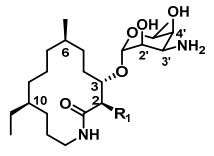
ZACA: zirconium-catalyzed asymmetric carboalumination

I. Introduction

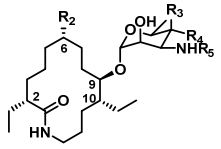
1. Fluvirucins

Fluvirucins, a class of macrolactam antibiotics, were isolated from fermentation broths of actinomycete isolates in 1991 by scientists at Bristol-Myers Squibb including fluvirucin A_{1-2}, B_{1-5} (**1-7**).[1-4] Scientists at Schering-Plough also independently isolated fluvirucin B_{1-3} (**3-5**) from *Actinomadura vulgaris* in 1990 and named them Sch 381516, Sch 38158 and Sch 38185, respectively. [5, 6] 6-Desmethyl-*N*-methylfluvirucin A_1 **8** and *N*-methylfluvirucin A_1 **9**, isolated from *Nonomuraea terkmeniaca* MA7364, were newly reported by scientists at Merck in 2007, and fluvirucin B_0 **10** was isolated from *Nonomuraea terkmeniaca* MA7381 in 2008 by the same group (Fig 1).[7, 8]

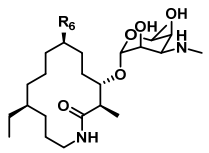
Fig 1. Fluvirucins



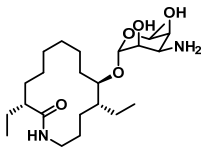
Fluvirucin A_1 (1) R_1=Me
A_2 (2) R_1=CH(OH)Me



Fluvirucin B_1 (3) R_2=Me, R_3=OH, R_4=H, R_5=H
B_2 (4) R_2=Et, R_3=H, R_4=OH, R_5=H
B_3 (5) R_2=Et, R_3=OH, R_4=H, R_5=H
B_4 (6) R_2=Et, R_3=H, R_4=OH, R_5=$CONHCH_2CH_2C_6H_5$
B_5 (7) R_2=Et, R_3=OH, R_4=H, R_5=$CONHCH_2CH_2C_6H_5$



6-desmethyl-N-methylfluvirucin A_1 (8) R_6=H
N-methylfluvirucin A_1 (9) R_6=Me



Fluvirucin B_0 (10)

These natural products have a 2,6-dialkyl-10-ethyl-3(or 9)-hydroxy-13-trodecanelactam of a 14-membered macrolactam that is called fluvirucinine. The fluvirucinine has stereogenic centers at carbons 2, 3 (or 9), (6) and 10 and is connected with a carbohydrate by a glycosidic linkage at the hydroxyl of 3 (or 9). [9, 10] The carbohydrate, 3,6-dideoxy-3-

(methyl)amino-*L*-talose, possesses a (methyl)amine group at carbon 3', and all substituents are positioned the same direction, on the β face, except for the carbohydrates of fluvirucin B_2 **4** and B_4 **6**. This conformation is unique and highly congested among the reported carbohydrates of natural products.

Fluvirucins B_1, B_2, and B_3 (**3-5**) have potent inhibitory effects against Gram (+) bacteria, bacteroides fragilis and yeast, whereas fluvirucins A_1 **1** and A_2 **2** are less potent. No activity of the fluvirucin series has been reported against Gram (-) bacteria, Gram (+) anaerobic bacteria or filamentous fungi. Most of all, fluvirucins exhibit considerable inhibitory activity against influenza A virus in Madin-Darby canine kidney (MDCK) cells, especially fluvirucins A_1, A_2, B_1 and B_3 (**1-3, 5**) (ID_{50} : 2.3-4.6 μg/mL). [3, 4]

2. Total Syntheses of Fluvirucin A Series By The Aza-Claisen Rearrangement(ACR)

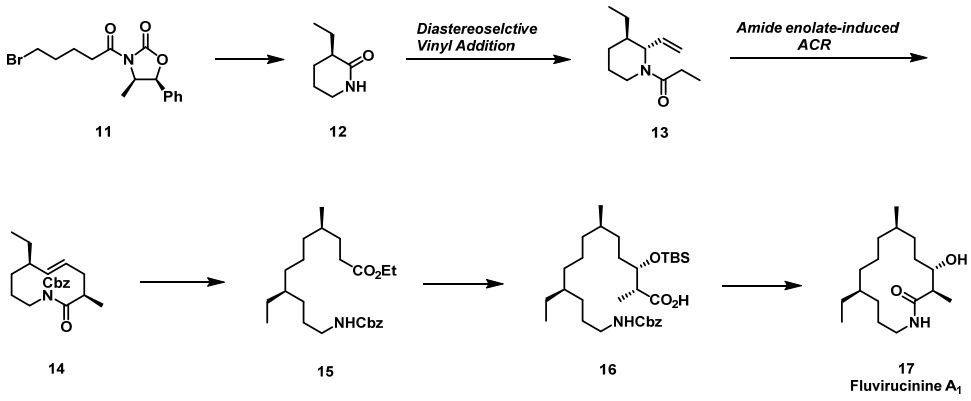
Our group has explored the total synthesis of natural products by the aza-Claisen rearrangement (ACR) since the 1990s. Medium or macro-rings were generated through ring expansion along with controlling the distant stereogenic centers, or a fused heterocycle ring was formed by the subsequent diastereoselective transannulation. To date, we have reported the tremendous and concise synthesis of alkaloids, including benzo[*a*]quinolizidine, indole, indolizidine and macrolactam. [11-18] The syntheses of the fluvirucinine A series exploiting ACR are presented here.

2-1. Synthesis of fluvirucinine A_1[11]

The synthesis was commenced by the preparation of the optically active *trans*-2,3-disubstituted piperidine **13**, as a precursor for the aza-Claisen rearrangement, from 3-

ethylvalerolactam **12**. We developed a direct diastereoselective vinyl addition to the lactam carbonyl group with the assistance of $LiAl(OEt)_3H$. The facile aza-Claisen rearrangement of **13**, induced by an amide enolate, afforded the ring-expanded lactam **14** which possesses the second requisite stereogenic center corresponding to C6 of the target molecule. The lactam **14** was converted into the ester **15** by a three-step sequence: Reduction with DIBAL followed by the direct Wittig olefination of the resulting aldehyde and the subsequent reduction of the olefin with $NaBH_4$. The C2 and C3 chiral units with the requisite configurations were effectively elaborated by reduction, followed by condensation with the boron enolate of propionyloxazolidinone. For the completion of the synthesis, acid **16** was cyclized to furnish fluvirucinine A_1 **17** after desilylation (Fig 2).

Fig 2. Synthesis of fluvirucinine A_1

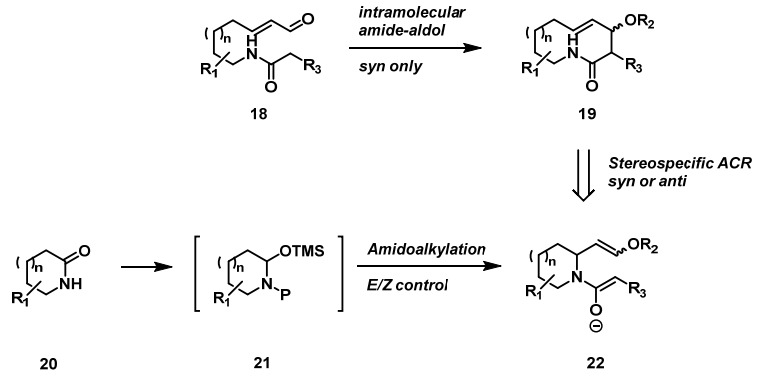


2-2. Synthesis of fluvirucinine A_2[13]

Since we reported the first asymmetric total synthesis of fluvirucinine A_1, we have been interested in iterative ring-expansion strategies as one of the most efficient approaches to the synthesis of macrolactam alkaloids. Direct cyclization approaches to the synthesis of macrocyclic rings are often limited because of entropic considerations, highly dilute

conditions and the lack of functional diversity. The ACR-induced ring expansion offers an opportunity for the rapid assembly of complex alkaloids. However, it has been under emphasized, partly as a result of limited access to the requisite precursors. In particular, the direct ring-expansion of medium-sized lactam precursors **20** via ACR has been limited, primarily because of the susceptibility of their lactam carbonyl to ring-opening during the requisite amidoalkylation. Our ring expansion strategy arises from the facile and diastereoselective amidoalkylation followed by the generation of the geometry-defined enol ether **22** and, finally, the ring expanded products, *β*-alkoxy-*α*-substituted macrolactams **19** of diverse ring sizes *via* the aza-Claisen rearrangement (Fig 3)

Fig 3. Amidoalkylation via *N,O*-acetal

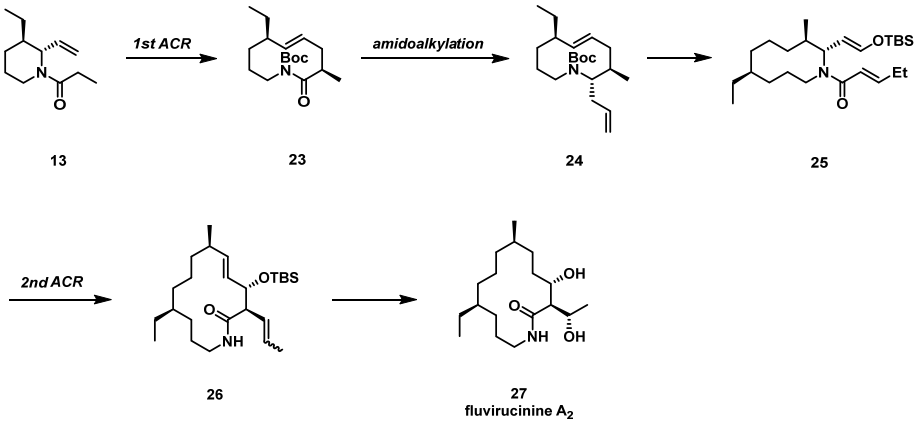


We reported an approach to the synthesis of the *N*-acyliminium ion from *N, O*-acetal TMS ether, which was conveniently prepared from lactam. The *N,O*-acetal TMS ether proved to be an excellent acyliminium ion precursor in terms of convenience of preparation, chemical stability, and functional versatility, in addition to the accessible structural diversity of the cyclic and acyclic *N*-acyliminium ions.

Taking advantage of our protocol *via N, O*-acetal TMS ether, we could provide the requisite allylazacycle **24** (Fig 4). Silylation under mild conditions (TBSCl, DBU, DCM,

reflux) resulted in the highly stereoselective formation of the (*E*)-enol TMS ether **25**. Expecting a chairlike transition state during the second ACR, stereoselective (*E*)-enol ether formation was required to facilitate the introduction of the newly generated stereochemistry at C3 as desired. The vinylogous amide enolate-induced ACR was conducted, followed by the selective olefin cleavage of **26** and the stereoselective Grignard addition, TBS deprotection and hydrogenation of the remaining olefin afforded fluvirucinine A_2 **27**.

Fig 4. Synthesis of Fluvirucinine A_2



3. Reported Synthetic Studies by Other Groups

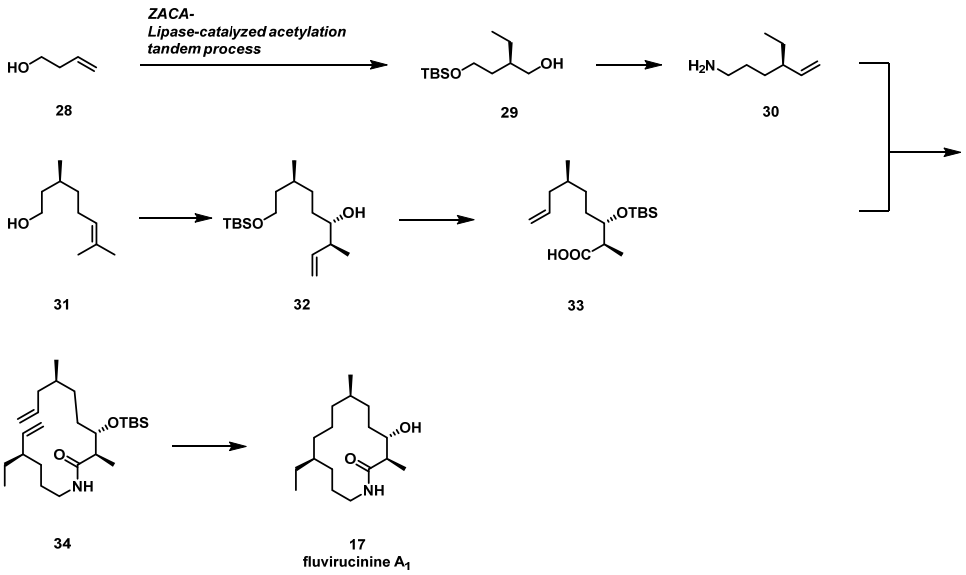
The difficulty of controlling the creation of the distant stereogenic centers of fluvirucins during the total syntheses has drawn the attention of several research groups. So far, four research groups have accomplished the total synthesis of fluvirucin or fluvirucinine including ours. [11, 14, 19-25] The synthesis of the carbohydrate parts has also posed a challenge due to its congested structure, and it has been reported by two synthetic groups: the A. H. Hoveyda group[10] and the S. Davies group.[26] The total synthesis of whole fluvirucin through a glycosylation step with a carbohydrate was reported by A. H. Hoveyda in 1997, the only

report to date. [21]

3-1. Fluvirucin A series

3-2-1. E.-I. Negishi's work [24]

Fig 5. Synthesis of fluvirucinine A_1 by Negishi.



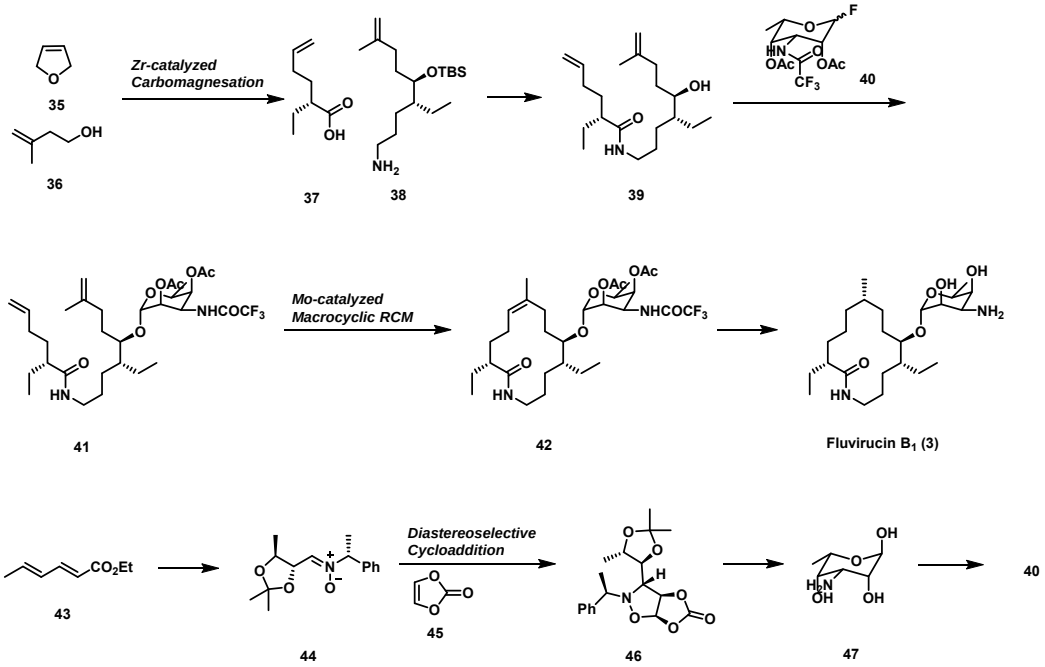
Since the fluvirucin A series was isolated in 1991, the total synthesis of fluvirucinine A_1 was reported only by our group, in the 1990s, as opposed to that of the fluvirucin B series, which has been actively reported. Recently, the Negishi group reported the concise synthesis of fluvirucinine A_1. The synthesis commenced with the conversion of 3-buten-1-ol **28** to 4-TBS-protected (*R*)-2-ethyl-1, 4-butanediol **29** of >98% ee. The reactions into **30** required six well-known steps including cyanation and reduction with the LAH of the nitrile formed. In view of the ready availability of (-)-(*S)-β*-citronellol **31**, its transformation into **32** was performed in nine steps, including the Brown crotylboration and OsO_4-

catalyzed oxidative alkene cleavage with $NaIO_4$ used twice. The conversion of the two key intermediates **30** and **33** into fluvirucinine A_1 **17** was achieved in two steps, RCM and desilylation (Fig 5).

3-2. Fluvirucins B series

3-2-1. A.H. Hoveyda's work [20] [21]

Fig 6. Synthesis of Fluvirucin B_1 by Hoveyda



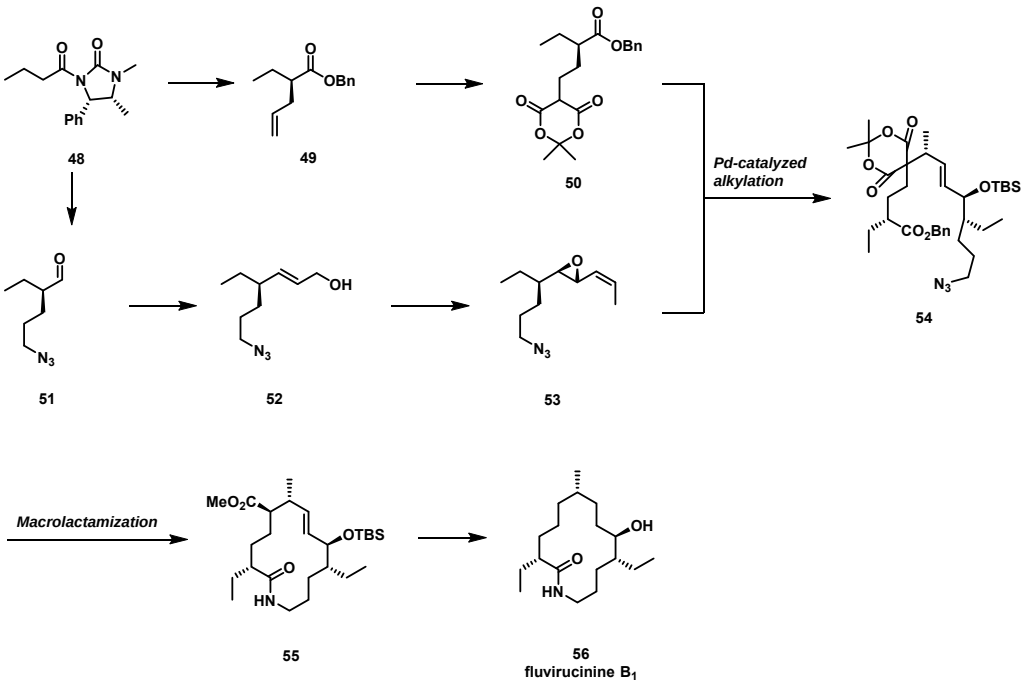
As depicted in Fig 6, the sequence began with the asymmetric catalytic ethylmagnesation of dihydrofuran **35**. The one-pot catalytic hydrovinylation of the terminal alkene and the Ru-catalyzed oxidation of the primary alcohol gave the derived acid **37**. The unsaturated amine **38** was prepared by the conversion of the homoallylic alcohol through a kinetic resolution and Zr-catalyzed asymmetric alkylation. Amine **38** and carboxylic acid **37** were

coupled to afford diene-amide **39**. For the carbohydrate synthesis, the asymmetric dihydroxylation of the commercially available ethyl sorbate **43** followed by acetal protection enable the establishment of the left part of **43**. The ethyl ester of **43** was reduced, ozonolysis provided carboaldehyde, and treatment with *N*-benzylhydroxylamine gave nitrone **44**. The diastereoselective [3+2] cycloaddition with vinylene carbonate **44** gave the cycloadduct **46**. The reduction of the *N-O* bond using Pearlman's catalyst gave the HCl salt of carbohydrate **47**, which was converted into fluoroglycoside **40** by a sequence of methoxy, acetoxy and thiophenyl substitution of acetal accompanied by protection steps. The glycosylation of **39** with fluoroglycoside **40** was carried out and the Mo-catalyzed ring closure, stereocontrolled hydrogenation, and deprotection delivered fluvirucin B_1 **3**.

3-2-2. B. M. Trost's work [22]

The stable imidazolidinone was chosen as the chiral auxiliary. Alkylation was performed to give **49** and **51**. The monosubstituted Meldrum's acid **50** was prepared by the reductive alkylation of the aldehyde produced by ozonolysis from **49** under Knoevenagel conditions. For the azide counterpart, the asymmetric epoxidation of the olefin **52** and the key Pd-catalyzed alkylation of **50** and **53** gave **54** as a single diastereomer. Alkene hydrogenation and hydrogenolysis of the benzyl ester and azide successfully effected macrolactamization. Decarboxylation, hydrogenation and desilylation were subsequently carried out to afford fluvirucinine B_1 **56** (Fig 7).

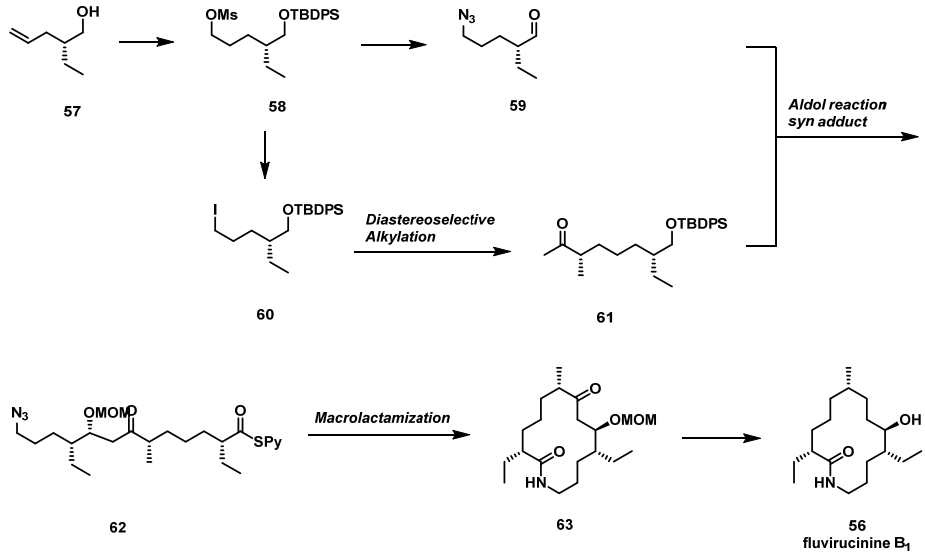
Fig 7. Synthesis of fluvirucinine B_1 by Trost



3-2-3. J. Vilarrasa's work [23, 25]

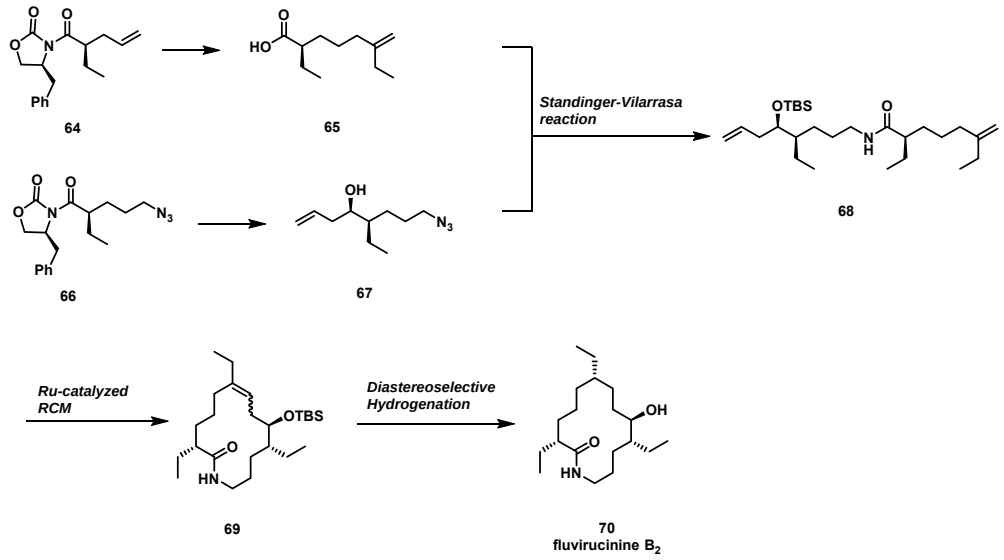
The synthesis of fluvirucinine B_1, reported in 1999, started from the oxazolidinone of Evans et al., which was converted as reported into enantiopure **57**. Hydroboration followed by oxidation, and reaction with MsCl afforded **58**. A fraction of **58** was converted into azide **59**, and the other portion was transformed to iodo derivative **60** by reaction with NaI in acetone. The diastereoselective alkylation of **60** with the *N*-propanoyl derivatives of (-)-pseudoephedrine gave the alkylation product; the addition of MeLi afforded the desired methyl ketone **61**. The boroon enolate of **61** was allowed to react with **59**, and the pure *syn* aldol adduct could be isolated. The protection of the hydroxyl group was accomplished with MOMCl. Cyclization afforded the desired macrolactam **63**. The ketone functionality of **63** was removed by reduction to the corresponding alcohol, followed by radical reduction and MOM deprotection (Fig 8).

Fig 8. Synthesis of fluvirucinine B_1 by Vilarrasa in 1999



The synthesis, announced in 2009, was started from the known oxazolidinone (Fig 9). Cross metathesis with ethyl vinyl ketone, simple catalytic hydrogenation of the double bond, selective methylenation and, finally, removal of the chiral auxiliary gave carboxylic acid **65**. The other fragment was synthesized from azide **66**. The standard reductive removal of the auxiliary, followed by the Swern reaction afforded an aldehyde product that was transferred to the *syn* adduct **67** by treatment with the Leighton reagent. The direct coupling of these two fragment gave amide **68** by using a catalytic variant of the Standinger-Vilarrasa reaction. To generate a macrocycle-embedded trisubstituted double bond, RCM was carried out in the presence of Hoveyda-Grubbs' 2nd initiator to give an *E/Z* isomeric mixture of product **69**, of which both components were smoothly converted to fluvirucinine B_2 **70** by hydrogenation and desilylation.

Fig 9. Synthesis of Fluvirucinine B_2 by Vilarrsa in 2009



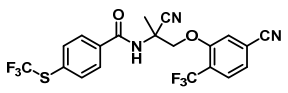
4. 6-Desmethyl-*N*-methylfluvirucin A_1 and *N*-Methylfluvirucin A_1[7, 8]

Recently, a drug-resistant hurdle has emerged in the livestock market. Novartis launched a new anthelmintics, Zolvix® (monopantel, **71**), in 2009 (Fig 10) as a result of this urgent problem. Three new macrolactams, 6-desmethyl-*N*-methylfluvirucin A_1 **8**, *N*-methyl fluvirucin A_1 **9** and fluvirucin B_0 **10**, and two known macrolactams, fluvirucin B_1, B_3, **3, 5**, were isolated by bioassay-guided fractionation as part of the search for new anthelmintics at Merck in 2007 and 2008. 6-Desmethyl-*N*-methylfluvirucin A_1 **8** exhibited *in vitro* activity (EC_{90} 15 ± 5 μg/mL) against *Haemonchus contortus* larvae, and fluvirucin B_0 **10** showed very potent activity (EC_{90} <1.0 μg/mL) along with fluvirucin B_1, B_3 **3, 5** (EC_{90} 1.5, 1.7 μg/mL, respectively). However, these natural compounds were restricted as new anthelmintics because of their modest *in vivo* activity against *Heligmosomoides polygyrus*

in mice. This limitation may be overcome *via* the process of chemical optimization for improving the *in vivo* activity. The syntheses of derivatives can enable the discovery of more powerful compounds as drug candidates.

Although the Hoveyda group reported the entire fluvirucin B_1 synthesis, a medicinal chemical limitation existed in the facile chemical modification in that the glycosylation was carried out before the 14-membered macrolactam framework was constructed. For this demand, we actively directed our efforts to the synthesis of 6-desmethyl-*N*-methylfluvirucin A_1, which could be acquired by glycosylation between the macrolactam aglycone part and the newly reported carbohydrate part. Fluvirucinine, the aglycone part, could be synthesized by our own ring expansion strategy.

Fig 10. New anthelmintics, Zolvix®, by Novartis co.



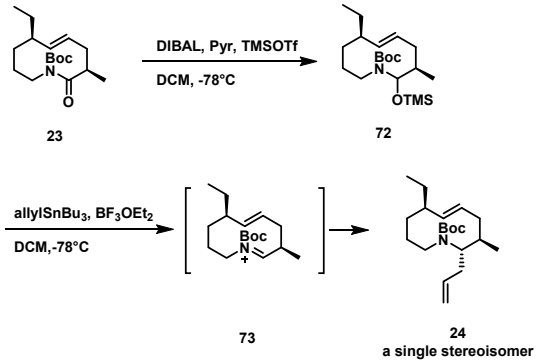
71
Zolvix (monopantel)

II. Results and Discussion

1. Diastereoselective Amidoalkylation Studies

To acquire a macrolactam through ring expansion, the facile protocol of azacyle syntheses was required from carbonyl group of a medium-sized lactam. We developed the diastereoselective amidoalkylation in the synthesis of the fluvirucinine A_2 for this reason, which is depicted in Scheme 1. Under optimized conditions (DIBAL, TMSOTf, pyr, -78℃ and then alkylating reagent, $BF_3{\cdot}OEt_2$, -78℃), the alkylation was performed stereoselectively without aminal generation. Moreover, the allyl group was introduced in the *anti* direction to the adjacent methyl group.

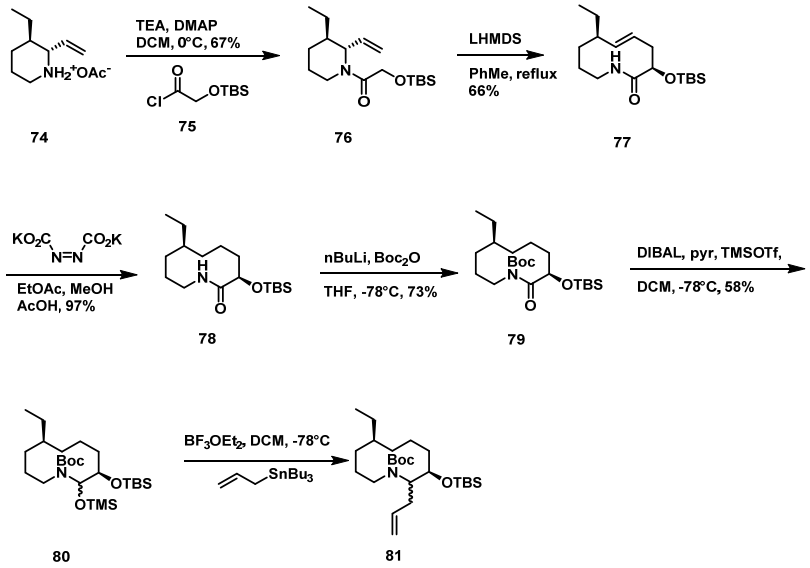
Scheme 1. Amidoalkylation in the synthesis of fluvirucinine A_2



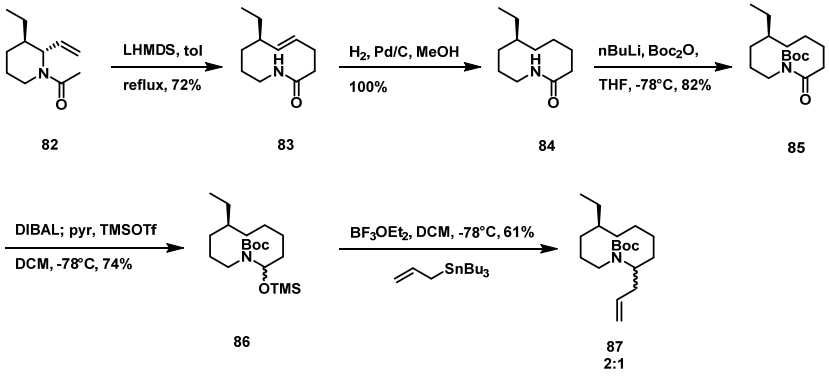
Because a stereogenic center of C6 was missing in 6-desmethyl-*N*-methylfluvirucin A_1, we considered other substituents as a surrogate for the methyl group to control the selectivity of the amidoalkylation. Acetoxy salt **74** was coupled with OTBS acetyl chloride, followed by an aza-Claisen rearrangement to give lactam **77** (Scheme 2). With the ACR product **77**, we carried out diimide hydrogenation, followed by Boc protection and DIBAL reduction directly trapped by TMSOTf to afford *N, O*-acetal TMS ether **80**.

Amidoalkylation was conducted in the treatment of BF_3•OEt_2 and allyltributyltin and gave diastereomeric mixtures of **81** with no stereoselectivity. This result implied that amidoalkylation is not always introduced an alkyl group in the *anti* direction to an adjacent group, but other factors may also be involved.

Scheme 2. OTBS as an auxiliary



Scheme 3. Amidoalkylation without auxiliary



It is known that when one or more double bonds are present in a medium sized ring, a stereoselective reaction is induced by the intrinsic ring strain. Therefore, we decided to conduct an amidoalkylation without an auxiliary. The ACR precursor **82**, prepared as a racemate, was converted into ring-expanded product **83,** which was further transformed to *N, O*-acetal TMS ether **86** by an optimized reaction sequence. Although the amidoalkylation of **86** still displayed a low diastereoselectivity (2:1), a promising result was obtained (Scheme 3).

2. Retrosynthetic Strategy

Fig 11. Retrosynthesis of aglycone

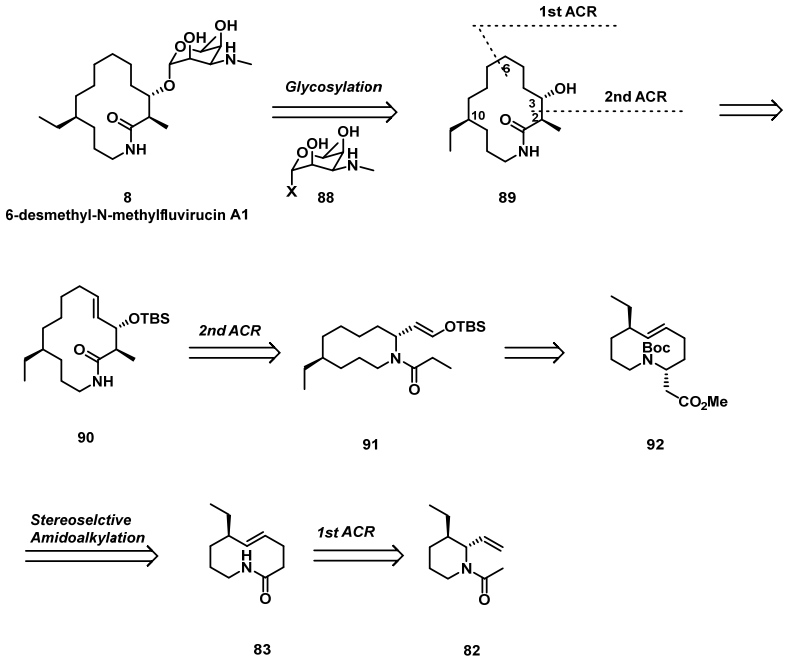
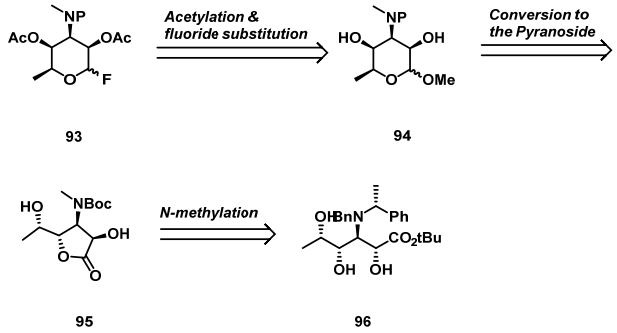


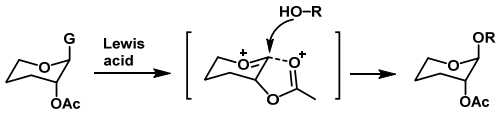
Fig 12. Retrosynthesis of carbohydrate



The retrosynthetic analysis of 6-desmethyl-*N*-methylfluvirucin A_1 **8** is shown in Fig 11 and 12. The final stage of the synthesis would be accomplished by glycosylation between a macrolactam aglycone and a carbohydrate. Our synthetic strategy for the aglycone part has taken full advantage of the previous studies of fluvirucinine A_1 and A_2 syntheses. The stereochemistries of C2 and C3 could be controlled by diastereoselective amidoalkylation of strained the 10-membered lactam and a highly ordered ring expansion *via* an aza-Claisen rearrangement.

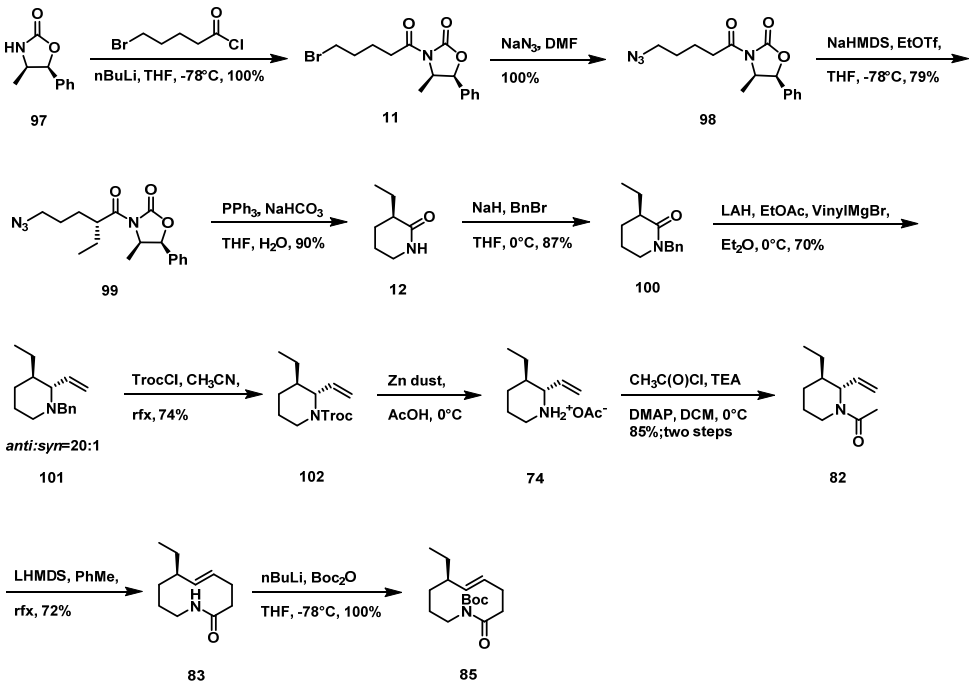
The reactive fluoroglycoside **93** was chosen as a counterpart, refering to Hoveyda's research. The protecting group of the two alcohols was an acetyl group to ensure *α* anomeric selectivity (Fig 13). The pyranoside structure **94** could be transformed from furan **95**. The *N*-methyl group would be introduced by *N*-methylation, and the substrate for **95** would be prepared from the known compound **96**.

Fig 13. *α* anomeric selectivity



3. Aglycone Synthesis: 6-Desmethyl-*N*-methylfluvirucinine A_1

Scheme 4. The first ACR mediated by LHMDS



The synthesis was commenced by the preparation of the optically active *trans*-2, 3-disubstituted piperidine **82** as a precursor for the first ACR from 3-ethylvalerolactam **12** *via* a well-established reaction sequence. The Evans' auxiliary was deprotonated with *n*BuLi and reacted with bromovaleryl chloride to give the corresponding amide **11**, which was converted to the azide **98**. The deprotonation of **98** with NaHMDS followed by the addition of EtOTf gave the desired diastereomer **99**. The six-membered piperidine **12** was constructed from the Staudinger reaction of azide **99**, directly protected with BnBr. The direct diastereoselective vinyl addition was carried out to afford the *trans*-substituted piperidine **101**. The ACR precursor **82** was obtained by debenzylation *via* Troc activation, followed by acetylation of the resulting amine. The facile ACR of **82** in the treatment of LHMDS afforded the ring-expanded lactam **83** as a sole product, possessing (*E*) olefin

geometry (Scheme 4).

From preliminary studies, we believed that the diastereoselective amidoalkylation of the ACR product lactam **89** could be carried out without an auxiliary's help *via* the rigid and one-isomer-favored conformation of the *N*-acyl iminium intermediate in the strained 10-membered ring (Scheme 5).[27] The Boc-protected 10-membered lactam **85** was reduced by DIBAL, and directly trapped by TMSOTf to obtain *N,O*-acetal TMS ether **102**. After the generation of the *N*-acyl iminium ion **103** by the treatment of $BF_3{\cdot}OEt_2$, highly stereoselective amidoalkylation was achieved as we hope to afford methyl ester **92** with separable small amounts of stereoisomer (ratio 10:1). We expect that the (*Z*) isomer would be more favorable, which will be confirmed soon by energy minimization calculation. The *Si* face attack was likely to happen in the case of the (*Z*) isomer of the *N*-acyl iminium intermediate (Fig 14).

Further modification for the preparation of the second ACR precursor was carried out. The hydrogenation of olefin followed by the DIBAL reduction gave aldehyde **105**. In the optimized condition of DBU and TBSCl, (*E*)-selective enol ether **106** was generated, which was transformed to the second ACR precursor **91** by subsequent Boc deprotection and a propionylation reaction. With the ACR precursor **91** available, we executed an aza-Claisen rearrangement *via* a chairlike transition state to establish the desired *anti* stereochemistry. The LHMDS-mediated ACR resulted in a low stereoselectivity of the *anti* product, which was instead mixed with the *syn* adduct in a ratio of 1.1~1.2:1. The low stereoselectivity by the treatment of LHMDS in 10-membered lactam system was also observed in previous studies in the synthesis of fluvirucinine A_2 (Eq 1 and 2, Scheme 6). We understood that both (*E*) and (*Z*) lithium amide enolates was generated in the system of the vinylogous amide groups. The formation of (*E*) enolate could be suppressed by elongating the alkyl chain of amide groups, and the *anti* stereoselectivity was acquired (Eq 3). In the case of an ACR substrate **91**, the outcome of a low stereoselectivity was explained by other factor because it

did not have a vinylogous amide group (Eq 4). Presumably the barrier of the energy level in the ACR substrate **91** became low between the chairlike transition state (TS) and boatlike TS due to the absence of an equatorial methyl group (Fig 15). We performed a trial with *i*PrMgCl, and the *anti* product **90** was obtained with high selectivity (19~21:1). Compared with a lithium amide enolate, the bigger magnesium complex can discriminate the transition state, and a chairlike transition state became more favorable.

Scheme 5. The second ACR mediated by *i*PrMgCl

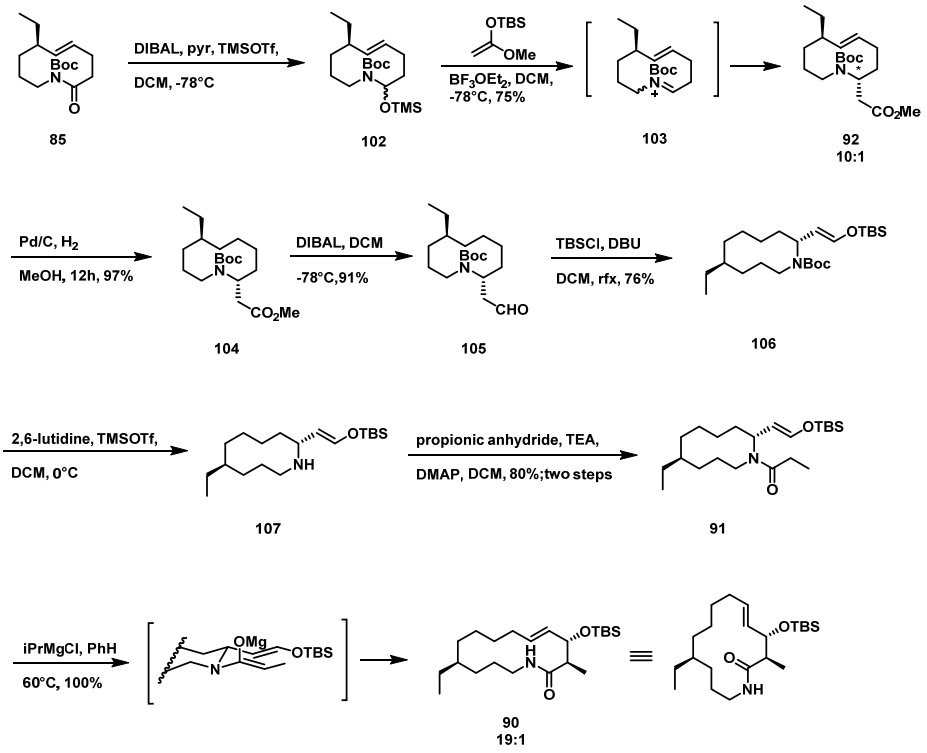
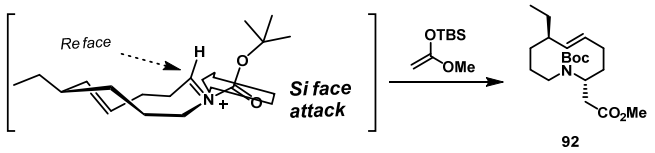


Fig 14. Rationale for asymmetric amidoalkylation



Scheme 6. Previous studies on ACR mediated by LHMDS

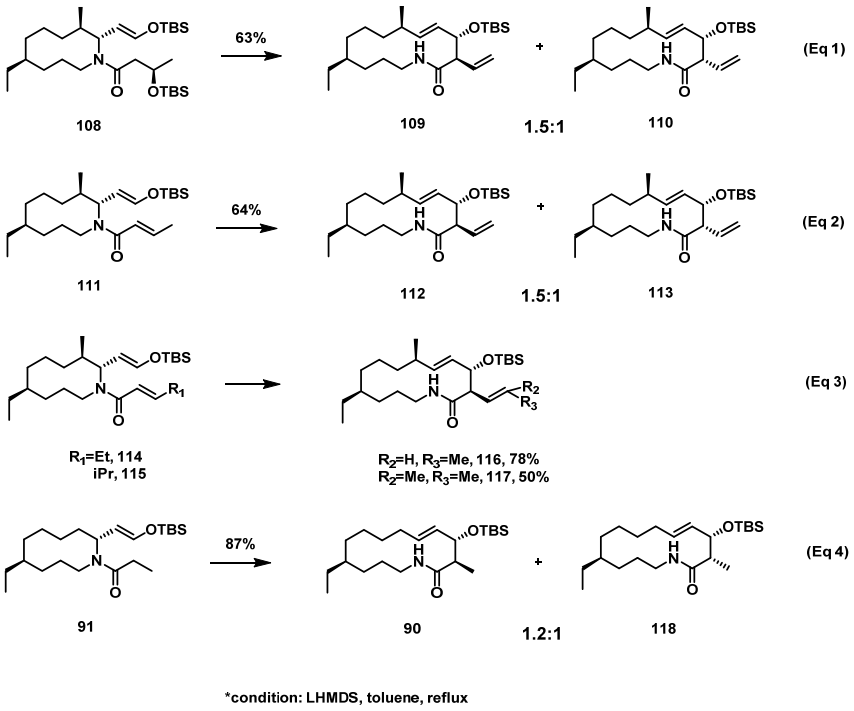
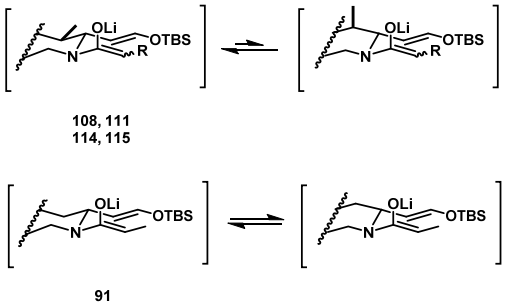


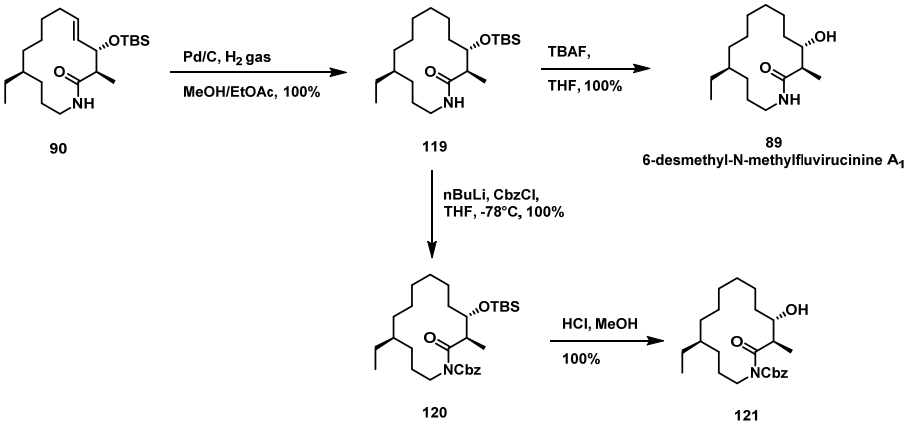
Fig 15. Chairlike vs boatlike TS



After the establishment of the macrolactam ring, the ACR product **90** was hydrogenated under Pd/C and 1 atm of hydrogen gas, and the synthesis of 6-desmethyl-*N*-methylfluvirucinine **89** was completed in high yield by the subsequent desilylation.

However, aglycone **89** was not soluble in aprotic solvents, such as Et_2O or DCM. This drawback was also noted in Hoveyda's report on the synthesis of fluvirucin B_1, so the glycosylation had to be performed with a linear aglycone before the macrolactam ring closure. This approach posed medicinal chemical limitation to the facile chemical modification of fluvirucins and their derivatives. We conducted a trial to improve the solubility of the 14-membered macrolactam and perceived that macrolactams **90** and **119** were methanol-insoluble liquids that were soluble in aprotic solvents, whereas fluvirucinine **89** had an opposite solubility. Inspired by this dramatic change in solubility, the amide protection on fluvirucinine **89** may help the solubility increase in aprotic solvent. Compound **121** was synthesized from the subsequent Cbz protection and desilylation of **1119** and exhibited acceptable solubility in aprotic solvents (Scheme 7).

Scheme 7. Completion of the aglycone synthesis

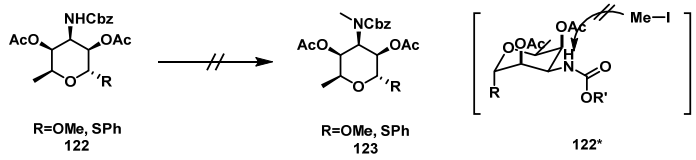


4. Carbohydrate Synthesis: 3,6-Dideoxy-3-methylamino-*L*-talose

After finishing the synthesis of aglycone part and solving the solubility drawback, we focused our efforts on the synthesis of the carbohydrate part, 3, 6-dideoxy-3-methylamino-*L*-talose, for the glycosylation. We basically utilized the synthetic method of 3, 6-dideoxy-3-amino-*L*-talose, which is a methyl-deleted amino sugar of the other fluvirucin series, that was reported by S. Davies. [26]

The initial synthetic studies focused on the induction of the methyl group on the amine. An *N*-methylation trial on pyranoside **122** was first carried out. Due to the steric hindrance of the two adjacent pre-existing OAc groups (see **122***), *N*-methylation did not succeeded under various conditions (Fig 16). We then conducted *N*-methylation before the conversion into pyranoside (Scheme 8). After the silyl protection of the known compound **124**, *N*-methylation was performed. Likely due to the bulkiness of the adjacent silyl alcohols on the lactone ring, the methyl group failed to be connected to the amine.

Fig 16. *N*-methylation trial in the pyranoside



Scheme 8. *N*-methylation trial I

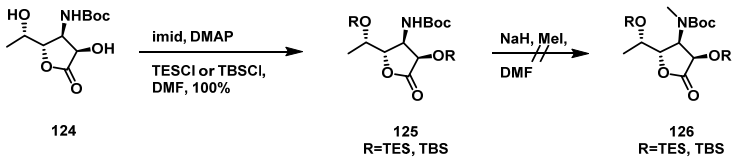
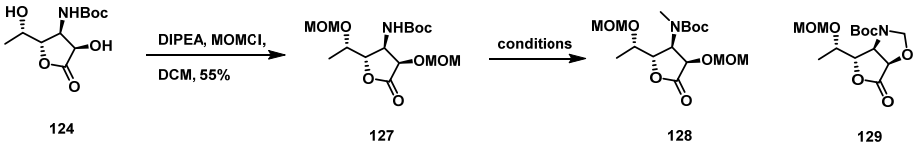


Table 1. *N*-methylation trial II



124 127 128 129

No.	conditions	Result
1	NaH, MeI, DMF	**128, 129**
2	NaH, MeOTf, DMF	No reaction
3	LHMDS, MeOTf, -78℃ to -15℃	No reaction
4	LHMDS, HMPA, MeOTf, -78℃ to -20℃	No reaction

Upon altering the silyl group to a smaller protecting group, MOM, *N*-methylation occurred to give compound **128** in condition of NaH, MeI, and DMF at room temperature (entry 1, Table 1). However, the *N*-methylation had low reproducibility because the amine attacked the MOM group of the vicinal alcohol to form oxazolidine ring **129** in basic conditions.

With a small amount of *N*-methylated product **128** available, a DIBAL reduction was performed to afford hemiacetal **130**, which was transformed under acidic conditions into pyranoside **131** with an unchanged furanoside **132** (0.8:1). Installation of an acetyl group in alcohols of **131**, especially at C2, was important for α anomeric selectivity in glycosylation as depicted above (Fig 13). However, our target carbohydrate, 3, 6-dideoxy-3-methylamino-*L*-talose, had a congested configuration in that all substituents existed in the same direction, with two alcohols lying in the axial position. When the acetylation of **131** was carried out, only the less-hindered alcohol of C2 was protected, leaving the alcohol of C4 naked (Fig 17). Based on the preliminary study that double acetylation smoothly occurred in the absence of the *N*-methyl group, the acetylation at C4 was presumably disturbed by the adjacent axial *N*-methyl group. Although the fluoroglycoside **136** was obtained from compound **133**, the total reaction yield and chemical stability were low

because of the unprotected alcohol. Moreover, we had difficulty in securing proper amounts of sugar for glycosylation (Scheme 9).

Scheme 9. Carbohydrate synthesis I

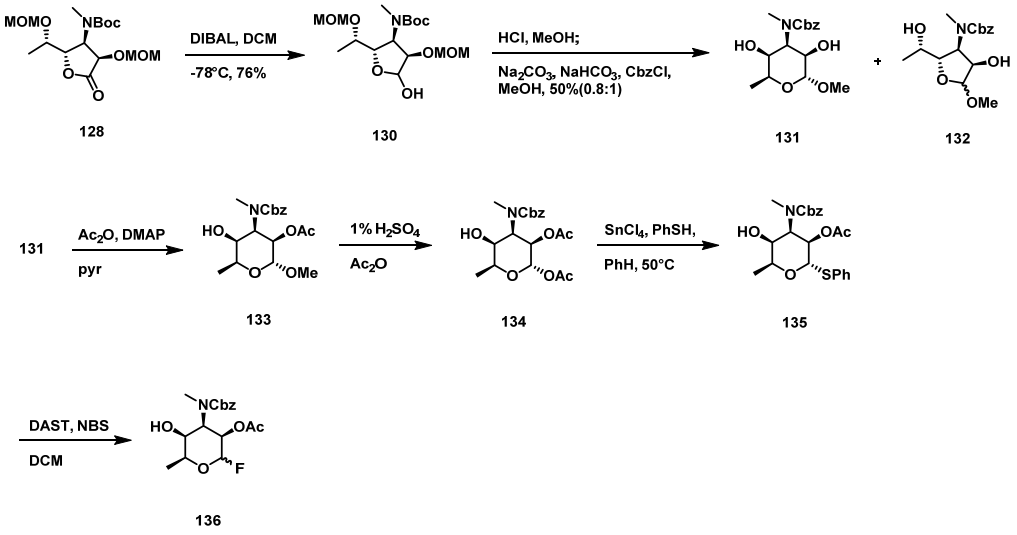
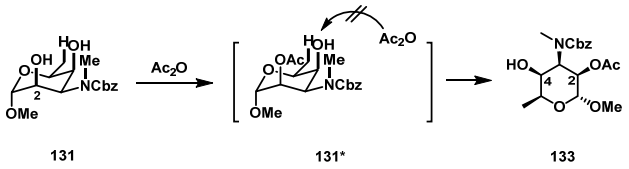


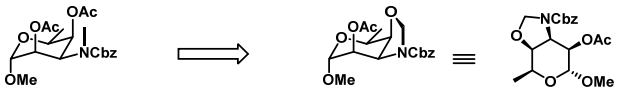
Fig 17. Limitation of acetylation at the alcohol of C4



We then searched for a surrogate of *N*-methylation to breakthrough the intrinsic congestion of the carbohydrate. We initially judged that two OAc groups, the *N*-methyl and *N*-protecting groups on the pyranoside were all required but seemed to be incompatible each other. To relieve this congestion, we designed the oxazolidine-fused pyranoside **137** acting as an alcohol protecting group as well as an *N*-methyl group (Fig 18). For the oxazolidine synthesis, we began with the MOM protection of the known aminoalcohol **138**, followed by the Upjohn dihydroxylation to obtain **140**, which was further converted to the Boc-substituted substrate **141** for oxazolidine ring formation. Under the catalytic PTSA and

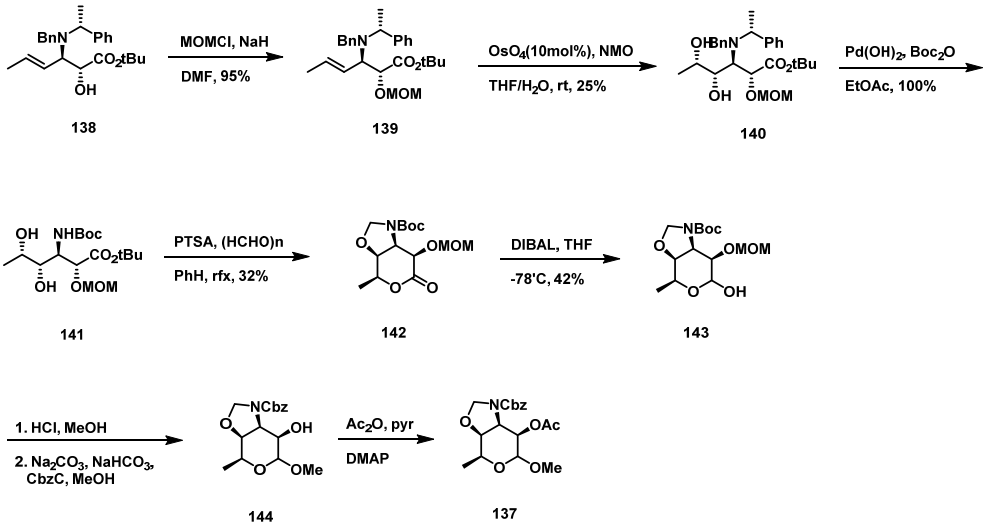
large amount of formaldehyde condition, the oxazolidine ring **142** was produced simultaneously with the 6-membered lactone formation. Without an additional pyranoside transformation step and unwanted furanoside generation, we successfully achieved what we targeted, from the sequence of a well-established procedure. However, the diastereomeric ratio at the dihydroxylation step was not satisfied and the oxazolidine ring formation yield was also low (Scheme 10).

Fig 18. Idea of oxazolidine



137

Scheme 10. Synthesis of oxazilidine-fused carbohydrate I

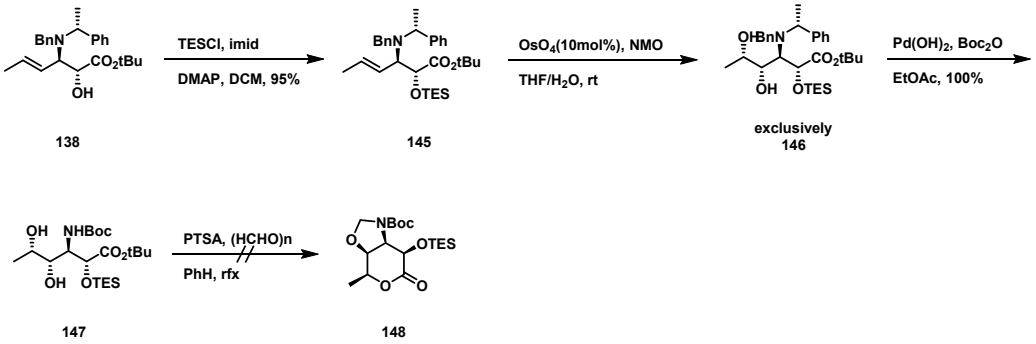


138 139 140 141 142 143 144 137

To increase the diastereomeric ratio at the dihydroxylation step, the MOM group was altered to a proper-sized silyl group, TES (in the case of TBS, the dihydroxylation reaction did not occurred, likely due to steric bulkiness). Although the desired dihydroxyl diastereomer **146** was synthesized exclusively, the oxazolidine ring product **148** was not

formed, but there were multiple unidentified products (Scheme 11).

Scheme 11. Synthesis of oxazolidine-fused carbohydrate II

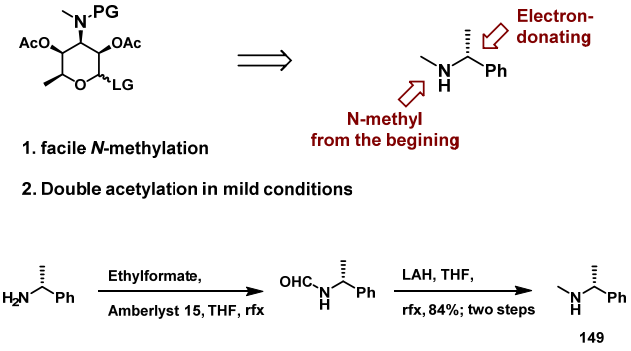


From previous trials and errors, we decided to install the *N*-methyl group from the beginning to avoid the laborious *N*-methylation step, and posed a phenylethyl group to a protecting group on pyranoside (Scheme 12). The phenylethyl group of amine, which was initially used for controlling the enantioselectivity in the aminohydroxylation step, can make the nucleophilicities of vicinal alcohols increase so that double acetylation could occur in mild conditions. Compared with Cbz, a phenylethyl group has more electron donating character.

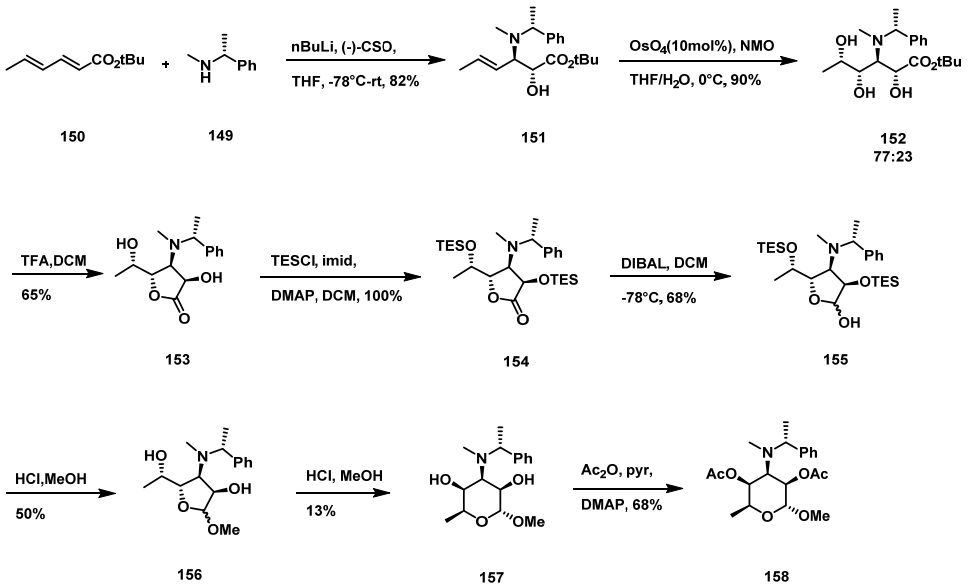
Methylamine **149**, the starting material, was prepared by a two-step sequence in high yield from (*R*)-(+)-1-phenylethylamine and directly used in aminohydroxylation step without the purification of column chromatography. The asymmetric aminohydroxylation of *t*-butyl sorbate **150** and methylamine **149** was performed with Davies' oxaziridine to give *N*-methyl aminoalcohol compound **151**, which was converted into the desired dihydroxylation product **152** under Upjohn condition with an acceptable diastereomeric ratio (77:23) (Scheme 13). The furan ring was spontaneously generated by the treatment of TFA with the detachment of the *t*-butyl group. Because the hemiacetal formation tended to a good result when the two alcohols were protected, a TES (or MOM) protection reaction was performed

to give **154** before DIBAL reduction. However, the pyranoside transformation seemed to be interrupted by the protecting groups. The rate of TES deprotection is presumably slower than that of the methoxy pyranoside transformation. Methoxy furanoside **156** was mainly obtained with trace amounts of methoxy pyranoside **157** (2~6%) in a 0.1~0.4 M HCl methanol solution, and the conversion yield was not satisfactory.

Scheme 12. Breakthrough: (*R*)-*N*-methyl-1-phenylethan-1-amine



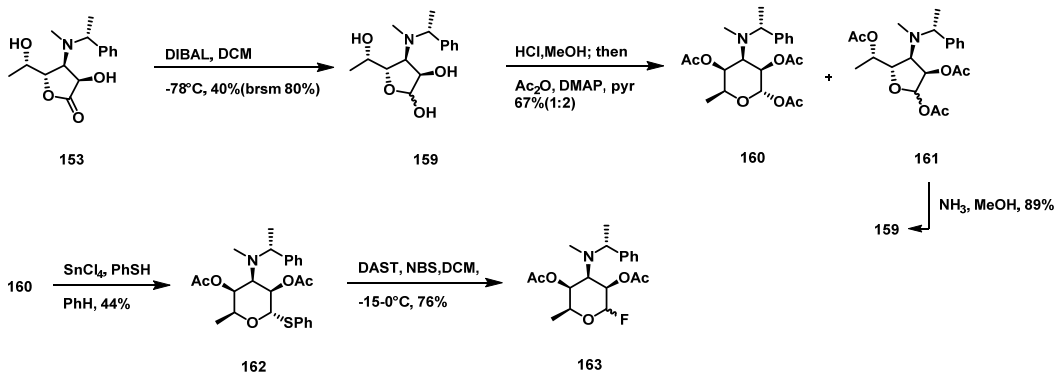
Scheme 13. Carbohydrate synthesis from *N*-methylamine



We then conducted a hemiacetal formation reaction with free alcohols (Scheme 14). Although the yield of the DIBAL reduction was lower than that of **154**, a sufficient result was acquired *via* an optimization process to afford hemiacetal **159**. In the treatment of HCl and MeOH, the hemiacetal **159** was transformed into pyranoside framework and didn't seem to be converted hemiacetal into methoxy group dissimilar to the case of **156**. The reaction mixture was evaporated *in vacuo*, and then directly used in an acetylation reaction.

We then focused on installing the acetyl groups on the two axial alcohols. As we hoped, the acetylation of both the alcohols of C2 and C4 took place smoothly, along with the direct conversion of the hemiacetal into an acetoxy group **160**. Although what we wanted was only a minor product, acetoxy furanoside **161** was recovered to the starting substance **159** in ammonia and methanol. Acetoxyl glycoside **160** was reacted with thiophenol and $SnCl_4$, followed by reaction with DAST and NBS to finally give fluoroglycoside **163**. Compared with fluoroglycoside **136** having one alcohol naked, the chemical stability was much improved. The synthesis of the carbohydrate part was accomplished in seven steps.

Scheme 14. Success of carbohydrate synthesis

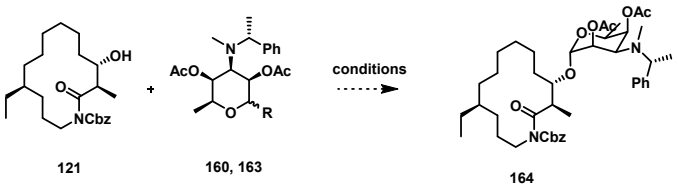


5. Glycosylation Studies

The glycosylation could eventually be attempted with the Cbz-protected aglycone **121** and fluoroglycoside **163** (Table 2). Several trials on glycosylation revealed that the carbohydrate part was smoothly converted into an oxonium ion under treatment by Lewis acids, and seemed to be more stabilized by Et_2O than DCM. The aglycone part, on the other hand, did not have enough reactivity to attack this oxonium ion, presumably due to the steric hindrance derived from the Cbz group. This assumption was supported by the previous study that macrolactam **119** was easily desilylated by TBAF to afford 6-desmethyl-*N*-methylfluvirucinine A_1 **89**. However, the Cbz-protected macrolactam **120** could not be desilylated by TBAF but only by the smaller hydrogen chloride.

We now consider a smaller protecting group of the amide with the solubility in aprotic solvent unchanged. After the glycosylation and deprotection reactions, we hope that the total synthesis of 6-desmethyl-*N*-methylfluvirucine A_1 could be accomplished at an early date.

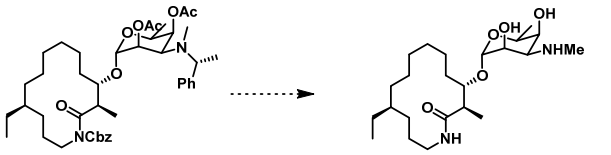
Table 2. Glycosylation study



No.	R	conditions	Solvent	T(℃)	Result
1	F	$SnCl_2$ (1.7), $AgClO_4$ (1.7)	Et_2O	-15	No reaction
2	F	$SnCl_2$ (3), $AgClO_4$ (3)	Et_2O	-15	No reaction
3	F	BF_3OEt_2 (1)	DCM	0	Degradation of **163**
4	F	BF_3OEt_2 (1)	DCM	-78	Partial degradation of **163**
5	OAc	BF_3OEt_2 (3)	DCM	rt	Partial degradation of **160**

All reaction materials were prepared by azeotropic distillation (benzene, 3 times), and flame-dried molecular sieve 4Å was added.

Scheme 15. Completion of the synthesis of 6-desmethyl-*N*-methylfluvirucin A_1



164 6-desmethyl-*N*-methylfluvirucin A_1 (8)

III. Conclusion

We accomplished the synthesis of 6-desmethyl-*N*-methylfluvirucinine A_1 **89** in 13 steps from the known piperidine salt **74** and also prepared an aprotic solvent-soluble glycosylation substrate **121**. The key reactions included a stereoselective amidoalkylation which was carried out in a 10-membered ACR product lactam having the intrinsic ring strain *via* rigid and one-isomer-favored *N*-acyl iminium. The ACR reaction was then conducted to give the desired ring expanded *anti* product **90** in high selectivity. For improving the solubility of aglycone, Cbz group was installed at amide group.

We also completed the synthesis of 3,6-dideoxy-3-methylamino-$_L$-talose as a fluoroglycoside figure. The synthesis of this aminosugar was challenged due to its congested structure in that all substituents lie in the same direction and the methylamine group was attached at carbon 3'. We brought the *N*-methyl group from the beginning to avoid the laborious *N*-methylation. Moreover, when the phenylethyl group was posed to a protecting group on pyranoside, the double acetylation occurred smoothly in a mild condition, which was crucial to the anomeric selectivity and chemical stability.

The glycosylation was eventually attempted with the Cbz-protected aglycone and fluoroglycoside. After glycosylation and deprotection reactions, we hope that the total synthesis of 6-desmethyl-*N*-methylfluvirucine A_1 could be accomplished at an early date.

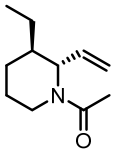
IV. Experimental

General experimental

Unless otherwise described, all commercial reagents and solvents were purchased from commercial suppliers and used without further purification, and all anhydrous reactions were carried out under argon gas (1 atm) in flame or oven-dried glassware. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, triethylamine, were freshly distilled with calcium hydride. Flash column chromatography was carried out using silica-gel 60 (230-400 mesh, Merck) and preparative thin layer chromatography was used with glass-backed silica gel plates (1mm, Merck). Thin layer chromatography was performed to monitor reactions. Optical rotations were measured using a JASCO DIP-2000 digital polarimeter at 20 ℃ using 10 or 100 mm cells of 3 mm diameter. Infrared spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. Mass spectra were obtained using a VG Trio-2 GC-MS instrument, and high resolution mass spectra were obtained using a JEOL JMS-AX 505WA unit. ^{1}H and ^{13}C NMR spectra were recorded on either a JEOL JNM-LA 300 (300MHz), JEOL JNM-GCX (400MHz), BRUKERAMX-500 (500MHz) or JEOL (600MHz) spectrometers. Chemical shifts are provided in parts per million (ppm, δ) downfield from tetramethylsilane (internal standard) with coupling constant in hertz (Hz). Multiplicity is indicated by the following abbreviations: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), quintet (quin), quartet of doublet (qd) multiplet (m) and broad (br). The purity of the compounds was determined by normal phase high performance liquid chromatography (HPLC), (Gilson or Waters, CHIRALPAK® AD-H (4.6 × 250 mm) or CHIRALPAK® OD-H (4.6 × 250 mm))

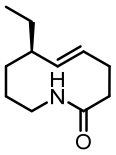
Aglycone part:

1-(2*S*, 3*R*)-3-ethyl-2-vinylpiperidin-1-yl)ethan-1-one (82)



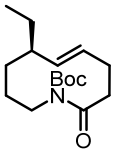
The salt of acetoxy (*2S,3R*)-3-ethyl-2-vinylpiperidin-1-ium (crude, 5 mmol) and DMAP (cat.) were dissolved by DCM (15 ml). To a stirred solution was added TEA (15 mmol, 2 l) followed by an addition of acetyl chloride (7.5 mmol, 0.53 ml) at 0℃. The resultant mixture was allowed to warm to rt and stirred until complete consumption of the starting material on TLC. The reaction mixture was quenched by adding water and diluted with CH_2Cl_2. The aqueous phase was extracted with DCM (3 x 15 ml). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 1 : 2) afforded 770 mg (4.25 mmol, 85%; two steps) of **82**: FT-IR (thin film, neat) *v* max 3477, 2937, 1651,1423, 1267 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.82-5.73 (m, 1H), 5.23-5.19 (m, 1H), 5.07-5.01 (m, 1H), 4.46 (d, 0.5H), 4.18 (s, 0.5H), 3.54 (d, 0.5H), 3.17 (t, 0.5H), 2,64 (t, 0.5H), 2.11(s, 1H), 2.05 (s, 2H), 1.64 (m, 3H), 1.50-1.43 (m, 3H), 1.40-1.28 (m, 1H), 0.94-0.91 (t, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 170.7, 136.9, 115.9, 59.6, 53.5, 42.4, 39.7, 38.7, 37.0, 24.1, 23.2, 21.3, 19.6, 12.2; LR-MS (ESI) *m/z* 182 ($M+H^+$); HR-MS (ESI) calcd for $C_{11}H_{19}NO$ ($M+H^+$) 182.1539; found 182.1524

(*R,E*)-7-ethyl-3,4,7,8,9,10-hexahydroazecin-2(1*H*)-one (83)



LHMDS (1M in toluene, 12.7 ml) was added dropwise to a stirred solution of 46 (4.25 mmol, 770 mg) in toluene (38 ml) at reflux. The reaction mixture was stirred for 1h and then allowed to cool to rt. The reaction mixture was quenched with adding minimum amount of water and filtrated through Celite® followed by concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 1 : 1, 10% DCM) afforded 554 mg (3.06 mmol, 72%) of **83**: FT-IR (thin film, neat) *v* max 3309, 2926, 1645, 1554 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 5.76 (broad s, NH), 5.30-5.25 (m, 1H), 5.02-4.97 (dd, 1H), 3.42-3.37 (m, 1H), 2.77-2.74 (m, 1H), 2.22-2.11 (m, 3H), 1.95 (td, 1H), 1.74-1.70 (m, 2H), 1.59-1.57 (m, 1H), 1.25-1.14 (m, 3H), 1.13-1.06 (m, 1H), 0.69 (t, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 173.0, 138.7, 126.6, 45.8, 40.5, 38.5, 35.7, 29.5, 28.2, 26.7, 11.8; LR-MS (ESI) *m/z* 182 ($M+H^+$); HR-MS (ESI) calcd for $C_{11}H_{19}NO$ ($M+H^+$) 182.1539; found 182.1532

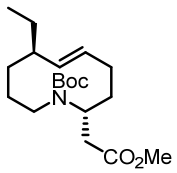
***tert*-butyl (*R,E*)-5-ethyl-10-oxo-3,4,5,8,9,10-hexahydroazecine-1(2*H*)-carboxylate (85)**



To a solution of lactam **83** (554mg, 3.06 mmol) in THF (9ml) was added *n*BuLi (2.5M in hexane, 1.8 ml) at -78℃. After the mixture was stirred for 10min, a solution of Boc_2O (6.1 mmol, 2.8 ml) in THF (3 ml) was added and the mixture was stirred for 2h. The reaction

was quenched with water and the mixture was allowed to warm to rt. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 10ml). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 20) to afford 860 mg (3.06 mmol, 100%) of **85**: FT-IR (thin film, neat) *v* max 1725, 1691, 1369, 1148 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.36-5.26 (m, 1H), 5.01(broad s, 1H), 3.70-3.56 (m, 2H), 3.21 (broad s, 1H), 2.80 (broad s, 1H), 2.80-2.31 (m, 2H), 1.71-1.67 (m, 2H), 1.56 (s, 1H), 1.53 (s, 10H), 1.34-1.22 (m, 3H), 0.80 (t, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 177.5, 153.5, 146.7, 138.9, 85.1, 82.5, 46.3, 39.2, 28.4, 28.1, 12.1; LR-MS (ESI) *m/z* 304 ($M+Na^+$); HR-MS (ESI) calcd for $C_{16}H_{27}NO_3$ ($M+Na^+$) 304.1883; found 304.1867

***tert*-butyl (5*R*,10*R*,*E*)-5-ethyl-10-(2-methoxy-2-oxoethyl)-3,4,5,8,9,10-hexahydroazecine-1(2H)-carboxylate (92)**

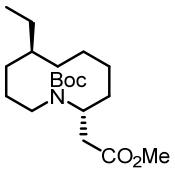


To a solution of lactam **85** (860mg, 3.06 mmol) in DCM (9 ml) was added DIBAL (1.0M in toluene, 5.51 ml) dropwise at -78℃. After the mixture was stirred for 10min, pyridine (15.3 mmol, 1.2 ml) and TMSOTf (7.67 mmol, 1.4 ml) were added. The mixture was stirred for 10min and allowed to warm to 0℃, quenched with satd aqueous Rochelle's soln (2 ml), and diluted with Et_2O. The resultant mixture was warmed to rt and stirred vigorously until two layers were completely separated. The mixture was extracted with Et_2O and combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 20, silica gel deactivated with Et_3N) to afford 870 mg (2.45 mmol, 80%) of

102.

To a solution of *N,O*-acetal TMS ether **102** in DCM (9 ml) were added 1-(*tert*-butyldimethylsilyloxyl)-1-methoxyethane (4.90 mmol, 1.1 ml) and $BF_3 \cdot OEt_2$ (2.7 mmol, 0.33 ml) at -78℃. The resultant mixture was stirred for 30min, and then slowly warmed to 0℃. The reaction mixture was quenched with TEA and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 10) to afford 783 mg (2.31 mmol, 94%) of **92**: FT-IR (thin film, neat) *v* max 2961, 2930, 1740, 1692, 1365, 1171 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.51-5.42 (m, 1H), 5.2-5.13 (m, 1H), 3.71 (m, 0.5H), 3.61 (s, 3H), 3.2 (broad s, 0.5H), 3.11-3.1 (m, 1H), 2.82 (dd, 0.5H), 2.53-2.47 (m, 1H), 2.43-2.37 (m, 0.5H), 2.31-2.26 (m, 1.5H), 2.19 (broad s, 0.5H), 2.08 (broad s, 0.5H), 1.98-1.89 (m, 1.5H), 1.83-1.76 (m, 1H), 1.67-1.62 (m, 1H), 1.45 (s, 4H), 1.422 (s, 2H), 1.39 (s, 5H), 1.36-1.29 (m, 1.5H), 1.27-1.15 (m, 2H), 0.93 (t, 1H), 0.82 (t, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 173.0, 155.0, 134.6, 131.5, 79.6, 78.9, 51.6, 51.4, 48.3, 40.3, 38.5, 35.8, 34.1, 33.5, 28.6, 28.5, 12.5; LR-MS (FAB) *m/z* 340 ($M+H^+$); HR-MS (FAB) calcd for $C_{19}H_{33}NO_4$ ($M+H^+$) 340.2410; found 340.2484

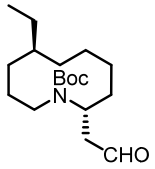
***tert*-butyl (2*R*,7*S*)-7-ethyl-2-(2-methoxy-2-oxoethyl)azecane-1-carboxylate (104)**



A solution of the methylester **92** (783mg, 2.31 mmol) and 10% Pd/C (78.3 mg) in anhydrous MeOH (10 ml) was placed under an atmosphere of hydrogen. After stirring for 19h, the reaction mixture was filtered through Celite® (eluent MeOH) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 10) to afford 764 mg (2.24 mmol, 97%) of **104**: FT-IR (thin film,

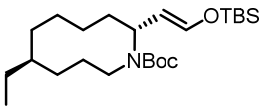
neat) ν max 2924, 1741, 1696, 1171 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 3.75 (broad s, 1H), 3.6 (s, 3H), 3.49 (broad s, 1H), 2.99-2.65 (m, 2H), 2.44-2.40 (m, 1H), 2.06-1.91 (m, 1H), 1.67 (broad s, 2H), 1.41 (s, 15H), 1.30 (s, 2H), 1.25-1.20 (m, 2H), 1.09 (broad s, 2H), 0.81 (t, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 172.6, 155.8, 79.6, 79.1, 51.6, 39.1, 38.5, 36.9, 32.4, 30.1, 28.4, 26.7, 25.8, 22.4, 11.9; LR-MS (FAB) *m/z* 342 ($M+H^+$); HR-MS (FAB) calcd for $C_{19}H_{35}NO_4$ ($M+H^+$) 342.4991; found 342.2644

***tert*-butyl (2*R*,7*S*)-7-ethyl-2-(2-oxoethyl)azecane-1-carboxylate (105)**



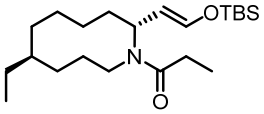
DIBAL (1M in toluene, 2.92 ml) was added dropwise to a stirred solution of **92** (2.24 mmol, 764 mg) in DCM (8 ml) at -78℃. The resultant mixture was stirred for 30min before quenched by the dropwise addition of satd aqueous Rochelle's soln (5 ml). The resultant mixture was diluted with DCM and allowed to warm to rt, and stirred vigorously until two layers were completely separated. The mixture was extracted with DCM and combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 10) to afford 635 mg (2.04 mmol, 91%) of **105**, which was directly used in next reaction because of its unstability.

***tert*-butyl (2*R*,7*S*)-2-((*E*)-2-((tert-butyldimethylsilyl)oxy)vinyl)-7-ethylazecane-1-carboxylate (106)**



To a mixture of aldehyde **105** (63.5 mg, 0.204 mmol), TBSCl (1.02 mmol, 150 mg) in DCM (3 ml) was added DBU (2.04 mmol, 0.3 ml). The resultant mixture was stirred at 40℃ for 1h and concentrated under reduced pressure to 0.5 ml. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 30, silica gel deactivated with Et_3N) to give 70.3 mg (0.16 mmol, 76%) of **106** with unseparable diastereoisomer: FT-IR (thin film, neat) *v* max 2958, 2929, 1695, 1169, 838 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.31 (dd, 1H), 5.10 (d, 1H), 3.64 (m, 1H), 2.85-2.78 (m, 1H), 2.04 (m, 1H), 1.74 (broad s, 1H), 1.66-1.63 (m, 1H), 1.54 (s, 1H), 1.44 (s, 11H), 1.35 (m, 3H), 1.25-1.18 (m, 4H), 1.14 (broad s, 2H), 0.89 (s, 9H), 0.86-0.84 (m, 4H), 0.11 (s, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 156.3, 141.3, 111.9, 79.2, 78.8, 57.2, 36.4, 32.6, 30.0, 28.5, 26.2, 25.7, 25.6, 22.8, 18.4, 11.9, -2.5, -4.7; LR-MS (FAB) *m/z* 426 ($M+H^+$); HR-MS (FAB) calcd for $C_{24}H_{47}NO_3Si$ ($M+H^+$) 426.3403; found 426.3394

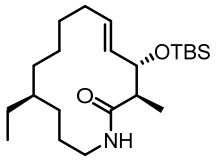
1-((2*R*,7*S*)-2-((*E*)-2-((*tert*-butyldimethylsilyl)oxy)vinyl)-7-ethylazecan-1-yl)propan-1-one (91)



To a solution of (*E*)-enol TBS ether **106** (70.3 mg, 0.16 mmol) in DCM (2 ml) were added 2,6-lutidine (0.64 mmol, 0.07ml) and TMSOTf (0.48 mmol, 0.086 ml) at 0℃. The resultant mixture was stirred for 30 min and then quenched by the dropwise addition of MeOH. The reaction mixture was allowed to warm to rt and concentrated *in vacuo*. The crude of **107** and DMAP (cat.) were dissolved in DCM (2 ml), which was treated with TEA (0.48 mmol,

0.07 ml) and propionic anhydride (0.32 mmol, 0.04 ml). The resultant mixture was stirred for 1h at ambient temperature and concentrated under reduced pressure to 0.5 ml. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 10, silica gel deactivated with Et_3N) to give 46.6 mg (0.13 mmol, 80%) of **91**: FT-IR (thin film, neat) *v* max 2956, 2930, 1652, 839 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.31 (d, 1H), 6.22 (d, 1H), 5.23 (broad s, 1H), 4.93 (dd, 1H), 4.13 (t, 1H), 3.49-3.37 (m, 2H), 3.08-2.92 (m, 2H), 2.38-2.27 (m, 2H), 2.24 (qd, 3H), 2.03 (m, 1H), 1.89-1.86 (m, 1H), 1.75 (broad s, 1H), 1.65-1.55 (m, 2H), 1.49-1.47 (m, 1H), 1.39 (m, 1H), 1.26-1.13(m, 2H), 1.11-1.06 (m, 2H), 0.85 (s, 9H), 0.82 (t, 3H), 0.07 (s, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 175.0, 141.7, 111.6, 56.6, 56.1, 37.4, 31.63, 29.7, 27.8, 27.4, 25.6, 25.5, 23.3, 18.3, 11.9, 9.4, -5.3; LR-MS (FAB) *m/z* 382 ($M+H^+$); HR-MS (FAB) calcd for $C_{22}H_{43}NO_2Si$ ($M+H^+$) 382.3141; found 382.3139

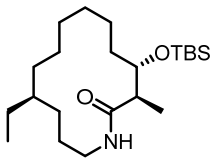
(3*R*,4*S*,11*S*,*E*)-4-((*tert*-butyldimethylsilyl)oxy)-11-ethyl-3-methylazacyclotetradec-5-en-2-one (90)



To a solution of silyl enol ether **91** (46.6 mg, 0.13 mmol) in benzene (3 ml) was added dropwise *i*PrMgCl (1.0M solution in hexane, 0.5 ml) at 60℃ and resulting solution was heated for 40 min. After addition of water, the solvent was evaporated and the residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 10) to give 46.6 mg (0.13 mmol, 95%) of **90** as a white solid: FT-IR (thin film, neat) *v* max 3279, 2928, 1638, 775cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.25 (s, NH), 5.59-5.54 (m, 1H), 5.37 (dd, 1H), 4.18 (t, 1H), 3.89-3.83 (m, 1H), 2.51 (tt, 1H), 2.27 (quintet, 1H), 2.01 (m, 2H), 1.56 (s, 1H), 1.48-1.38 (m, 2H), 1.36-1.20 (m, 8H), 1.17 (d, 3H), 1.07-0.99 (m, 2H), 0.89 (s, 9H),

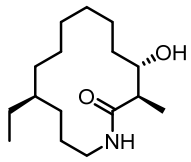
0.83 (t, 3H), 0.06 (s, 3H), 0.02 (s,3H);^{13}C-NMR ($CDCl_3$, 125 MHz) δ 173.9, 131.8, 130.7, 75.0, 48.4, 39.4, 37.7, 31.0, 30.9, 27.2, 27.1, 26.4, 25.9, 23.8, 23.6, 18.1, 15.1, 12.0, -4.3, -4.9; LR-MS (FAB) *m/z* 382 ($M+H^+$); HR-MS (FAB) calcd for $C_{22}H_{43}NO_2Si$ ($M+H^+$) 382.3141; found 382.3140

(3*R*,4*S*,11*S*)-4-((*tert*-butyldimethylsilyl)oxy)-11-ethyl-3-methylazacyclotetradecan-2-one (119)



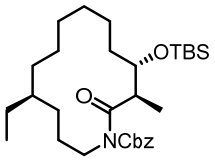
A solution of the macrolactam **90** (46.6mg, 0.13 mmol) and 10% Pd/C (4.7 mg) in anhydrous MeOH and EtOAc (2 ml, 1:1) was placed under an atmosphere of hydrogen. After stirring for 12h, the reaction mixture was filtered through Celite® (eluent EtOAc) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 15) to afford 49.8 mg (0.13 mmol, 100%) of **119**: FT-IR (thin film, neat) ν max 3285, 2957, 2931, 2857, 1637, 773 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.52 (d, NH), 3.99-3.88 (m, 1H), 3.75 (td, 1H), 2.58-2.52 (m, 1H), 2.40 (qiuntet, 1H), 1.70 (s, 1H), 1.54-1.23 (m, 18H), 1.09 (d, 3H), 0.89 (s, 3H), 0.83 (t, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 174.1, 74.7, 46.2, 38.9, 38.8, 31.3, 30.8, 27.6, 27.0, 26.8, 26.0, 25.9, 24.4, 23.6, 21.1, 18.0, 14.8, 11.8, -4.6, -4.6

6-desmethyl-*N*-methylfluvirucinine (89)



To a solution of lactam **119** (50 mg, 0.13 mmol) in THF (1 ml) was added TBAF (1.0M solution in THF, 0.16 ml) and the reaction mixture was stirred at rt for 1h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 1, 2% MeOH) to afford 35 mg (0.13 mmol, 100%) of **89**: FT-IR (thin film, neat) *v* max 3388, 3305, 1637, 789 cm^{-1}; ^{1}H-NMR (MeOD, 500 MHz) δ 4.58 (s, NH), 3.68-3.62 (m, 2H), 2.69 (qd, 1H), 2.37-2.31(m, 1H), 1.62-1.52 (m, 2H), 1.50-1.45 (m, 4H), 1.43-1.41 (m, 4H), 1.39-1.32 (m, 3H), 1.30-1.26 (m, 2H), 1.24-1.10 (m, 4H), 1.17 (d, 3H), 0.86 (t, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 178.7, 74.6, 48.8, 40.3, 38.5, 35.3, 32.6, 29.8, 28.9, 28.7, 27.8, 27.5, 24.2, 22.7, 16.8, 12.7; LR-MS (ESI) *m/z* 270 ($M+H^+$); HR-MS (ESI) calcd for $C_{16}H_{31}NO_2$ ($M+H^+$) 270.2426; found 270.2426

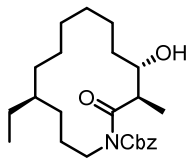
benzyl (3*R*,4*S*,11*S*)-4-((*tert*-butyldimethylsilyl)oxy)-11-ethyl-3-methyl-2-oxoazacyclotetradecane-1-carboxylate (120)



To a solution of lactam **119** (0.14 mmol, 54 mg) in THF (3 ml) was added *n*BuLi (1.6M in hexane, 0.1 ml) at -78℃. After the mixture was stirred for 10min, CbzCl (0.168 mmol, 0.02 ml) was added and the mixture was stirred for 2h. The reaction mixture was quenched by

adding water, and allowed to warm to rt. The mixture was extracted with EtOAc (3x40 ml) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification via flash column chromatography (EtOAc:Hexane=1:40) gave 72 mg (0.14 mmol, 100%) of **120**: FT-IR (thin film, neat) *v* max 2931, 1735, 1160, 774 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.37-7.32 (m, 5H), 5.23 (d, 2H), 4.09 (dt, 1H), 4.00 (dt, 1H), 3.75-3.72 (m, 1H), 3.53 (t, 1H), 1.54 (s, 4H), 1.44-1.35 (m, 3H), 1.31-1.20 (m, 9H), 1.17 (d, 3H), 1.14-1.09 (m, 3H), 0.87 (s, 9H), 0.80 (t, 3H), 0.03 (d, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 178.5, 154.8, 135.1, 128.7, 128.6, 74.3, 68.6, 45.0, 44.3, 38.0, 33.1, 31.3, 27.0, 26.4, 26.0, 25.9, 22.9, 22.3, 18.7, 18.1, 17.1, 12.0, -4.2, -4.6

benzyl (3*R*,4*S*,11*S*)-11-ethyl-4-hydroxy-3-methyl-2-oxoazacyclotetradecane-1-carboxylate (121)

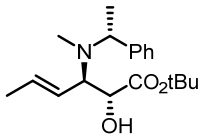


To a solution of lactam **120** (72 mg, 0.14 mmol) in MeOH:DCM (1.5 ml, 2:1) was added 1.25M HCl (0.25 ml) and the reaction mixture was stirred at rt for 2h 30min. The reaction mixture was quenched by adding satd aqueous $NaHCO_3$ soln, and extracted with DCM (3x3 ml) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification via flash column chromatography (EtOAc:Hexane=1:4) gave 56 mg (0.14 mmol, 100%) of **121**: FT-IR (thin film, neat) *v* max 2930, 1731, 1688, 1363, 1174 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.37-7.32 (m, 5H), 5.30-5.14 (m, 2H), 4.11 (dq, 1H), 3.89-3.80 (m, 1H), 3.68-3.59 (m, 1H), 3.56-3.49 (m, 1H), 1.86-1.79 (m, 1H), 1.65 (s, OH), 1.65-1.45 (m, 2H), 1.40-1.28 (m, 6H), 1.26-1.20 (m, 4H), 1.24 (d, 3H), 1.18-1.13 (m, 2H), 1.12-1.07 (m, 3H), 1.03-0.95 (m, 1H), 0.79 (t, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ

179.1, 154.9, 135.0, 128.7, 128.6, 128.4, 74.3, 68.6, 45.6, 44.4, 37.9, 33.3, 31.4, 27.7, 26.8, 26.1, 25.9, 24.2, 23.4, 21.5, 14.9, 11.6

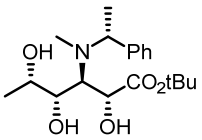
Carbohydrate part:

***tert*-butyl (2*R*,3*R*,*E*)-2-hydroxy-3-(methyl((*R*)-1-phenylethyl)amino)hex-4-enoate (151)**



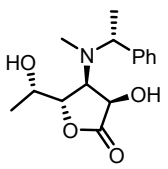
*n*BuLi (2.5M in hexane, 24 ml) was added dropwise to a stirred solution of (*R)-N*-methyl-*N-(α*-methylbenzyl)amine **149** (20 mmol, 2.7 g) in THF (50 ml) at -78℃. After stirring for 1h 30min, a solution of *tert*-butyl sorbate **150** (21 mmol, 3.53 g) in THF (21 ml) at -78℃ was cannulated. The reaction mixture was stirred for a further 1h, before the addition of (-)-CSO (24 mmol, 5g). The resultant mixture was allowed to warm to rt and heated to 40℃ over 12h. The reaction mixture was quenched with water and then aqueous phase was extracted with EtOAc. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification via flash column chromatography (EtOAc:Hexane=1:5) gave 3.96 g (12.4 mmol, 62%) of **151**: FT-IR (thin film, neat) *v* max 2975, 1726, 1366, 1169, 1152 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.3-7.13(m, 5H), 5.58-5.54 (m, 2H), 4.26 (d, 1H), 3.9 (q, 1H), 3.34 (dd, 1H), 2.09 (s, 3H), 1.63 (d, 3H), 1.37 (s, 9H), 1.24 (d, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 171.7, 143.7, 129.3, 127.4, 126.7, 125.9, 125.1, 80.5, 70.9, 64.8, 59.0, 33.1, 27.2, 17.2, 15.8; LR-MS (FAB) *m/z* 320 ($M+H^+$); HR-MS (FAB) calcd for $C_{19}H_{29}NO_3$ ($M+H^+$) 320.2226; found 320.2223

***tert*-butyl *(2R,3R,4S,5S)*-2,4,5-trihydroxy-3-(methyl*((R)*-1-phenylethyl)amino)hexanoate (152)**



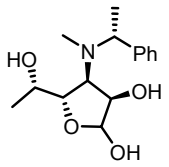
OsO4 (0.1M in toluene, 12.4 ml) was added to a stirred solution of **151** (3.96g, 12.4 mmol) in THF: H_2O (40ml, 2.5:1), followed by addition of NMO (49.6 mmol, 5.8 g) at 0℃. The resultant mixture was stirred at 0℃ for 12h. Satd aqueous Na_2SO_3 (40 ml) was then added and the reaction mixture was left to stir at rt for a further 1h. The mixture was extracted with EtOAc (3x40 ml) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification via flash column chromatography (EtOAc:Hexane=1:2) gave a separable 77: 23 mixture of **152** and its diastereomer respectively (3.9 g, 90%): FT-IR (thin film, neat) *v* max 3460, 2977, 1728, 1163 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.33-7.29 (m, 4H), 7.26-7.23 (m, 1H), 4.32 (s, OH), 4.03 (qd, 1H)m 3.83 (t, 1H), 3.64 (q, 1H), 3.26 (s, OH), 3.14 (d, 1H), 2.42 (s, 3H), 1.78 (d, 1H), 1.4 (d, 3H), 1.39 (s, 9H), 0.99 (d, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 174.6, 144.8, 128.6, 127.9, 127.5, 82.6, 70.2, 67.5, 66.8, 62.5, 34.9, 28.0, 20.9, 18.3; LR-MS (FAB) *m/z* 354 ($M+H^+$); HR-MS (FAB) calcd for $C_{19}H_{31}NO_5$ ($M+H^+$) 354.2280; found 354.2287

***(3R,4S,5S)*-3-hydroxy-5-*((S)*-1-hydroxyethyl)-4-(methyl*((R)*-1-phenylethyl)amino)dihydrofuran-2(3H)-one (153)**



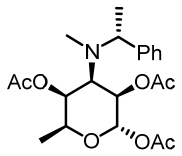
To a solution of triol **152** (3g, 8.5 mmol) in DCM (28 ml) was added TFA (2.8 ml) dropwise. The resultant mixture was stirred for 16h and neutralised by aqueous $NaHCO_3$ solution. The mixture was extracted with DCM (3x30 ml) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification via flash column chromatography (EtOAc:Hexane=1:1) gave 1.5 g (5.5 mmol, 65%) of **153**: FT-IR (thin film, neat) *v* max 3429, 1772, 772 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.31-7.28 (m, 2H), 7.26-7.22 (m, 3H), 4.38 (d, 1H), 3.91 (q, 1H), 3.78-3.75 (m, 2H), 3.66-3.65 (m, 1H), 2.17 (s, 3H), 1.40 (d, 3H), 1.07 (d, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 177.8, 141.3, 128.5, 127.7, 127.3, 81.4, 67.9, 64.6, 63.3, 31.1, 31.1, 19.4, 18.4; LR-MS (FAB) *m/z* 280 ($M+H^+$); HR-MS (FAB) calcd for $C_{15}H_{21}NO_4$ ($M+H^+$) 280.1549; found 280.1551

***(3R,4S,5S)*-5-((*S*)-1-hydroxyethyl)-4-(methyl((*R*)-1-phenylethyl)amino)tetrahydrofuran-2,3-diol (159)**



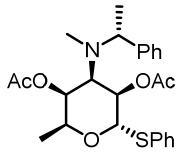
To a solution of lactone **153** (1.5g, 5.5 mmol) in DCM (91 ml) was added DIBAL (1.0M in toluene, 18 ml) dropwise at -78℃. The resultant mixture was stirred for 30min, and quenched by subsequent addtion of MeOH (12 ml) and satd aquoues Rochelle's solution (6 ml). The reaction mixture was allowed to warm to rt and stirred for 16h before being filtered through Celite® (eluent DCM). The filtrate was concentrated under reduced pressure. the residue was purified by flash column chromatography on silica gel (DCM : MeOH = 20: 1) to afford 618 mg (2.2 mmol, 40%(brsm 80%)) of **159**: LR-MS (FAB) *m/z* 282 ($M+H^+$); HR-MS (FAB) calcd for $C_{15}H_{23}NO_4$ ($M+H^+$) 282.1705; found 282.1703

***(2S,3R,4R,5S,6S)*-6-methyl-4-(methyl*((R)*-1-phenylethyl)amino)tetrahydro-2*H*-pyran-2,3,5-triyl triacetate (160)**



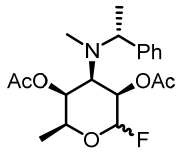
To a stirred solution of lactol **159** (618 mg, 2.2 mmol) in MeOH (20 ml) was added 1.25M HCl (4 ml) dropwise. The resultant mixture was stirred for 16h and concentrated *in vacuo*. The crude resultant and DMAP (cat.) were dissolved in pyridine: Ac_2O (1:1, 8 ml) and stirred for 24h. The reaction mixture was diluted with DCM and quenched by the addition of satd aqueous $CuSO_4$ solution (5 ml). The mixture was extracted with DCM (3x5 ml). The combined organic extracts were washed with satd $NaHCO_3$ soln and dried over $MgSO_4$, followed by concentration under reduced pressure. Purification via flash column chromatography (EtOAc:Hexane=1:4) allowed separation of **160** from furanoside **161** (200 mg, 67%, 1:2): FT-IR (thin film, neat) *v* max 1743, 1220, 772 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.31-7.19 (m, 5H), 5.93 (s, 1H), 5.18 (d, 1H), 4.89-4.83 (m, 1H), 4.16 (dd, 1H), 3.70 (q, 1H), 3.41 (dd, 1H), 2.39 (s, 3H), 2.08 (s, 3H), 1.93 (s, 3H), 1.88 (s, 3H), 1.34 (d, 3H), 1.23 (d, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 170.1, 169.8, 169.3, 144.3, 128.5, 127.3, 127.2, 98.6, 81.1, 76.2, 69.3, 63.1, 60.1, 34.1, 21.2, 21.0, 20.4, 16.8; LR-MS (FAB) *m/z* 408 ($M+H^+$); HR-MS (FAB) calcd for $C_{21}H_{29}NO_7$ ($M+H^+$) 408.2022; found 408.2038.

***(2S,3S,4R,5R,6S)-2*-methyl-4-(methyl((*R*)-1-phenylethyl)amino)-6-(phenylthio)tetrahydro-2H-pyran-3,5-diyl diacetate (162)**



To a benzene solution (7 ml) of triacetate glycoside **160** (200 mg, 0.49 mmol) was added PhSH (2.45 mmol, 0.25 ml), followed by $SnCl_4$ (1M in DCM, 0.73 ml). The resulting mixture was moved to the preheated bath (50℃) and stirred for 30 min. The reaction was quenched by the addition of a 14 ml of aqueous $NaHCO_3$, and diluted with DCM. Organic and aqueous layers were separated and the aqueous layer was washed with DCM (3x 20 ml portions). The combined organic layers were dried over anhydrous MgSO4, filtered and evaporated under reduced pressure. Purification via flash column chromatography (EtOAc:Hexane=1:5) afforded **162** (98mg, 44%): ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.49-7.44 (m, 2H), 7.31-7.21 (m, 8H), 5.25-5.24 (d, 1H), 5.21-5.19 (m, 1H), 4.86 (qd, 1H), 4.10 (dd, 1H), 3.67 (q, 1H), 3.55-3.52 (m, 1H), 2.36 (s, 3H), 2.06 (s, 3H), 1.93 (s, 3H), 1.32 (d, 3H), 1.27 (d, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.3, 169.8, 143.9, 133.7, 132.4, 128.8, 128.5, 127.5, 127.2, 90.4, 80.8, 77.8, 69.3, 63.1, 60.4, 33.9, 21.3, 21.2, 20.5, 16.8.

***(3R,4R,5S,6S)*-2-fluoro-6-methyl-4-(methyl((*R*)-1-phenylethyl)amino)tetrahydro-*2H*-pyran-3,5-diyl diacetate (163)**



Thioglycoside **162** (29 mg, 0.06 mmol) was dried through azeotropic distillation in benzene (3x 3 ml) and then dissloved in DCM (1 ml). The resulting solution was treated with DAST (0.08 mmol, 0.01 ml) at -15℃ and stirred for 2 min. NBS (0.09 mmol, 17 mg) was added and the reaction mixture was stirred for 1h at -15℃, and then for 2h at 0℃. The reaction mixture was quenched by addition of satd aqueous $NaHCO_3$ soln. The mixture was extracted with DCM (3x3 ml) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification via flash column chromatography

(EtOAc:Hexane=1:5) gave 16..5 mg (0.045 mmol, 71%) of **163** as mixture of anomers: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.30-7.18 (m, 5H), 5.91(d, 0.5H), 5.69 (d, 0.5H), 4.89-4.73 (m, 2H), 4.14 (dd, 1H), 3.79 (q, 1H), 3.33 (q, 1H), 2.52 (s, 3H), 2.15 (s, 3H), 1.83 (s, 3H), 1.33 (d, 3H), 1.23 (d, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.0, 169.9, 144.8, 128.6, 127.2, 127.2, 108.7, 106.9, 81.8, 73.8, 73.6, 69.2, 63.2, 56.9, 34.1, 21.5, 21.0, 20.8, 16.4, 1.1.

V. References

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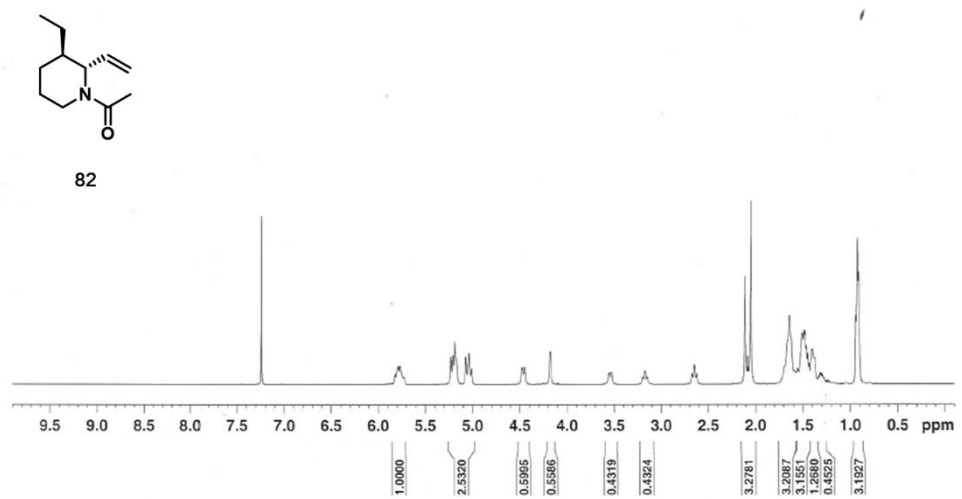
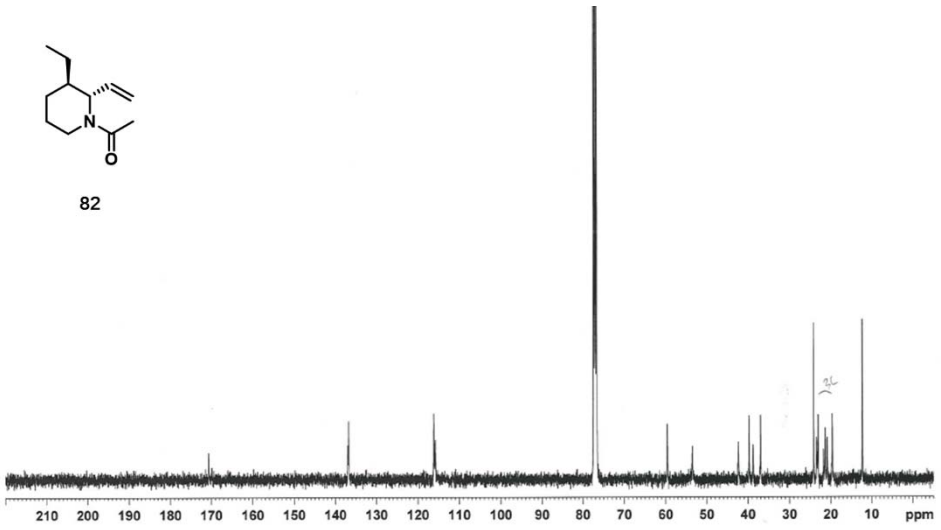
VI. Appendix

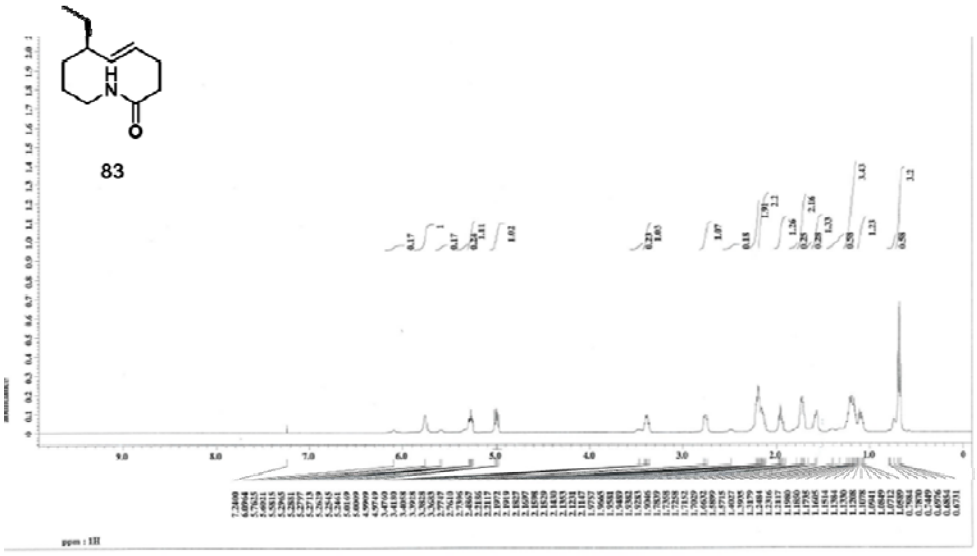
▼ ^{1}H-NMR ($CDCl_3$, 500 MHz)



▼ ^{13}C-NMR ($CDCl_3$, 100 MHz)



▼ ^{1}H-NMR ($CDCl_3$, 600 MHz)



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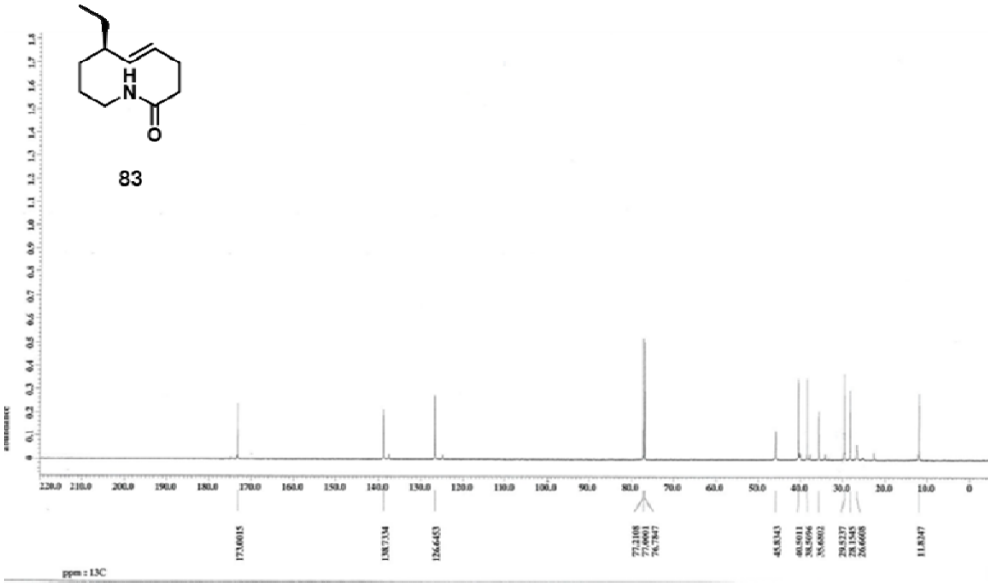

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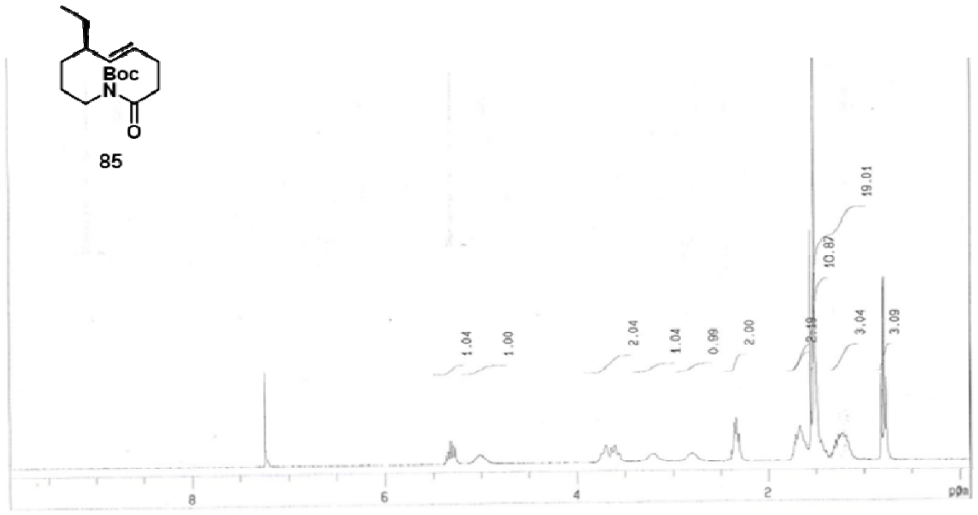

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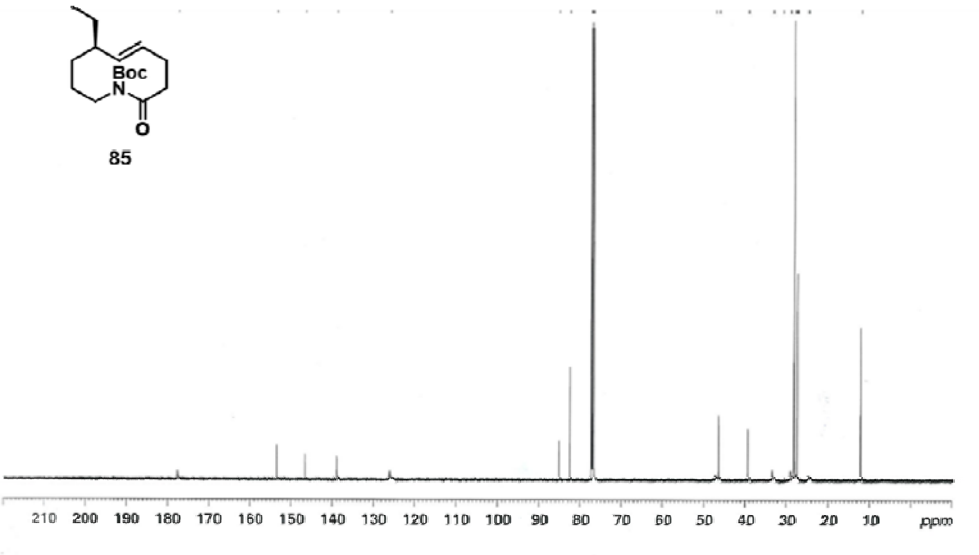

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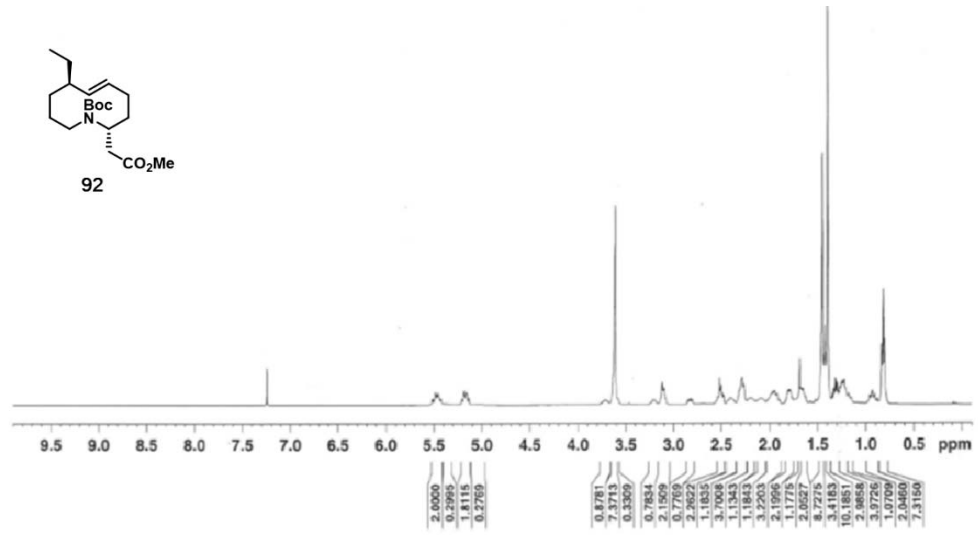

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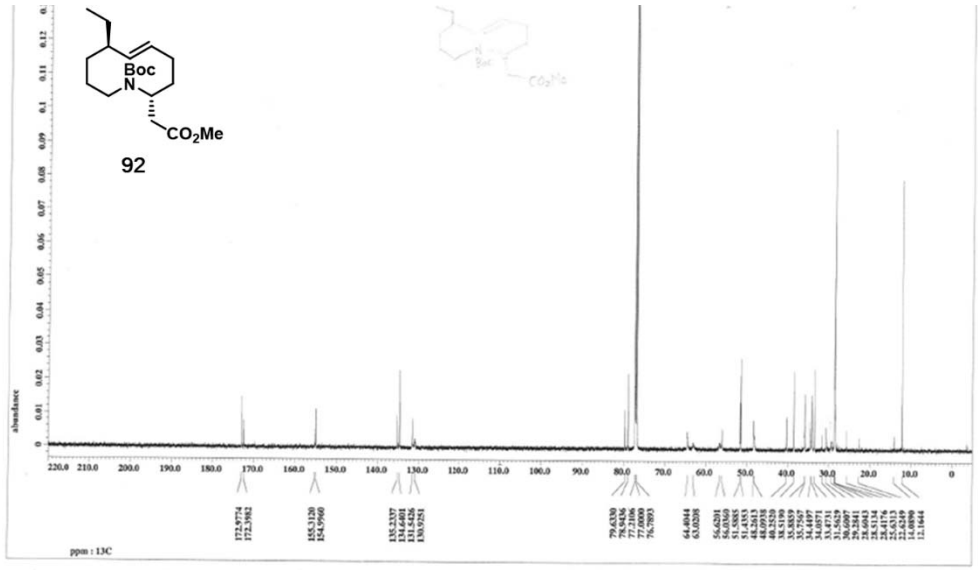

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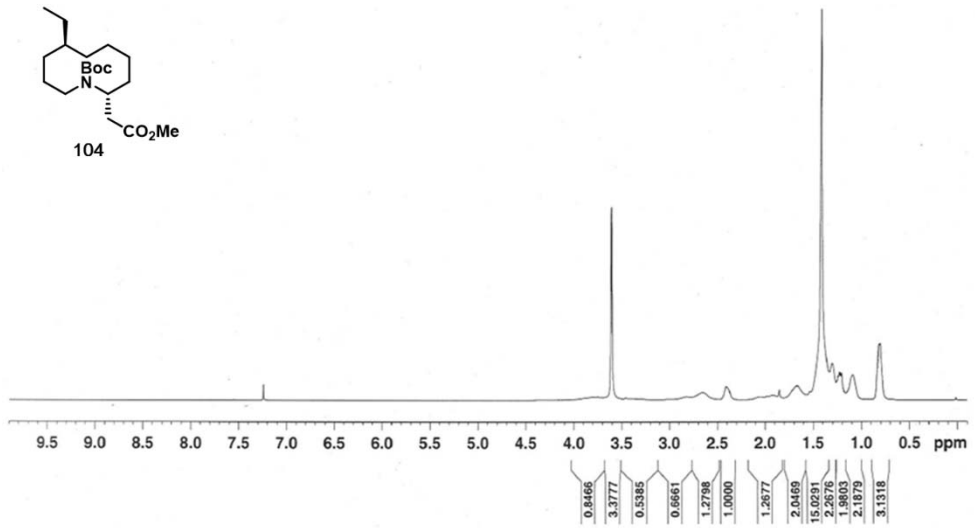

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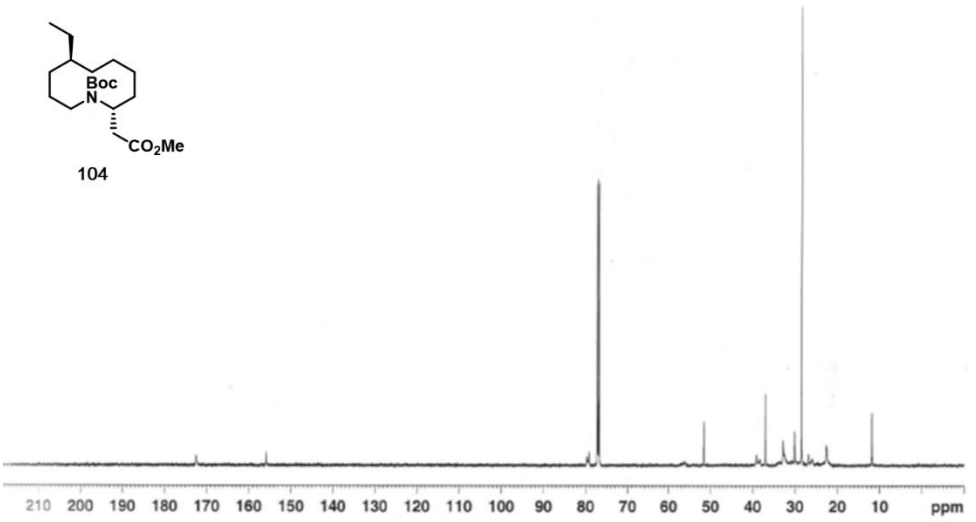

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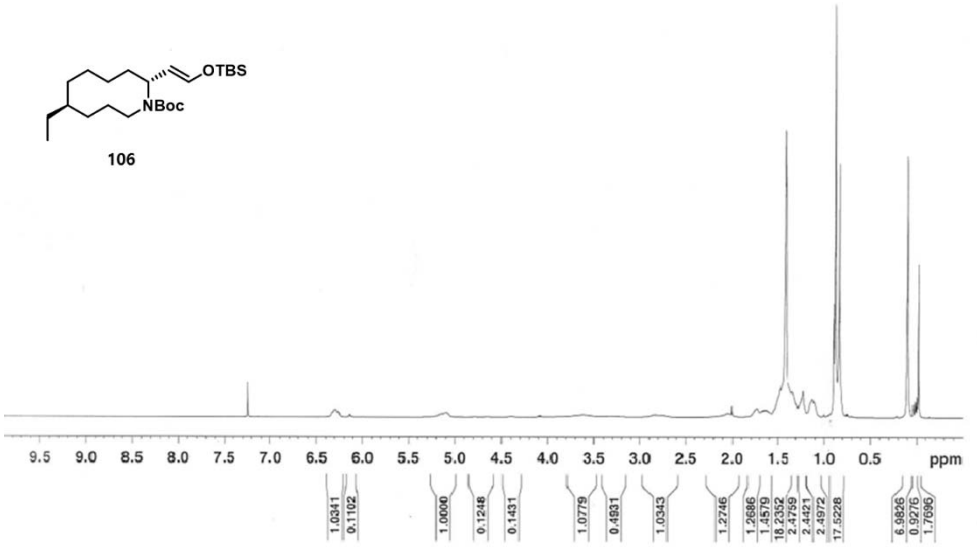

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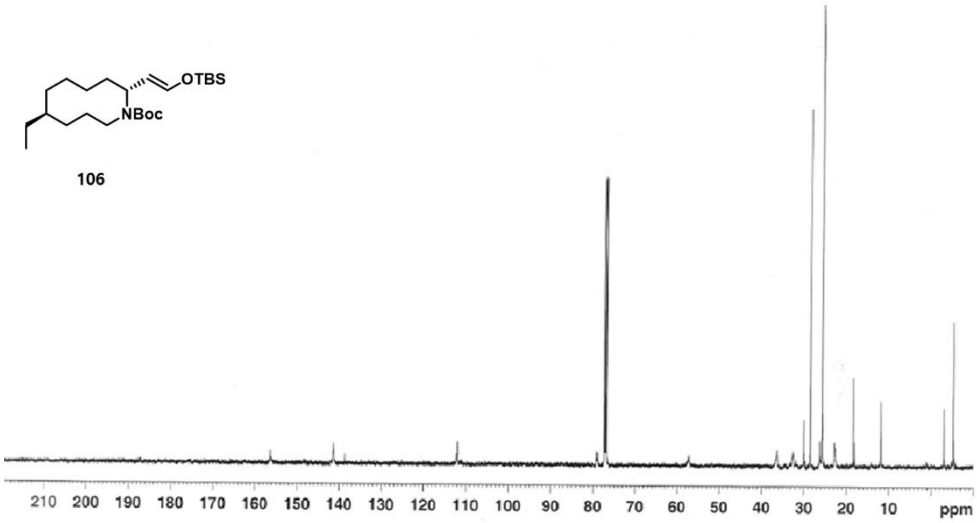

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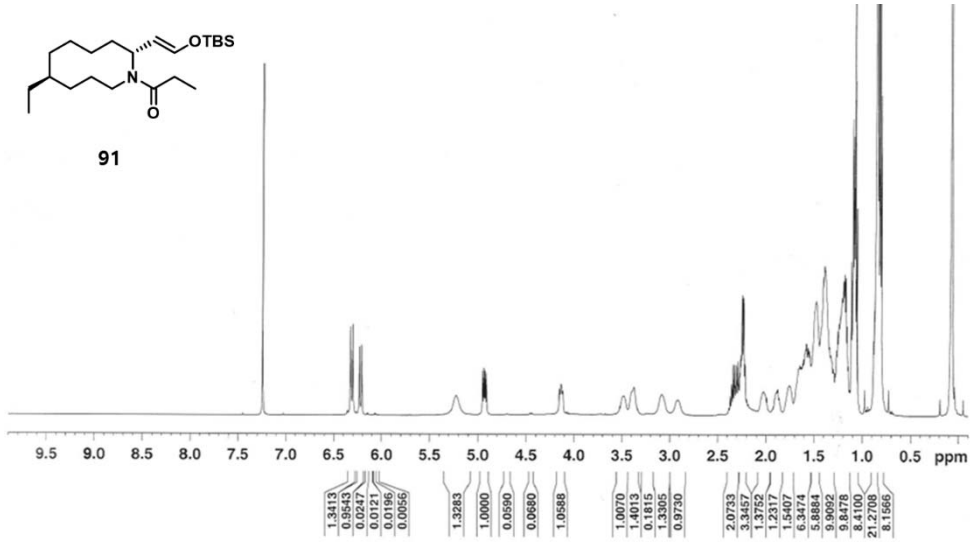

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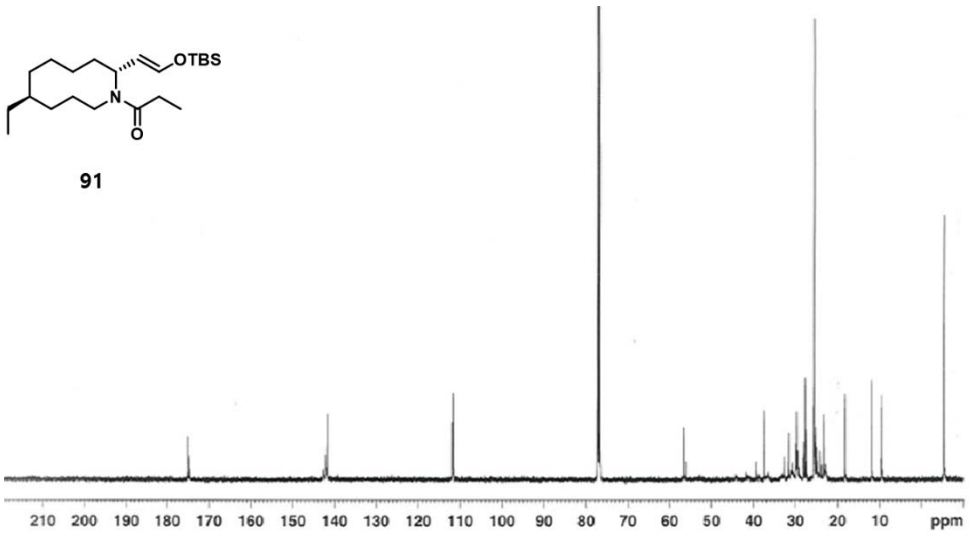

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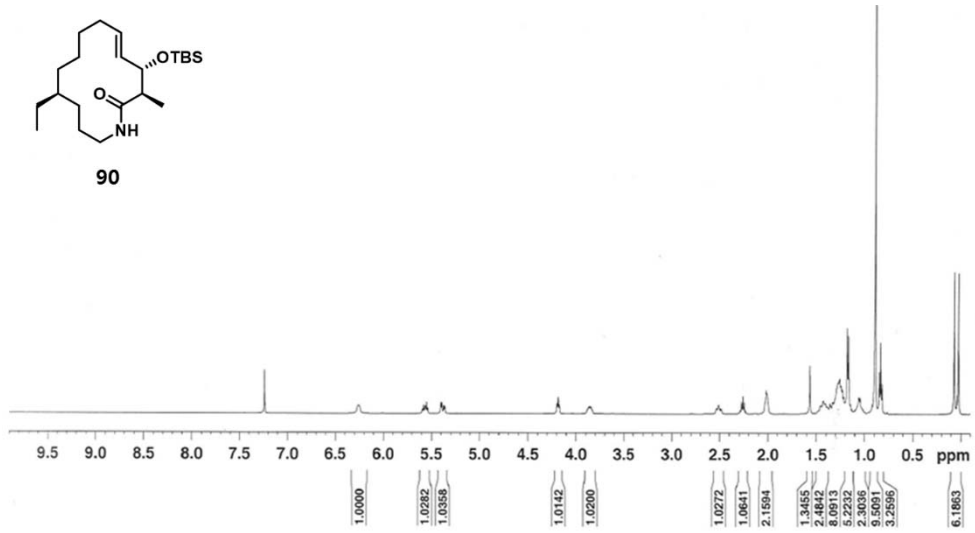

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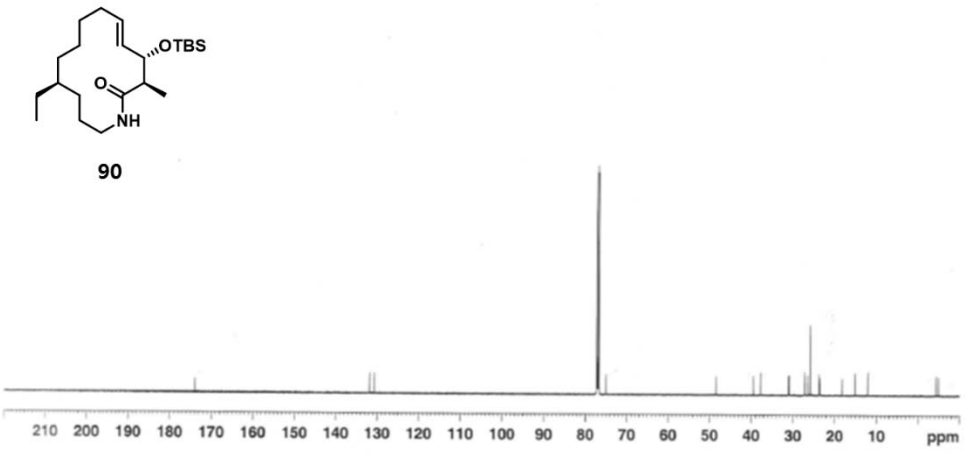

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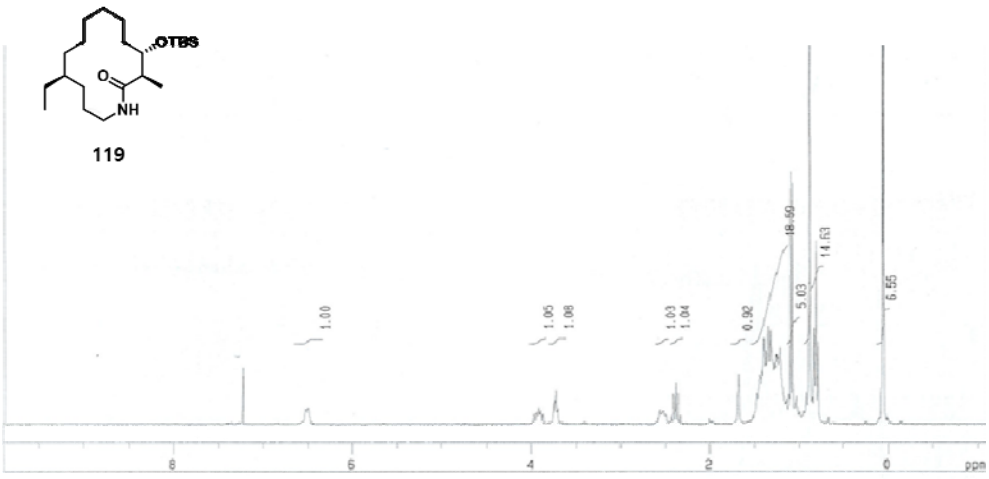

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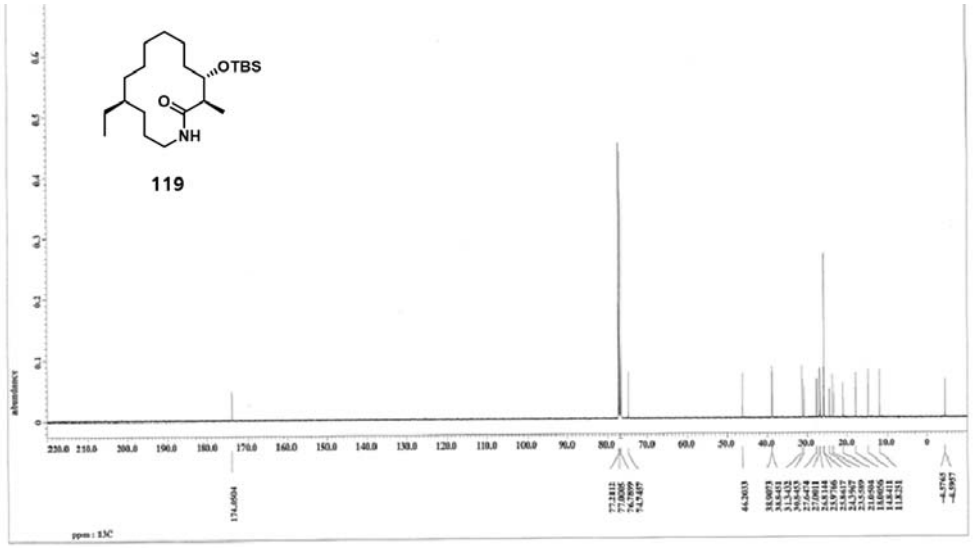

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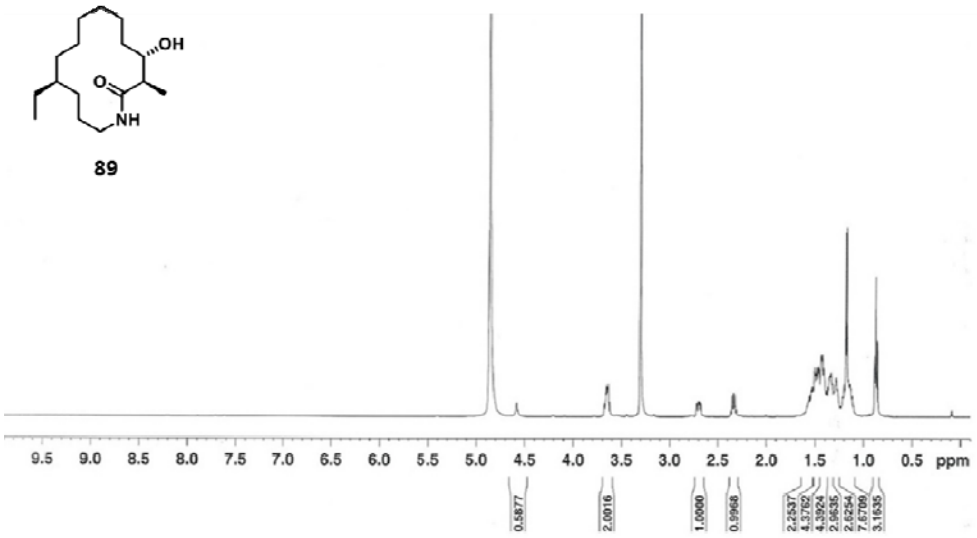

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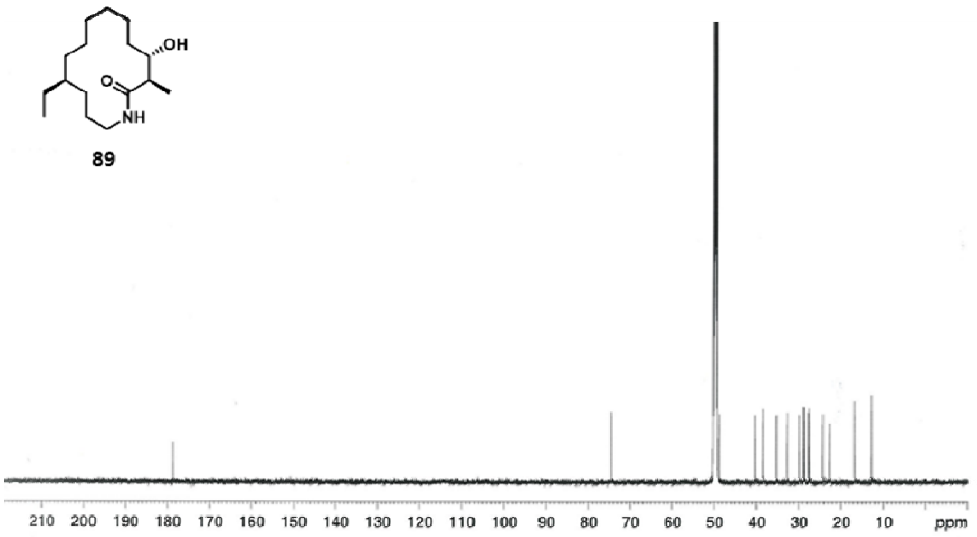

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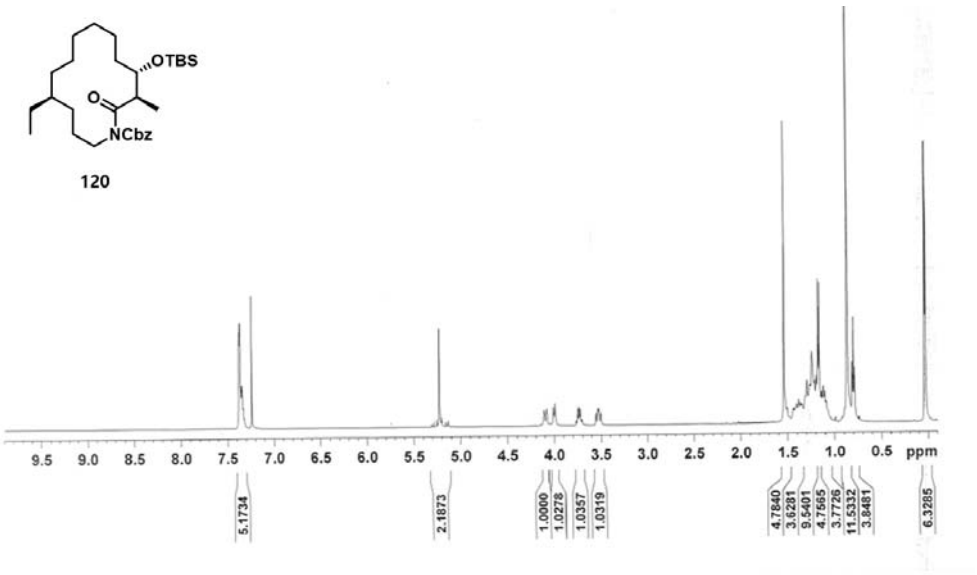

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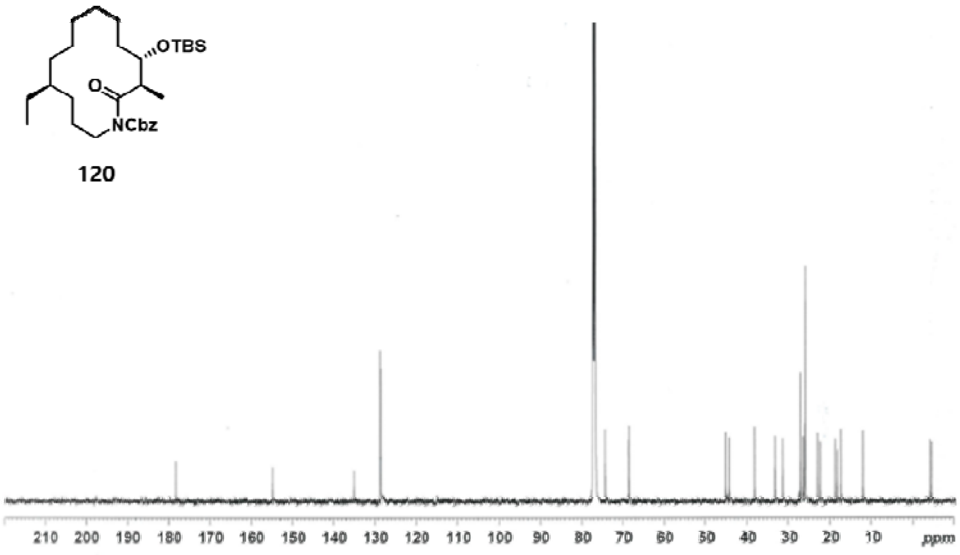

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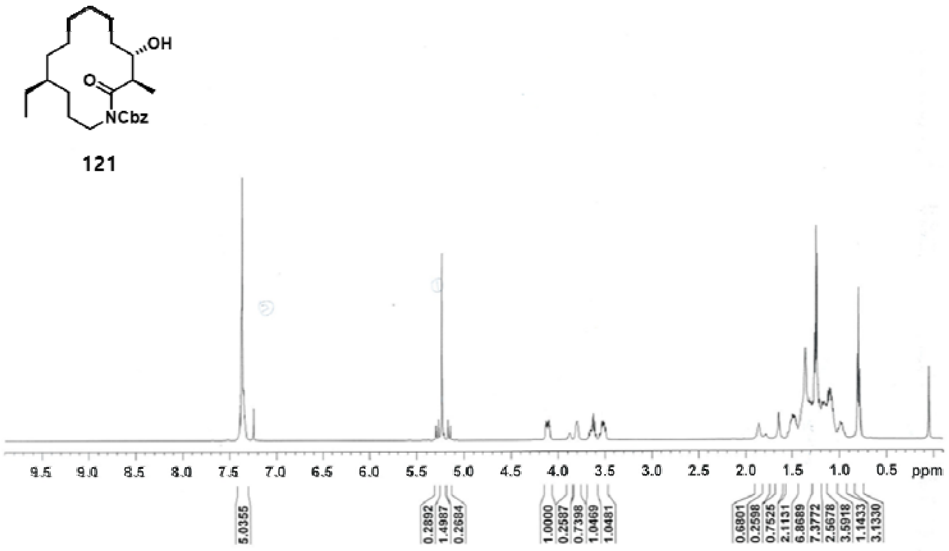

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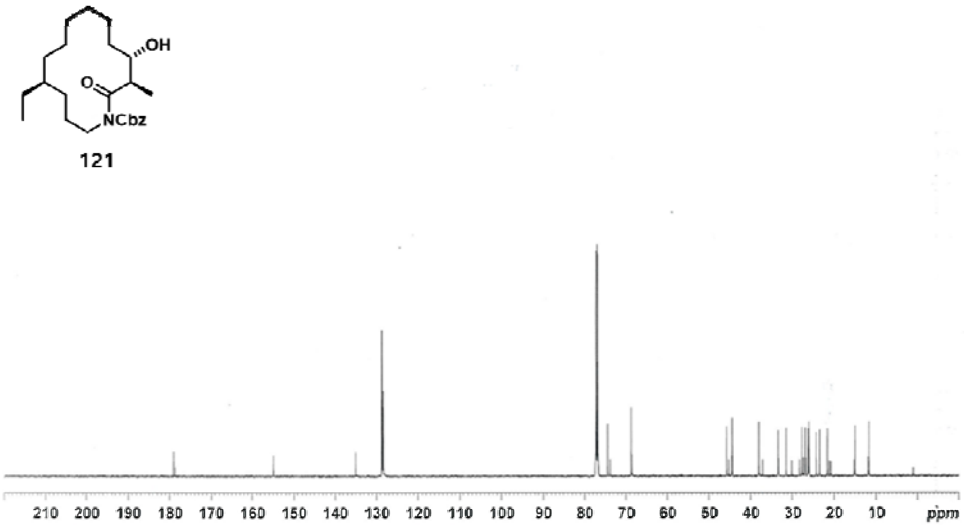

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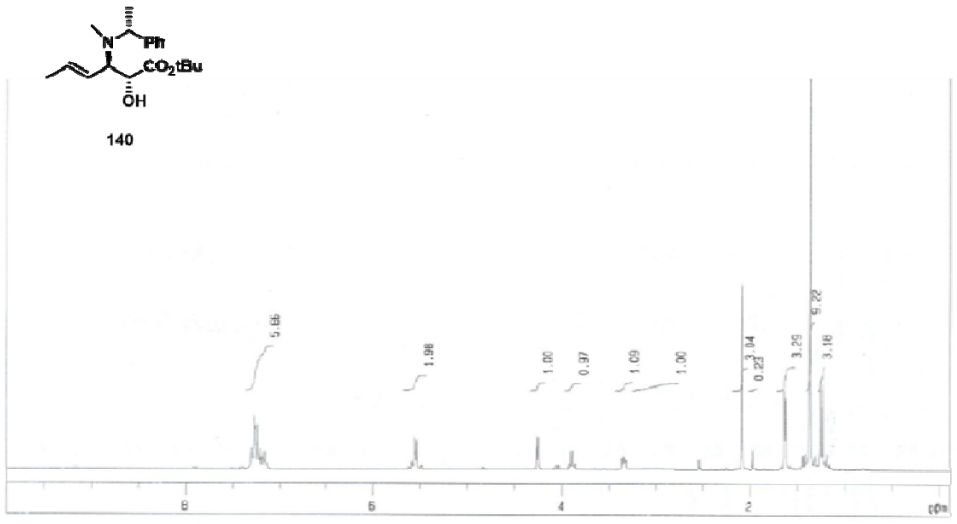

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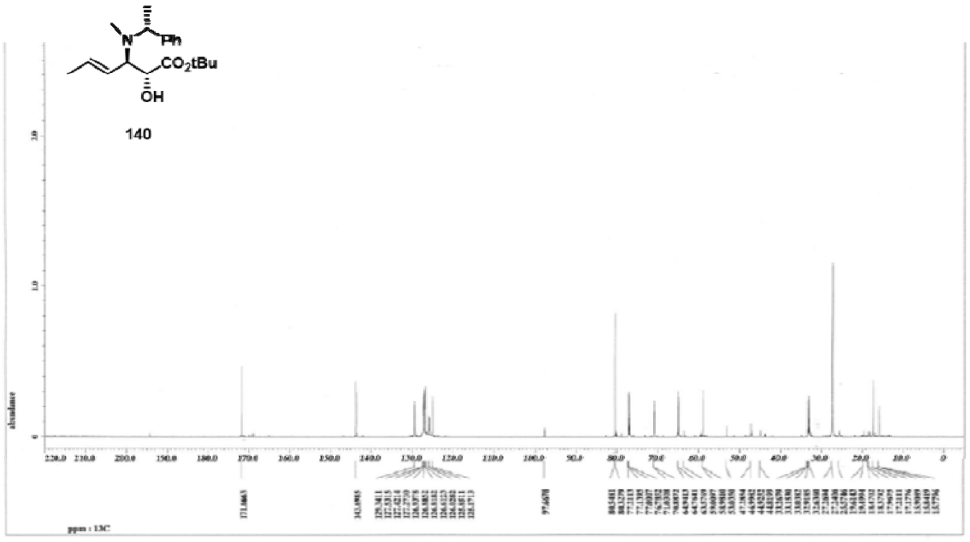

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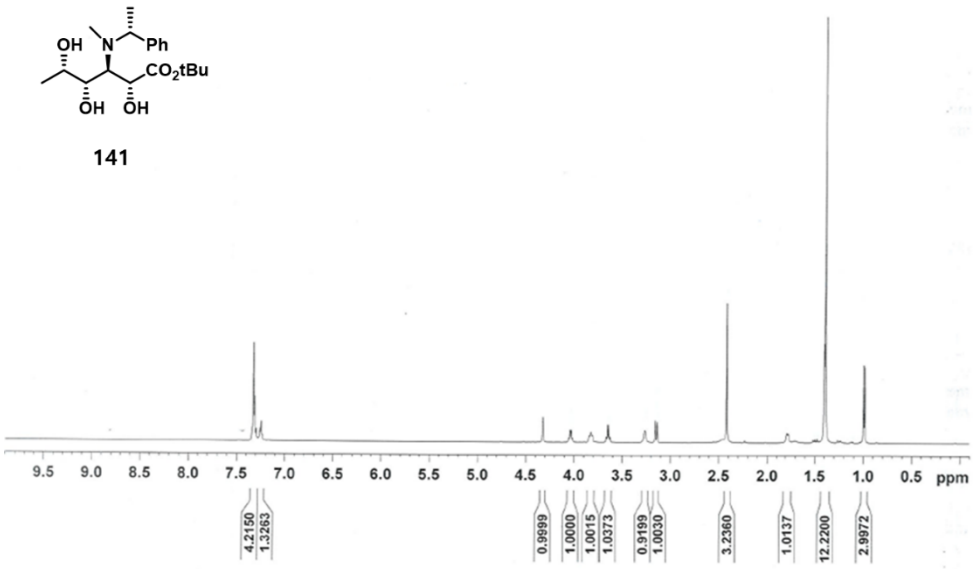

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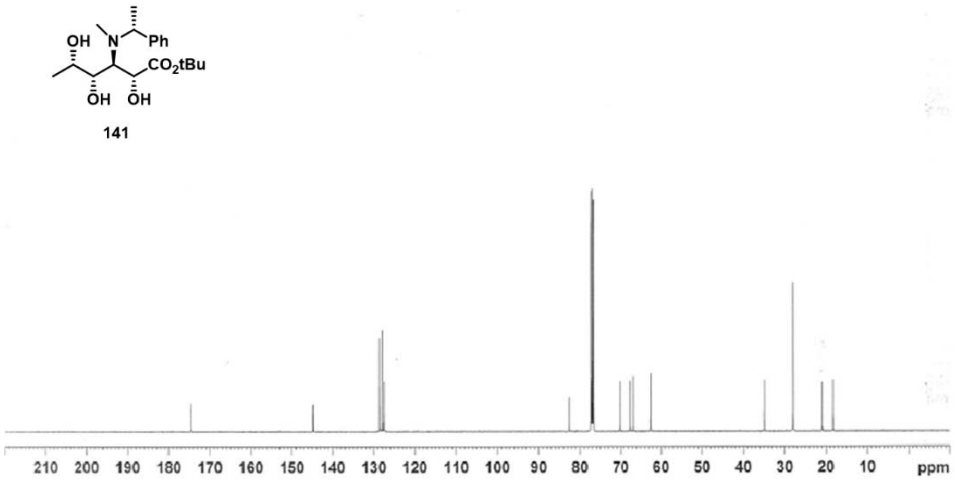

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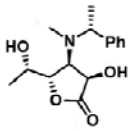

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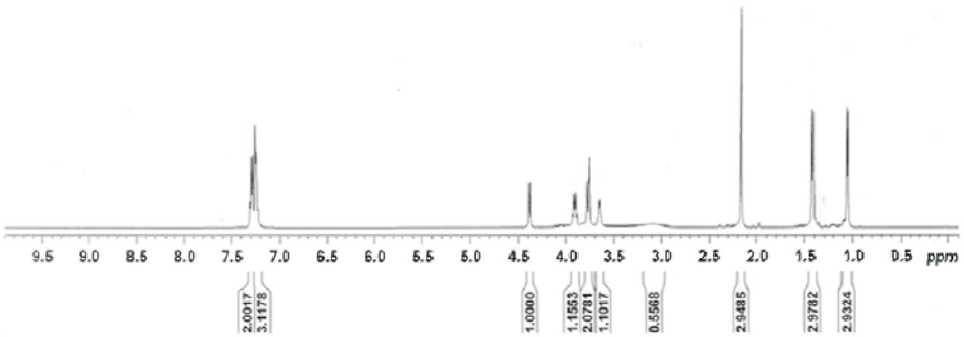

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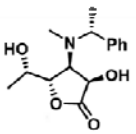

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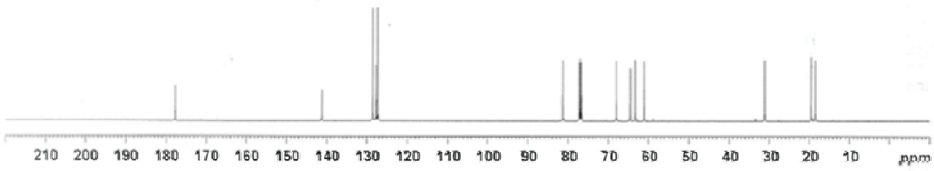

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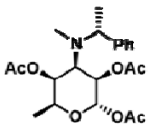

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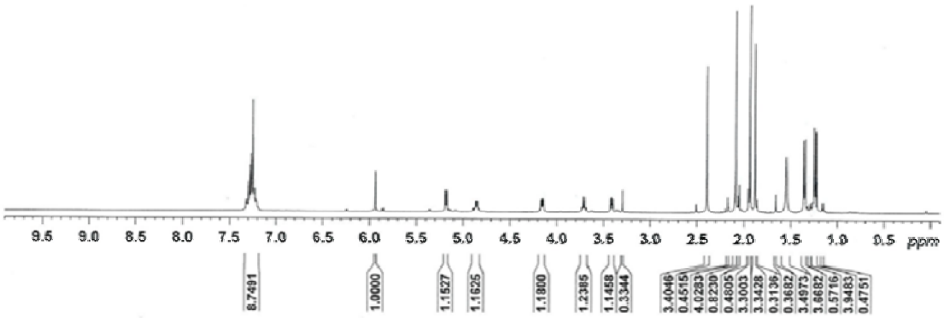

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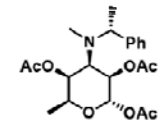

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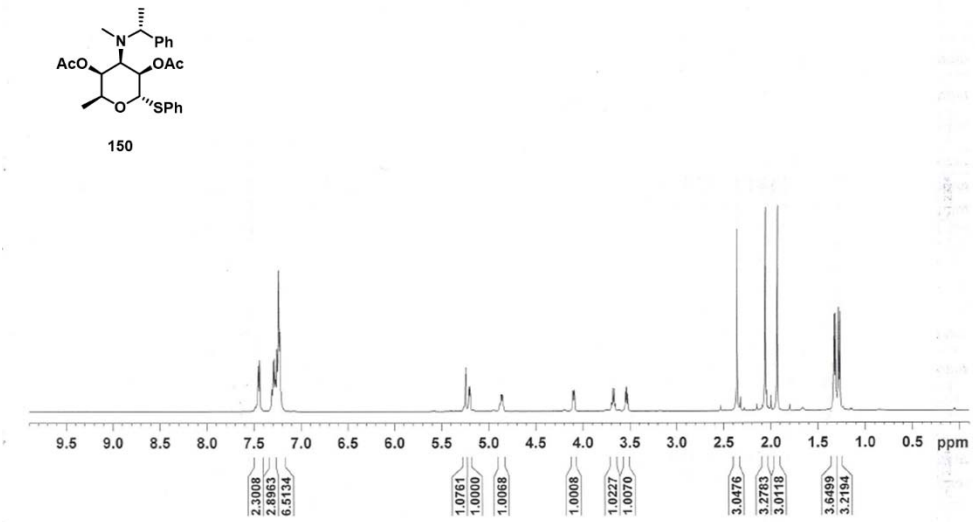

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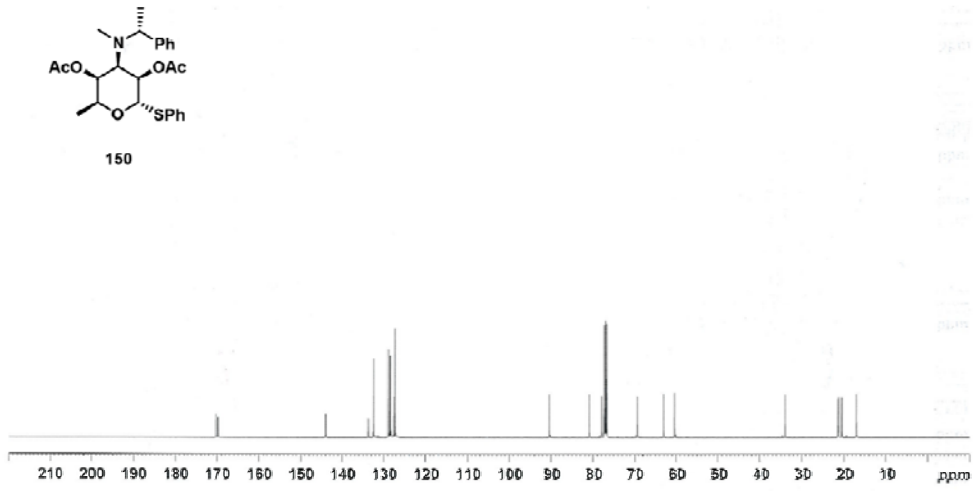

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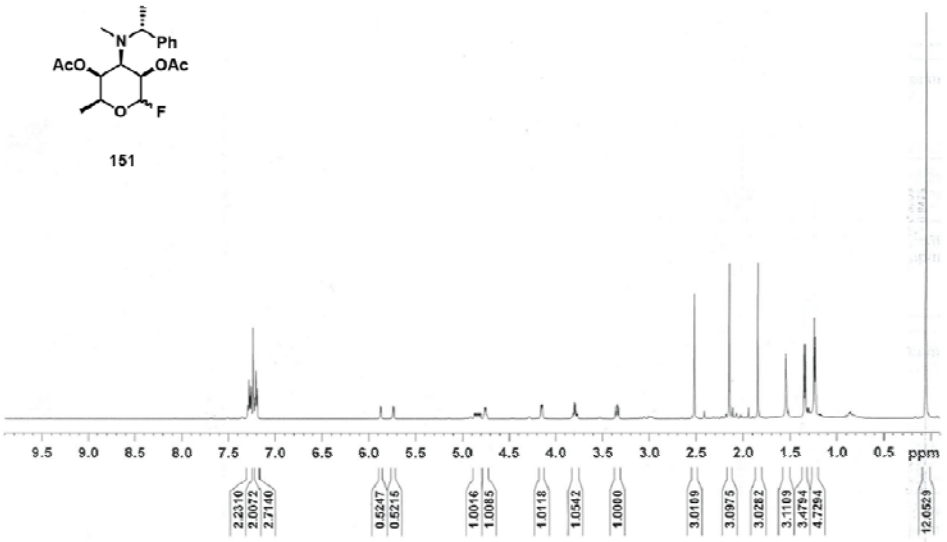

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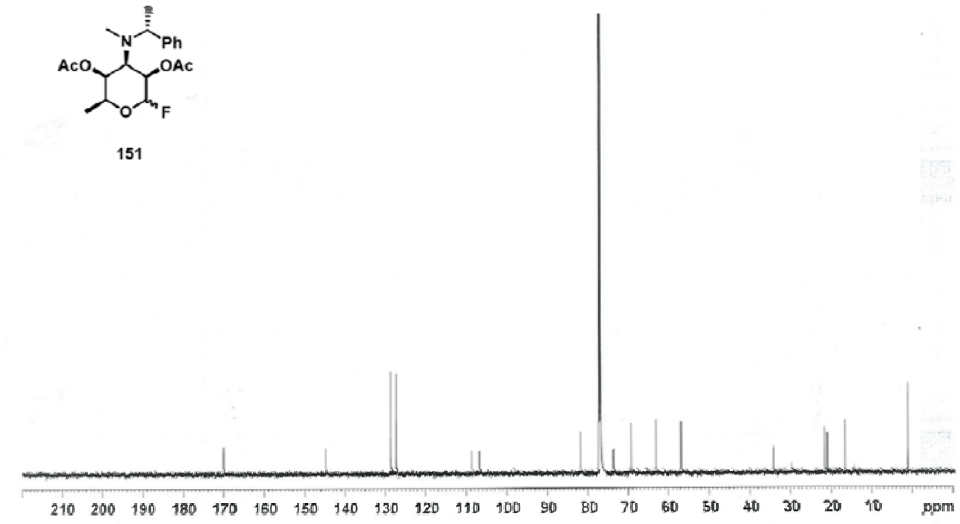

VII. 국문초록

Fluvirucin은 actinomycete에 속하는 토양 미생물로부터 분리된 macrolactam 계 항생물질로서 fluvirucin A_{1-2}, B_{1-5} 등 7종류가 보고되었다. 최근 보고된 천연물로는 *Nonomuraea terkmeniaca* MA7364 및 MA7381로부터 분리된 6-desmethyl-N-methylfluvirucin A_1, N-methylfluvirucin A_1, 그리고 fluvirucin B_0이 있다.

이 천연물들은 14원환의 macrolactam의 2,6-dialkyl-10-ethyl-3(or 9)-hydroxy-13-trodecanelactam핵을 가지고 있으며 이 핵을 fluvirucinine이라고 한다. Fluvirucinine은 2번, 3번 (혹은 9번), (6번) 그리고 10번 탄소에 비대칭 탄소가 존재하고 있으며, 3번 또는 9번의 hydroxyl 기에 carbohydrate가 glycosidic linkage로 연결되어 있다. Fluvirucin $B_{2,4}$ 를 제외한 모든 fluvirucins의 carbohydrate는 3'번 탄소에 amine group이 존재하고 모든 치환기가 한 방향으로 위치하는 독특하고 매우 congested된 구조를 가지고 있다.

6-Desmethyl-N-methyl Fluvirucin A_1, N-methyl Fluvirucin A_1 그리고 Fluvirucin B_0, B_1, B_3 의 경우에는 *Haemonchus contortus* larvae 에 대한 *in vitro*에서의 강력한 항구충효과가 보고된 바 있고, *in vivo*에서 다소 약한 활성을 보여 이를 극복하기 위한 다양한 유도체들의 합성 및 최적화 과정이 필요할 것으로 보인다. 따라서 본 연구자는 선행 연구를 통해 확립된 두 번의 ACR 반응을 통한 ring expansion 전략을 응용하여, 6-Desmethyl-N-methyl Fluvirucin A_1 의 aglycone인 fluvirucinine을 합성하고, 한편 3,6-Dideoxy-3-methylamino-*L*-talose 을 최초로 합성한 뒤 성공적인 glycosylation을 통한 전합성을 완결하고자 하였으며, 의약화학적 유도체 합성 및 개발에 용이한 합성법 또한 확립하고자 하였다.

Acyl vinylpiperidine **82**으로부터 첫 번째 ACR을 통해 10원환의 *E* olefin lactam

83을 합성하였다. Medium-sized ring 본래의 strain만을 이용하여 높은 선택성으로 알킬화반응을 성공시킨 다음 두 번째 ACR을 통해 원하는 비대칭 치환기를 가지는 14원환의 fluvirucinine 구조를 확립하였다. 이후 macrolactam의 amine 기에 Cbz로 보호하여 glycosylation을 위한 용해도를 높였다.

현재까지 보고된 fluvirucin A series은 그의 aglycone인 fluvirucinine만을 합성 보고하였으며, 완전체의 합성은 Hoveyda 연구팀에 의한 Fluvirucin B_1이 유일하다. 또한 목적하는 천연물 6-Desmethyl-N-methylfluvirucin A_1의 carbohydrate는 기존의 fluvirucin series의 그것에 N-methyl 기가 존재하는 구조적 특징이 있으며 아직 합성된 예가 없다. 특히 glycoside의 모든 치환기가 한 방향으로 존재하는 구조적 congestion으로 인해 합성하기 어려운 화합물로 인식되어 왔다.

본 연구자는 methylamine **149**의 입체선택적 aminohydroxylation 및 dihydroxylation을 통해 치환기들의 비대칭성을 확립하였고, hemiacetal의 furanoside에서 pyranoside로의 변환을 유도하였다. 2,4번 alcohol를 acetylation한 다음 일련의 반응을 통해 fluoroglycoside **163**을 효과적으로 합성 완료하였다. 이미 합성 완료한 6-desmethyl-N-methylfluvirucinine A_1과 glycosylation 반응을 수행하여 6-Desmethyl-N-methylfluvirucin A_1 의 합성을 완결하고자 현재 연구를 계속 진행 중이다.

주요어: 6-desmethyl-N-methylfluvirucin A1, N-methylfluvirucin A1, 3,6-dideoxy-3-methylamino-$_L$-talose, glycosylation, ring expansion, aza-Claisen rearrangement

학번 : 2007-21810

약학박사학위논문

Total Syntheses of (-)-Protoemetinol and 6-Desmethyl-*N*-methylfluvirucin A_1 via Aza-Claisen Rearrangement

aza-Claisen 전이를 이용한 생리활성 알칼로이드의 전합성 연구 : protoemetinol 및 6-desmethyl-*N*-methylfluvirucin A_1의 전합성

2016년 2월

서울대학교 대학원
제약학과 약품제조화학전공
문 현 영

Part I. Total Synthesis of (-)-Protoemetinol and Studies on the Synthesis of (-)-Emetine

Abstract

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Benzo[*α*]quinolizidine alkaloids, mainly isolated from the two different families, *Alangium lamarckii* and *Psychotria ipecacuanha*, have received constant attention because of their multiple pharmacological interests. A number of benzo[*α*]quinolizine derivatives have been synthesized in the pharmaceutical industry to evaluate their biological activities in numerous cell lines.

After the completion of the (+)-tetrabenazine synthesis, we directed our synthetic efforts to establish a unified and stereoselective strategy for the synthesis of benzo[α]quinolizidine alkaloids. Subsequently, we realized that protoemetinol could be an excellent intermediate for the synthesis of other benzo[α]quinolizidine alkaloids including emetine, tubulosine because the structure of protoemetinol is identical to that of the core upper part of those alkaloids.

Our approach relies on a sequential diastereoselective aza-Claisen rearrangement of *N*-acyl-*α*-vinyl-tetrahydroisoquinoline, efficiently prepared utilizing cross metathesis, and diastereoselective acid-promoted transannulation for the construction of the benzo[α]quinolizine framework as well as three stereogenic centers. The concise asymmetric synthesis of (-)-protoemetinol has been accomplished through nine steps (17% overall yield) from the known homoallylic amine. Our unique strategy envisages a unified and versatile synthetic strategy for structurally diverse benzo[α]quinolizidine alkaloids.

Keywords : (-)-Protoemetinol, benzo[α]quinolizidine alkaloids, aza-Claisen rearrangement, transannulation, cross metathesis, asymmetric allylation

Student Number : 2007-21801

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Abbreviations

ACR: aza-Claisen rearrangement

Bn: benzyl

Boc: t-butyloxycarbonyl

BQ: 1, 4-benzoquinone

CM: cross metathesis

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DIBAL: diisobutylaluminum hydride

DMF: *N,N*-dimethylformamide

dNs: 2,4-dinitrophenylsulfonyl

ee: enantiomeric excess

FDA: US food and drug administration

H-G2: Hoveyda-Grubbs' 2nd generation catalyst

HPLC: high-performance liquid chromatography

iPrMgCl: isopropyl magnesium chloride

G2: Grubbs' 2nd generation catalyst

LC/MS: liquid chromatography-mass spectrometry

LHMDS: lithium bis(trimethylsilyl)amide

NMO: *N*-methylmorpholine *N*-oxide

NMR: nuclear magnetic resonance

Ns: 4-nitrophenylsulfonyl

PMB: 4-methoxybenzyl ether

PTSA: *p*-toluenesulfonic acid

SM: starting material

TBS: *tert*-butyldimethylsilyl

TES: triethylsilyl

THF: tetrahydrofuran

TMSOTf: trimethylsilyl trifluoromethanesulfonate

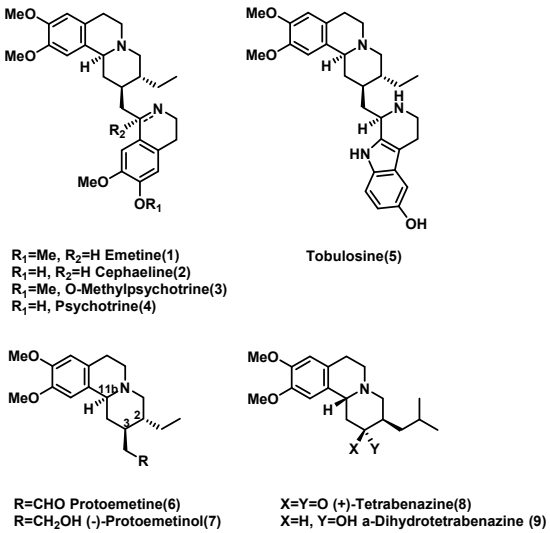
Ts: tosyl, 4-toluenesulfonyl

I. Introduction

1. Benzo[α]quinolizidine alkaloids and Protoemetinol

Benzo[α]quinolizidine alkaloids[1], which are mainly isolated from the two different families, *Alangium lamarckii* and *Psychotria ipecacuanha*, have received constant attention because of their multiple pharmacological interests.[2] Particularly, emetine **1** (Fig. 1), which acts as a protein synthesis inhibitor and DNA interacting agent, has been clinically used for the treatment of a protozoan infection. Recently, additional biological activities including antiviral properties and NF-κB signaling inhibitory effects were reported.[3] Tubulosine **5** also exhibits various biological activities[4] such as broad cytotoxicity in cancer cell lines, antimalarial activity, HIV reverse transcriptase inhibitory activity, and HIF-1 transcriptional inhibitory activity. Accordingly, numerous syntheses of benzo[α]quinolizine alkaloids including emetine and tubulosine have been attempted due to their biological importance and the unique structural features.[5]

Fig 1. The representative benzo[α]quinolizidine alkaloids and derivatives



Benzo[α]quinolizine has been considered as one of the privileged structure from the viewpoint of biological and medicinal chemistry.[6] Therefore, a number of benzo[α]quinolizine derivatives have been synthesized in the pharmaceutical industry to evaluate their biological activities in numerous cell lines. Tetrabenazine **8**,[7] the first and only drug approved by the U. S. FDA as a racemate for the treatment of chorea, represents a major advancement for Huntington's disease patients. The urgent demand for an optically pure drug to reduce or eliminate undesired effects invoked the enantioselective synthesis of (+)-tetrabenazine included in our work.[8]

After the accomplishment of the synthesis of (+)-tetrabenazine, we directed our synthetic efforts to establish an original and unified strategy for the synthesis of benzo[α]quinolizidine alkaloids, because the reported syntheses were limited on utilizing similar procedures such as Michael addition, Bischler-Napierlski or Pictet-Spengler reaction. We chose protoemetinol[9] **7** as our target, which is an excellent intermediate for the syntheses of other benzo[α]quinolizidine alkaloids including emetine **1**, tubulosine **5**, cephaeline **2**, *O*-methylpsychotrine **3**, and psychotrine **4** in that the structure of protoemetinol is identical to that of the core upper part of those alkaloids.

2. Reported Synthetic Studies of (-)-Protoemetinol

Most of the reported protoemetinol synthetic strategies have been limited to racemic approaches.[10] Recently, the several enantioselective syntheses have been reported, but all synthetic approaches, except the first one, based on the same proline-catalyzed Micheal addition as a key reaction (see below) to construct the stereogenic centers. In addition, they had mainly employed the conventional procedure such as Bischler-Napieralski cyclization/reduction or Pictet-Spengler synthesis to elaborate the tetrahydroisoquinoline

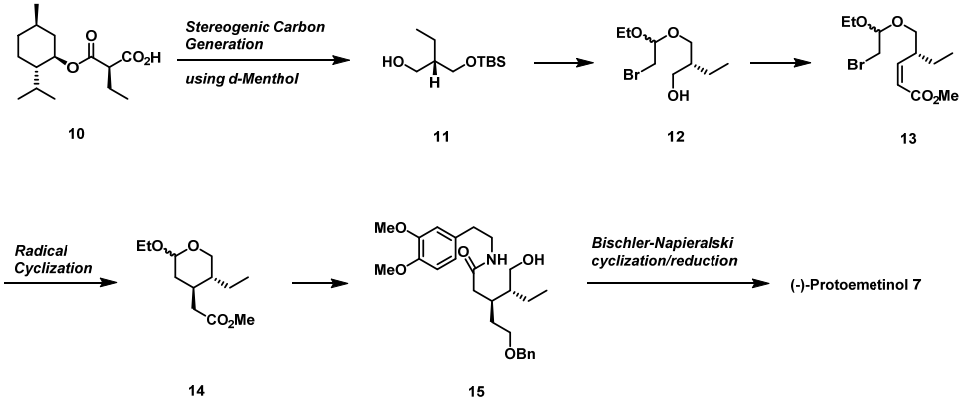
system.[11]

2-1. Asymmetric syntheses

2-1-1. K. Fukumoto's work [10g]

The unsymmetrical silyl-protected propane-1,3-diol **11**, derived from an acid **10** produced by the condensation of ethylmalonic acid with *d*-menthol, was reacted with the 1,2-dibromoethyl ethyl ether and deprotected to afford the alcohol **12**. After its conversion into the corresponding aldehyde, the (*Z*)-*α,β*-unsaturated ester **13** was selectively synthesized by the Still's method. Radical cyclization of **13** under irradiation in the presence of nBu_3SnH produced methyl ester **14**, which was converted into the lactone. Further transformation via amidation and Bischler-Napieralski cyclization/reduction process produced (-)-protoemetinol **7** (Fig 2).

Fig 2. (-)-Protoemetinol synthesis *via* radical cyclization as a key step by Fukumoto.

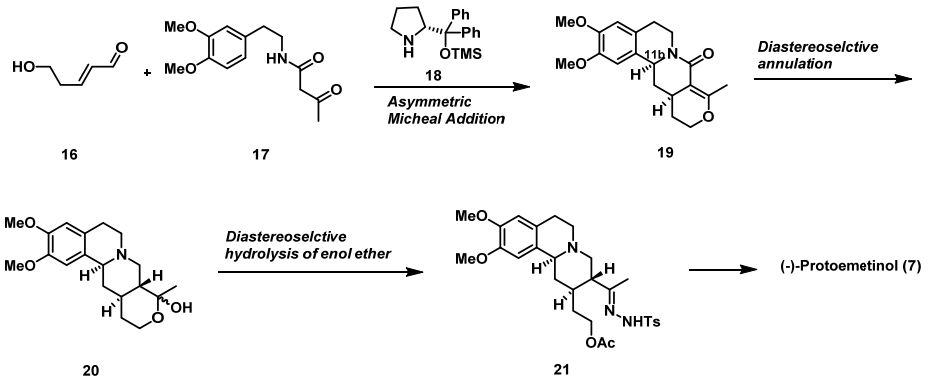


2-1-2. J. Franzén's work [10i]

The *β*-Ketoamide **17** reacted with the *α,β*-unsaturated aldehyde **16** in the presence of catalyst **18** to give a Michael adduct, which was spontaneously converted into

diastereomeric mixture of lactols *in situ*. The crude mixtures of lactol were quenched by addition of $SnCl_4$ to give the desired *β* stereoisomer **19** of C11b (78:22). Hydration of the dihydropyran of **19**, followed by acetylation of resulting lactol, gave the ketone form of **21** which was transformed the hydrazone in the treatment of tosyl hydrazide in AcOH/MeOH. DIBAL reduction of hydrazone with prolonged reaction time at elevated temperature gave the (-)-protoemetinol (Fig 3).

Fig 3. (-)-Protoemetinol synthesis *via* asymmetric Micheal addition as a key step by Franzén.

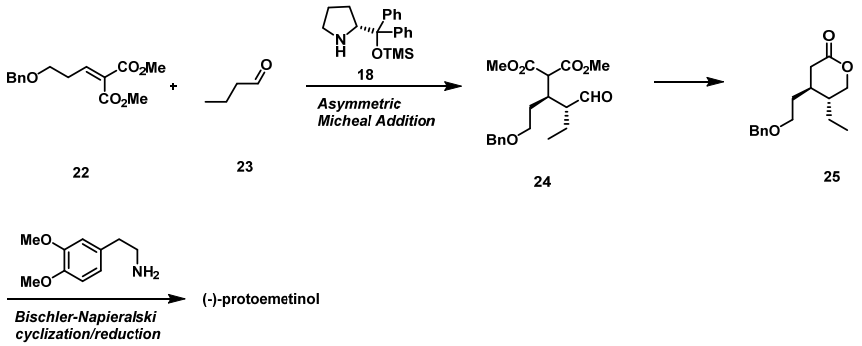


2-1-3 D. Ma's work [10h]

The Córdova group had demonstrated that an OTMS-protected diphenylproline **18** was the best catalyst for promoting the Michael addition of aldehydes to simple arylidene malonates in terms of diastereo- and enantioselectivity. Ma group also explored the Micheal reaction of *n*-butanal **23** with an alkylidene malonate **22** in the presence of catalyst **18** (Fig 4). The stereochemistry of C2 and C3 were established from this early stage. Lactone **25** was assembled from a Michael adduct **24** by a reduction, lactonization and decarboxylation reaction sequence. Following the procedure reported by Fukumoto et al.[10g], lactone **25** was transformed into tricyclic intermediate by the condensation with 3,4-

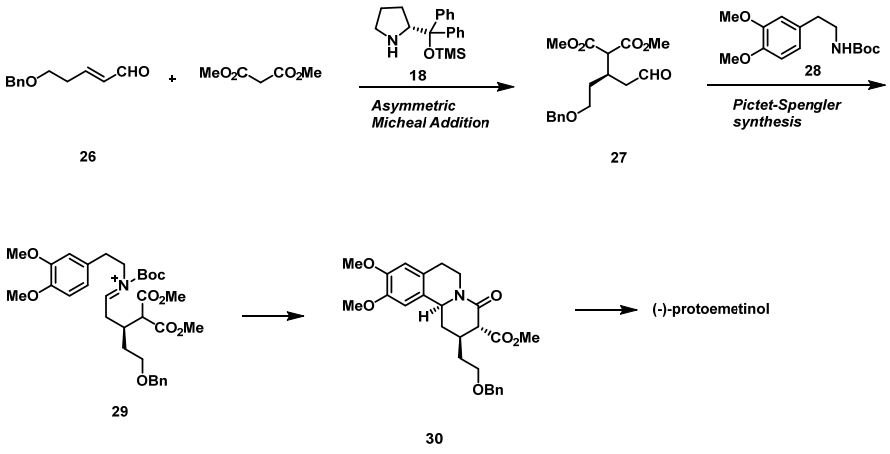
dimethoxyphenethylamine, treatment of the resulting amide with $POCl_3$ and subsequent reduction with $NaBH_4$ to give (-)-protoemetinol **7**.

Fig 4. (-)-Protoemetinol synthesis *via* asymmetric Micheal addition as a key step by Ma.



2-1-4. A. Córdova's work [10j]

Fig 5. (-)-Protoemetinol synthesis via asymmetric Micheal addition as a key step by Córdova.



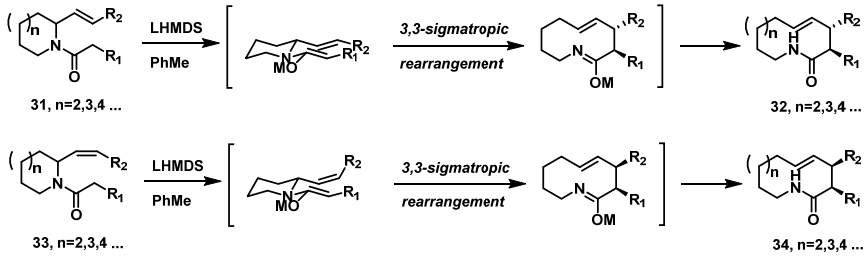
They investigated the one-pot three-component asymmetric Michael reaction sequence between enal **26**, malonate, and Boc-protected 3,4-dimethoxyphenethylamine **28** in the presence of a organocatalyst **18** as similar as the syntheses above. The Pictet-Spengler

reaction occurred smoothly, then a tricyclic compound **30** was synthesized by a lactamization. In the treatment of LAH, the carbonyl group of lactam and methyester of **30** were reduced, and the resulting alcohol intermediate was converted into (-)-protoemetinol by the sequence of Swern oxidation, Wittig olefination, hydrogenation and deprotection of a benzyl group (Fig 5).

3. Aza-Claisen Rearrangement and Acid-Promoted Transannulation Sequence

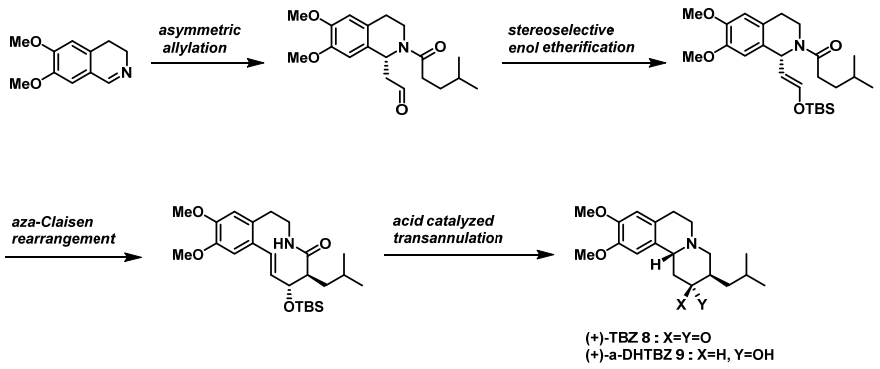
The principle of aza-Claisen rearrangement (ACR) is shown in Fig 6. To the amide **31** or **33** is treated LHMDS at reflux condition, the 3,3-sigmatropic rearrangement occurs to afford the ring-expanded products. The chirality is transferred *via* a chairlike transition state, 1, 2-*anti* for (*E)* enol ether and 1, 2-*syn* for (*Z)* enol ether. Our group had demonstrated that an ACR was proceeded at various ring size systems *via* a chairlike transition state, and the ACR-induced ring expansion could provide an opportunity for the rapid assembly of complex macrolactams or other types of alkaloids.

Fig 6. The principle of Aza-Claisen rearrangement (ACR)



The ring-expanded resultants could be transformed to the fused-ring system in diastereoselective manners *via* succeeding transannulation reaction. The fused ring framework was found in various natural products including benzo[α]quinolizidine alkaloids. We reported the total syntheses of (+)-tetrabenazine **8** and (+)-dihydrotetrabenazine **9** *via* the subsequent *i*PrMgCl-mediated ACR and acid-promoted transannulation as key reactions (Fig 7), which showed not only the ring could be expanded to medium or macro-sized ring but also the diastereoselective fused-ring system could be constructed by an additional transannulation reaction.

Fig 7. Total syntheses of (+)-Tetrabenazine and (+)-α-Dihydrotetrabenazine

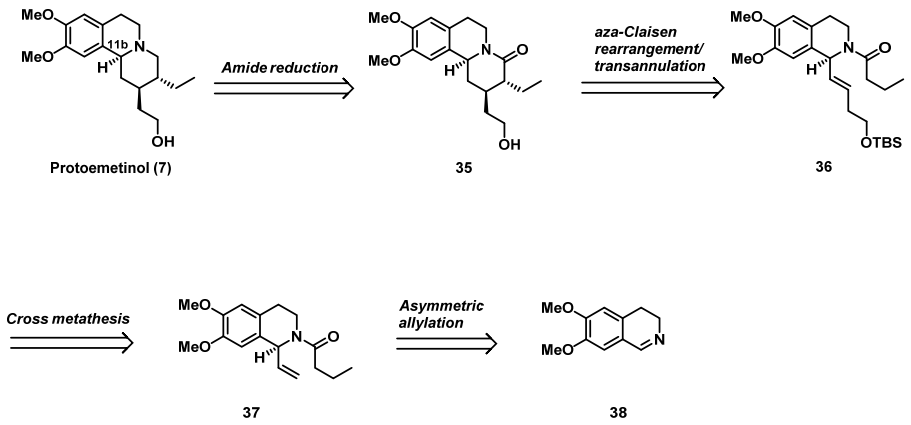


II. Results and Discussion

1. Retrosynthetic Strategy

Our approach relies on a sequential diastereoselective aza-Claisen rearrangement of *N*-acyl-*α*-vinyl-tetrahydroisoquinoline **36**, efficiently prepared utilizing a cross metathesis, and diastereoselective acid-promoted transannulation for the construction of the benzo[α]quinolizine framework as well as three stereogenic centers. Our unique approach provides easy access to structurally diverse benzo[α]quinolizines. The retrosynthetic analysis of (-)-protoemetinol **7** is shown in Fig 8.

Fig 8. Retrosynthetic analysis of (-)-protoemetinol



We planned to pursue a stereoselective sequence of aza-Claisen rearrangement (ACR)[12] and acid-promoted transannulation[13] as the key reactions to readily create the required stereogenic centers via 1, 4 and 1, 5 remote chiral transfers and to diastereoselectively elaborate the benzo[α]quinolizine skeleton. The benzo[α]quinolizine intermediate **35** can be

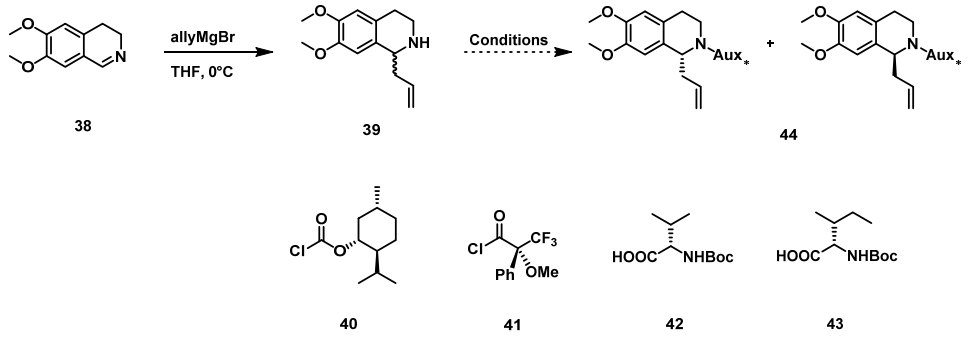
effectively transformed into protoemetinol **7** by the lactam reduction. Intermediate (*E*)-olefin **36** can be conveniently synthesized from amide **37** by a cross metathesis reaction. The initial stereogenic center C11b is introduced by an optimized Nakamura's asymmetric allylation[8b,14] of commercially available dihydroisoquinoline **38**.

2. Preparation of Cross Metathesis Precursors

2-1. Chemical resolution by a chiral auxiliary

Before executing an asymmetric allylation for establishing an initial stereogenic center of C11b[14], we searched more facile way for introducing the allyl group stereoselectively. Racemic allylation was carried out in the treatment of allylMgBr, and then the chemical resolution of allyl tetrahydroisoquinoline **39** was investigated in with chiral auxiliaries or amino acids such as (-)-menthyl chloroformate **40**, Mosher's ester **41**, *N*-Boc-*L*-valine **42** and *N*-Boc-*L*-isoleucine **43**. Unfortunately, none of these auxiliaries could discriminate among enantiomers of **39** (Scheme 1).

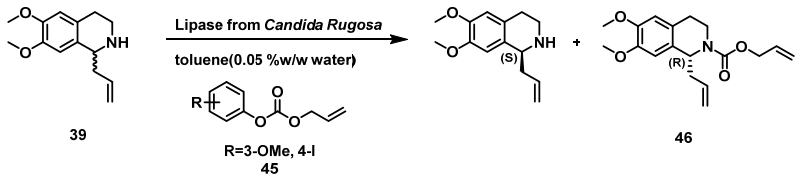
Scheme 1. The trial on Chemical resolution



2-2. Enzymatic resolution

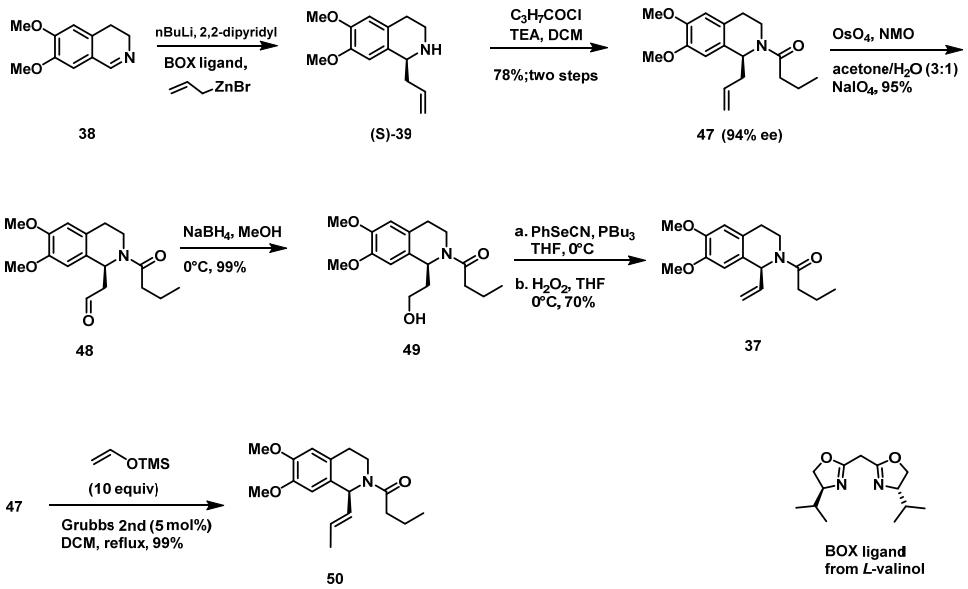
We also conducted a trial on enzymatic resolution (Scheme 2), and chose the lipase from *Candida Rugosa* as the enzyme and the allyl carbonates **45** as an acylating reagent. Although the allyl carbonates was reacted with the (*R*)-allyl tetraisoquinoline of **39** to afford **46** enantioselectively, the conversion yield was too low (9~12 %).

Scheme 2. The trial on enzymatic resolution



2-3. Substrate preparation *via* an asymmetric allylation

Scheme 3. Preparation of cross metathesis substrates



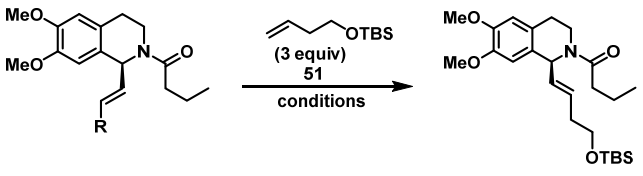
Our synthesis commenced with the preparation of precursors **37** and **50** for cross metathesis as shown in Scheme 3. The known homoallylic amine[15] **39** possessing the stereogenic center C11b was prepared by an asymmetric allylation of the commercially available dihydroisoquinoline **38** in the presence of an enantiomerically enriched bisoxazoline (BOX) ligand and allyl zinc bromide. The amidation of the resulting amine **(*S*)-39** with butyryl chloride followed by an dihydroxylation and the $NaIO_4$ treatment of the resulting diol intermediate provided the aldehyde **48** in an excellent yield. The aldehyde **48** was reduced with sodium borohydride and the resulting alcohol **49** was converted to the vinyl-substituted dihydroisoquinoline **37** utilizing Grieco's protocol.[17] The olefin-isomerized product **50** as another precursor for cross metathesis, was also prepared by the treatment of **47** with excess vinyloxytrimethylsilane in the presence of Grubbs' 2nd generation catalyst[16] in high yield.

3. Cross Metathesis

We conducted the cross metathesis of olefins **37** or **50** with a counterpart **51** to secure an ACR precursor **36** as outlined in Table 1. In case of **50**, the desired product was not detected under both Grubbs' 2nd and Hoveyda-Grubbs' 2nd catalyst presumably due to the insufficient reactivity of the methyl vinyl group of compound **50**. After numerous attempts of cross metathesis with the vinyl tetrahydroisoquinoline **37**, the Hoveyda-Grubbs' 2nd catalyst turned out to be superior over Grubbs' 2nd catalyst in terms of yield, of which the best result was observed with 20 mol%. Addition of 1, 4-benzoquinone (BQ) minimized the isomerization[16] of **51**. Other endeavour such as altering solvent, adding Lewis acid, prolonged reaction time did not improve the outcome. It is noted that the substantially

different results were made depending on the amount of substrates **37**. The yield tended to diminish in the relatively large scale (above 1.0 mmol) (entry 6).

Table 1. Cross metathesis studies



R=H, **37**
R=Me, **50**

36

entry	Substrate(mmol)	Catalyst(mol%)	Additive(eq)	T(hrs)	Result
1	**50**	G2 (20)	-		No reaction
2	**50**	H-G2 (20)	-		No reaction
3	**37** (0.5)	G2 (20)	BQ(3)	48	6% (brsm 14%)
4	**37** (0.5)	H-G2 (10)	BQ(3)	48	15% (brsm 29%)
5	**37** (0.2)	H-G2 (20)	BQ(3)	48	**52% (brsm 73%)**
6	**37** (1.0)	H-G2 (20)	BQ(3)	48	12% (brsm 18%)

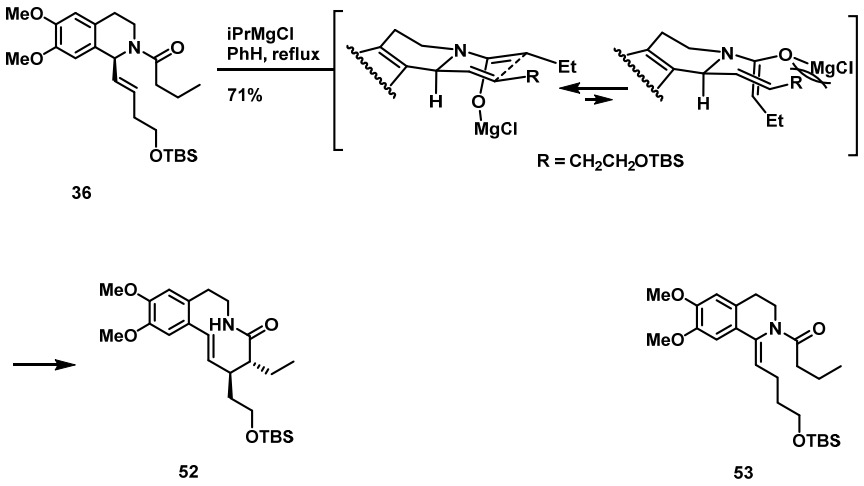
G2: Grubbs' 2nd catalyst
H-G2: Hoveyda-Grubbs' 2nd catalyst
BQ: 1, 4-benzoquinone

4. Aza-Claisen Rearrangement(ACR) and Transannulation Sequence, and Completion of Total Synthesis of (-)-Protoemetinol

We executed the key aza-Claisen rearrangement (ACR) to obtain the lactam intermediate **52** and two stereogenic centers as well as a *trans*-ring olefin (Table 2). The lithium amide enolate, derived from the LHMDS treatment of **36**, afford the isomerized side product[19] **53** exclusively instead of the rearranged product, which resulted from the abstraction of a benzylic proton of C11b. In contrast, the ACR with *i*-PrMgCl proceeded smoothly to give

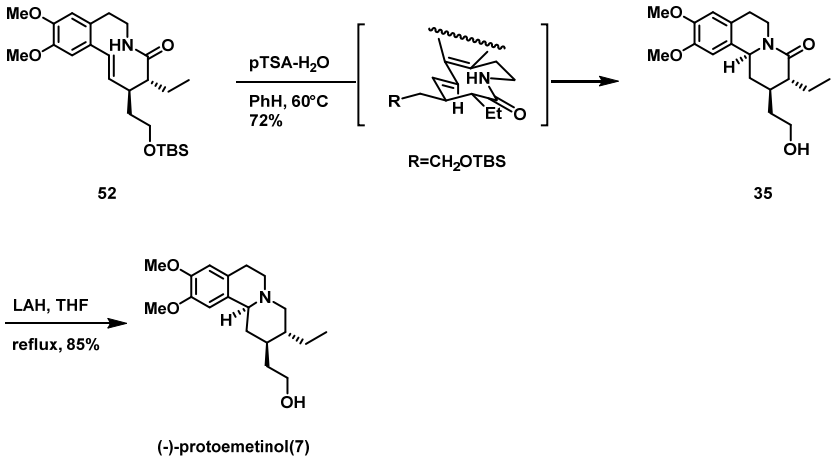
the ring-expansion product[20] **52**. The superiority of *i*-PrMgCl over LHMDS can be explained by the gauche interaction between the bulky MgCl complex and the silyloxyethyl group. This interaction may forces the highly ordered chair-like transition state. The ACR product **52** underwent the facile acid-promoted transannulation to give alcohol **35** as a sole product with the desired diastereoselectivity under the optimized condition (pTSA·H_2O in benzene, 60 °C, 2 hours). The tricyclic lactam **35** was finally reduced with LAH to produce the (-)-protoemetinol **7** (Scheme 4).

Table 2. Aza-Claisen rearrangement studies



entry	Base(eq)	solvent	T(hr)	Result
1	LHMDS (3)	PhMe	2	**53** (21 %)
2	LHMDS (5)	PhMe	2	**53** (51 %)
3	iPrMgCl (3)	PhH	5	**52** (48 %)
4	iPrMgCl (4)	PhH	3	**52** (**71 %**)

Scheme 4. Diastereoselective transannulation and Completion of the synthesis



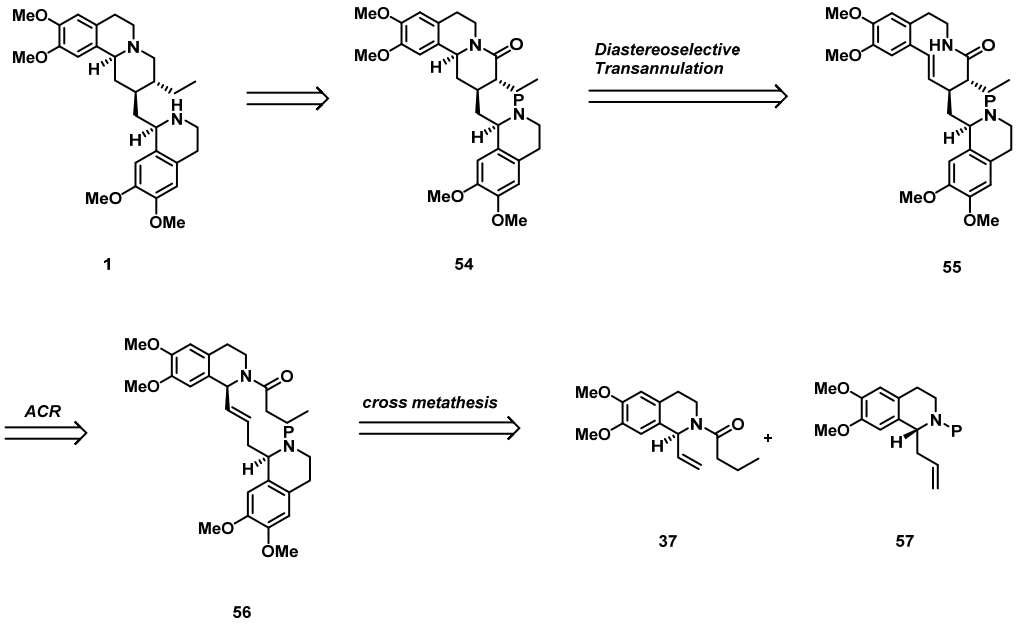
5. Further Studies on the Synthesis of (-)-Emetine

5-1. Retrosynthetic analysis

After the total synthesis of (-)-protoemetinol was accomplished, we further explored the synthesis of (-)-emetine **1**, one of the representative benzo[α]quinolizine alkaloids. Emetine is a well-known alkaloid because of the multiple biological activities as mentioned earlier.

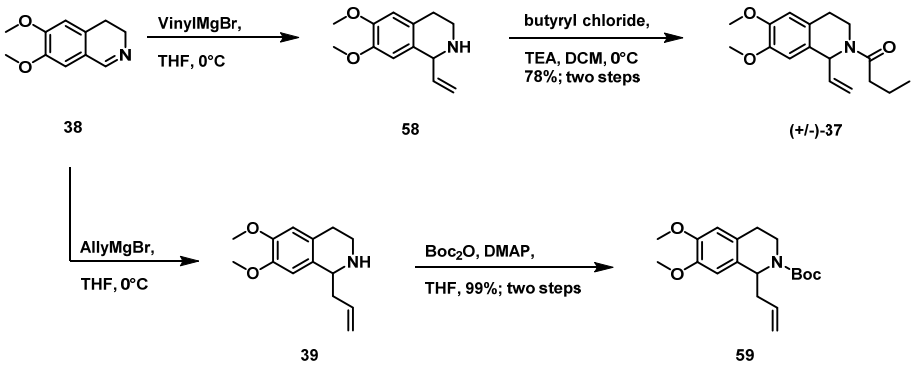
The retrosynthetic analysis is shown in Fig 9. The reported total syntheses of emetine almost started from protoemetinol or its relatives, because it possesses a tetrahydroisoquinoline moiety at lower part. Therefore, we focus on the convergent synthetic approach. Two tetrahydroisoquinoline fragments are prepared and then coupled *via* optimized cross metathesis. With the major building blocks constructed, the key sequence reactions are conducted to build the benzo[α]quinolizine framework. Formation of a proper chairlike transition state will be major concern for the desired stereoselectivity on the ACR and transannulation reactions.

Fig 9. Retrosynthesis of (-)-emetine



5-2. Cross metathesis

Scheme 5. Preparation of cross metathesis precursors

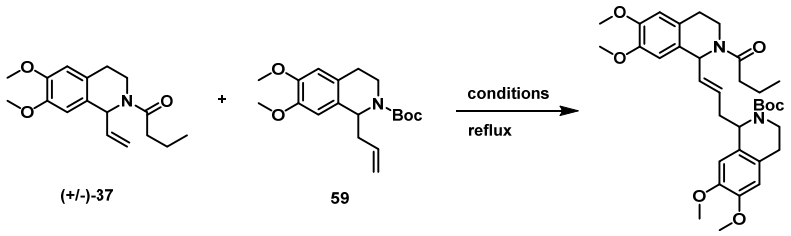


For efficiency, the cross metathesis precursors were prepared as racemates (Scheme 5). The dihydroisoquinoline **38** was converted in the treatment of vinylMgBr, followed by a butyryl amidation to give the vinyl counterpart **37**. A portion of **38** was also reacted with

allylMgBr, followed by Boc protection to obtain allyl counterpart **59**.

We conducted a cross metathesis reaction of **37** and **59** under the various conditions. The isomerized and dimer compounds of **59** were mainly identified in entry 3 because of the sufficient reactivity of allyl tetrahydroisoquinoline, while either isomerization or dimerization of vinyl counter **37** were not observed. We conducted a lot of trials to increase the yield of cross metathesis such as extending the loading amount of catalyst up to 50 mol%, adding Lewis acid like Cy_2BCl, (entry 9 and 10) or changing the solvent such as hexafluorobenzene, 1,2-difluorobenzene or xylene (entry 6, 7 and 8). However, little improvement was shown, and the low reactivity of **37** was likely the main cause (Table 3).

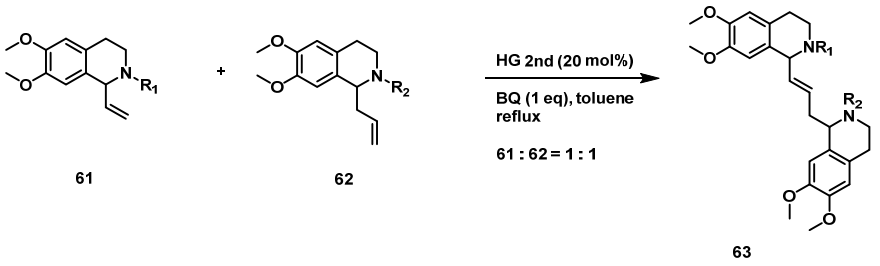
Table 3. Trial on cross metathesis I



(+/-)-37 59 60

entry	Catalyst(mol%)	Additives(eq)	solvent	t	result
1	G2 (30)	-	toluene	74hr	Trace
2	Schrock (30)	-	benzene	30hr	Trace
3	HG2 (20)	-	toluene	2hr	3%
4	HG2 (20)	BQ (2)	toluene	67hr	6%
5	HG2 (30)	BQ (1)	toluene	140hr	14%
6	HG2 (20)	BQ (1)	hexafluorobenzene	69hr	6%
7	HG2 (20)	BQ (1)	1,2-difluorobenzene	72hr	8%
8	HG2 (20)	BQ (1)	xylene	94hr	9%
9	HG2 (20)	BQ (1), Cy_2BCl (20 mol%)	toluene	30hr	10%
10	HG2 (50)	BQ (1), Cy_2BCl (10 mol%)	toluene	72hr	19%

Table 4. Trial on cross metathesis II



61 62 63

No.	R_1	R_2	t	Result
1	butyryl	PMB	72hr	no rxn
2	butyryl	Bn	73hr	no rxn
3	α -bromobutyryl	Boc	87hr	22%
4	α -bromobutyryl	Ts	72hr	Ts dimer 36% (E/Z isomer 2:1)
5	α -bromobutyryl	CO_2Me	69hr	CO_2Me dimer 60%
6	α -bromobutyryl	Bn	64hr	no rxn
7	α -bromobutyryl	Me	53hr	no rxn
8	CO_2Me	Boc	66hr	43%
9	CO_2Me	Bn	60hr	5%
10	CO_2Me	Ts	45hr	30%, Ts dimer 25%
11	$COCF_3$	Boc	66hr	Boc dimer 49%
12	Ts	Boc	56hr	**65%**
13	Ns*	Boc	61hr	**73%**
14	dNs**	Boc	56hr	**75%**

*:4-Nitrophenylsulfonyl
**:2,4-Dinitrophenylsulfonyl

We decided to alter the electronic properties of two substrates, especially the vinyl counterpart, for increasing the yield of cross metathesis. The alkyl chain of a vinyl counterpart **37** and the Boc protecting group of an allyl counterpart **59** were converted to electron withdrawing or donating groups. Substituting the Boc group to more electron donating groups such as benzyl or PMB, the cross metathesis reaction did not occur (entry 1 and 2, Table 4). The cross metathesis is well-known for the preference of electron withdrawing conditions. Adding the Lewis acid like Cy_2BCl, seen above, can be understood in the same context. Therefore, when the Boc group was transformed to the tosyl or CO_2Me,

the dimer of **62** was formed because of the excessively increasing reactivity (entry 4, 5 and 10). When we altered the butyryl group of vinyl substrate **61** to the electron withdrawing groups such as α-bromobutyryl, CO_2Me, $COCF_3$, Ts, Ns(4-nitrophenylsulfonyl) or dNs(2, 4-dinitrophenylsulfonyl), the big improvement was shown. Especially in case of Ts, Ns and dNs, the best yields were obtained (entry 13, 17 and 18). The preparation of Ts and dNs-protected substrate is shown in Scheme 6.

Scheme 6. Preparation of the Ts or dNs-protected substrate

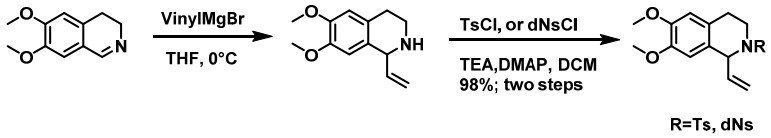
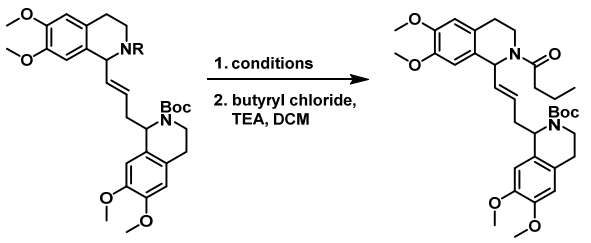


Table 5. Re-introduction of butyryl group: Ts and dNs deprotection



64 60

Entry	R	condition	Solvent	T	result
1	Ts	LiOH	THF/H_2O	rt	no reaction
2	Ts	5% Na-Hg, NaH_2PO_4•$2H_2O$	MeOH	〃	no reaction
3	Ts	Na•Np	DME	-56℃	side reaction
4	Ts	Na, NH_3, 20min	-	-78℃	10%
5	Ts	Na, NH_3, 10min	-	-42℃	**59%**
6	dNs	$HSCH_2CO_2H$, TEA	DCM	rt	no reaction
7	dNs	$HSCH_2CO_2H$, LiOH•H_2O(4eq)	DCM	〃	no reaction
8	dNs	$HSCH_2CO_2H$, LiOH(4eq)	DMF	〃	43%
9	dNs	$HSCH_2CO_2H$, LiOH(excess)	DMF	〃	degradation
10	dNs	$HSCH_2CO_2H$, LiOH•H_2O(4eq)	DMF	〃	**45%**
11	dNs	$HSCH_2CO_2H$(2eq), LiOH•H_2O(4eq)	DMF	60℃	20%

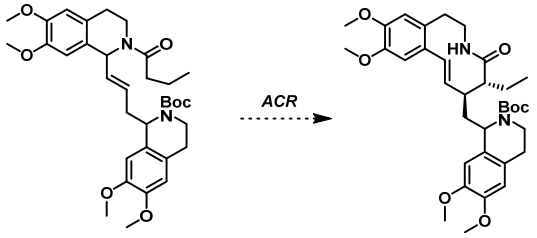
With the cross metathesis product **64** in our hand, we re-introduced the butyryl group on amine group (Table 5). Among the various deprotection conditions, entry 8 turned out to be the best result for the tosyl group and entry 13 for the dNs group.

5-3. Studies on aza-Claisen rearrangement

We executed the key ACR to obtain the 10-membered lactam intermediate **65** with two desired stereogenic centers. Because we observed the superiority of *i*-PrMgCl in the benzylic proton-presence ACR (see Table 2), *i*-PrMgCl was the first choice of an ACR base. When the ACR precursor **60** was treated in the optimized condition (*i*PrMgCl, benzene, reflux), the rearrangement did not occur, but there was the degradation. The TMS trapping was also failed in the use of TMSOTf. We then examined the LHMDS-mediated ACR as well. Although the substrate of ACR **60** was survived in the treatment of LHMDS, neither the rearranged or even isomerized products were detected. Other base screening resulted in failure (Table 6).

Reformatsky-type aza-Claisen rearrangement was attempted as well. However, we could not observe either the silyl trapped or rearranged product in several conditions, but only a de-bromide compound **60** and the degradation eventually (Table 7).

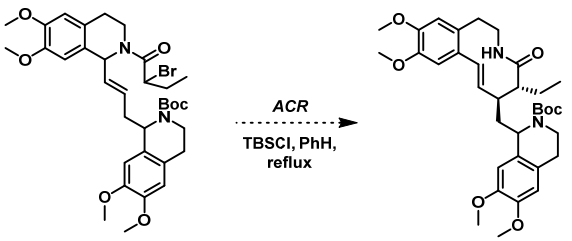
Table 6. Aza-Claisen rearrangement studies



60 **65**

Entry	base	Additive	solvent	temperature	Result
1	iPrMgCl	-	toluene	120℃	Degradation
2	iPrMgCl	-	benzene	90℃	Remained SM, Degradation
3	iPrMgCl	TMSOTf	benzene	-78℃ to reflux	Degradation
4	iPrMgCl	TMSOTf,	THF	-78℃ to reflux	Degradation
5	iPrMgCl	TMSOTf,	toluene	-78℃ to reflux	Degradation
6	LHMDS	-	toluene	120℃	Remained SM
7	LHMDS	TMSOTf,	toluene	-78℃ to reflux	Remained SM
8	LHMDS	TBSOTf	toluene	-78℃ to reflux	Remained SM
9	LHMDS	TBSCl	toluene	-78℃ to reflux	Remained SM
10	nPrMgCl	TMSOTf	toluene	-78℃ to reflux	Remained SM
11	nPrMgCl	TMSOTf,	THF	-78℃ to reflux	Remained SM
12	EtMgBr	-	benzene	90℃	Degradation
13	EtMgBr	LiCl	benzene	90℃	Remained SM
14	MesitylMgBr	-	benzene	90℃	Remained SM
15	PropenylMgBr	LiCl	benzene	90℃	Remained SM
16	nBuLi	TMSOTf	toluene	-78℃ to reflux	Remained SM
17	NaHMDS	-	toluene	120℃	Remained SM
18	KHMDS	-	toluene	120℃	Remained SM

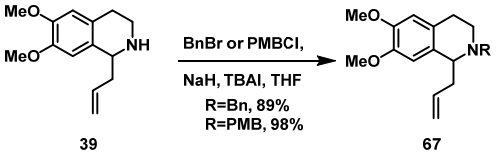
Table 7. Reformatsky-type ACR studies



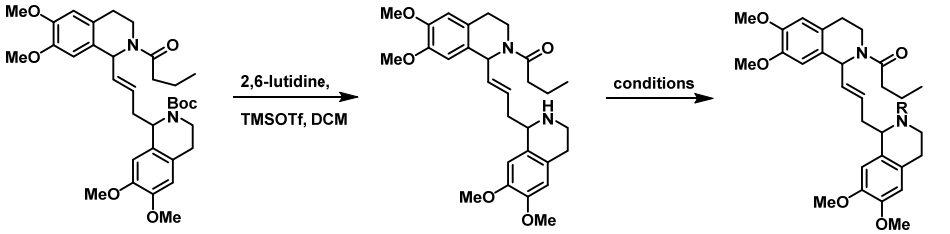
No.	Base (2.4 eq)	Result
1	iPrMgCl	degradation
2	EtMgCl	degradation
3	PhMgCl	degradation
4	CyclopentylMgBr	degradation
5	MesitylMgBr	degradation

We then considered modifying a protecting group of ACR substrate left with the fundamental framework intact. The preparation of the modified precursors was shown in Table 9. We altered the Boc group to the more electron rich groups such as benzyl or PMB. Although the benzylation and PMB protection were carried out smoothly in tetrahydroisoquinoline system (Eq 1), those reactions were struggled in the emetine scaffold. The yield of PMB protection particularly was too low enough to secure the next reaction sequence (entry 5 and 6).

Table 8. Trials on the Bn and PMB protection



39 67 (Eq 1)

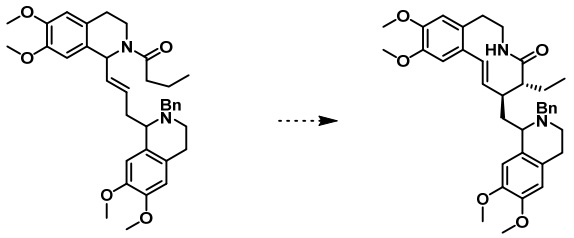


61 68 69 (Eq 2)

No.	R	Base	solvent	Result
1	Bn	K_2CO_3, BnBr, TBAI	EtOH	10%
2	Bn	TEA, BnBr, DMAP	DCM	36%
3	Bn	NaH, BnBr, TBAI	THF	47%
4	Bn	PhCHO, TEA, $NaCNBH_3$	MeOH	**65%**
5	PMB	NaH, PMBCl, TBAI	THF	10%
6	PMB	4-methoxyPhCHO, $Na(OAc)_3BH$	DCM	No reaction

With a small amount of the benzyl substrate **69** available, we conducted the aza-Claisen rearrangement. Although, the stability seemed to be much higher in the *i*-PrMgCl treatment, the reaction did not take place. Isomerized product was detected at a strictly-controlled LHMDS-mediated condition (entry 3, Table 10). The ACR studies for the completion of emetine synthesis are under investigation.

Table 9. ACR study on benzyl substrate



70 71

No.	Base(eq)	Solvent (0.01M)	T	t	Result
1	iPrMgCl (3)	benzene	reflux	2hr	Remained SM
2	LHMDS (2)	toluene	reflux	-	Remained SM
3	LHMDS (3)	toluene	90℃	6hr	Isomerized, 25%*
4	LHMDS (3)	toluene	reflux	2hr	degradation
5	LHMDS (4)	toluene	reflux	3hr	degradation
6	LHMDS (5)	toluene	reflux	1hr	degradation

III. Conclusion

In summary, the concise asymmetric synthesis of (-)-protoemetinol **7** has been accomplished through nine steps (17% overall yield) from the known homoallylic amine **12**. The efficient synthetic procedure employed a sequence of diastereoselective amide enolate-induced ACR of an appropriately substituted dihydroisoquinoline, which is readily prepared via the cross metathesis of *N*-acyl-*a*-vinyl-tetrahydroisoquinoline, and the acid-catalyzed transannulation of the ring-expanded lactam. This unique strategy envisages a unified and versatile synthetic strategy for structurally diverse benzo[α]quinolizidine alkaloids.

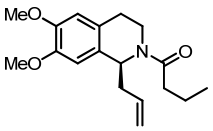
In addition, we further explored the synthesis of one of the representative benzo[α]quinolizine alkaloids, emetine **1**. The reported total syntheses of emetine almost started from protoemetinol or its relatives, because it possesses a tetrahydroisoquinoline moiety at lower part. Therefore, we focus on the convergent synthetic approach. We conducted a cross metathesis reaction of **37** and **59** under the various conditions, but the yield was not satisfactory. We altered the electronic property of the vinyl counterpart, and the big improvement was shown, especially in case of dNs group. Aza-Claisen rearrangement was then conducted in the optimized condition (*i*PrMgCl, benzene, reflux), but the reaction did not occur. The ACR studies for the completion of emetine synthesis are under investigation.

IV. Experimental

General experimental

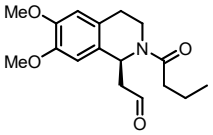
Unless otherwise described, all commercial reagents and solvents were purchased from commercial suppliers and used without further purification, and all anhydrous reactions were carried out under argon gas (1 atm) in flame or oven-dried glassware. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, triethylamine, were freshly distilled with calcium hydride. Flash column chromatography was carried out using silica-gel 60 (230-400 mesh, Merck) and preparative thin layer chromatography was used with glass-backed silica gel plates (1mm, Merck). Thin layer chromatography was performed to monitor reactions. Optical rotations were measured using a JASCO DIP-2000 digital polarimeter at 20 ℃ using 10 or 100 mm cells of 3 mm diameter. Infrared spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. Mass spectra were obtained using a VG Trio-2 GC-MS instrument, and high resolution mass spectra were obtained using a JEOL JMS-AX 505WA unit. ^{1}H and ^{13}C NMR spectra were recorded on either a JEOL JNM-LA 300 (300MHz), JEOL JNM-GCX (400MHz), BRUKERAMX-500 (500MHz) or JEOL (600MHz) spectrometers. Chemical shifts are provided in parts per million (ppm, δ) downfield from tetramethylsilane (internal standard) with coupling constant in hertz (Hz). Multiplicity is indicated by the following abbreviations: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), quintet (quin), quartet of doublet (qd) multiplet (m) and broad (br). The purity of the compounds was determined by normal phase high performance liquid chromatography (HPLC), (Gilson or Waters, CHIRALPAK® AD-H (4.6 × 250 mm) or CHIRALPAK® OD-H (4.6 × 250 mm))

(S)-1-(1-allyl-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)butan-1-one (47)



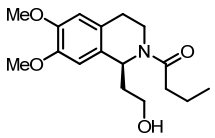
To a solution of the (S)-1-allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (crude, 1.29 mmol) in CH_2Cl_2 (6 mL) was added triethylamine (0.27 ml, 1.93 mmol) followed by an addition of butyryl chloride(1.62 ml, 1.55 mmol) under argon gas at 0℃. The reaction mixture was stirred until complete consumption of the starting material on TLC at ambient temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with CH_2Cl_2. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 1 : 2) afforded 305 mg (78%; two steps) of **47:** $[\alpha]_D^{20}$ +118.6 (*c* 0.93, $CHCl_3$); FT-IR (thin film, neat) *v* max 2960, 1639, 1440 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz, mixture of rotamers) δ 6.41 (d, 1H), 6.64 (d, 1H), 5.97(td, 1H, *J*=5.62, 2.45 Hz), 4.88 (m, 1H), 4.76 (m, 1H), 5.40 (dd, 1H, *J*=6.95, 2.4 Hz), 4.62 (dd, *J*=6.93, 2.55 Hz), 4.46 (dd, *J*=9.28, 5.55 Hz), 3.58 (m, 7H), 3.25 (td, 1H, *J*=12.23, 4.15 Hz), 2.78 (dd, *J*=12.4, 4.15 Hz), 2.64-2.56 (m, 1H), 2.5-2.47 (m, 1H), 2.39-2.24 (m, 2H), 2.21-2.03 (m, 2H), 1.46-1.39 (m, 2H), 0.75-0.67 (m, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.8, 147.0, 146.9, 134.5, 128.5, 124.8, 116.1, 110.7, 109.7, 55.2, 55.1, 50.6, 40.4, 39.1, 34.8, 28.1, 18.0, 13.3; LR-MS (FAB) *m/z* 304 ($M+H^+$); HR-MS (FAB) calcd for $C_{18}H_{26}NO_3$ ($M+H^+$) 304.1913; found 304.1913

(S)-2-(2-butyryl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)acetaldehyde (43)



To a solution of the terminal olefin **47** (305 mg, 1.01 mmol) in Acetone: H_2O (3 mL: 1 mL) was added N-methylmorpholine N-oxide (355 mg, 3.03 mmol) followed by an addition of OsO4 0.1M in toluene (0.76 ml, 0,076 mmol) dropwise at 0℃. The reaction mixture was stirred overnight at ambient temperature and was added sodium periodate (648 mg, 3.03 mmol). The reaction mixture was further stirred for one hour and was quenched with saturated aqueous $Na_2S_2O_3$ and diluted with EtOAc. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 1 : 2) afforded 293 mg (95%) of **43**: $[\alpha]_D^{20}$ +147.2 (*c* 2.0, $CHCl_3$); FT-IR (thin film, neat) *v* max 2961, 1720, 1636 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 9.70 (s, 1H), 6.58 (s, 1H), 6.51 (s, 1H), 5.93 (t, 1H, *J*=4.4 Hz), 3.74 (m, 7H), 3.40 (m, 1H), 2.78-2.74 (m, 2H), 2.69-2.65 (m, 2H), 2.32-2.17 (m, 2H), 1.57-1.53 (m, 2H), 0.87-0.84 (m, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 199.8, 171.9, 147.8, 147.7, 127.6, 125.4, 111.1, 109.5, 55.8, 55.7, 50.9, 47.5, 39.9, 35.2, 28.4, 18.2, 13.6; LR-MS (FAB) *m/z* 306 ($M+H^+$); HR-MS (FAB) calcd for $C_{17}H_{24}NO_4$ ($M+H^+$) 306.1705; found 306.1708

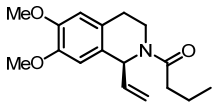
(S)-1-(1-(2-hydroxyethyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)butan-1-one (49)



To a solution of the aldehyde **43** (293 mg, 0.96 mmol) in methanol (5 mL) was added sodium borohydride (18 mg, 0.48 mmol) at room temperature and stirred until complete consumption of the starting material on TLC. The reaction mixture was evaporated and diluted with EtOAc and water. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 2 : 1) afforded 292 mg (99%) of **49**: $[\alpha]_D^{20}$

+81.9 (*c* 1.7, $CHCl_3$); FT-IR (thin film, neat) *v* max 3399, 2958, 1613 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz, mixture of rotamers) δ 6.60 (s, 1H), 6.52 (s, 1H), 5.46 (d, 1H, *J*=11.35 Hz), 3.84 (d, 1H, *J*=12.6 Hz), 3.77 (s, 6H), 3.56 (d, 1H, *J*=10.65 Hz), 3.37-3.27 (m, 2H), 2.88-2.81 (m, 1H), 2.69-2.66 (m,1H), 2.45-2.40 (m, 1H), 2.34-2.28 (m, 1H), 2.08-2.03 (m, 1H), 1.73-1.60 (m, 3H), 0.93(t, 3H, *J*=7.35 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 173.3, 147.8, 147.6, 129.1, 124.8, 111.1, 109.8, 58.0, 55.9, 55.8, 48.9, 39.7, 38.4, 35.2, 28.5, 18.7, 13.8; LR-MS (FAB) *m/z* 308 ($M+H^+$); HR-MS (FAB) calcd for $C_{17}H_{26}NO_4$ ($M+H^+$) 308.1862; found 308.1866.

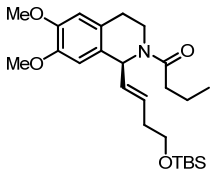
(S)-1-(6,7-dimethoxy-1-vinyl-3,4-dihydroisoquinolin-2(1H)-yl)butan-1-one (37)



To a solution of the alcohol **49** (292 mg, 0.95 mmol) and 1-nitro-2-selenocyanatobenzene (259 mg, 1.14 mmol) in THF (5 mL) was added tributhylphosphine (0.36 ml, 1.43 mmol) slowly at 0℃ under argon gas. The reaction mixture was stirred until complete consumption of the starting material on TLC and was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 2 : 1) afforded (S)-1-(6,7-dimethoxy-1-(2-(2-nitrophenylselanyl)ethyl)-3,4-dihydroisoquinolin-2(1H)-yl)butan-1-one intermediate. Hydrogen peroxide was added dropwise in the solution of the selenide intermediate in THF (5 mL) at 0℃. The reaction mixture was stirred until complete consumption of the starting material on TLC and was quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on

silica gel (EtOAc : Hexane = 1 : 2) afforded 192 mg (70%; two steps) of **37**: $[\alpha]_D^{20}$ +145.7 (*c* 1.99, $CHCl_3$); FT-IR (thin film, neat) *v* max 2960, 1643, 1254 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz, mixture of rotamers) δ 6.57-6.55 (m, 2H), 6.02 (d, 1H, *J*=4.5 Hz), 5.96-8.85 (m, 1H), 5.23-5.22 (m), 5.81 (dd, 1H, *J*=10.2 Hz), 5.01 (dd, 1H, *J*=17.05 Hz), 3.80-3.77 (m, 7H), 3.40 (td, 1H, *J*=12.19, 4.05 Hz), 2.97 (td, *J*=12.05, 3.85 Hz), 2.84-2.75 (m, 1H), 2.68-2.56 (m, 1H), 2.40-2.25 (m, 2H), 1.67-1.61 (m, 2H), 0.94-0.89 (m, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 171.3, 147.7, 147.4, 137.3, 126.6, 125.9, 116.4, 111.0, 110.9, 55.8, 55.7, 53.8, 40.0, 35.4, 28.6, 18.6, 13.9; LR-MS (FAB) *m/z* 290 ($M+H^+$); HR-MS (FAB) calcd for $C_{17}H_{24}NO_3$ ($M+H^+$) 290.1756; found 290.1760.

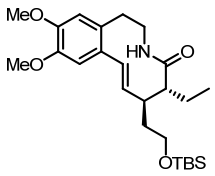
(S,E)-1-(1-(4-(tert-butyldimethylsilyloxy)but-1-enyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)butan-1-one (36)



To a solution of the allylamide **37** (45 mg, 0.16 mmol) and (but-3-enyloxy)(tert-butyl)dimethylsilane (87 mg, 0.47 mmol) in anhydrous toluene (1.5 mL) was added Hoveyda-Grubbs' 2nd generation catalyst (20mg, 0.032 mmol), followed by an addition of 1,4-benzoquinone (51 mg, 0.47 mmol) under argon gas. The reaction mixture was refluxed for 2 days and cooled to room temperature followed by an addition of Dimethyl sulfoxide (0.1 ml, 50 equiv per 1 equiv Hoveyda-Grubbs' cat.). The reaction mixture was stirred open to the air for 12hr and purified by flash column chromatography directly on silica gel (EtOAc : Hexane = 1 : 2) directly afforded 37 mg (52%; brsm 73%) of **36**: $[\alpha]_D^{20}$ +106.9 (*c* 1.5, $CHCl_3$); FT-IR (thin film, neat) *v* max 2956, 1255, 836 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz, mixture of rotamers) δ 6.57 (s, 2H), 6.04 (d, 1H, *J*=5.49 Hz), 5.63-5.36 (m, 2H),

5.23(d, *J*=5.49 Hz), 3.83-3.81 (m, 6H), 3.80-3.76 (m, 1H), 3.62-3.54 (m, 2H), 3.49-3.45 (m, 1H), 3.00 (m), 2.81-2.58 (m, 2H), 2.41-2.31 (m, 2H), 2.28-2.20 (m, 2H), 1.72-1.64 (m, 2H), 0.98-0.92 (m, 3H), 0.88-0.83 (m, 9H), 0.00- -0.02 (m, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 171.4, 147.8, 147.5, 131.2, 129.7, 119.4, 116.1, 111.1, 111.0, 62.6, 55.9, 55.8, 53.3, 39.9, 35.7, 35.5, 28.7, 27.9, 25.8, 25.8, 25.8, 18.7, 13.9, -5.4, -5.4; LR-MS (FAB) *m/z* 448 ($M+H^+$); HR-MS (FAB) calcd for $C_{25}H_{42}NO_4Si$ ($M+H^+$) 448.2883; found 448.2863.

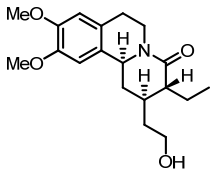
(5R,6S,E)-6-(2-(tert-butyldimethylsilyloxy)ethyl)-5-ethyl-10,11-dimethoxy-2,3,5,6-tetrahydrobenzo[d]azecin-4(1H)-one (54)



To a solution of the (*E*)-olefin **36** (37 mg, 0.083 mmol) in anhydrous benzene (8 mL) was added iPrMgCl (2.0M in THF, 0.17 ml) dropwise at reflux condition under argon gas. The reaction mixture was further refluxed for 6hr and quenched with water. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 1 : 2) afforded 20 mg (55%) of **54**: $[\alpha]_D^{20}$ +144.9 (*c* 0.76, $CHCl_3$); FT-IR (thin film, neat) *v* max 2956, 1509, 837 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.73 (s, 1H), 6.64 (s, 1H), 6.57 (d, 1H, *J*=16.0 Hz), 5.18 (dd, 1H, *J*=16.0, 9.5 Hz), 4.05-4.01 (m, 1H), 3.86 (m, 6H), 3.75-3.70 (m, 1H), 3.67-3.62 (m, 1H), 3.49 (td, 1H, *J*=13.45, 3.35 Hz), 2.78-2.72 (m, 1H), 2.41 (qd, 1H, *J*=10.35, 2.45 Hz), 2.23 (d, 1H, *J*=14.35 Hz), 1.99-1.93 (m, 1H), 1.77-1.70 (m, 1H), 1.62-1.48 (m, 2H), 1.40-1.33 (m, 1H), 0.89-0.81 (m, 12H), 0.06 (s, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 176.1, 147.9, 147.9, 137.7, 133.0, 132.9, 130.4, 113.4, 109.4, 61.9, 56.5, 56.1, 56.1, 44.3, 43.9, 34.8, 30.8, 26.0, 26.0, 26.0, 21.3, 18.3, 12.8, -5.2, -5.2; LR-MS

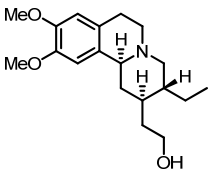
(FAB) *m/z* 448 ($M+H^+$); HR-MS (FAB) calcd for $C_{25}H_{42}NO_4Si$ ($M+H^+$) 448.2883; found 448.2891.

(2R,3R,11bS)-3-ethyl-2-(2-hydroxyethyl)-9,10-dimethoxy-2,3,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-4(11bH)-one (35)



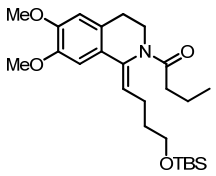
To a solution of the (*E*)-olefin **54** (20 mg, 0.045 mmol) in benzene (4 mL) was added pTSA·H_2O (11 mg, 0.067 mmol). The reaction mixture was stirred stirred at 60℃ until complete consumption of the starting material on TLC and quenched with water. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : MeOH = 10 : 1) afforded 11 mg (72%) of **35**: $[\alpha]_D^{20}$ -55.5 (*c* 0.54, $CHCl_3$); FT-IR (thin film, neat) *v* max 3403, 2925, 1614 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz, mixture of rotamers) *δ* 6.64 (s, 1H), 6.59 (s, 1H), 4.85 (dq, 1H, *J*=11.65, 1.9 Hz), 4.58 (dd, *J*=11.18, 3.35 Hz), 3.85 (s, 3H), 3.84 (s, 3H), 3.83-3.74 (m, 2H), 2.84 (td, 1H, *J*=13.5, 4.7 Hz), 2.75 (td, 1H, *J*=12.1, 2.45 Hz), 2.59 (d, 1H, *J*=15.2 Hz), 2.50 (dt, 1H, *J*=13.2, 3.6 Hz), 2.15-2.09 (m, 2H), 2.09-2.00 (m, 1H), 1.89-1.82 (m, 1H), 1.72-1.63 (m, 1H), 1.46-1.39 (m, 1H), 1.38-1.3 (m, 1H), 1.27-1.19 (m, 1H), 0.91-0.86 (m, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) *δ* 171.4, 147.8, 147.8, 129.1, 127.4, 111.5, 108.6, 60.4, 56.2, 55.9, 55.7, 48.1, 39.6, 37.3, 37.2, 30.9, 28.6, 22.4, 10.0; LR-MS (FAB) *m/z* 334 ($M+H^+$); HR-MS (FAB) calcd for $C_{19}H_{28}NO_4$ ($M+H^+$) 334.2018; found 334.2037.

(-)-Protoemetinol (7)



To a solution of the alcohol **35** (11 mg, 0.033 mmol) in anhydrous THF (1 mL) was added LAH powder (3.75 mg, 0.099 mmol) under argon gas. The reaction mixture was refluxed until complete consumption of the starting material on TLC and cooled to room temperature. The reaction mixture was quenched with saturated aqueous potassium sodium tartrate and diluted with EtOAc. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : MeOH = 10 : 1) afforded 9 mg (85%) of **7**: $[\alpha]_D^{22}$ -44.25 (*c* 0.09, MeOH); FT-IR (thin film, neat) *v* max 2925, 1366, 1257 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.67 (s, 1H), 6.55 (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.81-3.71 (m, 2H), 3.13-3.05 (m, 3H), 2.98-2.96 (m, 1H), 2.61 (d, 1H, *J*=15.35 Hz), 2.47 (td, 1H), 2.32 (d, 1H, *J*=12.9 Hz), 2.02-1.98 (m, 1H), 1.97-1.92 (m, 1H), 1.70-1.63 (m, 1H), 1.44-1.43 (m, 3H), 1.28-1.24 (m, 1H), 1.16-1.08 (m, 1H), 0.91 (t, 3H, *J*=7.5 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 147.5, 147.2, 129.4, 126.7, 111.5, 108.3, 62.7, 61.4, 60.7, 56.1, 55.8, 52.5, 41.2, 37.6, 37.3, 35.9, 29.1, 23.5, 11.1; LR-MS (FAB) *m/z* 320 ($M+H^+$); HR-MS (FAB) calcd for $C_{19}H_{30}NO_3$ ($M+H^+$) 320.2226; found 320.2212.

(Z)-1-(1-(4-(tert-butyldimethylsilyloxy)butylidene)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)butan-1-one (55)



To a solution of the (*E*)-olefin **36** (37 mg, 0.083 mmol) in anhydrous benzene (8 mL) was added LHMDS (1.0M in THF, 0.34 ml) dropwise at reflux condition under argon gas. The reaction mixture was further refluxed for 6hr and quenched with water. The organic phase was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 1 : 2) afforded 19 mg (51%) of **55:** ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.93 (s, 1H), 6.54 (s, 1H), 5.88-5.85 (q, 1H), 4.92-4.89 (q, 1H), 3.89 (s, 3H), 3.87-3.83 (m, 1H), 3.84 (s, 3H), 3.68-3.56 (m, 3H), 3.09-3.02 (td, 1H), 2.97-2.91 (td, 1H), 2.58-2.54 (dd, 1H), 2.33-2.09 (m, 3H), 1.73-1.57 (m, 2H), 0.87 (s, 9H), 0.79-0.76 (t, 3H), 0.03 (s, 6H); LR-MS (FAB) *m/z* 448 ($M+H^+$); HR-MS (FAB) calcd for $C_{25}H_{41}NO_4Si$ ($M+H^+$) 447.28; found 448.2876.

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15. Intermediate **13** is an antipode of the reported homoallylic amine. Refer to references 14 and 8b .

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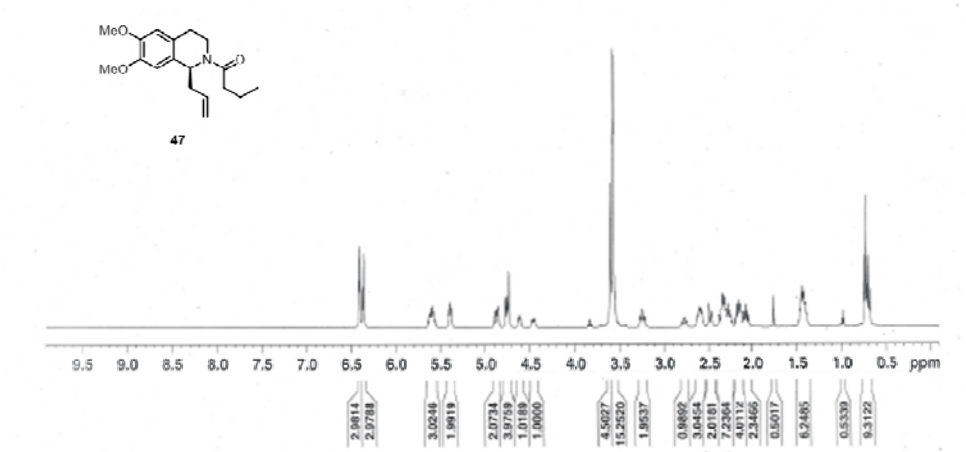
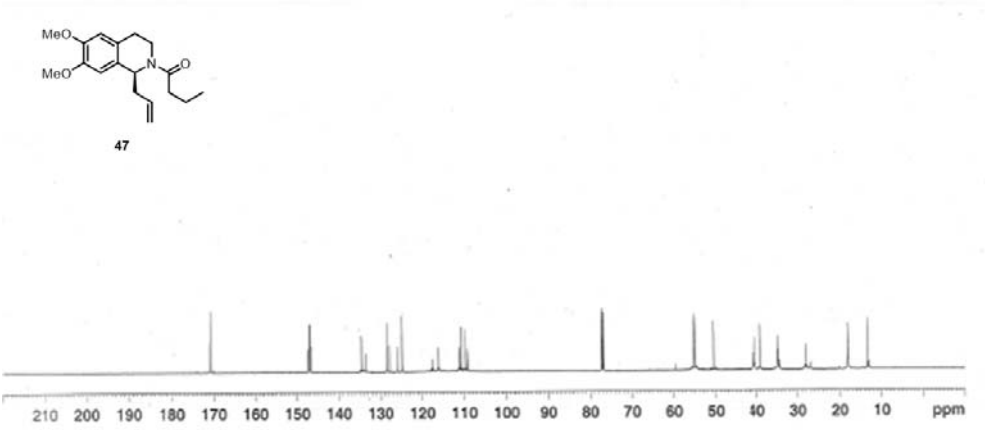
18. All spectral data of the synthetic (-)-protoemetinol were identical to those of the authentic **7.**

VI. Appendix

▼ ^{1}H-NMR ($CDCl_3$, 500 MHz)



▼ ^{13}C-NMR ($CDCl_3$, 125 MHz)



▼ HPLC (chiral AD-H, Hex: ProH= 4: 1)

Thu Aug 25 2011 15:02:37 Results Report Page 1

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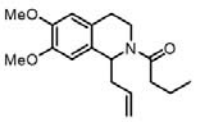
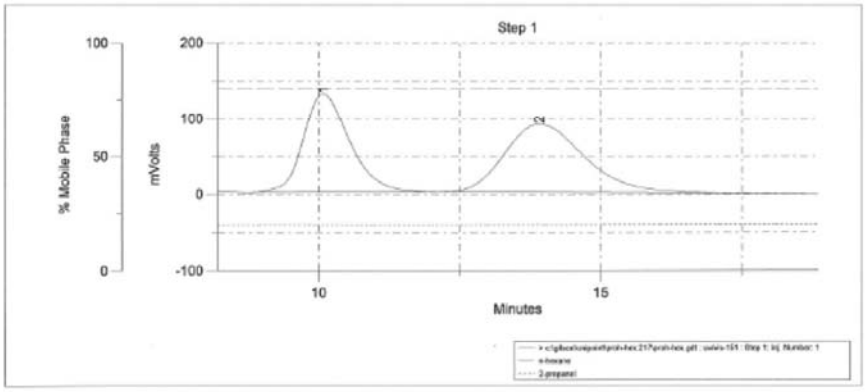


(+/-)-47



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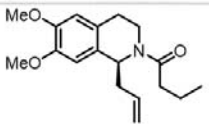

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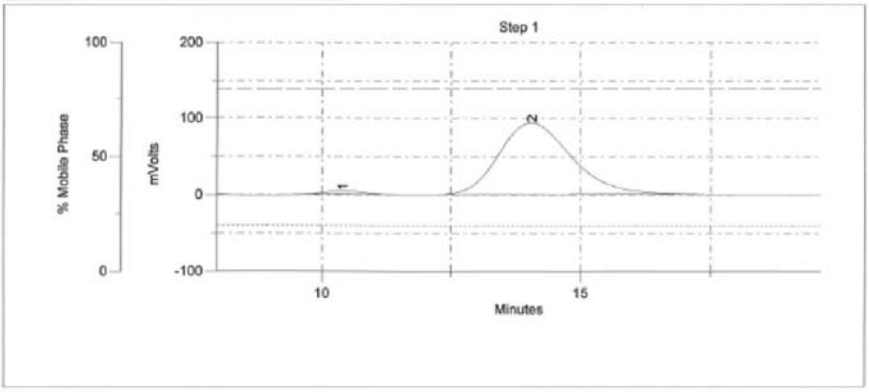

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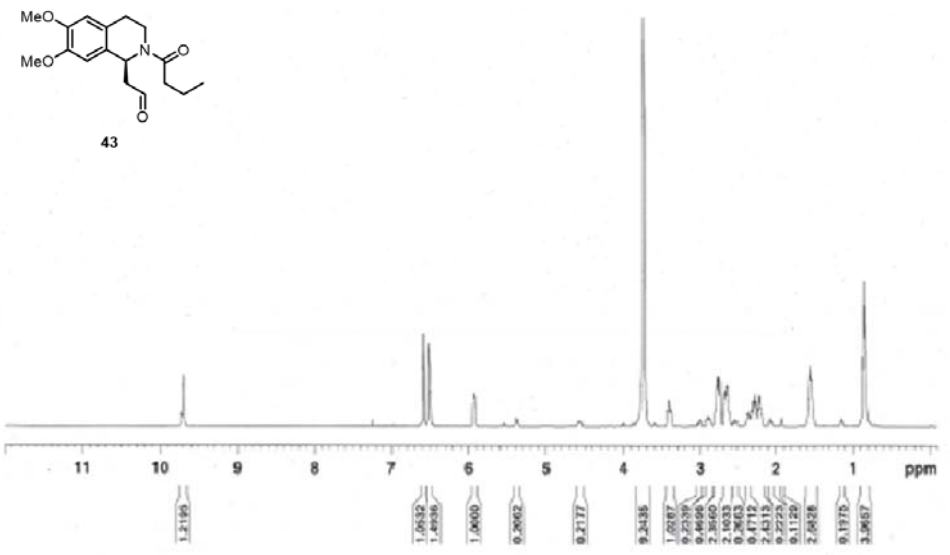
▼ ^{1}H-NMR ($CDCl_3$, 500 MHz)



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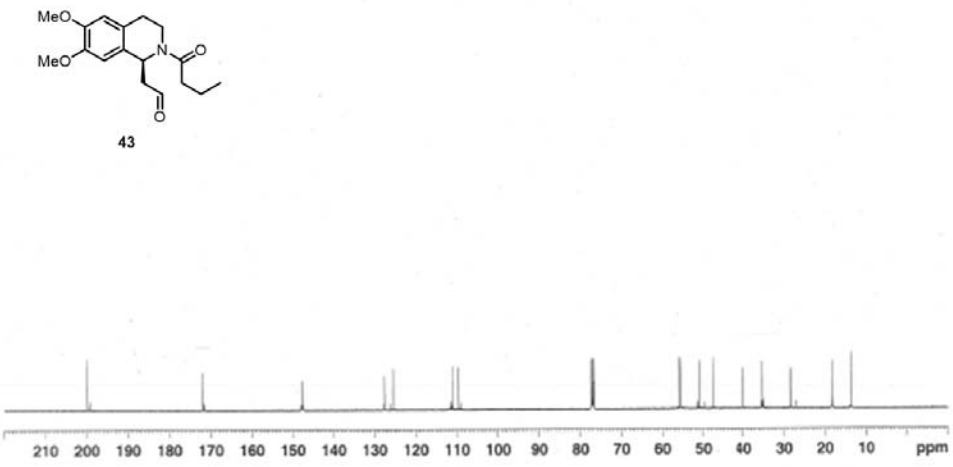

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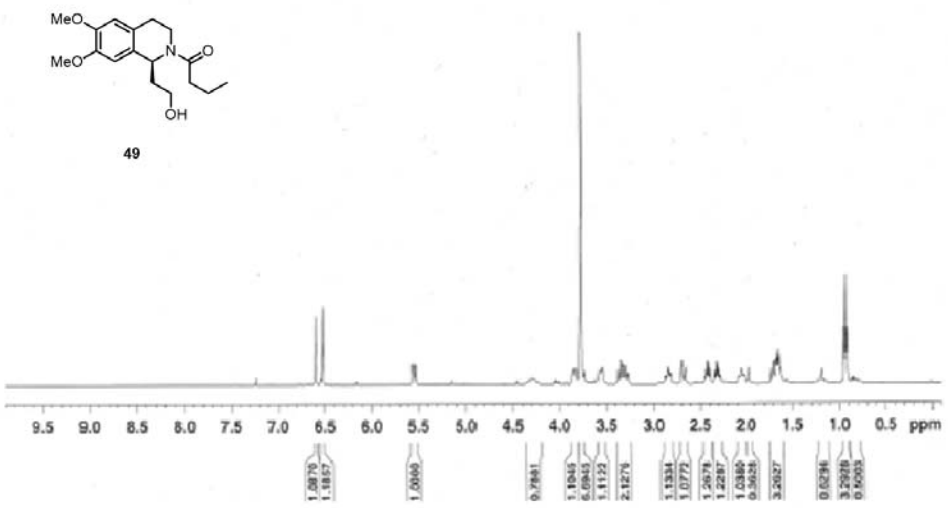

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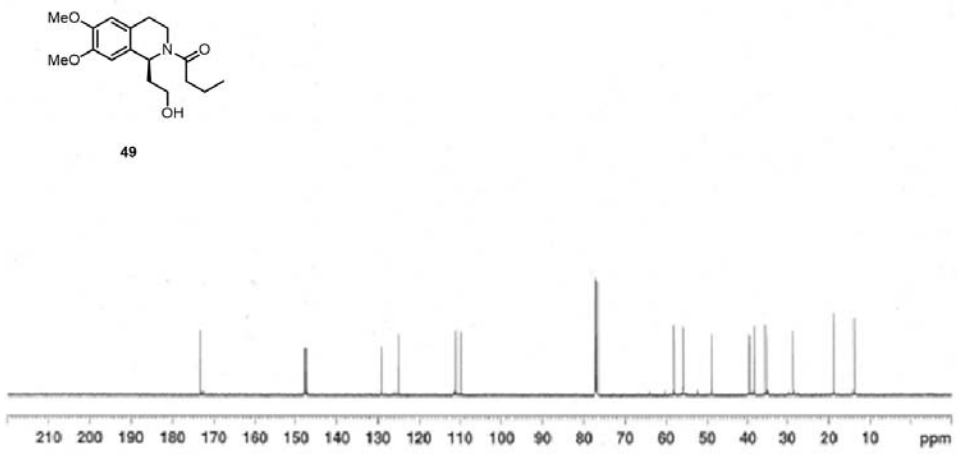

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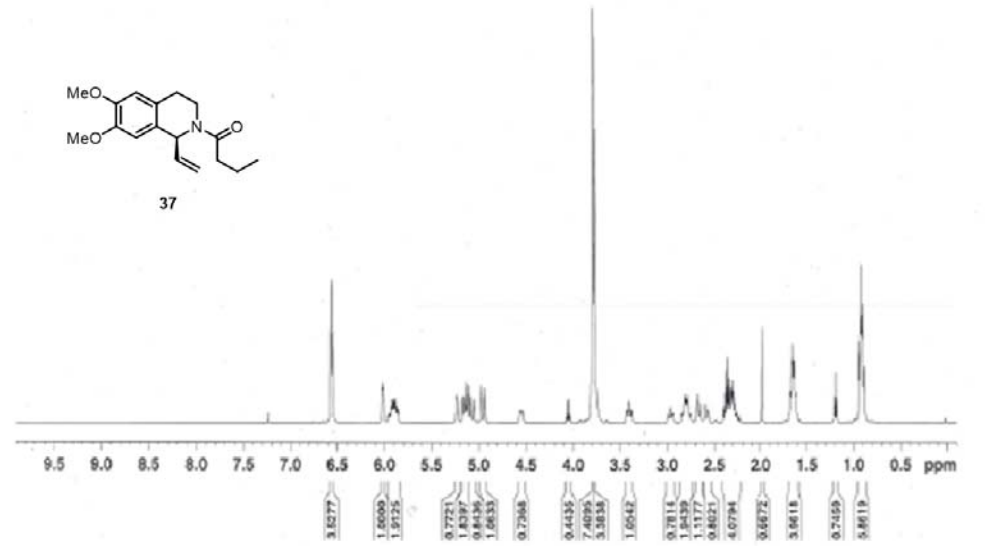

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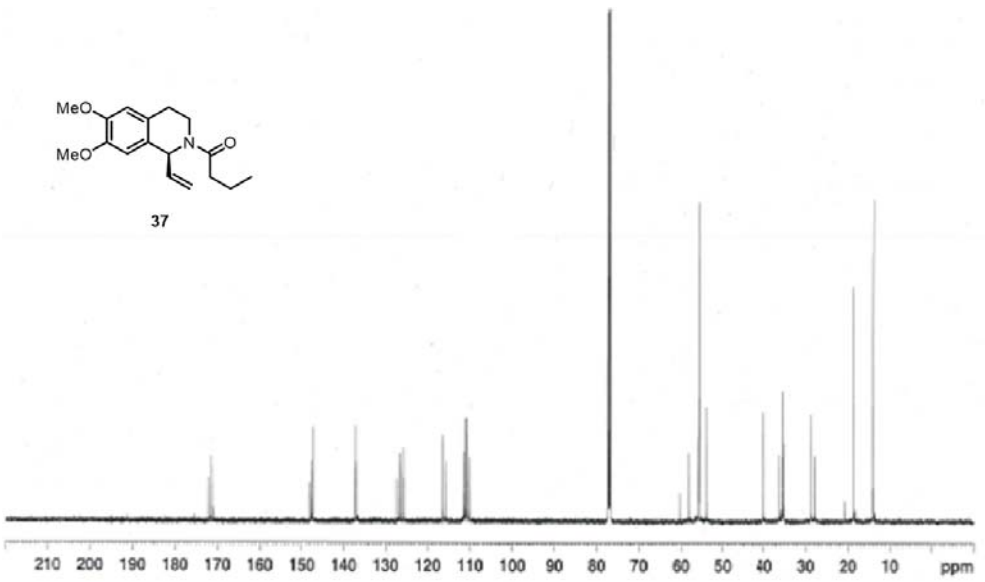

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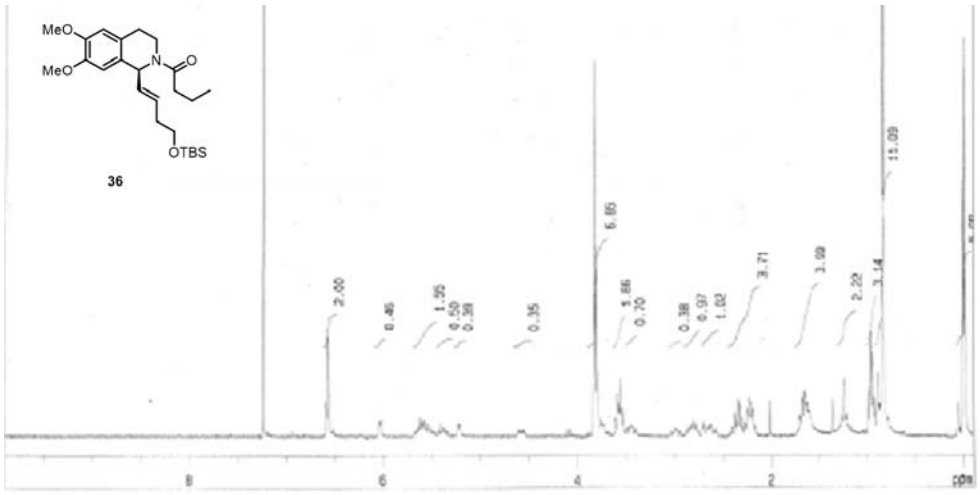
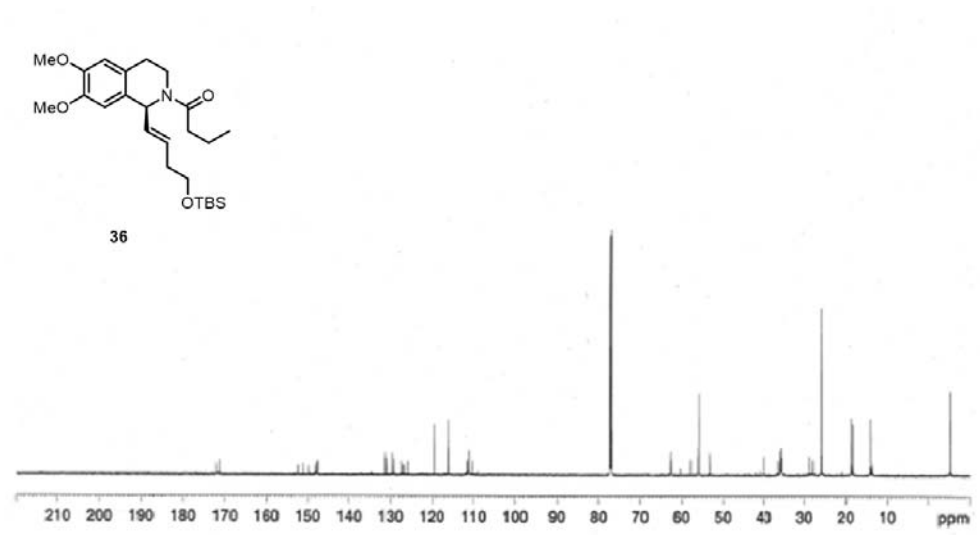
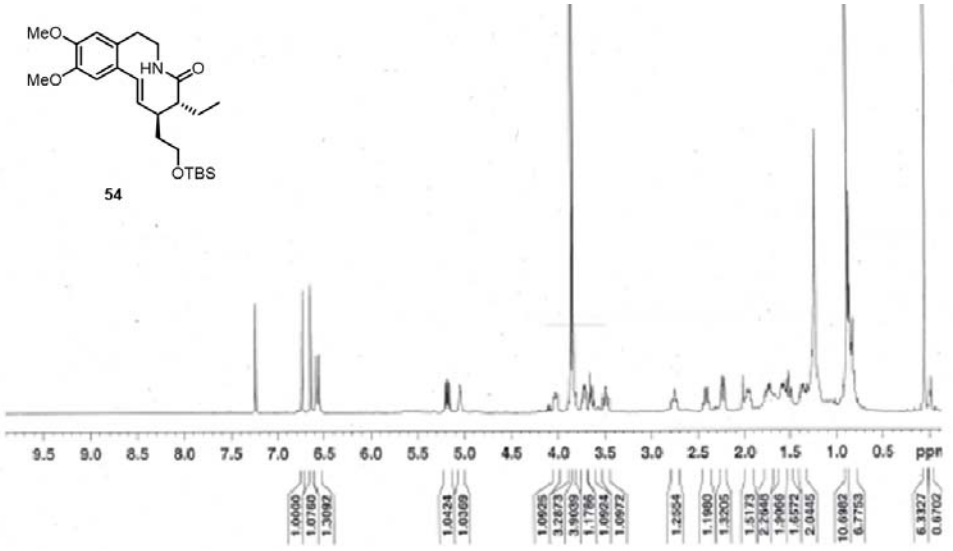


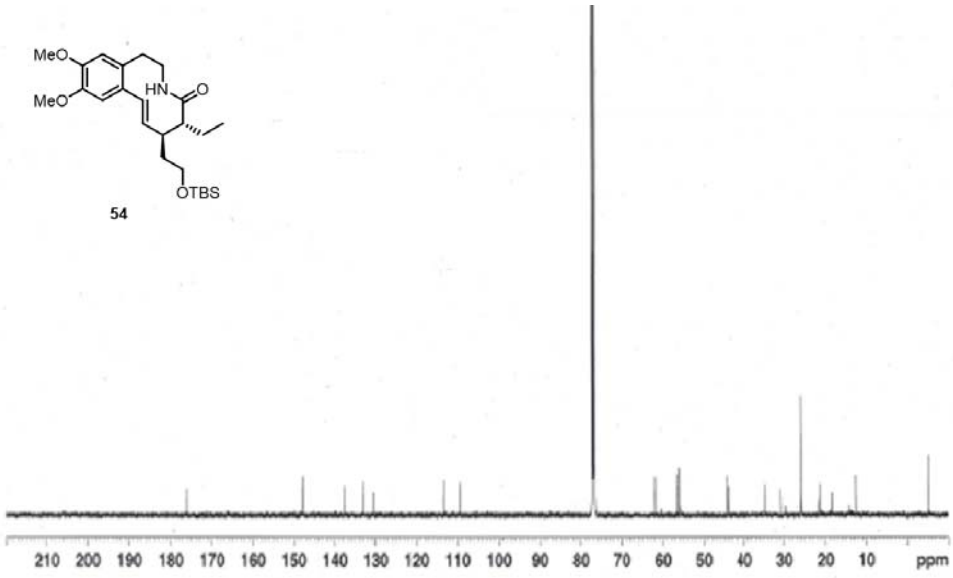
▼ ^{13}C-NMR ($CDCl_3$, 125 MHz)



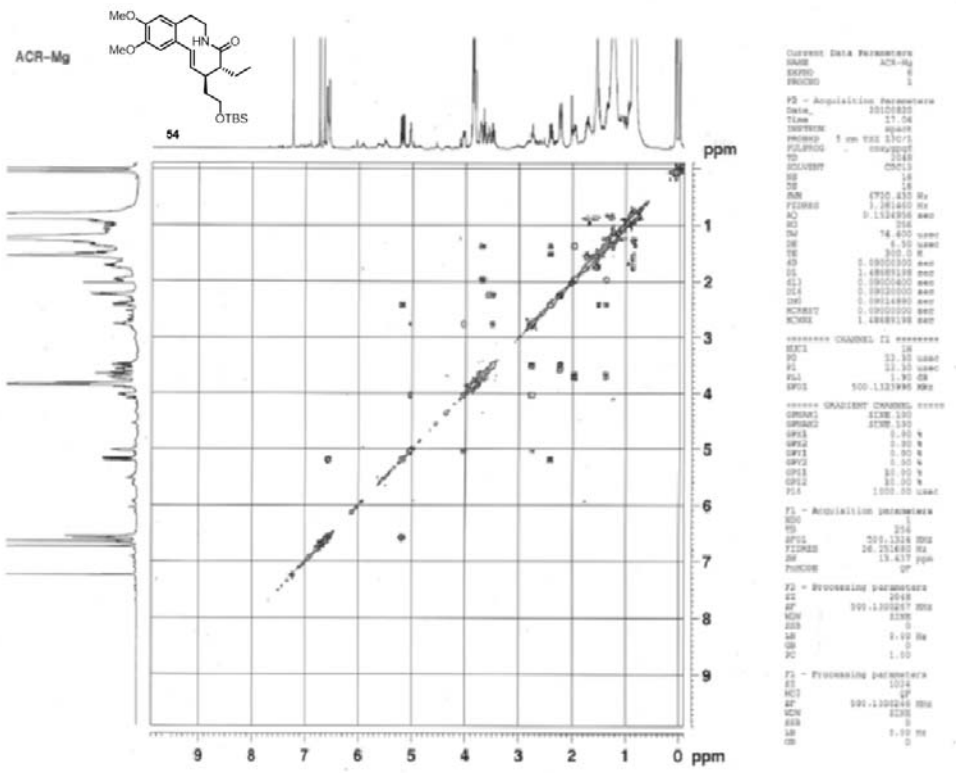
▼ ^{1}H-NMR ($CDCl_3$, 500 MHz)



▼ ^{13}C-NMR ($CDCl_3$, 125 MHz)



▼ COESY



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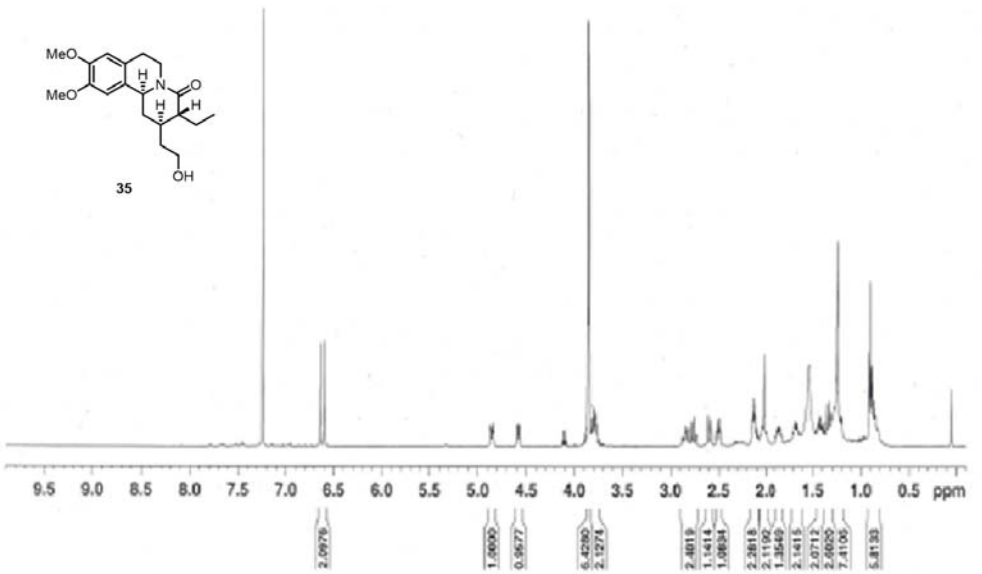
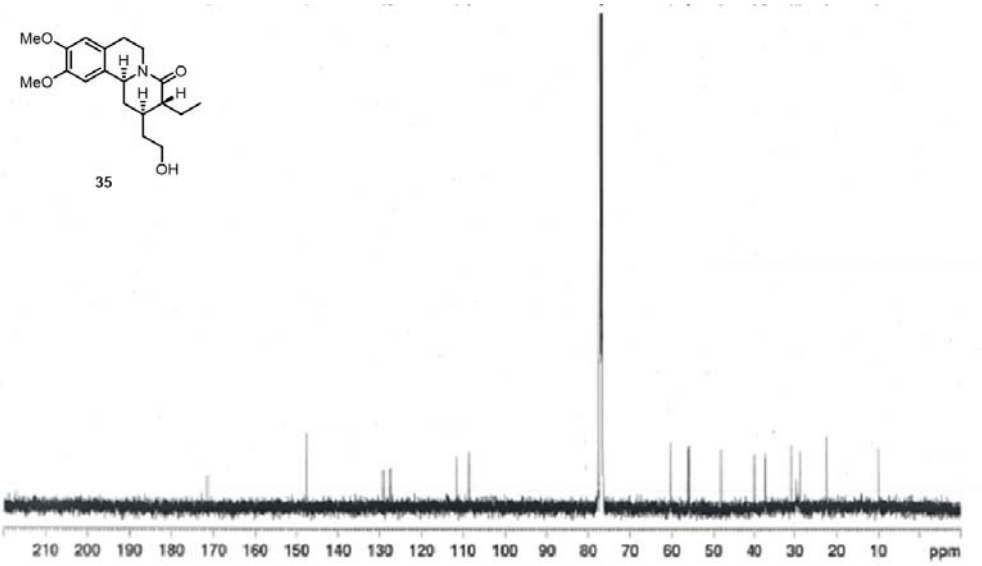


▼ ^{13}C-NMR ($CDCl_3$, 125 MHz)



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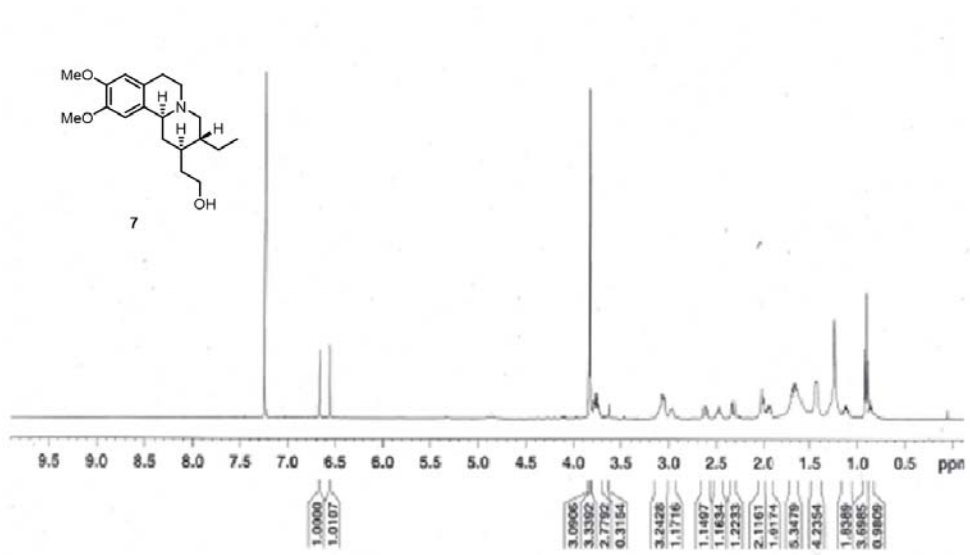
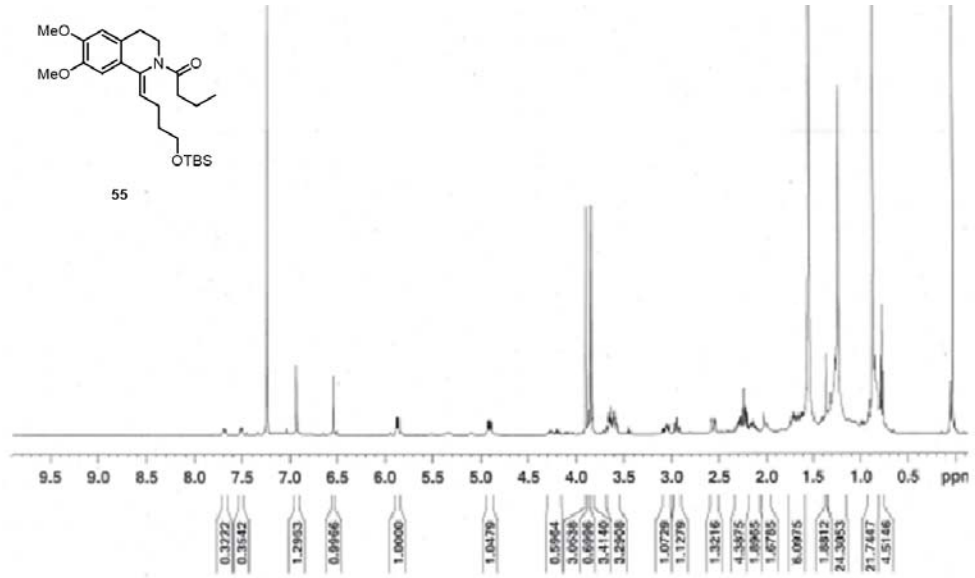
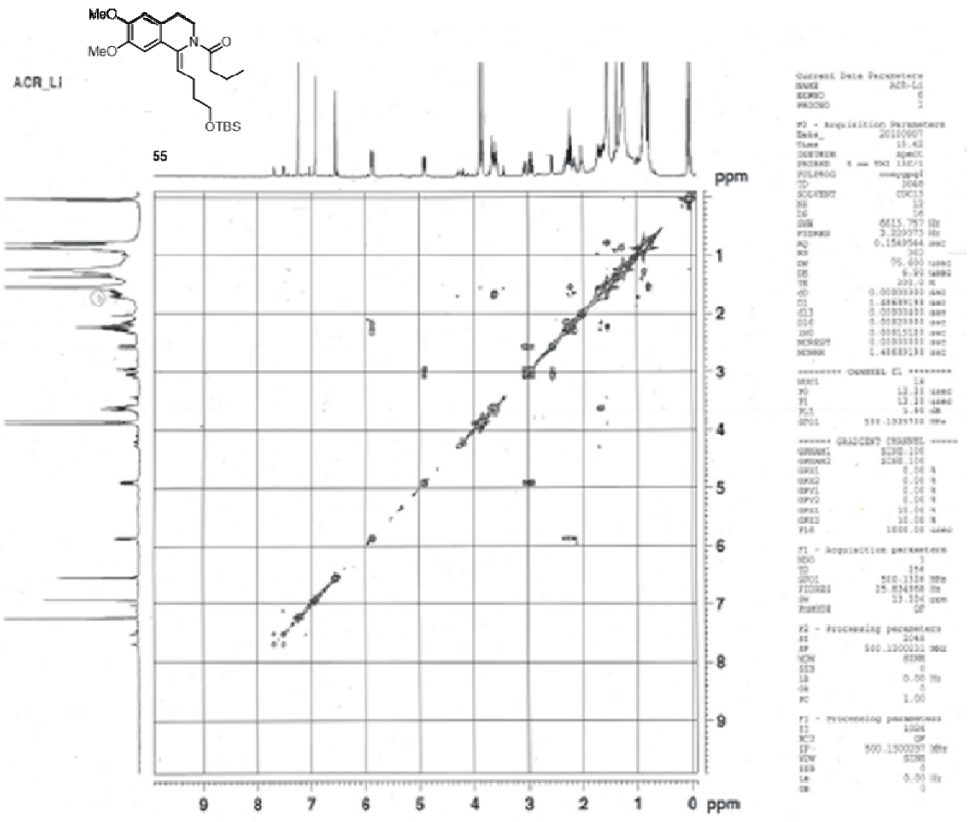


▼ ^{1}H-NMR ($CDCl_3$, 500 MHz)



▼ COESY



VII. 국문초록

Benzo[α]quinolizidine 계 알칼로이드는 *alangium lamarckii*와 *psychotria ipecacuanha*에서 주로 분리되는 천연물로써, Emetine, Tobulosine, Cephaeline, Psychotrine 등이 보고되었고, 이들의 다양한 약리효과로 인해 오랜 기간 학계로부터 지속적인 주목을 끌어왔다. 이들의 생물학적 중요성과 구조적 특징으로 인해 효과적인 합성법 개발을 위한 많은 시도가 있었고, 본 연구실은 헌팅톤 병에 의한 무도증 치료제로 2008년 FDA승인된 바 있는 benzo[α]quinolizidine 계 알칼로이드 유도체인 Tetrabenazine의 입체선택적 합성법을 개발 보고하였다.

현재까지 보고된 tetrahydroisoquinoline 골격의 입체선택적 합성은 Bischler-Napierlaski cyclization과 Pictet-Spengler synthesis을 이용하는데 국한되어 있다. 이에 본 연구자는 선행 연구를 통해 확립된 ACR(aza-Claisen rearrangement)-transannulation cascade을 응용하여, 2번, 3번 그리고 11b번 탄소에 원하는 입체선택성을 지닌 (-)-Protoemetinol의 합성을 완료하였고, 이를 중간체로 하는 2,3-disubstituted benzo[α]quinolizidine계 알칼로이드의 활발한 합성 연구를 기대한다. 핵심반응을 위한 기질은 Hoveyda-Grubbs' 2nd 촉매를 사용한 cross metathesis 을 통해 *(E)*-selective하게 합성하였고, 처음의 11b 탄소의 입체 중심은 최적화된 Nakamura's asymmetric allylation을 통해 확립하였다.

한편 benzo[α]quinolizidine계 알칼로이드의 대표적 천연물인 emetine의 합성 연구도 진행하였다. 대부분의 보고된 전합성이 protoemetinol 혹은 이의 관련 화합물로부터 linear한 합성을 통해 완결된 점에 착안하여, 본 연구자는 최적화된 선행 연구를 응용하여 두 tetrahydroisoquinoline fragments을 먼저 합성하고 이를 연결한 뒤 benzo[α]quinolizidine 골격을 완성하는 convergent한 접근법을 통해 합성 가능하리라 기대하였다. electron deficient한 기질로부터 성공적인 cross metathesis를 진행하였고 현재 aza-Claisen 전이에 대한 연구를

진행 중이다.

주요어 : (-)-Protoemetinol, (-)-emetine, benzo[α]quinolizidine 알칼로이드, aza-Claisen 전이, transannulation, cross metathesis, convergent synthesis

학번 : 2007-21810

Part II. First Total Synthesis of 6-Desmethyl-*N*-methylfluvirucin A_1

Abstract

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College of Pharmacy

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Fluvirucins, a class of macrolactam antibiotics, were isolated from fermentation broths of actinomycete isolates in 1991 and reported seven species including fluvirucin $A_{1\text{-}2}$, $B_{1\text{-}5}$. Recently, a drug-resistant hurdle have emerged in the livestock market. Three new macrolactams, 6-desmethyl-*N*-methylfluvirucin A_1, *N*-methylfluvirucin A_1 and fluvirucin B_0, and two known macrolactams, fluvirucin B_1, B_3, were isolated by bioassay-guided fractionation as part of the search for new anthelmintics in 2007 and 2008.

6-Desmethyl-*N*-methylfluvirucin A_1 exhibited *in vitro* activity (EC_{90} 15 ± 5 μg/mL) against *Haemonchus contortus* larvae, and fluvirucin B_0 showed very potent activity (EC_{90} <1.0 μg/mL) along with fluvirucin B_1, B_3 (EC_{90} 1.5, 1.7 μg/mL, respectively). But these natural compounds were restricted as new anthelmintics because of their modest *in vivo* activity against *Heligmosomoides polygyrus* in mice. This limitation may be overcome *via* the process of chemical optimization for improving *in vivo* activity. The syntheses of derivatives *via* a pre-established synthetic route can enable the discovery of more powerful compounds as drug candidates.

For this demand, we actively directed our efforts to the synthesis of 6-desmethyl-*N*-methylfluvirucin A_1. Our approach relies on the stereoselective amidoalkylation on the 10-membered lactam *via N*-acyl iminium intermediate taking advantage of the intrinsic ring strain, and *i*PrMgCl-mediated aza-Claisen rearrangemnet to give the ring-expanded *anti* product in high stereoselectivity.

The synthesis of a carbohydrate of 6-desmethyl-*N*-methylfluvirucin A_1 has posed a challenge due to its congested structure in that all substituents are positioned the same

direction, on the β face and a methylamine group was attached at carbon 3'. We installed the *N*-methyl group from the beginning to avoid the difficulty of *N*-methylation and posed the protecting group of amine to a pre-existed phenylethyl group for the double acetylation.

Glycosylation was attempted with the Cbz-protected aglycone and fluoroglycoside. Optimization of glycosylation is under investigation. After the glycosylation and deprotection steps, we hope that the total synthesis of 6-desmethyl-*N*-methylfluvirucin A_1 could be accomplished at an early date.

Keyword: 6-desmethyl-*N*-methylfluvirucin A_1, *N*-methylfluvirucin A_1, 3,6-dideoxy-3-methylamino-*L*-talose, glycosylation, aza-Claisen rearrangement, amidoalkylation, solubility

Student Number : 2007-21801

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Abbreviations

Ac: acetyl

Bn: benzyl

Boc: t-butyloxycarbonyl

Cbz: benzyloxy carbamate

CM: cross metathesis

(-)-CSO: (2*S*, 8*aR*)-(-)-(camphorylsulfonyl)-oxaziridine

DAST: diethylaminosulfur trifluoride

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCM: dichloromethane, methylene chloride, MC

DIBAL: diisobutylaluminum hydride

DMAP: *N,N*-dimethylaminopyridine

DMF: *N,N*-dimethylformamide

EtOAc: ethyl acetate

ee: Enantiomeric Excess

FDA: US Food and Drug Administration

Fmoc: fluorenylmethyloxycarbonyl

iPrMgCl: isopropyl magnesium chloride

LHMDS: lithium bis(trimethylsilyl)amide

MeOH: methanol

MOM: methyloxy methyl

Ms: methansulfonyl

NaHMDS: sodium bis(trimethylsilyl)amide

NBS: *N*-bromosuccinimide

NMO: *N*-methylmorpholine *N*-oxide

NMR: nuclear magnetic resonance

Pd/C: palladium/carbon

RCM: ring closing metathesis

TBAF: tetra-*n*-butylammonium fluoride

TBS: *tert*-butyldimethylsilyl

TEA: triethylamine

TES: triethylsilyl

TFA: trifluoroacetic acid

THF: tetrahydrofuran

Troc: 2,2,2-trichloroethoxycarbonyl

TS: transition state

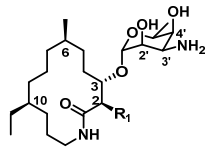
ZACA: zirconium-catalyzed asymmetric carboalumination

I. Introduction

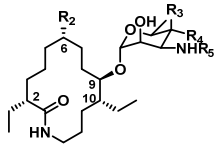
1. Fluvirucins

Fluvirucins, a class of macrolactam antibiotics, were isolated from fermentation broths of actinomycete isolates in 1991 by scientists at Bristol-Myers Squibb including fluvirucin A_{1-2}, B_{1-5} (**1-7**).[1-4] Scientists at Schering-Plough also independently isolated fluvirucin B_{1-3} (**3-5**) from *Actinomadura vulgaris* in 1990 and named them Sch 381516, Sch 38158 and Sch 38185, respectively. [5, 6] 6-Desmethyl-*N*-methylfluvirucin A_1 **8** and *N*-methylfluvirucin A_1 **9**, isolated from *Nonomuraea terkmeniaca* MA7364, were newly reported by scientists at Merck in 2007, and fluvirucin B_0 **10** was isolated from *Nonomuraea terkmeniaca* MA7381 in 2008 by the same group (Fig 1).[7, 8]

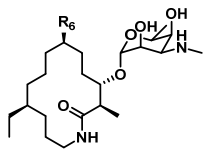
Fig 1. Fluvirucins



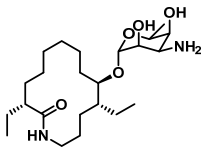
Fluvirucin A_1 (1) R_1=Me
A_2 (2) R_1=CH(OH)Me



Fluvirucin B_1 (3) R_2=Me, R_3=OH, R_4=H, R_5=H
B_2 (4) R_2=Et, R_3=H, R_4=OH, R_5=H
B_3 (5) R_2=Et, R_3=OH, R_4=H, R_5=H
B_4 (6) R_2=Et, R_3=H, R_4=OH, R_5=$CONHCH_2CH_2C_6H_5$
B_5 (7) R_2=Et, R_3=OH, R_4=H, R_5=$CONHCH_2CH_2C_6H_5$



6-desmethyl-N-methylfluvirucin A_1 (8) R_6=H
N-methylfluvirucin A_1 (9) R_6=Me



Fluvirucin B_0 (10)

These natural products have a 2,6-dialkyl-10-ethyl-3(or 9)-hydroxy-13-trodecanelactam of a 14-membered macrolactam that is called fluvirucinine. The fluvirucinine has stereogenic centers at carbons 2, 3 (or 9), (6) and 10 and is connected with a carbohydrate by a glycosidic linkage at the hydroxyl of 3 (or 9). [9, 10] The carbohydrate, 3,6-dideoxy-3-

(methyl)amino-*L*-talose, possesses a (methyl)amine group at carbon 3', and all substituents are positioned the same direction, on the β face, except for the carbohydrates of fluvirucin B_2 **4** and B_4 **6**. This conformation is unique and highly congested among the reported carbohydrates of natural products.

Fluvirucins B_1, B_2, and B_3 (**3-5**) have potent inhibitory effects against Gram (+) bacteria, bacteroides fragilis and yeast, whereas fluvirucins A_1 **1** and A_2 **2** are less potent. No activity of the fluvirucin series has been reported against Gram (-) bacteria, Gram (+) anaerobic bacteria or filamentous fungi. Most of all, fluvirucins exhibit considerable inhibitory activity against influenza A virus in Madin-Darby canine kidney (MDCK) cells, especially fluvirucins A_1, A_2, B_1 and B_3 (**1-3, 5**) (ID_{50} : 2.3-4.6 μg/mL). [3, 4]

2. Total Syntheses of Fluvirucin A Series By The Aza-Claisen Rearrangement(ACR)

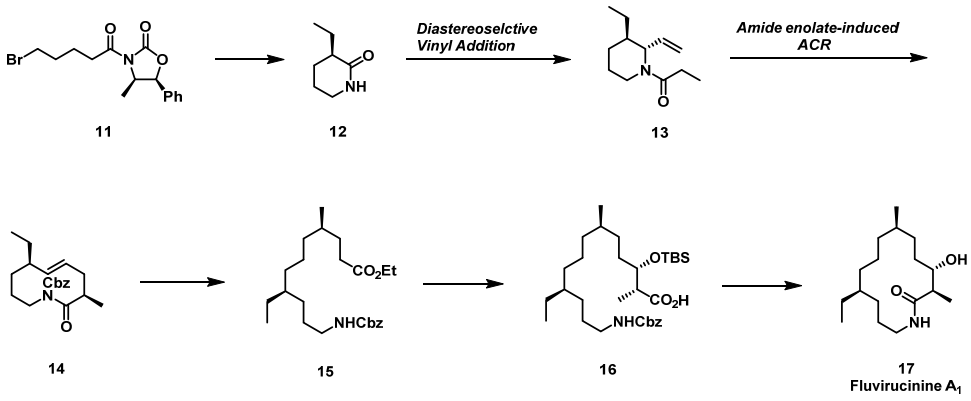
Our group has explored the total synthesis of natural products by the aza-Claisen rearrangement (ACR) since the 1990s. Medium or macro-rings were generated through ring expansion along with controlling the distant stereogenic centers, or a fused heterocycle ring was formed by the subsequent diastereoselective transannulation. To date, we have reported the tremendous and concise synthesis of alkaloids, including benzo[*a*]quinolizidine, indole, indolizidine and macrolactam. [11-18] The syntheses of the fluvirucinine A series exploiting ACR are presented here.

2-1. Synthesis of fluvirucinine A_1[11]

The synthesis was commenced by the preparation of the optically active *trans*-2,3-disubstituted piperidine **13**, as a precursor for the aza-Claisen rearrangement, from 3-

ethylvalerolactam **12**. We developed a direct diastereoselective vinyl addition to the lactam carbonyl group with the assistance of $LiAl(OEt)_3H$. The facile aza-Claisen rearrangement of **13**, induced by an amide enolate, afforded the ring-expanded lactam **14** which possesses the second requisite stereogenic center corresponding to C6 of the target molecule. The lactam **14** was converted into the ester **15** by a three-step sequence: Reduction with DIBAL followed by the direct Wittig olefination of the resulting aldehyde and the subsequent reduction of the olefin with $NaBH_4$. The C2 and C3 chiral units with the requisite configurations were effectively elaborated by reduction, followed by condensation with the boron enolate of propionyloxazolidinone. For the completion of the synthesis, acid **16** was cyclized to furnish fluvirucinine A_1 **17** after desilylation (Fig 2).

Fig 2. Synthesis of fluvirucinine A_1

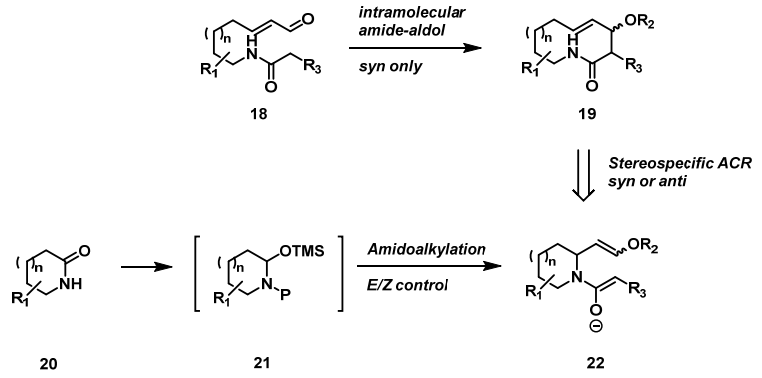


2-2. Synthesis of fluvirucinine A_2[13]

Since we reported the first asymmetric total synthesis of fluvirucinine A_1, we have been interested in iterative ring-expansion strategies as one of the most efficient approaches to the synthesis of macrolactam alkaloids. Direct cyclization approaches to the synthesis of macrocyclic rings are often limited because of entropic considerations, highly dilute

conditions and the lack of functional diversity. The ACR-induced ring expansion offers an opportunity for the rapid assembly of complex alkaloids. However, it has been under emphasized, partly as a result of limited access to the requisite precursors. In particular, the direct ring-expansion of medium-sized lactam precursors **20** via ACR has been limited, primarily because of the susceptibility of their lactam carbonyl to ring-opening during the requisite amidoalkylation. Our ring expansion strategy arises from the facile and diastereoselective amidoalkylation followed by the generation of the geometry-defined enol ether **22** and, finally, the ring expanded products, *β*-alkoxy-*α*-substituted macrolactams **19** of diverse ring sizes *via* the aza-Claisen rearrangement (Fig 3)

Fig 3. Amidoalkylation via *N,O*-acetal

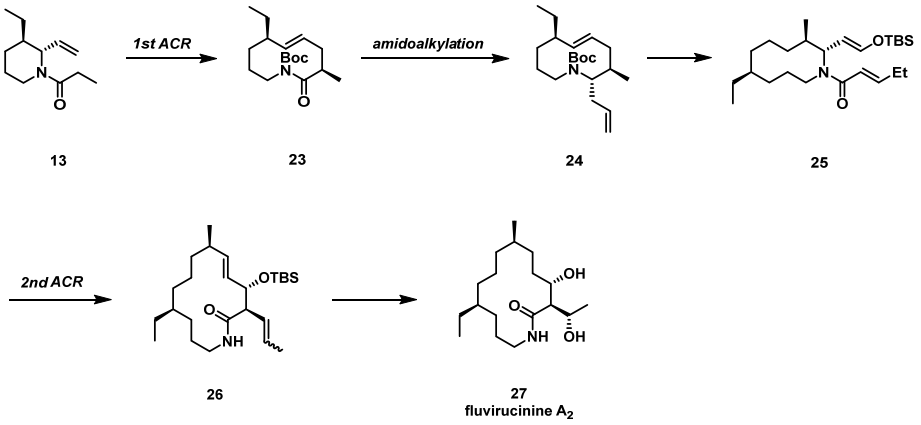


We reported an approach to the synthesis of the *N*-acyliminium ion from *N, O*-acetal TMS ether, which was conveniently prepared from lactam. The *N,O*-acetal TMS ether proved to be an excellent acyliminium ion precursor in terms of convenience of preparation, chemical stability, and functional versatility, in addition to the accessible structural diversity of the cyclic and acyclic *N*-acyliminium ions.

Taking advantage of our protocol *via N, O*-acetal TMS ether, we could provide the requisite allylazacycle **24** (Fig 4). Silylation under mild conditions (TBSCl, DBU, DCM,

reflux) resulted in the highly stereoselective formation of the (*E*)-enol TMS ether **25**. Expecting a chairlike transition state during the second ACR, stereoselective (*E*)-enol ether formation was required to facilitate the introduction of the newly generated stereochemistry at C3 as desired. The vinylogous amide enolate-induced ACR was conducted, followed by the selective olefin cleavage of **26** and the stereoselective Grignard addition, TBS deprotection and hydrogenation of the remaining olefin afforded fluvirucinine A_2 **27**.

Fig 4. Synthesis of Fluvirucinine A_2



3. Reported Synthetic Studies by Other Groups

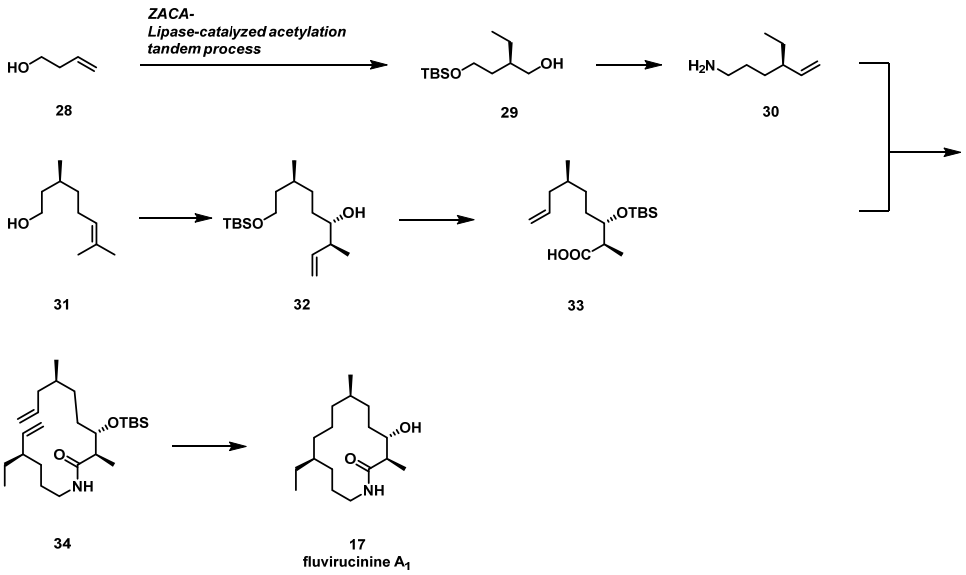
The difficulty of controlling the creation of the distant stereogenic centers of fluvirucins during the total syntheses has drawn the attention of several research groups. So far, four research groups have accomplished the total synthesis of fluvirucin or fluvirucinine including ours. [11, 14, 19-25] The synthesis of the carbohydrate parts has also posed a challenge due to its congested structure, and it has been reported by two synthetic groups: the A. H. Hoveyda group[10] and the S. Davies group.[26] The total synthesis of whole fluvirucin through a glycosylation step with a carbohydrate was reported by A. H. Hoveyda in 1997, the only

report to date. [21]

3-1. Fluvirucin A series

3-2-1. E.-I. Negishi's work [24]

Fig 5. Synthesis of fluvirucinine A_1 by Negishi.



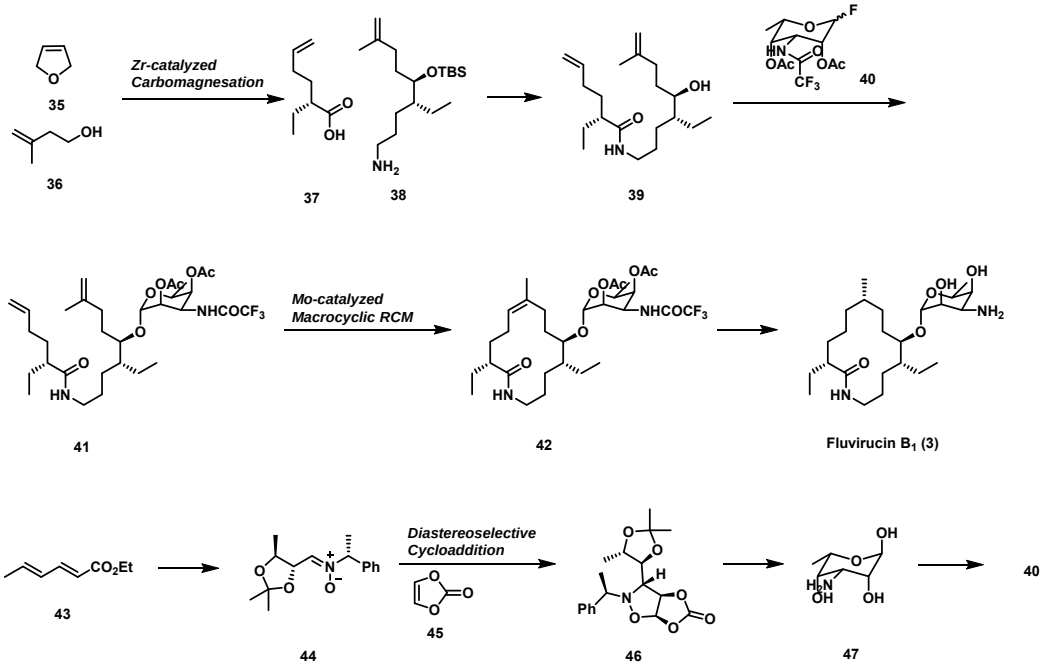
Since the fluvirucin A series was isolated in 1991, the total synthesis of fluvirucinine A_1 was reported only by our group, in the 1990s, as opposed to that of the fluvirucin B series, which has been actively reported. Recently, the Negishi group reported the concise synthesis of fluvirucinine A_1. The synthesis commenced with the conversion of 3-buten-1-ol **28** to 4-TBS-protected (*R*)-2-ethyl-1, 4-butanediol **29** of >98% ee. The reactions into **30** required six well-known steps including cyanation and reduction with the LAH of the nitrile formed. In view of the ready availability of (-)-(*S)-β*-citronellol **31**, its transformation into **32** was performed in nine steps, including the Brown crotylboration and OsO_4-

catalyzed oxidative alkene cleavage with $NaIO_4$ used twice. The conversion of the two key intermediates **30** and **33** into fluvirucinine A_1 **17** was achieved in two steps, RCM and desilylation (Fig 5).

3-2. Fluvirucins B series

3-2-1. A.H. Hoveyda's work [20] [21]

Fig 6. Synthesis of Fluvirucin B_1 by Hoveyda



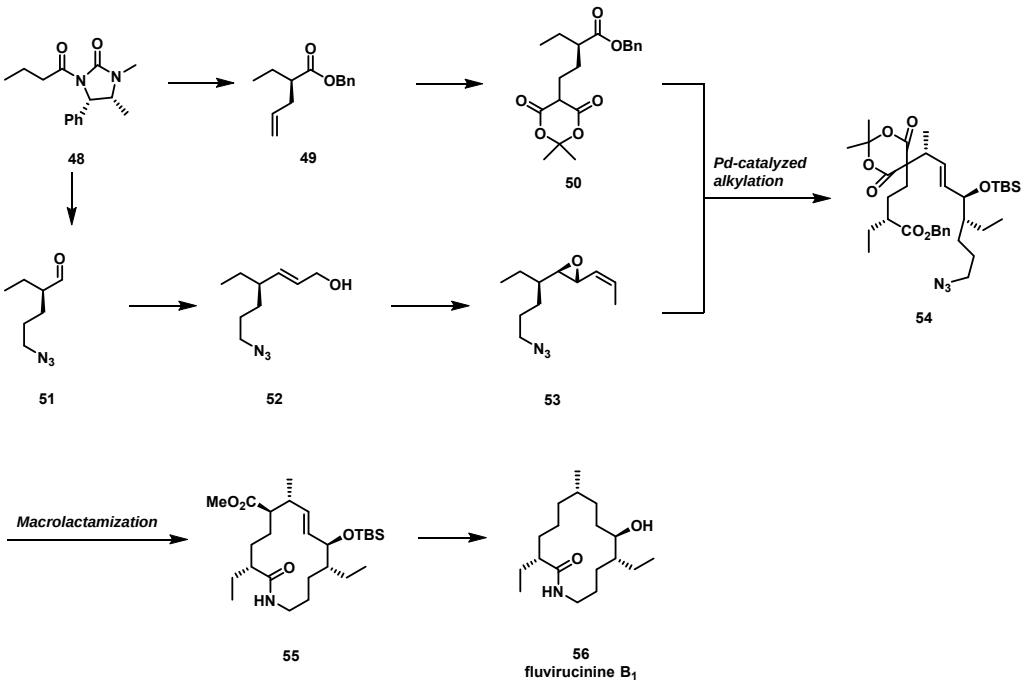
As depicted in Fig 6, the sequence began with the asymmetric catalytic ethylmagnesation of dihydrofuran **35**. The one-pot catalytic hydrovinylation of the terminal alkene and the Ru-catalyzed oxidation of the primary alcohol gave the derived acid **37**. The unsaturated amine **38** was prepared by the conversion of the homoallylic alcohol through a kinetic resolution and Zr-catalyzed asymmetric alkylation. Amine **38** and carboxylic acid **37** were

coupled to afford diene-amide **39**. For the carbohydrate synthesis, the asymmetric dihydroxylation of the commercially available ethyl sorbate **43** followed by acetal protection enable the establishment of the left part of **43**. The ethyl ester of **43** was reduced, ozonolysis provided carboaldehyde, and treatment with *N*-benzylhydroxylamine gave nitrone **44**. The diastereoselective [3+2] cycloaddition with vinylene carbonate **44** gave the cycloadduct **46**. The reduction of the *N-O* bond using Pearlman's catalyst gave the HCl salt of carbohydrate **47**, which was converted into fluoroglycoside **40** by a sequence of methoxy, acetoxy and thiophenyl substitution of acetal accompanied by protection steps. The glycosylation of **39** with fluoroglycoside **40** was carried out and the Mo-catalyzed ring closure, stereocontrolled hydrogenation, and deprotection delivered fluvirucin B_1 **3**.

3-2-2. B. M. Trost's work [22]

The stable imidazolidinone was chosen as the chiral auxiliary. Alkylation was performed to give **49** and **51**. The monosubstituted Meldrum's acid **50** was prepared by the reductive alkylation of the aldehyde produced by ozonolysis from **49** under Knoevenagel conditions. For the azide counterpart, the asymmetric epoxidation of the olefin **52** and the key Pd-catalyzed alkylation of **50** and **53** gave **54** as a single diastereomer. Alkene hydrogenation and hydrogenolysis of the benzyl ester and azide successfully effected macrolactamization. Decarboxylation, hydrogenation and desilylation were subsequently carried out to afford fluvirucinine B_1 **56** (Fig 7).

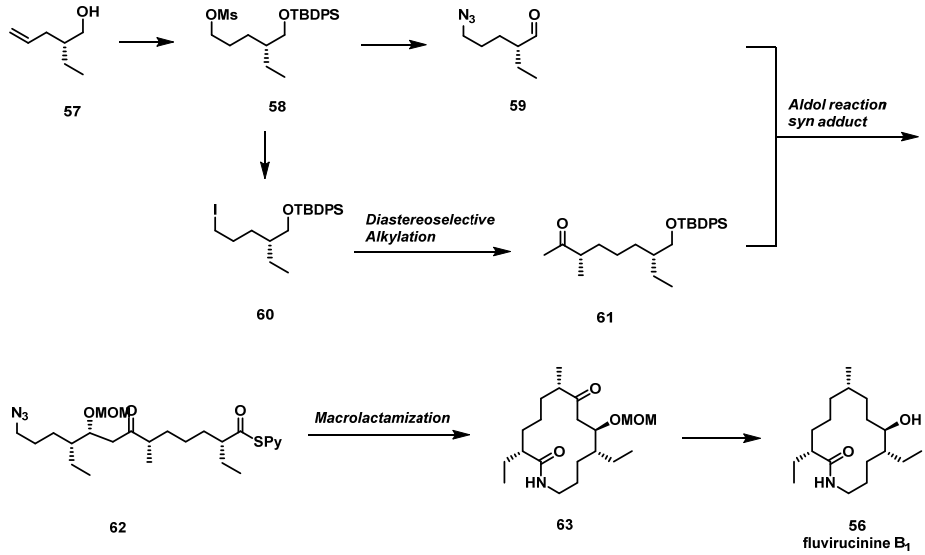
Fig 7. Synthesis of fluvirucinine B_1 by Trost



3-2-3. J. Vilarrasa's work [23, 25]

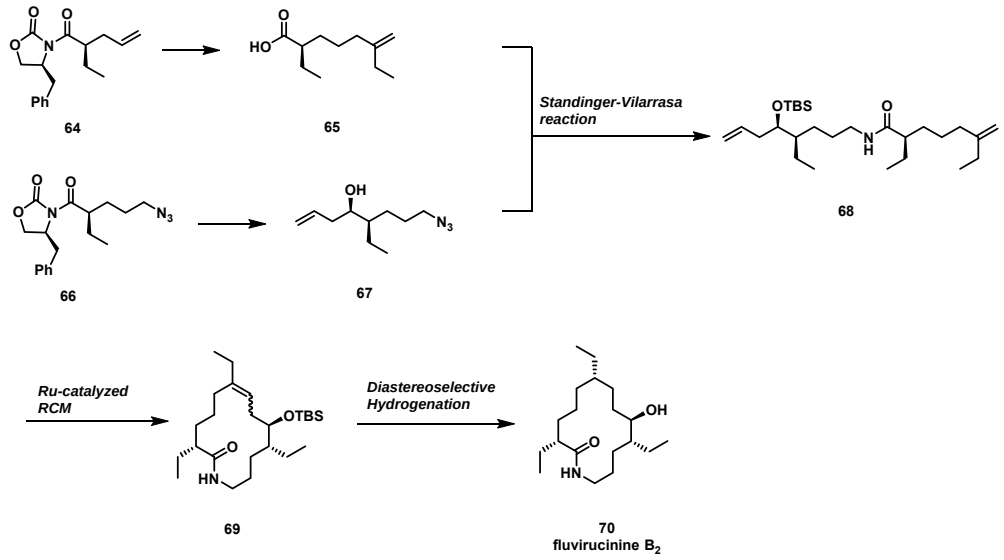
The synthesis of fluvirucinine B_1, reported in 1999, started from the oxazolidinone of Evans et al., which was converted as reported into enantiopure **57**. Hydroboration followed by oxidation, and reaction with MsCl afforded **58**. A fraction of **58** was converted into azide **59**, and the other portion was transformed to iodo derivative **60** by reaction with NaI in acetone. The diastereoselective alkylation of **60** with the *N*-propanoyl derivatives of (-)-pseudoephedrine gave the alkylation product; the addition of MeLi afforded the desired methyl ketone **61**. The boroon enolate of **61** was allowed to react with **59**, and the pure *syn* aldol adduct could be isolated. The protection of the hydroxyl group was accomplished with MOMCl. Cyclization afforded the desired macrolactam **63**. The ketone functionality of **63** was removed by reduction to the corresponding alcohol, followed by radical reduction and MOM deprotection (Fig 8).

Fig 8. Synthesis of fluvirucinine B_1 by Vilarrasa in 1999



The synthesis, announced in 2009, was started from the known oxazolidinone (Fig 9). Cross metathesis with ethyl vinyl ketone, simple catalytic hydrogenation of the double bond, selective methylenation and, finally, removal of the chiral auxiliary gave carboxylic acid **65**. The other fragment was synthesized from azide **66**. The standard reductive removal of the auxiliary, followed by the Swern reaction afforded an aldehyde product that was transferred to the *syn* adduct **67** by treatment with the Leighton reagent. The direct coupling of these two fragment gave amide **68** by using a catalytic variant of the Standinger-Vilarrasa reaction. To generate a macrocycle-embedded trisubstituted double bond, RCM was carried out in the presence of Hoveyda-Grubbs' 2nd initiator to give an *E/Z* isomeric mixture of product **69**, of which both components were smoothly converted to fluvirucinine B_2 **70** by hydrogenation and desilylation.

Fig 9. Synthesis of Fluvirucinine B_2 by Vilarrsa in 2009



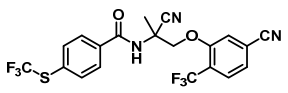
4. 6-Desmethyl-*N*-methylfluvirucin A_1 and *N*-Methylfluvirucin A_1[7, 8]

Recently, a drug-resistant hurdle has emerged in the livestock market. Novartis launched a new anthelmintics, Zolvix® (monopantel, **71**), in 2009 (Fig 10) as a result of this urgent problem. Three new macrolactams, 6-desmethyl-*N*-methylfluvirucin A_1 **8**, *N*-methyl fluvirucin A_1 **9** and fluvirucin B_0 **10**, and two known macrolactams, fluvirucin B_1, B_3, **3, 5**, were isolated by bioassay-guided fractionation as part of the search for new anthelmintics at Merck in 2007 and 2008. 6-Desmethyl-*N*-methylfluvirucin A_1 **8** exhibited *in vitro* activity (EC_{90} 15 ± 5 μg/mL) against *Haemonchus contortus* larvae, and fluvirucin B_0 **10** showed very potent activity (EC_{90} <1.0 μg/mL) along with fluvirucin B_1, B_3 **3, 5** (EC_{90} 1.5, 1.7 μg/mL, respectively). However, these natural compounds were restricted as new anthelmintics because of their modest *in vivo* activity against *Heligmosomoides polygyrus*

in mice. This limitation may be overcome *via* the process of chemical optimization for improving the *in vivo* activity. The syntheses of derivatives can enable the discovery of more powerful compounds as drug candidates.

Although the Hoveyda group reported the entire fluvirucin B_1 synthesis, a medicinal chemical limitation existed in the facile chemical modification in that the glycosylation was carried out before the 14-membered macrolactam framework was constructed. For this demand, we actively directed our efforts to the synthesis of 6-desmethyl-*N*-methylfluvirucin A_1, which could be acquired by glycosylation between the macrolactam aglycone part and the newly reported carbohydrate part. Fluvirucinine, the aglycone part, could be synthesized by our own ring expansion strategy.

Fig 10. New anthelmintics, Zolvix®, by Novartis co.



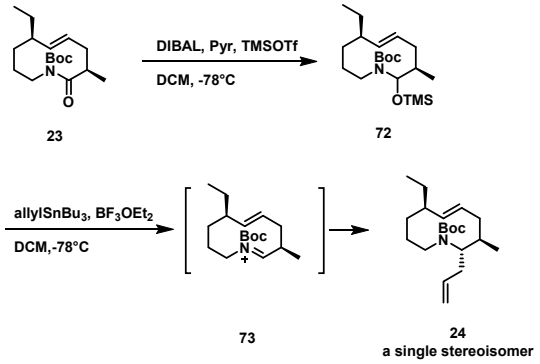
71
Zolvix (monopantel)

II. Results and Discussion

1. Diastereoselective Amidoalkylation Studies

To acquire a macrolactam through ring expansion, the facile protocol of azacyle syntheses was required from carbonyl group of a medium-sized lactam. We developed the diastereoselective amidoalkylation in the synthesis of the fluvirucinine A_2 for this reason, which is depicted in Scheme 1. Under optimized conditions (DIBAL, TMSOTf, pyr, -78℃ and then alkylating reagent, $BF_3{\cdot}OEt_2$, -78℃), the alkylation was performed stereoselectively without aminal generation. Moreover, the allyl group was introduced in the *anti* direction to the adjacent methyl group.

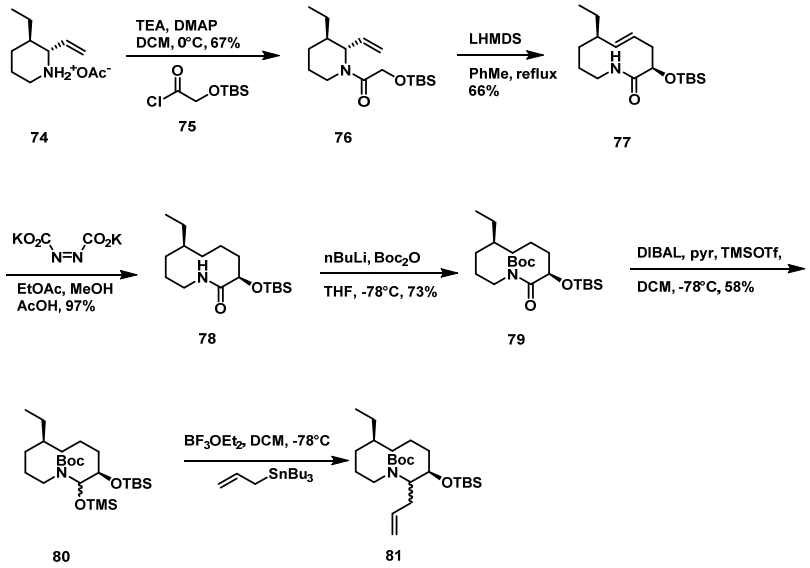
Scheme 1. Amidoalkylation in the synthesis of fluvirucinine A_2



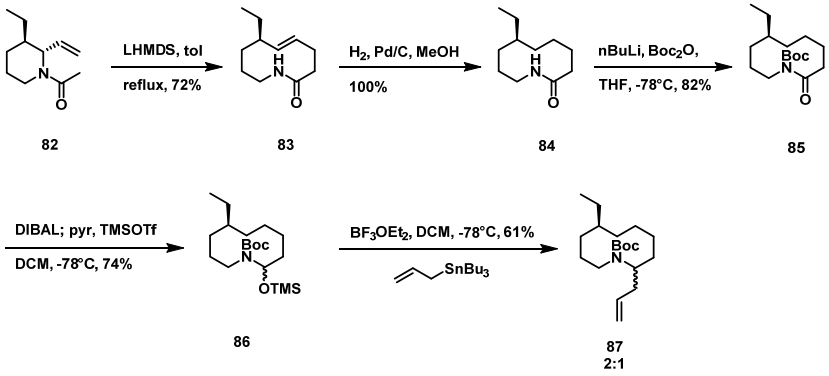
Because a stereogenic center of C6 was missing in 6-desmethyl-*N*-methylfluvirucin A_1, we considered other substituents as a surrogate for the methyl group to control the selectivity of the amidoalkylation. Acetoxy salt **74** was coupled with OTBS acetyl chloride, followed by an aza-Claisen rearrangement to give lactam **77** (Scheme 2). With the ACR product **77**, we carried out diimide hydrogenation, followed by Boc protection and DIBAL reduction directly trapped by TMSOTf to afford *N, O*-acetal TMS ether **80**.

Amidoalkylation was conducted in the treatment of BF_3•OEt_2 and allyltributyltin and gave diastereomeric mixtures of **81** with no stereoselectivity. This result implied that amidoalkylation is not always introduced an alkyl group in the *anti* direction to an adjacent group, but other factors may also be involved.

Scheme 2. OTBS as an auxiliary



Scheme 3. Amidoalkylation without auxiliary



It is known that when one or more double bonds are present in a medium sized ring, a stereoselective reaction is induced by the intrinsic ring strain. Therefore, we decided to conduct an amidoalkylation without an auxiliary. The ACR precursor **82**, prepared as a racemate, was converted into ring-expanded product **83,** which was further transformed to *N, O*-acetal TMS ether **86** by an optimized reaction sequence. Although the amidoalkylation of **86** still displayed a low diastereoselectivity (2:1), a promising result was obtained (Scheme 3).

2. Retrosynthetic Strategy

Fig 11. Retrosynthesis of aglycone

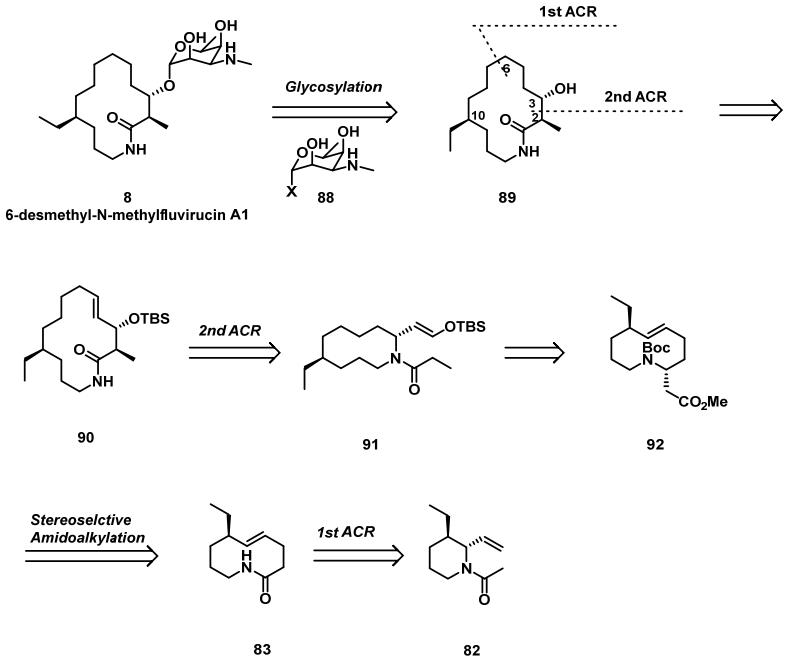
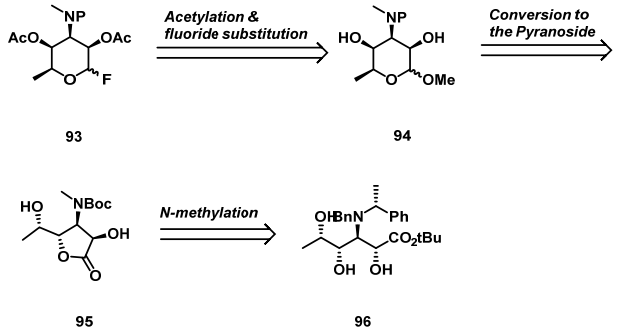


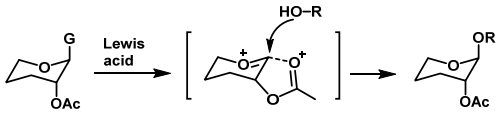
Fig 12. Retrosynthesis of carbohydrate



The retrosynthetic analysis of 6-desmethyl-*N*-methylfluvirucin A_1 **8** is shown in Fig 11 and 12. The final stage of the synthesis would be accomplished by glycosylation between a macrolactam aglycone and a carbohydrate. Our synthetic strategy for the aglycone part has taken full advantage of the previous studies of fluvirucinine A_1 and A_2 syntheses. The stereochemistries of C2 and C3 could be controlled by diastereoselective amidoalkylation of strained the 10-membered lactam and a highly ordered ring expansion *via* an aza-Claisen rearrangement.

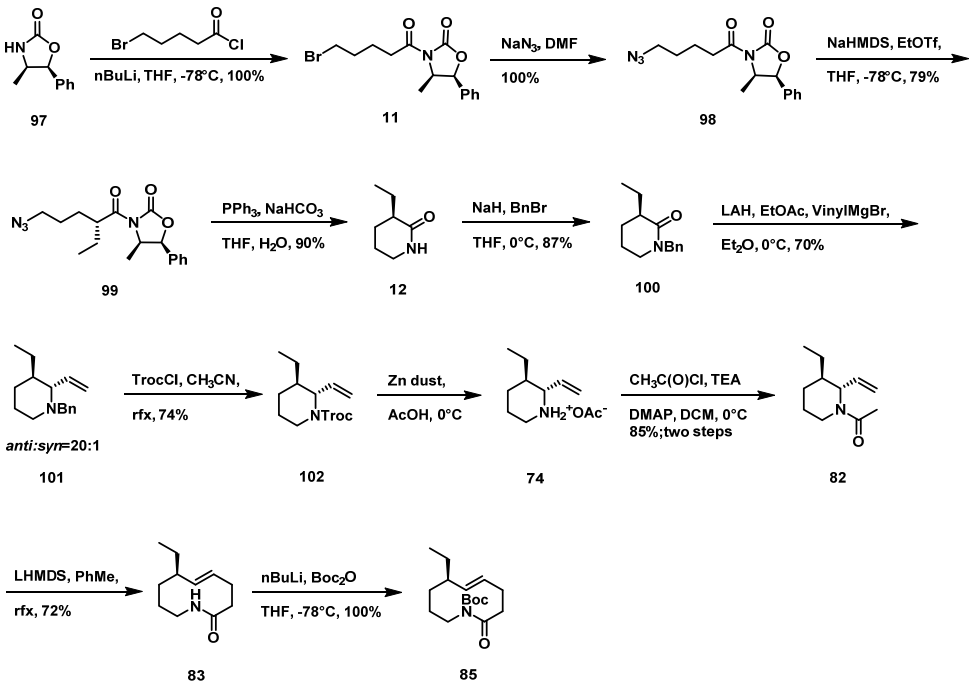
The reactive fluoroglycoside **93** was chosen as a counterpart, refering to Hoveyda's research. The protecting group of the two alcohols was an acetyl group to ensure *α* anomeric selectivity (Fig 13). The pyranoside structure **94** could be transformed from furan **95**. The *N*-methyl group would be introduced by *N*-methylation, and the substrate for **95** would be prepared from the known compound **96**.

Fig 13. *α* anomeric selectivity



3. Aglycone Synthesis: 6-Desmethyl-*N*-methylfluvirucinine A_1

Scheme 4. The first ACR mediated by LHMDS



The synthesis was commenced by the preparation of the optically active *trans*-2, 3-disubstituted piperidine **82** as a precursor for the first ACR from 3-ethylvalerolactam **12** *via* a well-established reaction sequence. The Evans' auxiliary was deprotonated with *n*BuLi and reacted with bromovaleryl chloride to give the corresponding amide **11**, which was converted to the azide **98**. The deprotonation of **98** with NaHMDS followed by the addition of EtOTf gave the desired diastereomer **99**. The six-membered piperidine **12** was constructed from the Staudinger reaction of azide **99**, directly protected with BnBr. The direct diastereoselective vinyl addition was carried out to afford the *trans*-substituted piperidine **101**. The ACR precursor **82** was obtained by debenzylation *via* Troc activation, followed by acetylation of the resulting amine. The facile ACR of **82** in the treatment of LHMDS afforded the ring-expanded lactam **83** as a sole product, possessing (*E*) olefin

geometry (Scheme 4).

From preliminary studies, we believed that the diastereoselective amidoalkylation of the ACR product lactam **89** could be carried out without an auxiliary's help *via* the rigid and one-isomer-favored conformation of the *N*-acyl iminium intermediate in the strained 10-membered ring (Scheme 5).[27] The Boc-protected 10-membered lactam **85** was reduced by DIBAL, and directly trapped by TMSOTf to obtain *N,O*-acetal TMS ether **102**. After the generation of the *N*-acyl iminium ion **103** by the treatment of $BF_3{\cdot}OEt_2$, highly stereoselective amidoalkylation was achieved as we hope to afford methyl ester **92** with separable small amounts of stereoisomer (ratio 10:1). We expect that the (*Z*) isomer would be more favorable, which will be confirmed soon by energy minimization calculation. The *Si* face attack was likely to happen in the case of the (*Z*) isomer of the *N*-acyl iminium intermediate (Fig 14).

Further modification for the preparation of the second ACR precursor was carried out. The hydrogenation of olefin followed by the DIBAL reduction gave aldehyde **105**. In the optimized condition of DBU and TBSCl, (*E*)-selective enol ether **106** was generated, which was transformed to the second ACR precursor **91** by subsequent Boc deprotection and a propionylation reaction. With the ACR precursor **91** available, we executed an aza-Claisen rearrangement *via* a chairlike transition state to establish the desired *anti* stereochemistry. The LHMDS-mediated ACR resulted in a low stereoselectivity of the *anti* product, which was instead mixed with the *syn* adduct in a ratio of 1.1~1.2:1. The low stereoselectivity by the treatment of LHMDS in 10-membered lactam system was also observed in previous studies in the synthesis of fluvirucinine A_2 (Eq 1 and 2, Scheme 6). We understood that both (*E*) and (*Z*) lithium amide enolates was generated in the system of the vinylogous amide groups. The formation of (*E*) enolate could be suppressed by elongating the alkyl chain of amide groups, and the *anti* stereoselectivity was acquired (Eq 3). In the case of an ACR substrate **91**, the outcome of a low stereoselectivity was explained by other factor because it

did not have a vinylogous amide group (Eq 4). Presumably the barrier of the energy level in the ACR substrate **91** became low between the chairlike transition state (TS) and boatlike TS due to the absence of an equatorial methyl group (Fig 15). We performed a trial with *i*PrMgCl, and the *anti* product **90** was obtained with high selectivity (19~21:1). Compared with a lithium amide enolate, the bigger magnesium complex can discriminate the transition state, and a chairlike transition state became more favorable.

Scheme 5. The second ACR mediated by *i*PrMgCl

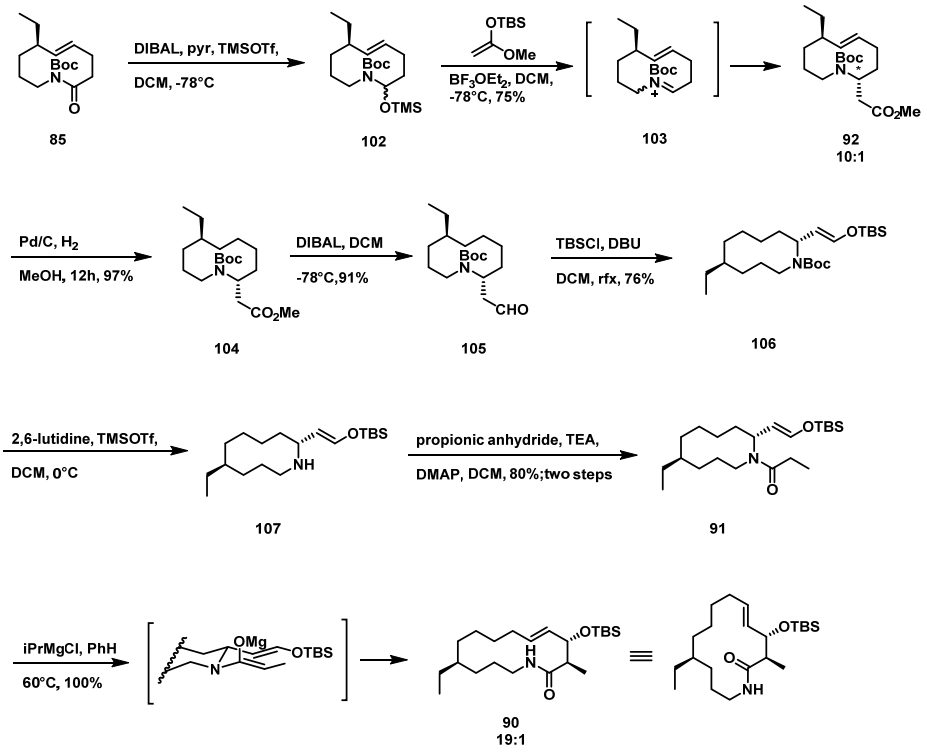
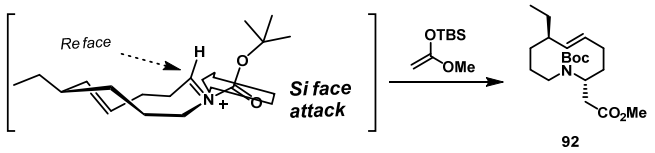


Fig 14. Rationale for asymmetric amidoalkylation



Scheme 6. Previous studies on ACR mediated by LHMDS

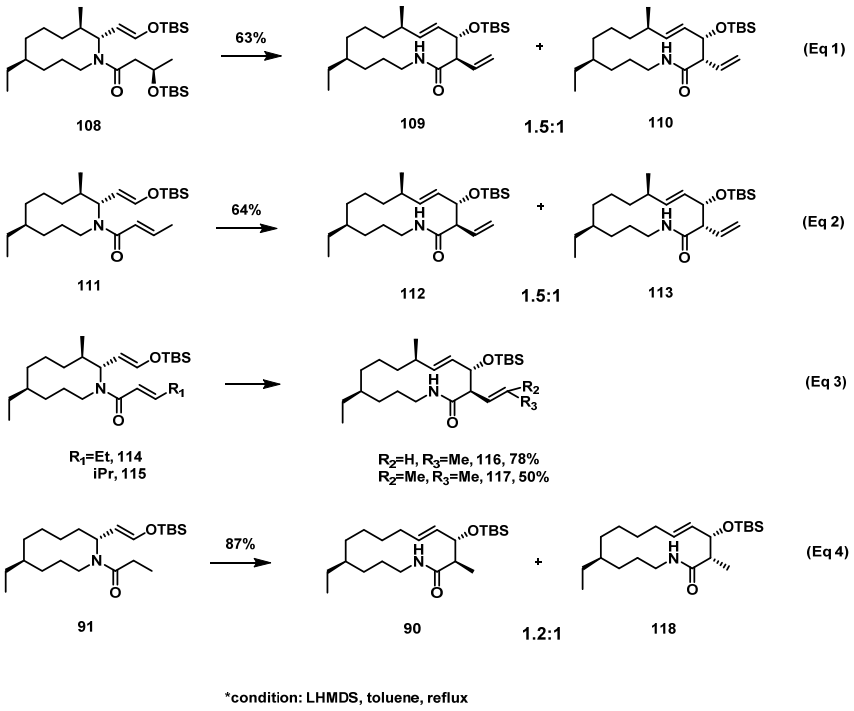
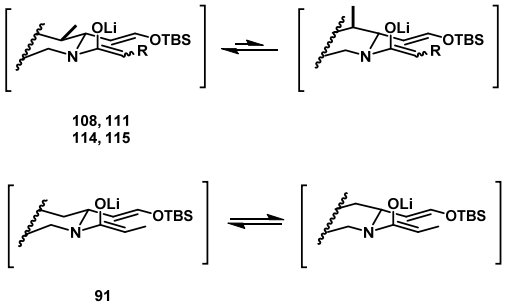


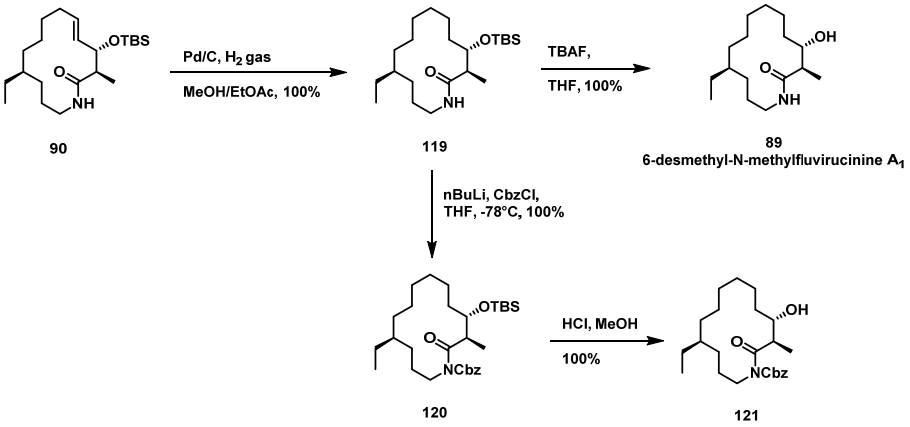
Fig 15. Chairlike vs boatlike TS



After the establishment of the macrolactam ring, the ACR product **90** was hydrogenated under Pd/C and 1 atm of hydrogen gas, and the synthesis of 6-desmethyl-*N*-methylfluvirucinine **89** was completed in high yield by the subsequent desilylation.

However, aglycone **89** was not soluble in aprotic solvents, such as Et_2O or DCM. This drawback was also noted in Hoveyda's report on the synthesis of fluvirucin B_1, so the glycosylation had to be performed with a linear aglycone before the macrolactam ring closure. This approach posed medicinal chemical limitation to the facile chemical modification of fluvirucins and their derivatives. We conducted a trial to improve the solubility of the 14-membered macrolactam and perceived that macrolactams **90** and **119** were methanol-insoluble liquids that were soluble in aprotic solvents, whereas fluvirucinine **89** had an opposite solubility. Inspired by this dramatic change in solubility, the amide protection on fluvirucinine **89** may help the solubility increase in aprotic solvent. Compound **121** was synthesized from the subsequent Cbz protection and desilylation of **1119** and exhibited acceptable solubility in aprotic solvents (Scheme 7).

Scheme 7. Completion of the aglycone synthesis

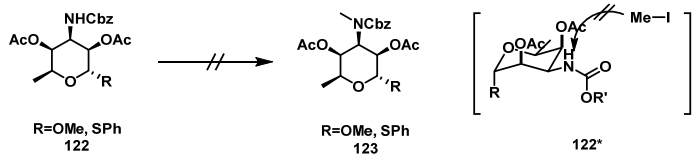


4. Carbohydrate Synthesis: 3,6-Dideoxy-3-methylamino-*L*-talose

After finishing the synthesis of aglycone part and solving the solubility drawback, we focused our efforts on the synthesis of the carbohydrate part, 3, 6-dideoxy-3-methylamino-*L*-talose, for the glycosylation. We basically utilized the synthetic method of 3, 6-dideoxy-3-amino-*L*-talose, which is a methyl-deleted amino sugar of the other fluvirucin series, that was reported by S. Davies. [26]

The initial synthetic studies focused on the induction of the methyl group on the amine. An *N*-methylation trial on pyranoside **122** was first carried out. Due to the steric hindrance of the two adjacent pre-existing OAc groups (see **122***), *N*-methylation did not succeeded under various conditions (Fig 16). We then conducted *N*-methylation before the conversion into pyranoside (Scheme 8). After the silyl protection of the known compound **124**, *N*-methylation was performed. Likely due to the bulkiness of the adjacent silyl alcohols on the lactone ring, the methyl group failed to be connected to the amine.

Fig 16. *N*-methylation trial in the pyranoside



Scheme 8. *N*-methylation trial I

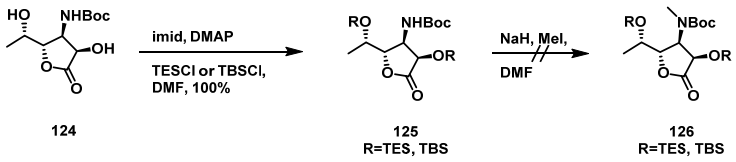
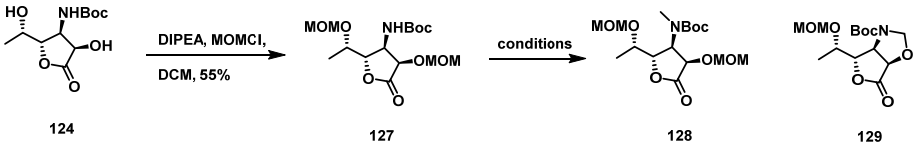


Table 1. *N*-methylation trial II



124 127 128 129

No.	conditions	Result
1	NaH, MeI, DMF	**128, 129**
2	NaH, MeOTf, DMF	No reaction
3	LHMDS, MeOTf, -78℃ to -15℃	No reaction
4	LHMDS, HMPA, MeOTf, -78℃ to -20℃	No reaction

Upon altering the silyl group to a smaller protecting group, MOM, *N*-methylation occurred to give compound **128** in condition of NaH, MeI, and DMF at room temperature (entry 1, Table 1). However, the *N*-methylation had low reproducibility because the amine attacked the MOM group of the vicinal alcohol to form oxazolidine ring **129** in basic conditions.

With a small amount of *N*-methylated product **128** available, a DIBAL reduction was performed to afford hemiacetal **130**, which was transformed under acidic conditions into pyranoside **131** with an unchanged furanoside **132** (0.8:1). Installation of an acetyl group in alcohols of **131**, especially at C2, was important for α anomeric selectivity in glycosylation as depicted above (Fig 13). However, our target carbohydrate, 3, 6-dideoxy-3-methylamino-*L*-talose, had a congested configuration in that all substituents existed in the same direction, with two alcohols lying in the axial position. When the acetylation of **131** was carried out, only the less-hindered alcohol of C2 was protected, leaving the alcohol of C4 naked (Fig 17). Based on the preliminary study that double acetylation smoothly occurred in the absence of the *N*-methyl group, the acetylation at C4 was presumably disturbed by the adjacent axial *N*-methyl group. Although the fluoroglycoside **136** was obtained from compound **133**, the total reaction yield and chemical stability were low

because of the unprotected alcohol. Moreover, we had difficulty in securing proper amounts of sugar for glycosylation (Scheme 9).

Scheme 9. Carbohydrate synthesis I

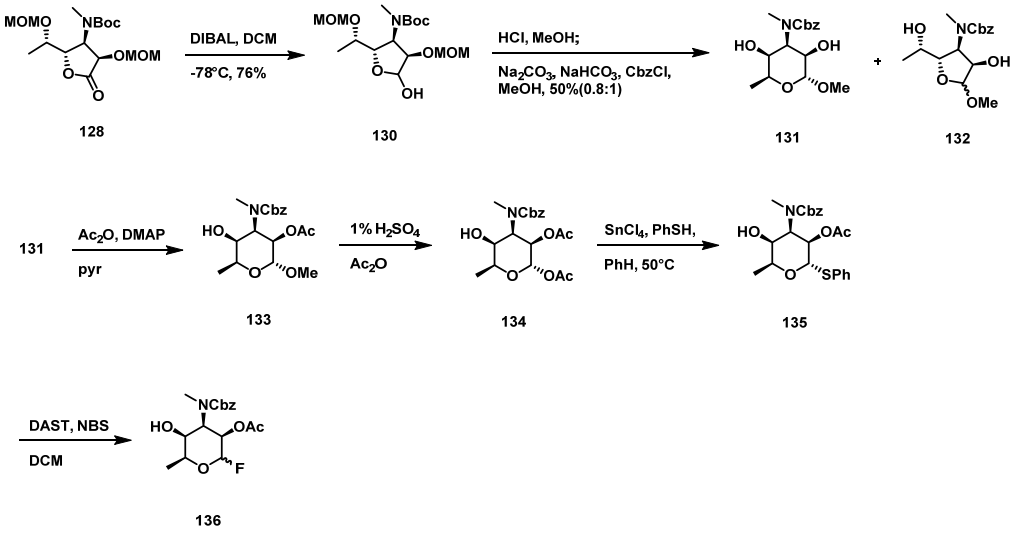
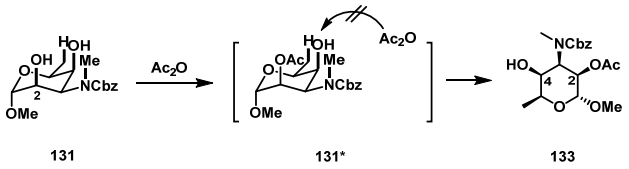


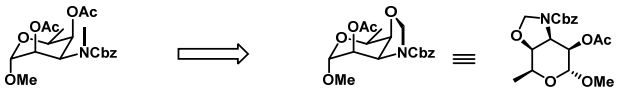
Fig 17. Limitation of acetylation at the alcohol of C4



We then searched for a surrogate of *N*-methylation to breakthrough the intrinsic congestion of the carbohydrate. We initially judged that two OAc groups, the *N*-methyl and *N*-protecting groups on the pyranoside were all required but seemed to be incompatible each other. To relieve this congestion, we designed the oxazolidine-fused pyranoside **137** acting as an alcohol protecting group as well as an *N*-methyl group (Fig 18). For the oxazolidine synthesis, we began with the MOM protection of the known aminoalcohol **138**, followed by the Upjohn dihydroxylation to obtain **140**, which was further converted to the Boc-substituted substrate **141** for oxazolidine ring formation. Under the catalytic PTSA and

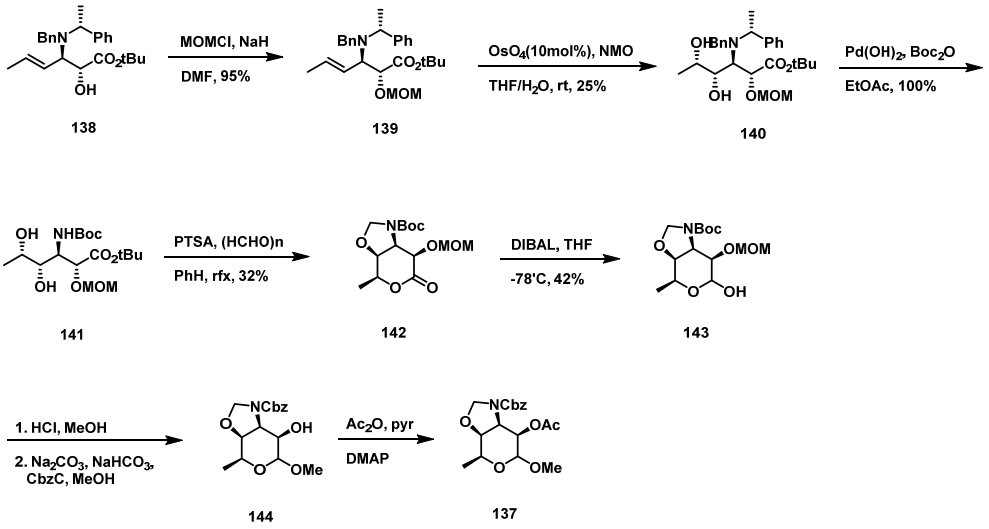
large amount of formaldehyde condition, the oxazolidine ring **142** was produced simultaneously with the 6-membered lactone formation. Without an additional pyranoside transformation step and unwanted furanoside generation, we successfully achieved what we targeted, from the sequence of a well-established procedure. However, the diastereomeric ratio at the dihydroxylation step was not satisfied and the oxazolidine ring formation yield was also low (Scheme 10).

Fig 18. Idea of oxazolidine



137

Scheme 10. Synthesis of oxazilidine-fused carbohydrate I

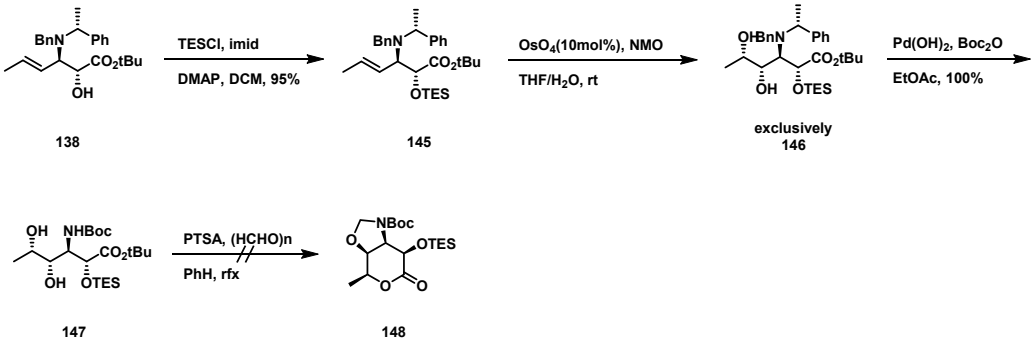


138 139 140 141 142 143 144 137

To increase the diastereomeric ratio at the dihydroxylation step, the MOM group was altered to a proper-sized silyl group, TES (in the case of TBS, the dihydroxylation reaction did not occurred, likely due to steric bulkiness). Although the desired dihydroxyl diastereomer **146** was synthesized exclusively, the oxazolidine ring product **148** was not

formed, but there were multiple unidentified products (Scheme 11).

Scheme 11. Synthesis of oxazolidine-fused carbohydrate II

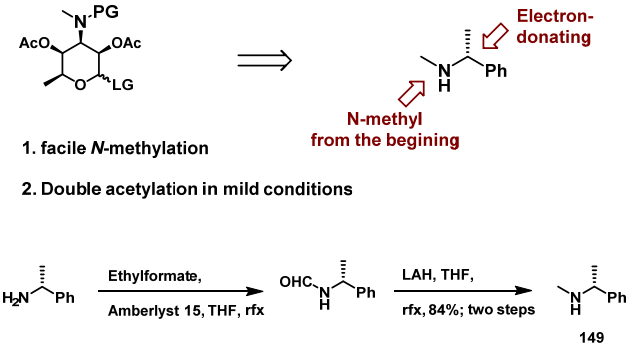


From previous trials and errors, we decided to install the *N*-methyl group from the beginning to avoid the laborious *N*-methylation step, and posed a phenylethyl group to a protecting group on pyranoside (Scheme 12). The phenylethyl group of amine, which was initially used for controlling the enantioselectivity in the aminohydroxylation step, can make the nucleophilicities of vicinal alcohols increase so that double acetylation could occur in mild conditions. Compared with Cbz, a phenylethyl group has more electron donating character.

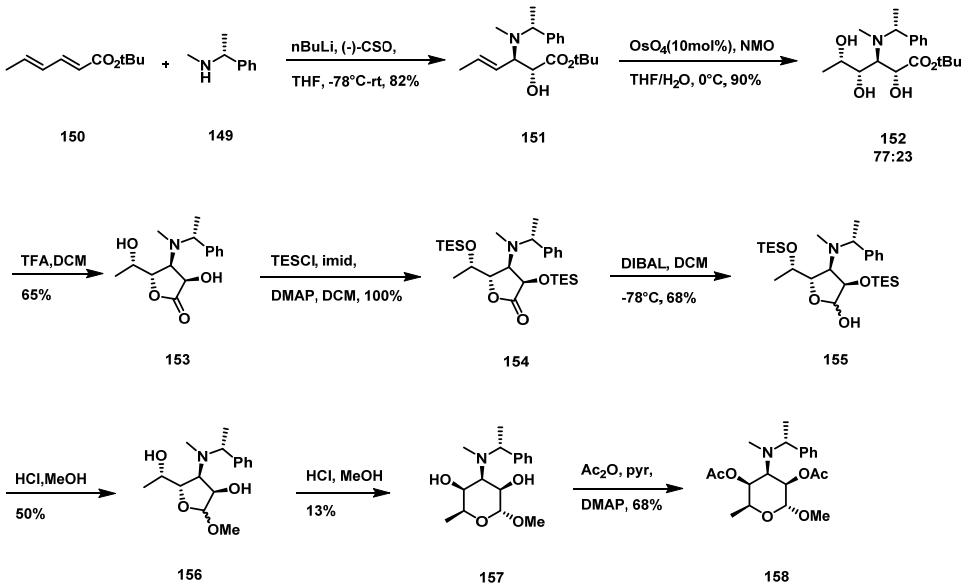
Methylamine **149**, the starting material, was prepared by a two-step sequence in high yield from (*R*)-(+)-1-phenylethylamine and directly used in aminohydroxylation step without the purification of column chromatography. The asymmetric aminohydroxylation of *t*-butyl sorbate **150** and methylamine **149** was performed with Davies' oxaziridine to give *N*-methyl aminoalcohol compound **151**, which was converted into the desired dihydroxylation product **152** under Upjohn condition with an acceptable diastereomeric ratio (77:23) (Scheme 13). The furan ring was spontaneously generated by the treatment of TFA with the detachment of the *t*-butyl group. Because the hemiacetal formation tended to a good result when the two alcohols were protected, a TES (or MOM) protection reaction was performed

to give **154** before DIBAL reduction. However, the pyranoside transformation seemed to be interrupted by the protecting groups. The rate of TES deprotection is presumably slower than that of the methoxy pyranoside transformation. Methoxy furanoside **156** was mainly obtained with trace amounts of methoxy pyranoside **157** (2~6%) in a 0.1~0.4 M HCl methanol solution, and the conversion yield was not satisfactory.

Scheme 12. Breakthrough: (*R*)-*N*-methyl-1-phenylethan-1-amine



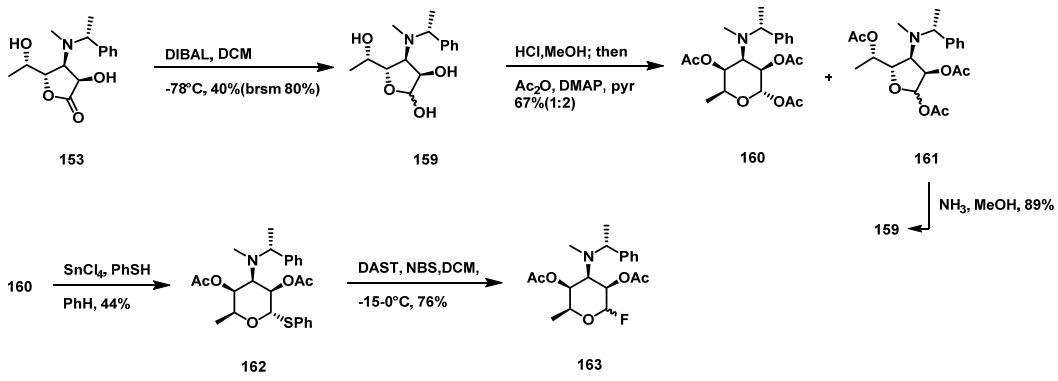
Scheme 13. Carbohydrate synthesis from *N*-methylamine



We then conducted a hemiacetal formation reaction with free alcohols (Scheme 14). Although the yield of the DIBAL reduction was lower than that of **154**, a sufficient result was acquired *via* an optimization process to afford hemiacetal **159**. In the treatment of HCl and MeOH, the hemiacetal **159** was transformed into pyranoside framework and didn't seem to be converted hemiacetal into methoxy group dissimilar to the case of **156**. The reaction mixture was evaporated *in vacuo*, and then directly used in an acetylation reaction.

We then focused on installing the acetyl groups on the two axial alcohols. As we hoped, the acetylation of both the alcohols of C2 and C4 took place smoothly, along with the direct conversion of the hemiacetal into an acetoxy group **160**. Although what we wanted was only a minor product, acetoxy furanoside **161** was recovered to the starting substance **159** in ammonia and methanol. Acetoxyl glycoside **160** was reacted with thiophenol and $SnCl_4$, followed by reaction with DAST and NBS to finally give fluoroglycoside **163**. Compared with fluoroglycoside **136** having one alcohol naked, the chemical stability was much improved. The synthesis of the carbohydrate part was accomplished in seven steps.

Scheme 14. Success of carbohydrate synthesis

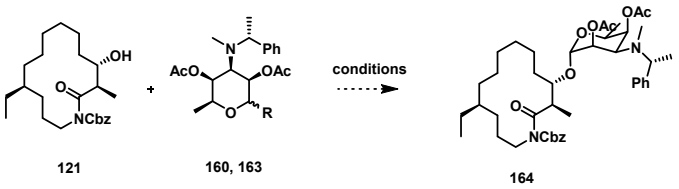


5. Glycosylation Studies

The glycosylation could eventually be attempted with the Cbz-protected aglycone **121** and fluoroglycoside **163** (Table 2). Several trials on glycosylation revealed that the carbohydrate part was smoothly converted into an oxonium ion under treatment by Lewis acids, and seemed to be more stabilized by Et_2O than DCM. The aglycone part, on the other hand, did not have enough reactivity to attack this oxonium ion, presumably due to the steric hindrance derived from the Cbz group. This assumption was supported by the previous study that macrolactam **119** was easily desilylated by TBAF to afford 6-desmethyl-*N*-methylfluvirucinine A_1 **89**. However, the Cbz-protected macrolactam **120** could not be desilylated by TBAF but only by the smaller hydrogen chloride.

We now consider a smaller protecting group of the amide with the solubility in aprotic solvent unchanged. After the glycosylation and deprotection reactions, we hope that the total synthesis of 6-desmethyl-*N*-methylfluvirucine A_1 could be accomplished at an early date.

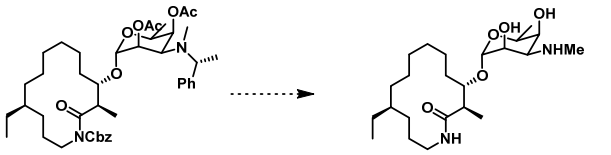
Table 2. Glycosylation study



No.	R	conditions	Solvent	T(℃)	Result
1	F	$SnCl_2$ (1.7), $AgClO_4$ (1.7)	Et_2O	-15	No reaction
2	F	$SnCl_2$ (3), $AgClO_4$ (3)	Et_2O	-15	No reaction
3	F	BF_3OEt_2 (1)	DCM	0	Degradation of **163**
4	F	BF_3OEt_2 (1)	DCM	-78	Partial degradation of **163**
5	OAc	BF_3OEt_2 (3)	DCM	rt	Partial degradation of **160**

All reaction materials were prepared by azeotropic distillation (benzene, 3 times), and flame-dried molecular sieve 4Å was added.

Scheme 15. Completion of the synthesis of 6-desmethyl-*N*-methylfluvirucin A_1



164 6-desmethyl-*N*-methylfluvirucin A_1 (8)

III. Conclusion

We accomplished the synthesis of 6-desmethyl-*N*-methylfluvirucinine A_1 **89** in 13 steps from the known piperidine salt **74** and also prepared an aprotic solvent-soluble glycosylation substrate **121**. The key reactions included a stereoselective amidoalkylation which was carried out in a 10-membered ACR product lactam having the intrinsic ring strain *via* rigid and one-isomer-favored *N*-acyl iminium. The ACR reaction was then conducted to give the desired ring expanded *anti* product **90** in high selectivity. For improving the solubility of aglycone, Cbz group was installed at amide group.

We also completed the synthesis of 3,6-dideoxy-3-methylamino-$_L$-talose as a fluoroglycoside figure. The synthesis of this aminosugar was challenged due to its congested structure in that all substituents lie in the same direction and the methylamine group was attached at carbon 3'. We brought the *N*-methyl group from the beginning to avoid the laborious *N*-methylation. Moreover, when the phenylethyl group was posed to a protecting group on pyranoside, the double acetylation occurred smoothly in a mild condition, which was crucial to the anomeric selectivity and chemical stability.

The glycosylation was eventually attempted with the Cbz-protected aglycone and fluoroglycoside. After glycosylation and deprotection reactions, we hope that the total synthesis of 6-desmethyl-*N*-methylfluvirucine A_1 could be accomplished at an early date.

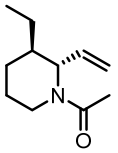
IV. Experimental

General experimental

Unless otherwise described, all commercial reagents and solvents were purchased from commercial suppliers and used without further purification, and all anhydrous reactions were carried out under argon gas (1 atm) in flame or oven-dried glassware. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, triethylamine, were freshly distilled with calcium hydride. Flash column chromatography was carried out using silica-gel 60 (230-400 mesh, Merck) and preparative thin layer chromatography was used with glass-backed silica gel plates (1mm, Merck). Thin layer chromatography was performed to monitor reactions. Optical rotations were measured using a JASCO DIP-2000 digital polarimeter at 20 ℃ using 10 or 100 mm cells of 3 mm diameter. Infrared spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. Mass spectra were obtained using a VG Trio-2 GC-MS instrument, and high resolution mass spectra were obtained using a JEOL JMS-AX 505WA unit. ^{1}H and ^{13}C NMR spectra were recorded on either a JEOL JNM-LA 300 (300MHz), JEOL JNM-GCX (400MHz), BRUKERAMX-500 (500MHz) or JEOL (600MHz) spectrometers. Chemical shifts are provided in parts per million (ppm, δ) downfield from tetramethylsilane (internal standard) with coupling constant in hertz (Hz). Multiplicity is indicated by the following abbreviations: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quartet (q), quintet (quin), quartet of doublet (qd) multiplet (m) and broad (br). The purity of the compounds was determined by normal phase high performance liquid chromatography (HPLC), (Gilson or Waters, CHIRALPAK® AD-H (4.6 × 250 mm) or CHIRALPAK® OD-H (4.6 × 250 mm))

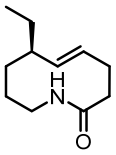
Aglycone part:

1-(2*S*, 3*R*)-3-ethyl-2-vinylpiperidin-1-yl)ethan-1-one (82)



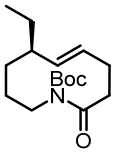
The salt of acetoxy (*2S,3R*)-3-ethyl-2-vinylpiperidin-1-ium (crude, 5 mmol) and DMAP (cat.) were dissolved by DCM (15 ml). To a stirred solution was added TEA (15 mmol, 2 l) followed by an addition of acetyl chloride (7.5 mmol, 0.53 ml) at 0℃. The resultant mixture was allowed to warm to rt and stirred until complete consumption of the starting material on TLC. The reaction mixture was quenched by adding water and diluted with CH_2Cl_2. The aqueous phase was extracted with DCM (3 x 15 ml). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 1 : 2) afforded 770 mg (4.25 mmol, 85%; two steps) of **82**: FT-IR (thin film, neat) *v* max 3477, 2937, 1651,1423, 1267 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.82-5.73 (m, 1H), 5.23-5.19 (m, 1H), 5.07-5.01 (m, 1H), 4.46 (d, 0.5H), 4.18 (s, 0.5H), 3.54 (d, 0.5H), 3.17 (t, 0.5H), 2,64 (t, 0.5H), 2.11(s, 1H), 2.05 (s, 2H), 1.64 (m, 3H), 1.50-1.43 (m, 3H), 1.40-1.28 (m, 1H), 0.94-0.91 (t, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 170.7, 136.9, 115.9, 59.6, 53.5, 42.4, 39.7, 38.7, 37.0, 24.1, 23.2, 21.3, 19.6, 12.2; LR-MS (ESI) *m/z* 182 ($M+H^+$); HR-MS (ESI) calcd for $C_{11}H_{19}NO$ ($M+H^+$) 182.1539; found 182.1524

(*R,E*)-7-ethyl-3,4,7,8,9,10-hexahydroazecin-2(1*H*)-one (83)



LHMDS (1M in toluene, 12.7 ml) was added dropwise to a stirred solution of 46 (4.25 mmol, 770 mg) in toluene (38 ml) at reflux. The reaction mixture was stirred for 1h and then allowed to cool to rt. The reaction mixture was quenched with adding minimum amount of water and filtrated through Celite® followed by concentrated *in vacuo.* Purification of the residue via flash column chromatography on silica gel (EtOAc : Hexane = 1 : 1, 10% DCM) afforded 554 mg (3.06 mmol, 72%) of **83**: FT-IR (thin film, neat) *v* max 3309, 2926, 1645, 1554 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz) δ 5.76 (broad s, NH), 5.30-5.25 (m, 1H), 5.02-4.97 (dd, 1H), 3.42-3.37 (m, 1H), 2.77-2.74 (m, 1H), 2.22-2.11 (m, 3H), 1.95 (td, 1H), 1.74-1.70 (m, 2H), 1.59-1.57 (m, 1H), 1.25-1.14 (m, 3H), 1.13-1.06 (m, 1H), 0.69 (t, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 173.0, 138.7, 126.6, 45.8, 40.5, 38.5, 35.7, 29.5, 28.2, 26.7, 11.8; LR-MS (ESI) *m/z* 182 ($M+H^+$); HR-MS (ESI) calcd for $C_{11}H_{19}NO$ ($M+H^+$) 182.1539; found 182.1532

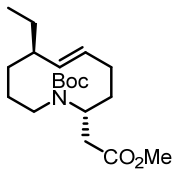
***tert*-butyl (*R,E*)-5-ethyl-10-oxo-3,4,5,8,9,10-hexahydroazecine-1(2*H*)-carboxylate (85)**



To a solution of lactam **83** (554mg, 3.06 mmol) in THF (9ml) was added *n*BuLi (2.5M in hexane, 1.8 ml) at -78℃. After the mixture was stirred for 10min, a solution of Boc_2O (6.1 mmol, 2.8 ml) in THF (3 ml) was added and the mixture was stirred for 2h. The reaction

was quenched with water and the mixture was allowed to warm to rt. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 x 10ml). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 20) to afford 860 mg (3.06 mmol, 100%) of **85**: FT-IR (thin film, neat) *v* max 1725, 1691, 1369, 1148 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 5.36-5.26 (m, 1H), 5.01(broad s, 1H), 3.70-3.56 (m, 2H), 3.21 (broad s, 1H), 2.80 (broad s, 1H), 2.80-2.31 (m, 2H), 1.71-1.67 (m, 2H), 1.56 (s, 1H), 1.53 (s, 10H), 1.34-1.22 (m, 3H), 0.80 (t, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 177.5, 153.5, 146.7, 138.9, 85.1, 82.5, 46.3, 39.2, 28.4, 28.1, 12.1; LR-MS (ESI) *m/z* 304 ($M+Na^+$); HR-MS (ESI) calcd for $C_{16}H_{27}NO_3$ ($M+Na^+$) 304.1883; found 304.1867

***tert*-butyl (5*R*,10*R*,*E*)-5-ethyl-10-(2-methoxy-2-oxoethyl)-3,4,5,8,9,10-hexahydroazecine-1(2H)-carboxylate (92)**

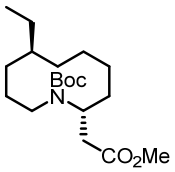


To a solution of lactam **85** (860mg, 3.06 mmol) in DCM (9 ml) was added DIBAL (1.0M in toluene, 5.51 ml) dropwise at -78℃. After the mixture was stirred for 10min, pyridine (15.3 mmol, 1.2 ml) and TMSOTf (7.67 mmol, 1.4 ml) were added. The mixture was stirred for 10min and allowed to warm to 0℃, quenched with satd aqueous Rochelle's soln (2 ml), and diluted with Et_2O. The resultant mixture was warmed to rt and stirred vigorously until two layers were completely separated. The mixture was extracted with Et_2O and combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 20, silica gel deactivated with Et_3N) to afford 870 mg (2.45 mmol, 80%) of

102.

To a solution of *N,O*-acetal TMS ether **102** in DCM (9 ml) were added 1-(*tert*-butyldimethylsilyloxyl)-1-methoxyethane (4.90 mmol, 1.1 ml) and $BF_3 \cdot OEt_2$ (2.7 mmol, 0.33 ml) at -78℃. The resultant mixture was stirred for 30min, and then slowly warmed to 0℃. The reaction mixture was quenched with TEA and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 10) to afford 783 mg (2.31 mmol, 94%) of **92**: FT-IR (thin film, neat) *v* max 2961, 2930, 1740, 1692, 1365, 1171 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 5.51-5.42 (m, 1H), 5.2-5.13 (m, 1H), 3.71 (m, 0.5H), 3.61 (s, 3H), 3.2 (broad s, 0.5H), 3.11-3.1 (m, 1H), 2.82 (dd, 0.5H), 2.53-2.47 (m, 1H), 2.43-2.37 (m, 0.5H), 2.31-2.26 (m, 1.5H), 2.19 (broad s, 0.5H), 2.08 (broad s, 0.5H), 1.98-1.89 (m, 1.5H), 1.83-1.76 (m, 1H), 1.67-1.62 (m, 1H), 1.45 (s, 4H), 1.422 (s, 2H), 1.39 (s, 5H), 1.36-1.29 (m, 1.5H), 1.27-1.15 (m, 2H), 0.93 (t, 1H), 0.82 (t, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 173.0, 155.0, 134.6, 131.5, 79.6, 78.9, 51.6, 51.4, 48.3, 40.3, 38.5, 35.8, 34.1, 33.5, 28.6, 28.5, 12.5; LR-MS (FAB) *m/z* 340 ($M+H^+$); HR-MS (FAB) calcd for $C_{19}H_{33}NO_4$ ($M+H^+$) 340.2410; found 340.2484

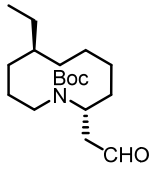
***tert*-butyl (2*R*,7*S*)-7-ethyl-2-(2-methoxy-2-oxoethyl)azecane-1-carboxylate (104)**



A solution of the methylester **92** (783mg, 2.31 mmol) and 10% Pd/C (78.3 mg) in anhydrous MeOH (10 ml) was placed under an atmosphere of hydrogen. After stirring for 19h, the reaction mixture was filtered through Celite® (eluent MeOH) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 10) to afford 764 mg (2.24 mmol, 97%) of **104**: FT-IR (thin film,

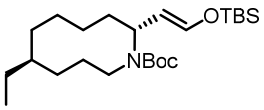
neat) ν max 2924, 1741, 1696, 1171 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 3.75 (broad s, 1H), 3.6 (s, 3H), 3.49 (broad s, 1H), 2.99-2.65 (m, 2H), 2.44-2.40 (m, 1H), 2.06-1.91 (m, 1H), 1.67 (broad s, 2H), 1.41 (s, 15H), 1.30 (s, 2H), 1.25-1.20 (m, 2H), 1.09 (broad s, 2H), 0.81 (t, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 172.6, 155.8, 79.6, 79.1, 51.6, 39.1, 38.5, 36.9, 32.4, 30.1, 28.4, 26.7, 25.8, 22.4, 11.9; LR-MS (FAB) *m/z* 342 ($M+H^+$); HR-MS (FAB) calcd for $C_{19}H_{35}NO_4$ ($M+H^+$) 342.4991; found 342.2644

***tert*-butyl (2*R*,7*S*)-7-ethyl-2-(2-oxoethyl)azecane-1-carboxylate (105)**



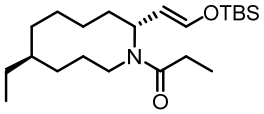
DIBAL (1M in toluene, 2.92 ml) was added dropwise to a stirred solution of **92** (2.24 mmol, 764 mg) in DCM (8 ml) at -78℃. The resultant mixture was stirred for 30min before quenched by the dropwise addition of satd aqueous Rochelle's soln (5 ml). The resultant mixture was diluted with DCM and allowed to warm to rt, and stirred vigorously until two layers were completely separated. The mixture was extracted with DCM and combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 10) to afford 635 mg (2.04 mmol, 91%) of **105**, which was directly used in next reaction because of its unstability.

***tert*-butyl (2*R*,7*S*)-2-((*E*)-2-((tert-butyldimethylsilyl)oxy)vinyl)-7-ethylazecane-1-carboxylate (106)**



To a mixture of aldehyde **105** (63.5 mg, 0.204 mmol), TBSCl (1.02 mmol, 150 mg) in DCM (3 ml) was added DBU (2.04 mmol, 0.3 ml). The resultant mixture was stirred at 40℃ for 1h and concentrated under reduced pressure to 0.5 ml. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 30, silica gel deactivated with Et_3N) to give 70.3 mg (0.16 mmol, 76%) of **106** with unseparable diastereoisomer: FT-IR (thin film, neat) *v* max 2958, 2929, 1695, 1169, 838 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.31 (dd, 1H), 5.10 (d, 1H), 3.64 (m, 1H), 2.85-2.78 (m, 1H), 2.04 (m, 1H), 1.74 (broad s, 1H), 1.66-1.63 (m, 1H), 1.54 (s, 1H), 1.44 (s, 11H), 1.35 (m, 3H), 1.25-1.18 (m, 4H), 1.14 (broad s, 2H), 0.89 (s, 9H), 0.86-0.84 (m, 4H), 0.11 (s, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 156.3, 141.3, 111.9, 79.2, 78.8, 57.2, 36.4, 32.6, 30.0, 28.5, 26.2, 25.7, 25.6, 22.8, 18.4, 11.9, -2.5, -4.7; LR-MS (FAB) *m/z* 426 ($M+H^+$); HR-MS (FAB) calcd for $C_{24}H_{47}NO_3Si$ ($M+H^+$) 426.3403; found 426.3394

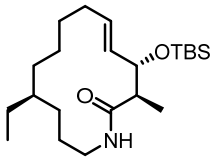
1-((2*R*,7*S*)-2-((*E*)-2-((*tert*-butyldimethylsilyl)oxy)vinyl)-7-ethylazecan-1-yl)propan-1-one (91)



To a solution of (*E*)-enol TBS ether **106** (70.3 mg, 0.16 mmol) in DCM (2 ml) were added 2,6-lutidine (0.64 mmol, 0.07ml) and TMSOTf (0.48 mmol, 0.086 ml) at 0℃. The resultant mixture was stirred for 30 min and then quenched by the dropwise addition of MeOH. The reaction mixture was allowed to warm to rt and concentrated *in vacuo*. The crude of **107** and DMAP (cat.) were dissolved in DCM (2 ml), which was treated with TEA (0.48 mmol,

0.07 ml) and propionic anhydride (0.32 mmol, 0.04 ml). The resultant mixture was stirred for 1h at ambient temperature and concentrated under reduced pressure to 0.5 ml. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 10, silica gel deactivated with Et_3N) to give 46.6 mg (0.13 mmol, 80%) of **91**: FT-IR (thin film, neat) *v* max 2956, 2930, 1652, 839 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.31 (d, 1H), 6.22 (d, 1H), 5.23 (broad s, 1H), 4.93 (dd, 1H), 4.13 (t, 1H), 3.49-3.37 (m, 2H), 3.08-2.92 (m, 2H), 2.38-2.27 (m, 2H), 2.24 (qd, 3H), 2.03 (m, 1H), 1.89-1.86 (m, 1H), 1.75 (broad s, 1H), 1.65-1.55 (m, 2H), 1.49-1.47 (m, 1H), 1.39 (m, 1H), 1.26-1.13(m, 2H), 1.11-1.06 (m, 2H), 0.85 (s, 9H), 0.82 (t, 3H), 0.07 (s, 6H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 175.0, 141.7, 111.6, 56.6, 56.1, 37.4, 31.63, 29.7, 27.8, 27.4, 25.6, 25.5, 23.3, 18.3, 11.9, 9.4, -5.3; LR-MS (FAB) *m/z* 382 ($M+H^+$); HR-MS (FAB) calcd for $C_{22}H_{43}NO_2Si$ ($M+H^+$) 382.3141; found 382.3139

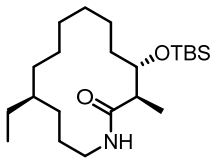
(3*R*,4*S*,11*S*,*E*)-4-((*tert*-butyldimethylsilyl)oxy)-11-ethyl-3-methylazacyclotetradec-5-en-2-one (90)



To a solution of silyl enol ether **91** (46.6 mg, 0.13 mmol) in benzene (3 ml) was added dropwise *i*PrMgCl (1.0M solution in hexane, 0.5 ml) at 60℃ and resulting solution was heated for 40 min. After addition of water, the solvent was evaporated and the residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 10) to give 46.6 mg (0.13 mmol, 95%) of **90** as a white solid: FT-IR (thin film, neat) *v* max 3279, 2928, 1638, 775cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 6.25 (s, NH), 5.59-5.54 (m, 1H), 5.37 (dd, 1H), 4.18 (t, 1H), 3.89-3.83 (m, 1H), 2.51 (tt, 1H), 2.27 (quintet, 1H), 2.01 (m, 2H), 1.56 (s, 1H), 1.48-1.38 (m, 2H), 1.36-1.20 (m, 8H), 1.17 (d, 3H), 1.07-0.99 (m, 2H), 0.89 (s, 9H),

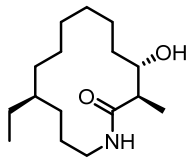
0.83 (t, 3H), 0.06 (s, 3H), 0.02 (s,3H);^{13}C-NMR ($CDCl_3$, 125 MHz) δ 173.9, 131.8, 130.7, 75.0, 48.4, 39.4, 37.7, 31.0, 30.9, 27.2, 27.1, 26.4, 25.9, 23.8, 23.6, 18.1, 15.1, 12.0, -4.3, -4.9; LR-MS (FAB) *m/z* 382 ($M+H^+$); HR-MS (FAB) calcd for $C_{22}H_{43}NO_2Si$ ($M+H^+$) 382.3141; found 382.3140

(3*R*,4*S*,11*S*)-4-((*tert*-butyldimethylsilyl)oxy)-11-ethyl-3-methylazacyclotetradecan-2-one (119)



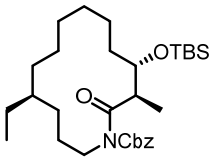
A solution of the macrolactam **90** (46.6mg, 0.13 mmol) and 10% Pd/C (4.7 mg) in anhydrous MeOH and EtOAc (2 ml, 1:1) was placed under an atmosphere of hydrogen. After stirring for 12h, the reaction mixture was filtered through Celite® (eluent EtOAc) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 15) to afford 49.8 mg (0.13 mmol, 100%) of **119**: FT-IR (thin film, neat) ν max 3285, 2957, 2931, 2857, 1637, 773 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 6.52 (d, NH), 3.99-3.88 (m, 1H), 3.75 (td, 1H), 2.58-2.52 (m, 1H), 2.40 (qiuntet, 1H), 1.70 (s, 1H), 1.54-1.23 (m, 18H), 1.09 (d, 3H), 0.89 (s, 3H), 0.83 (t, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 174.1, 74.7, 46.2, 38.9, 38.8, 31.3, 30.8, 27.6, 27.0, 26.8, 26.0, 25.9, 24.4, 23.6, 21.1, 18.0, 14.8, 11.8, -4.6, -4.6

6-desmethyl-*N*-methylfluvirucinine (89)



To a solution of lactam **119** (50 mg, 0.13 mmol) in THF (1 ml) was added TBAF (1.0M solution in THF, 0.16 ml) and the reaction mixture was stirred at rt for 1h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (EtOAc : Hexane = 1 : 1, 2% MeOH) to afford 35 mg (0.13 mmol, 100%) of **89**: FT-IR (thin film, neat) *v* max 3388, 3305, 1637, 789 cm^{-1}; ^{1}H-NMR (MeOD, 500 MHz) δ 4.58 (s, NH), 3.68-3.62 (m, 2H), 2.69 (qd, 1H), 2.37-2.31(m, 1H), 1.62-1.52 (m, 2H), 1.50-1.45 (m, 4H), 1.43-1.41 (m, 4H), 1.39-1.32 (m, 3H), 1.30-1.26 (m, 2H), 1.24-1.10 (m, 4H), 1.17 (d, 3H), 0.86 (t, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 178.7, 74.6, 48.8, 40.3, 38.5, 35.3, 32.6, 29.8, 28.9, 28.7, 27.8, 27.5, 24.2, 22.7, 16.8, 12.7; LR-MS (ESI) *m/z* 270 ($M+H^+$); HR-MS (ESI) calcd for $C_{16}H_{31}NO_2$ ($M+H^+$) 270.2426; found 270.2426

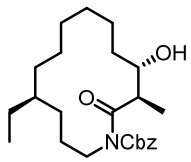
benzyl (3*R*,4*S*,11*S*)-4-((*tert*-butyldimethylsilyl)oxy)-11-ethyl-3-methyl-2-oxoazacyclotetradecane-1-carboxylate (120)



To a solution of lactam **119** (0.14 mmol, 54 mg) in THF (3 ml) was added *n*BuLi (1.6M in hexane, 0.1 ml) at -78℃. After the mixture was stirred for 10min, CbzCl (0.168 mmol, 0.02 ml) was added and the mixture was stirred for 2h. The reaction mixture was quenched by

adding water, and allowed to warm to rt. The mixture was extracted with EtOAc (3x40 ml) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification via flash column chromatography (EtOAc:Hexane=1:40) gave 72 mg (0.14 mmol, 100%) of **120**: FT-IR (thin film, neat) *v* max 2931, 1735, 1160, 774 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.37-7.32 (m, 5H), 5.23 (d, 2H), 4.09 (dt, 1H), 4.00 (dt, 1H), 3.75-3.72 (m, 1H), 3.53 (t, 1H), 1.54 (s, 4H), 1.44-1.35 (m, 3H), 1.31-1.20 (m, 9H), 1.17 (d, 3H), 1.14-1.09 (m, 3H), 0.87 (s, 9H), 0.80 (t, 3H), 0.03 (d, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 178.5, 154.8, 135.1, 128.7, 128.6, 74.3, 68.6, 45.0, 44.3, 38.0, 33.1, 31.3, 27.0, 26.4, 26.0, 25.9, 22.9, 22.3, 18.7, 18.1, 17.1, 12.0, -4.2, -4.6

benzyl (3*R*,4*S*,11*S*)-11-ethyl-4-hydroxy-3-methyl-2-oxoazacyclotetradecane-1-carboxylate (121)

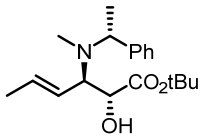


To a solution of lactam **120** (72 mg, 0.14 mmol) in MeOH:DCM (1.5 ml, 2:1) was added 1.25M HCl (0.25 ml) and the reaction mixture was stirred at rt for 2h 30min. The reaction mixture was quenched by adding satd aqueous $NaHCO_3$ soln, and extracted with DCM (3x3 ml) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification via flash column chromatography (EtOAc:Hexane=1:4) gave 56 mg (0.14 mmol, 100%) of **121**: FT-IR (thin film, neat) *v* max 2930, 1731, 1688, 1363, 1174 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.37-7.32 (m, 5H), 5.30-5.14 (m, 2H), 4.11 (dq, 1H), 3.89-3.80 (m, 1H), 3.68-3.59 (m, 1H), 3.56-3.49 (m, 1H), 1.86-1.79 (m, 1H), 1.65 (s, OH), 1.65-1.45 (m, 2H), 1.40-1.28 (m, 6H), 1.26-1.20 (m, 4H), 1.24 (d, 3H), 1.18-1.13 (m, 2H), 1.12-1.07 (m, 3H), 1.03-0.95 (m, 1H), 0.79 (t, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ

179.1, 154.9, 135.0, 128.7, 128.6, 128.4, 74.3, 68.6, 45.6, 44.4, 37.9, 33.3, 31.4, 27.7, 26.8, 26.1, 25.9, 24.2, 23.4, 21.5, 14.9, 11.6

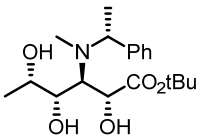
Carbohydrate part:

***tert*-butyl (2*R*,3*R*,*E*)-2-hydroxy-3-(methyl((*R*)-1-phenylethyl)amino)hex-4-enoate (151)**



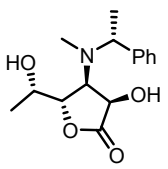
*n*BuLi (2.5M in hexane, 24 ml) was added dropwise to a stirred solution of (*R)-N*-methyl-*N-(α*-methylbenzyl)amine **149** (20 mmol, 2.7 g) in THF (50 ml) at -78℃. After stirring for 1h 30min, a solution of *tert*-butyl sorbate **150** (21 mmol, 3.53 g) in THF (21 ml) at -78℃ was cannulated. The reaction mixture was stirred for a further 1h, before the addition of (-)-CSO (24 mmol, 5g). The resultant mixture was allowed to warm to rt and heated to 40℃ over 12h. The reaction mixture was quenched with water and then aqueous phase was extracted with EtOAc. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification via flash column chromatography (EtOAc:Hexane=1:5) gave 3.96 g (12.4 mmol, 62%) of **151**: FT-IR (thin film, neat) *v* max 2975, 1726, 1366, 1169, 1152 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.3-7.13(m, 5H), 5.58-5.54 (m, 2H), 4.26 (d, 1H), 3.9 (q, 1H), 3.34 (dd, 1H), 2.09 (s, 3H), 1.63 (d, 3H), 1.37 (s, 9H), 1.24 (d, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ 171.7, 143.7, 129.3, 127.4, 126.7, 125.9, 125.1, 80.5, 70.9, 64.8, 59.0, 33.1, 27.2, 17.2, 15.8; LR-MS (FAB) *m/z* 320 ($M+H^+$); HR-MS (FAB) calcd for $C_{19}H_{29}NO_3$ ($M+H^+$) 320.2226; found 320.2223

***tert*-butyl *(2R,3R,4S,5S)*-2,4,5-trihydroxy-3-(methyl*((R)*-1-phenylethyl)amino)hexanoate (152)**



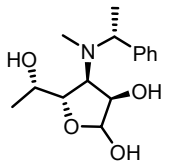
OsO4 (0.1M in toluene, 12.4 ml) was added to a stirred solution of **151** (3.96g, 12.4 mmol) in THF: H_2O (40ml, 2.5:1), followed by addition of NMO (49.6 mmol, 5.8 g) at 0℃. The resultant mixture was stirred at 0℃ for 12h. Satd aqueous Na_2SO_3 (40 ml) was then added and the reaction mixture was left to stir at rt for a further 1h. The mixture was extracted with EtOAc (3x40 ml) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification via flash column chromatography (EtOAc:Hexane=1:2) gave a separable 77: 23 mixture of **152** and its diastereomer respectively (3.9 g, 90%): FT-IR (thin film, neat) *v* max 3460, 2977, 1728, 1163 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.33-7.29 (m, 4H), 7.26-7.23 (m, 1H), 4.32 (s, OH), 4.03 (qd, 1H)m 3.83 (t, 1H), 3.64 (q, 1H), 3.26 (s, OH), 3.14 (d, 1H), 2.42 (s, 3H), 1.78 (d, 1H), 1.4 (d, 3H), 1.39 (s, 9H), 0.99 (d, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 174.6, 144.8, 128.6, 127.9, 127.5, 82.6, 70.2, 67.5, 66.8, 62.5, 34.9, 28.0, 20.9, 18.3; LR-MS (FAB) *m/z* 354 ($M+H^+$); HR-MS (FAB) calcd for $C_{19}H_{31}NO_5$ ($M+H^+$) 354.2280; found 354.2287

***(3R,4S,5S)*-3-hydroxy-5-*((S)*-1-hydroxyethyl)-4-(methyl*((R)*-1-phenylethyl)amino)dihydrofuran-2(3H)-one (153)**



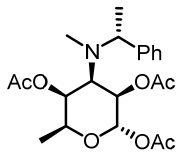
To a solution of triol **152** (3g, 8.5 mmol) in DCM (28 ml) was added TFA (2.8 ml) dropwise. The resultant mixture was stirred for 16h and neutralised by aqueous $NaHCO_3$ solution. The mixture was extracted with DCM (3x30 ml) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification via flash column chromatography (EtOAc:Hexane=1:1) gave 1.5 g (5.5 mmol, 65%) of **153**: FT-IR (thin film, neat) *v* max 3429, 1772, 772 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.31-7.28 (m, 2H), 7.26-7.22 (m, 3H), 4.38 (d, 1H), 3.91 (q, 1H), 3.78-3.75 (m, 2H), 3.66-3.65 (m, 1H), 2.17 (s, 3H), 1.40 (d, 3H), 1.07 (d, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 177.8, 141.3, 128.5, 127.7, 127.3, 81.4, 67.9, 64.6, 63.3, 31.1, 31.1, 19.4, 18.4; LR-MS (FAB) *m/z* 280 ($M+H^+$); HR-MS (FAB) calcd for $C_{15}H_{21}NO_4$ ($M+H^+$) 280.1549; found 280.1551

***(3R,4S,5S)*-5-((*S*)-1-hydroxyethyl)-4-(methyl((*R*)-1-phenylethyl)amino)tetrahydrofuran-2,3-diol (159)**



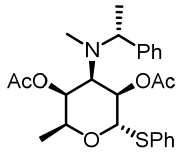
To a solution of lactone **153** (1.5g, 5.5 mmol) in DCM (91 ml) was added DIBAL (1.0M in toluene, 18 ml) dropwise at -78℃. The resultant mixture was stirred for 30min, and quenched by subsequent addtion of MeOH (12 ml) and satd aquoues Rochelle's solution (6 ml). The reaction mixture was allowed to warm to rt and stirred for 16h before being filtered through Celite® (eluent DCM). The filtrate was concentrated under reduced pressure. the residue was purified by flash column chromatography on silica gel (DCM : MeOH = 20: 1) to afford 618 mg (2.2 mmol, 40%(brsm 80%)) of **159**: LR-MS (FAB) *m/z* 282 ($M+H^+$); HR-MS (FAB) calcd for $C_{15}H_{23}NO_4$ ($M+H^+$) 282.1705; found 282.1703

***(2S,3R,4R,5S,6S)*-6-methyl-4-(methyl*((R)*-1-phenylethyl)amino)tetrahydro-2*H*-pyran-2,3,5-triyl triacetate (160)**



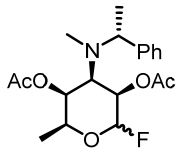
To a stirred solution of lactol **159** (618 mg, 2.2 mmol) in MeOH (20 ml) was added 1.25M HCl (4 ml) dropwise. The resultant mixture was stirred for 16h and concentrated *in vacuo*. The crude resultant and DMAP (cat.) were dissolved in pyridine: Ac_2O (1:1, 8 ml) and stirred for 24h. The reaction mixture was diluted with DCM and quenched by the addition of satd aqueous $CuSO_4$ solution (5 ml). The mixture was extracted with DCM (3x5 ml). The combined organic extracts were washed with satd $NaHCO_3$ soln and dried over $MgSO_4$, followed by concentration under reduced pressure. Purification via flash column chromatography (EtOAc:Hexane=1:4) allowed separation of **160** from furanoside **161** (200 mg, 67%, 1:2): FT-IR (thin film, neat) *v* max 1743, 1220, 772 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.31-7.19 (m, 5H), 5.93 (s, 1H), 5.18 (d, 1H), 4.89-4.83 (m, 1H), 4.16 (dd, 1H), 3.70 (q, 1H), 3.41 (dd, 1H), 2.39 (s, 3H), 2.08 (s, 3H), 1.93 (s, 3H), 1.88 (s, 3H), 1.34 (d, 3H), 1.23 (d, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 170.1, 169.8, 169.3, 144.3, 128.5, 127.3, 127.2, 98.6, 81.1, 76.2, 69.3, 63.1, 60.1, 34.1, 21.2, 21.0, 20.4, 16.8; LR-MS (FAB) *m/z* 408 ($M+H^+$); HR-MS (FAB) calcd for $C_{21}H_{29}NO_7$ ($M+H^+$) 408.2022; found 408.2038.

***(2S,3S,4R,5R,6S)-2*-methyl-4-(methyl((*R*)-1-phenylethyl)amino)-6-(phenylthio)tetrahydro-2H-pyran-3,5-diyl diacetate (162)**



To a benzene solution (7 ml) of triacetate glycoside **160** (200 mg, 0.49 mmol) was added PhSH (2.45 mmol, 0.25 ml), followed by $SnCl_4$ (1M in DCM, 0.73 ml). The resulting mixture was moved to the preheated bath (50℃) and stirred for 30 min. The reaction was quenched by the addition of a 14 ml of aqueous $NaHCO_3$, and diluted with DCM. Organic and aqueous layers were separated and the aqueous layer was washed with DCM (3x 20 ml portions). The combined organic layers were dried over anhydrous MgSO4, filtered and evaporated under reduced pressure. Purification via flash column chromatography (EtOAc:Hexane=1:5) afforded **162** (98mg, 44%): ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.49-7.44 (m, 2H), 7.31-7.21 (m, 8H), 5.25-5.24 (d, 1H), 5.21-5.19 (m, 1H), 4.86 (qd, 1H), 4.10 (dd, 1H), 3.67 (q, 1H), 3.55-3.52 (m, 1H), 2.36 (s, 3H), 2.06 (s, 3H), 1.93 (s, 3H), 1.32 (d, 3H), 1.27 (d, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.3, 169.8, 143.9, 133.7, 132.4, 128.8, 128.5, 127.5, 127.2, 90.4, 80.8, 77.8, 69.3, 63.1, 60.4, 33.9, 21.3, 21.2, 20.5, 16.8.

***(3R,4R,5S,6S)*-2-fluoro-6-methyl-4-(methyl((*R*)-1-phenylethyl)amino)tetrahydro-*2H*-pyran-3,5-diyl diacetate (163)**



Thioglycoside **162** (29 mg, 0.06 mmol) was dried through azeotropic distillation in benzene (3x 3 ml) and then dissloved in DCM (1 ml). The resulting solution was treated with DAST (0.08 mmol, 0.01 ml) at -15℃ and stirred for 2 min. NBS (0.09 mmol, 17 mg) was added and the reaction mixture was stirred for 1h at -15℃, and then for 2h at 0℃. The reaction mixture was quenched by addition of satd aqueous $NaHCO_3$ soln. The mixture was extracted with DCM (3x3 ml) and the combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification via flash column chromatography

(EtOAc:Hexane=1:5) gave 16..5 mg (0.045 mmol, 71%) of **163** as mixture of anomers: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.30-7.18 (m, 5H), 5.91(d, 0.5H), 5.69 (d, 0.5H), 4.89-4.73 (m, 2H), 4.14 (dd, 1H), 3.79 (q, 1H), 3.33 (q, 1H), 2.52 (s, 3H), 2.15 (s, 3H), 1.83 (s, 3H), 1.33 (d, 3H), 1.23 (d, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz) δ 170.0, 169.9, 144.8, 128.6, 127.2, 127.2, 108.7, 106.9, 81.8, 73.8, 73.6, 69.2, 63.2, 56.9, 34.1, 21.5, 21.0, 20.8, 16.4, 1.1.

V. References

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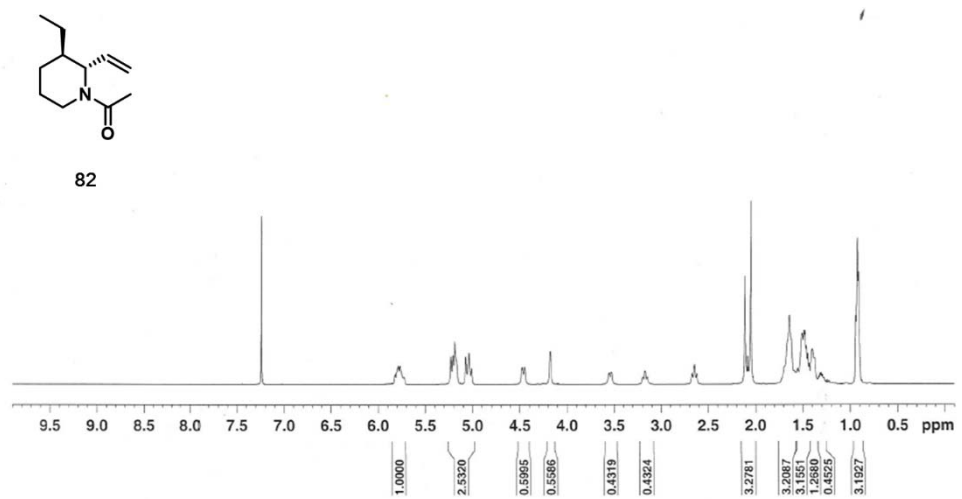
VI. Appendix

▼ ^{1}H-NMR ($CDCl_3$, 500 MHz)



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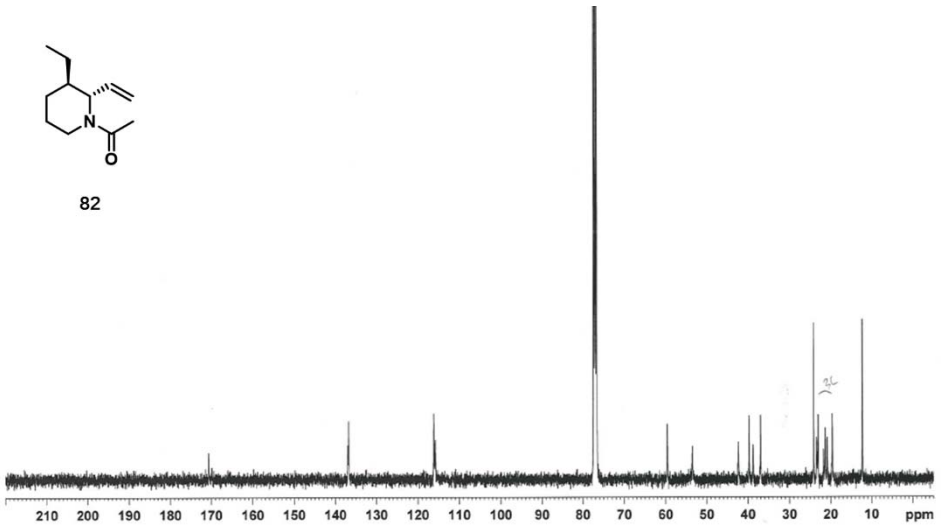

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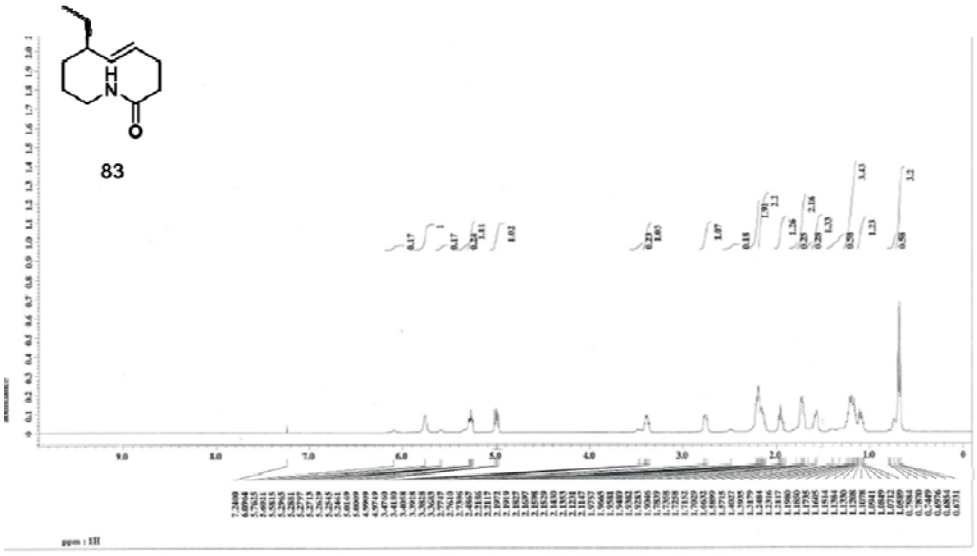

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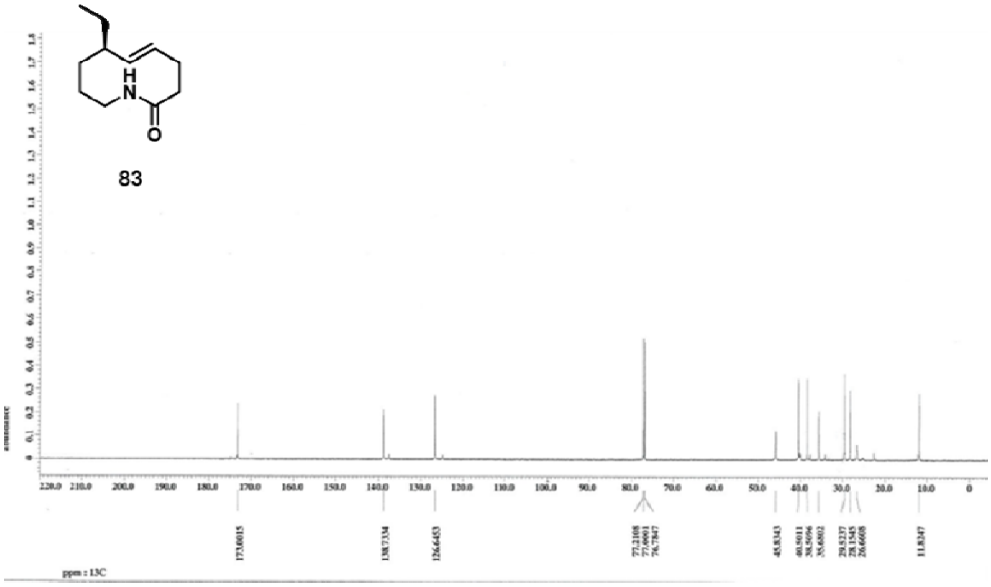

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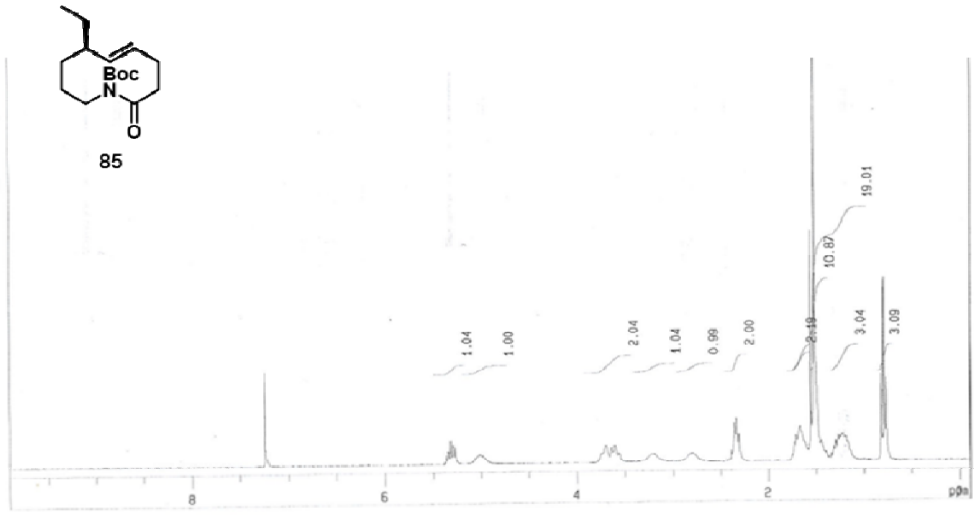

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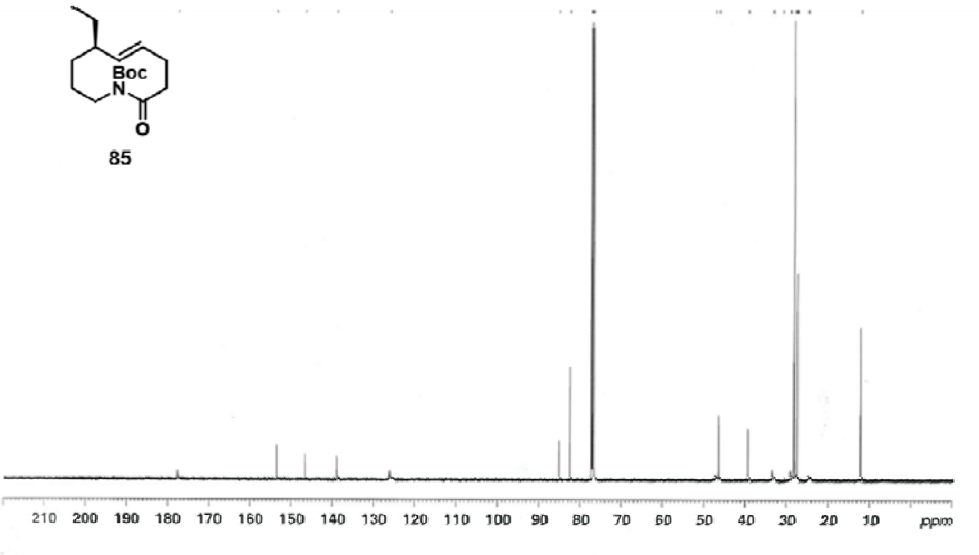

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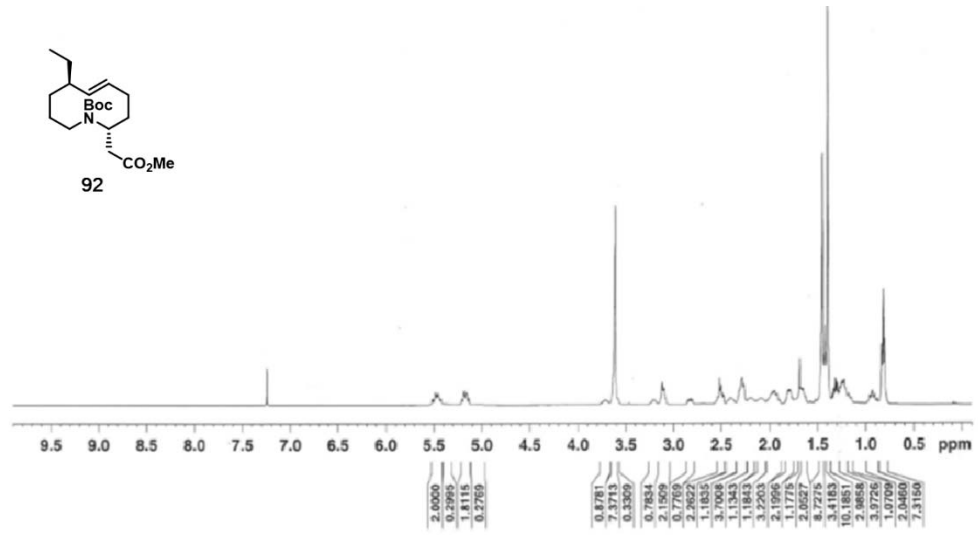

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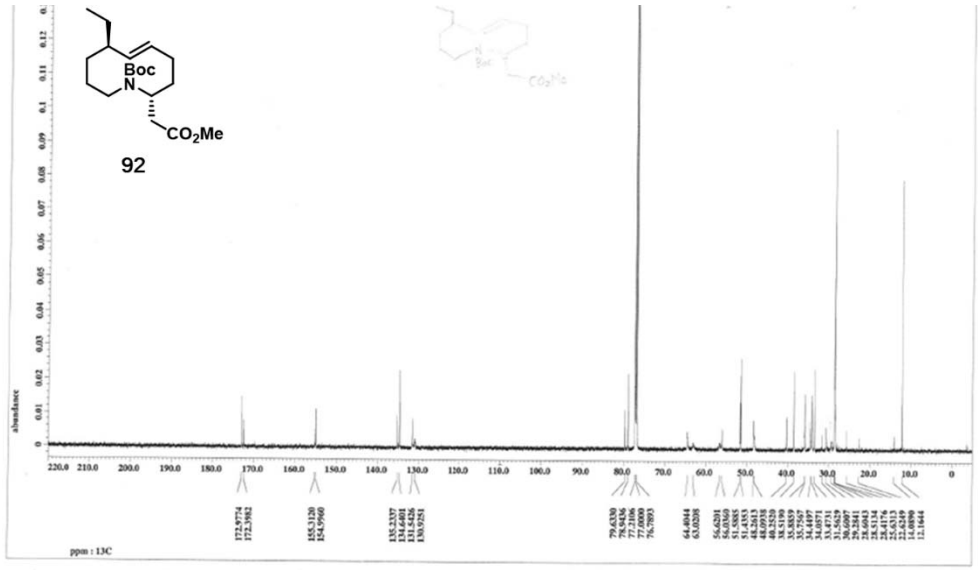

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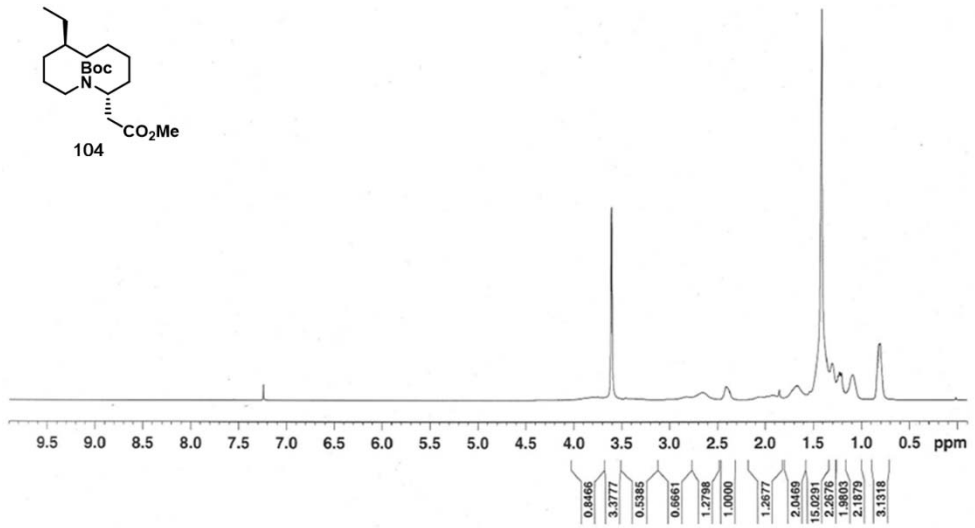

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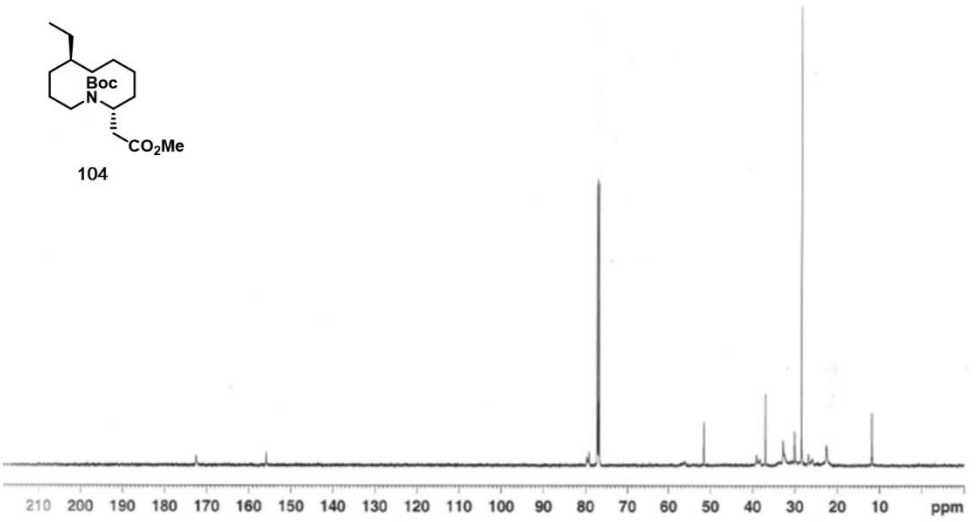

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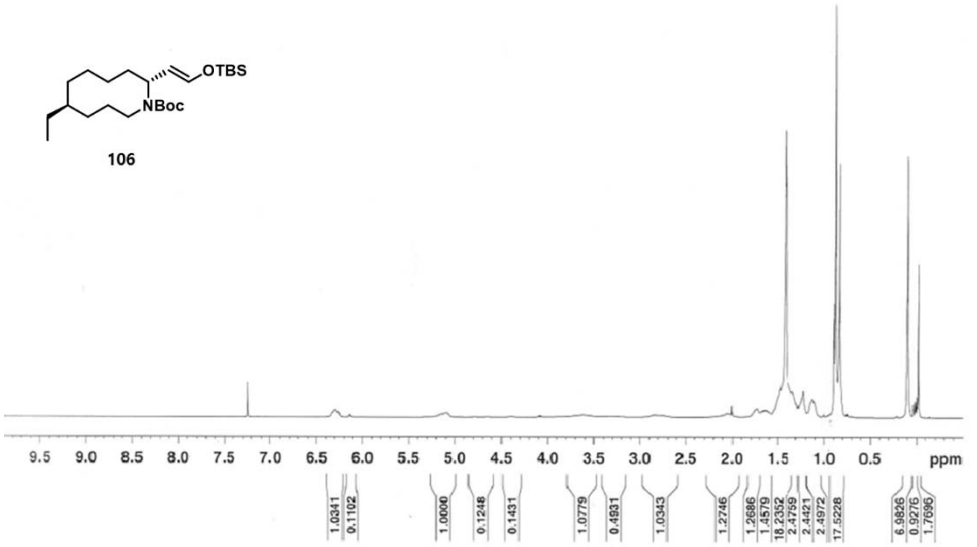

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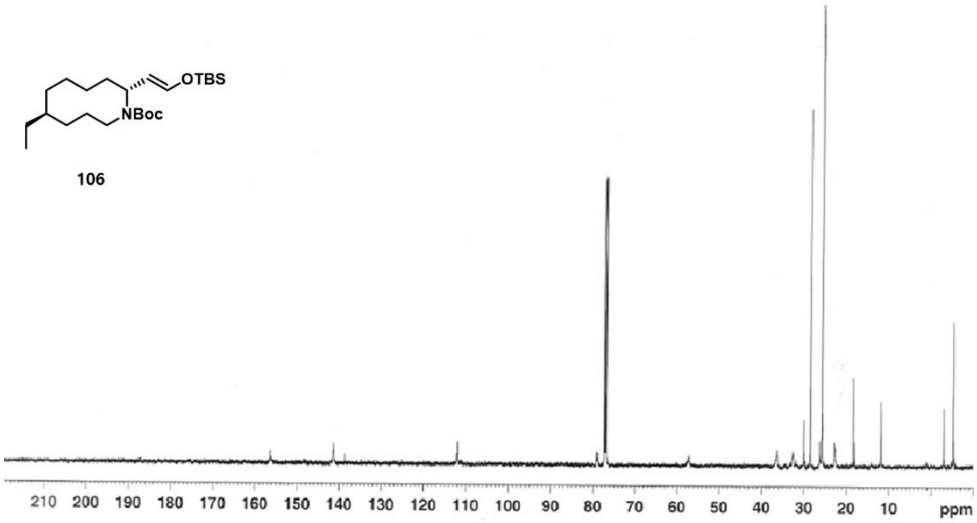

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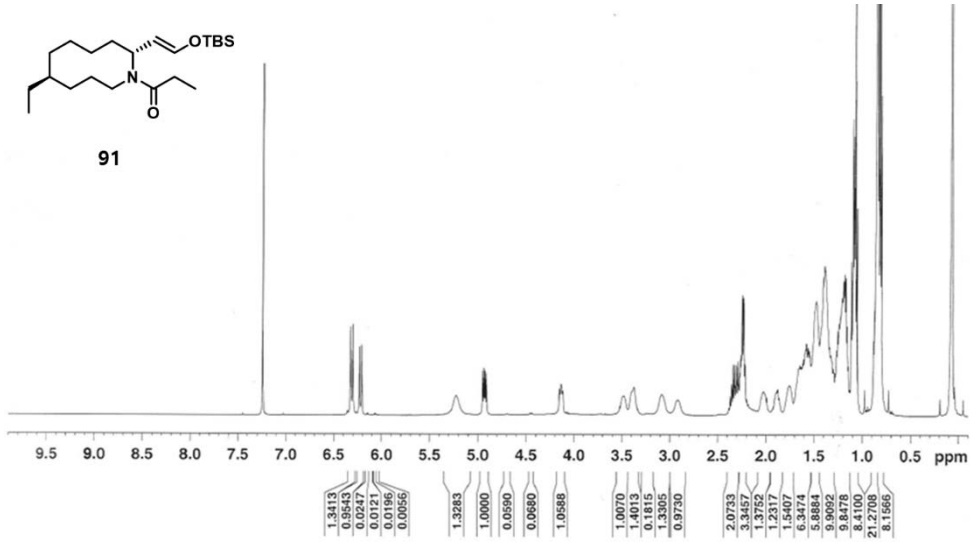

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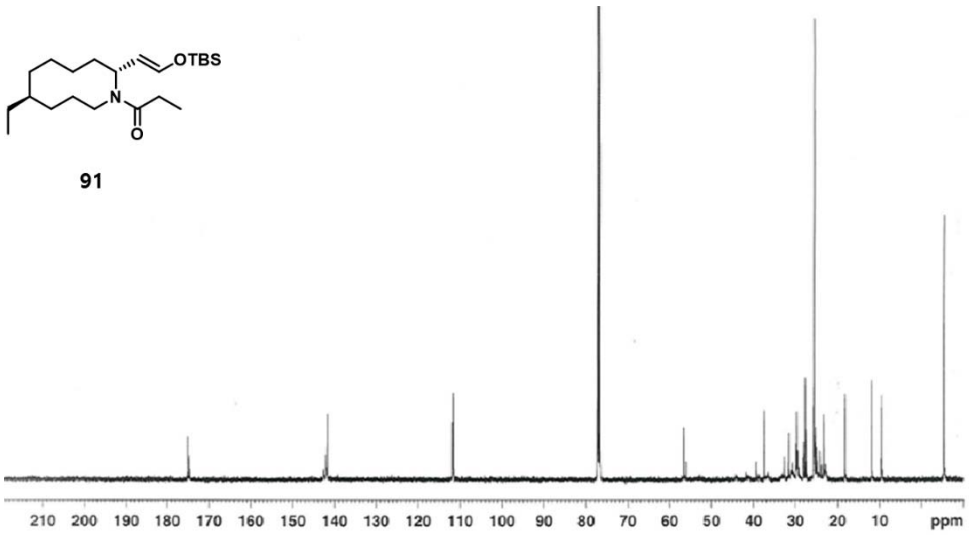

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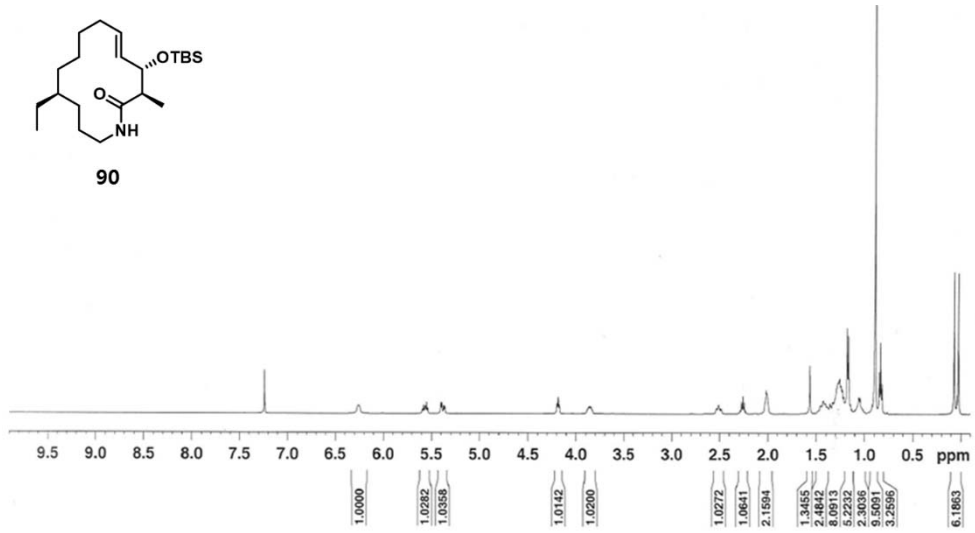

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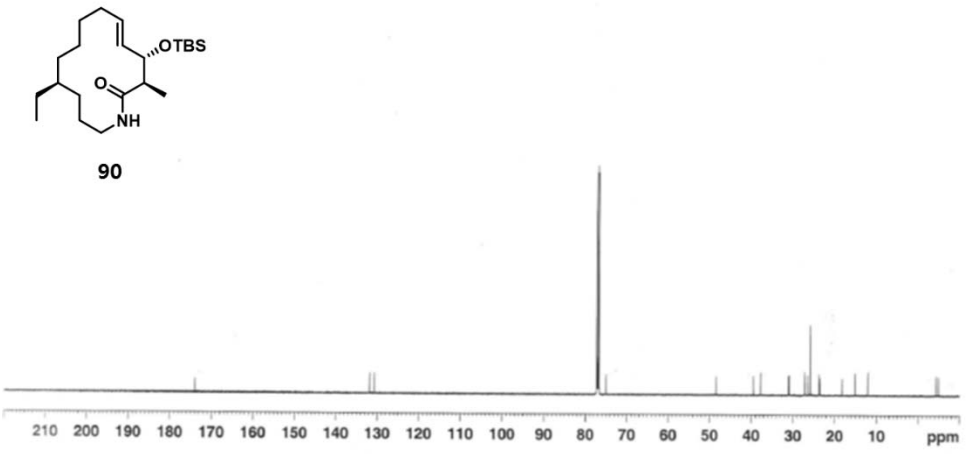

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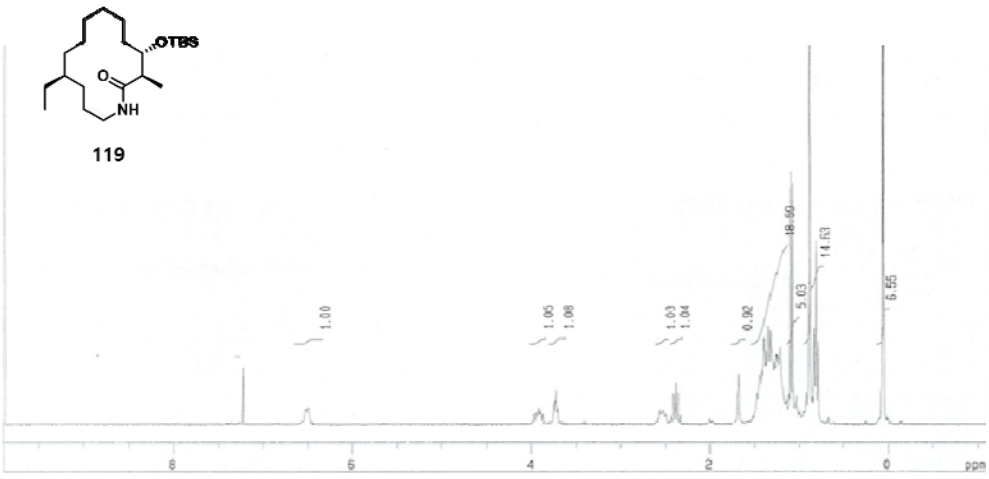

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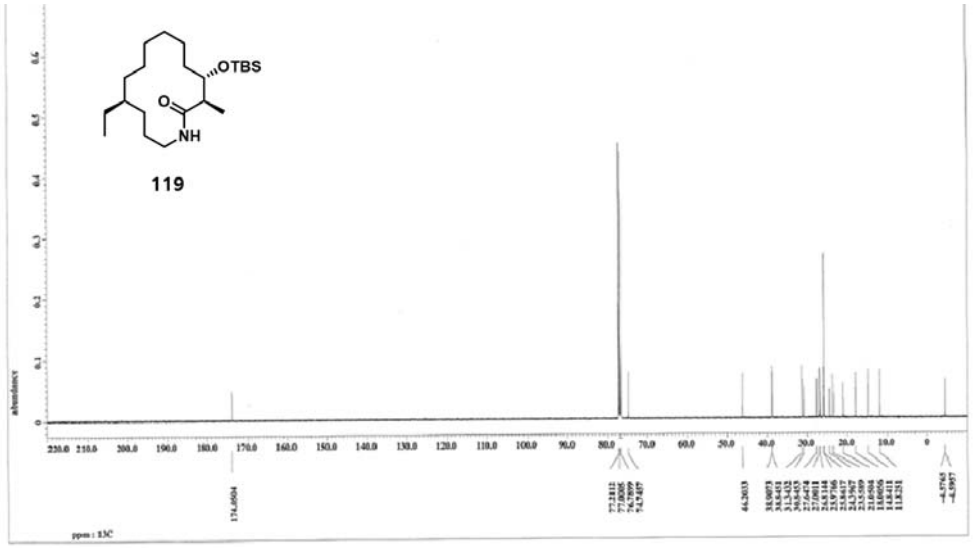

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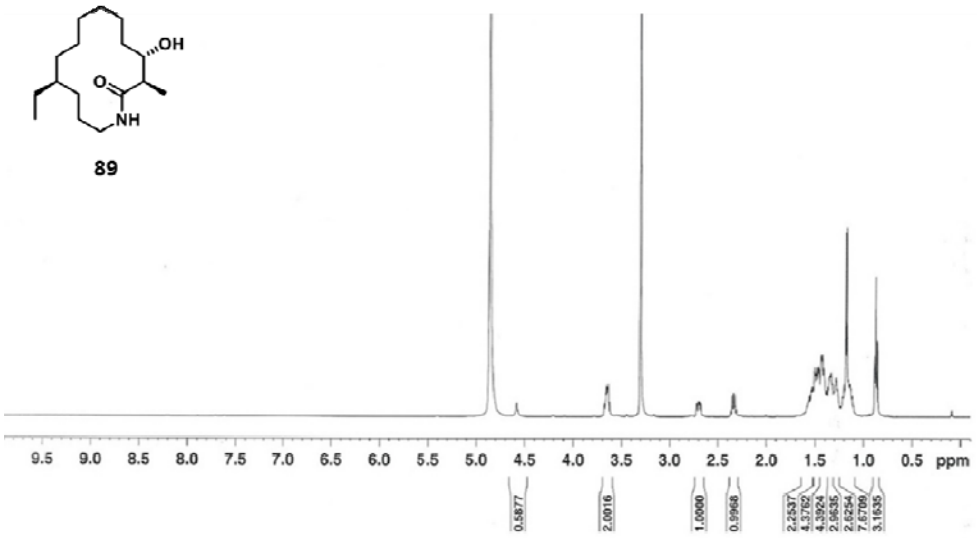

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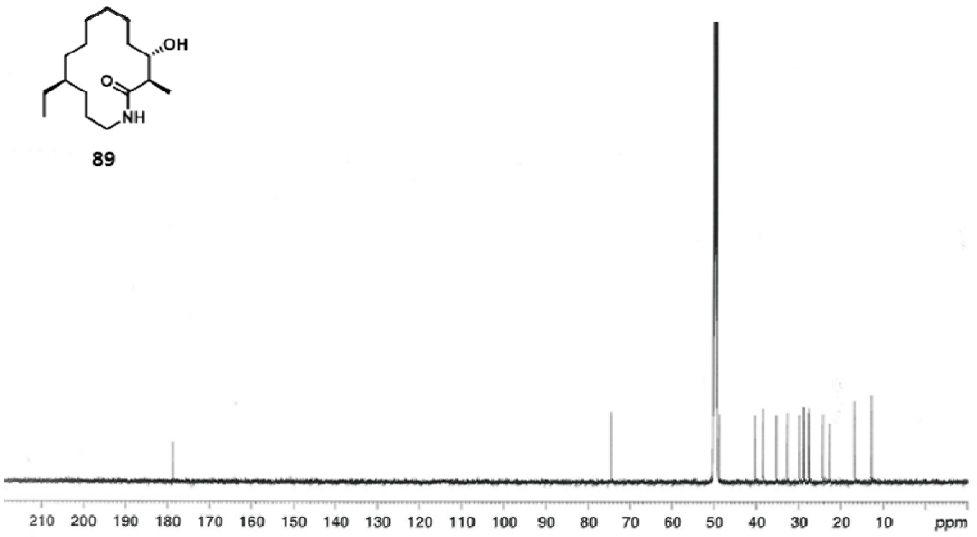

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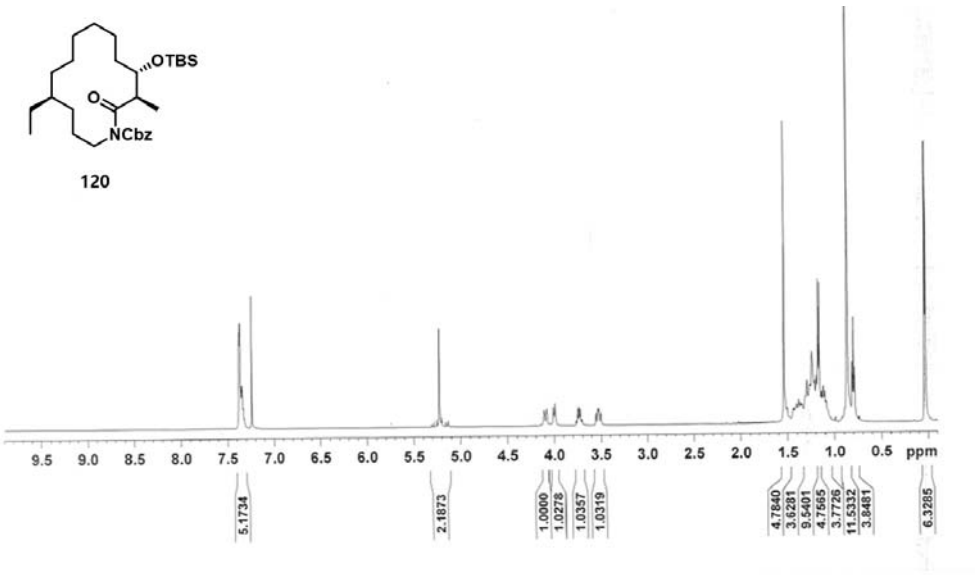

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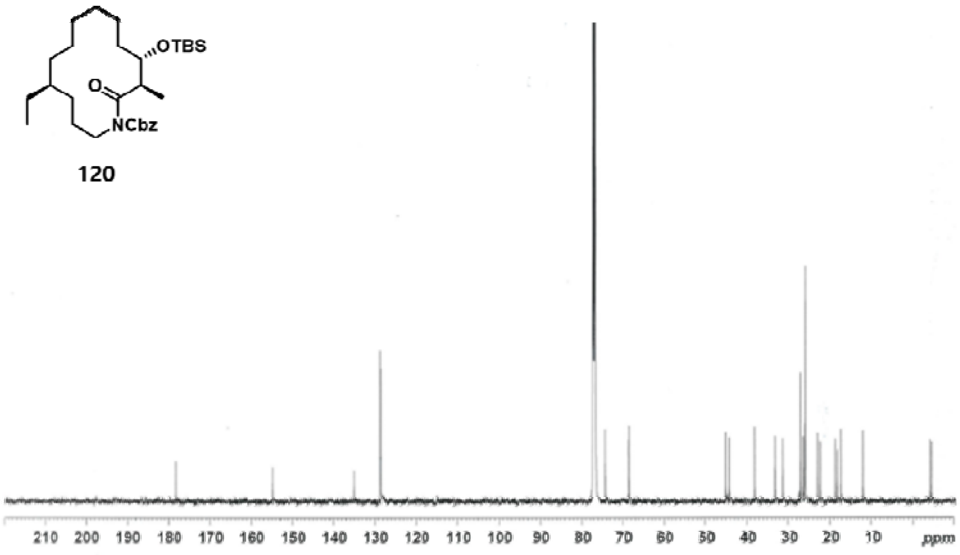

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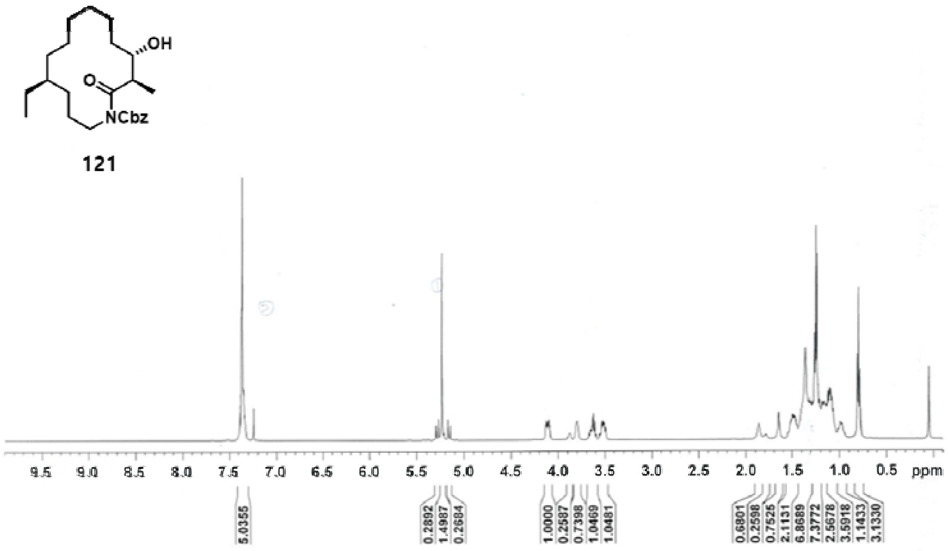

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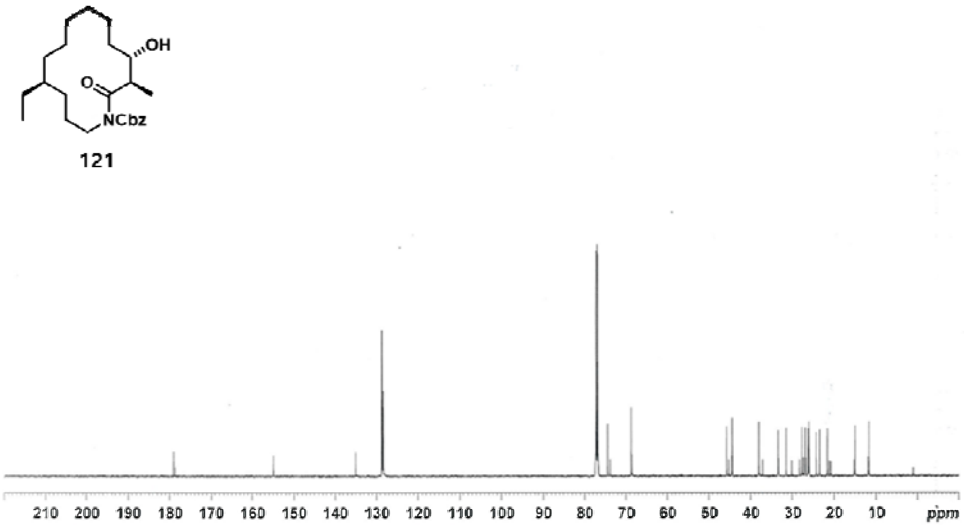

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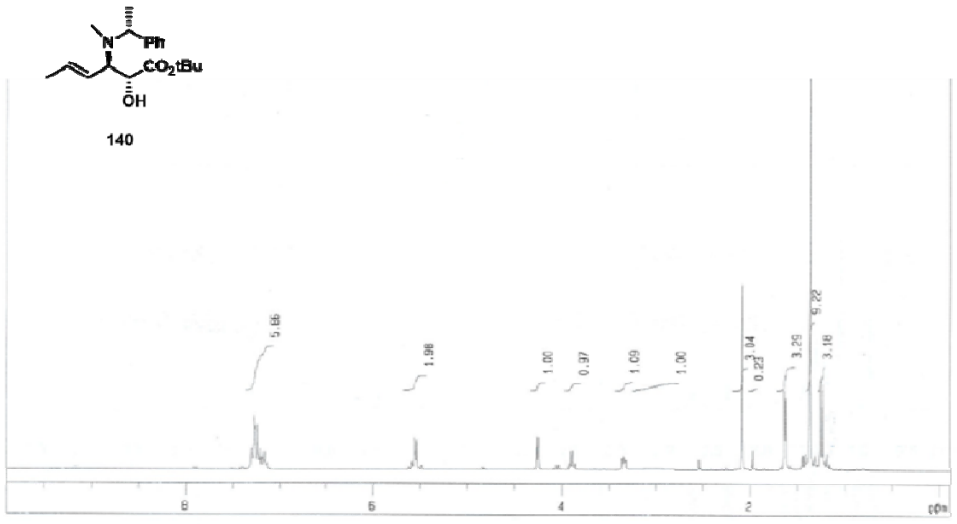

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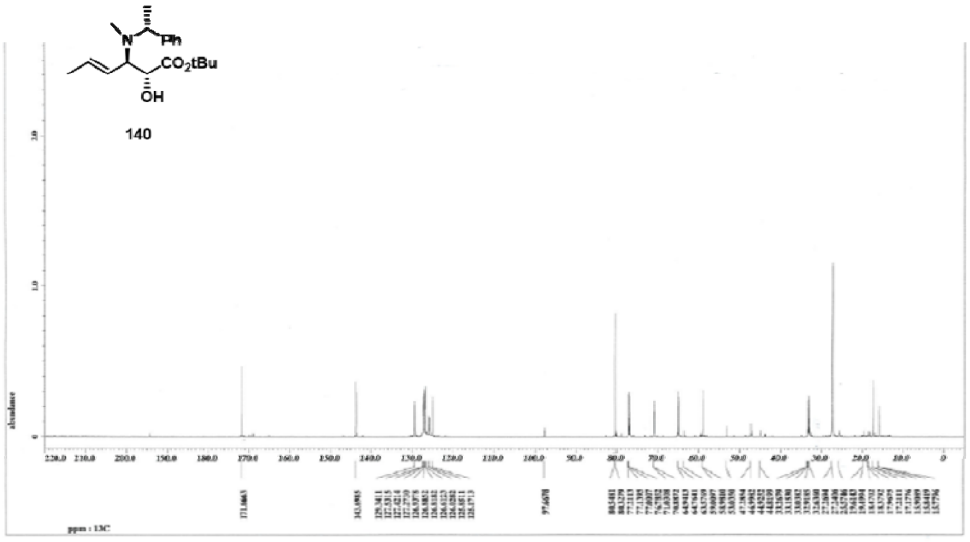

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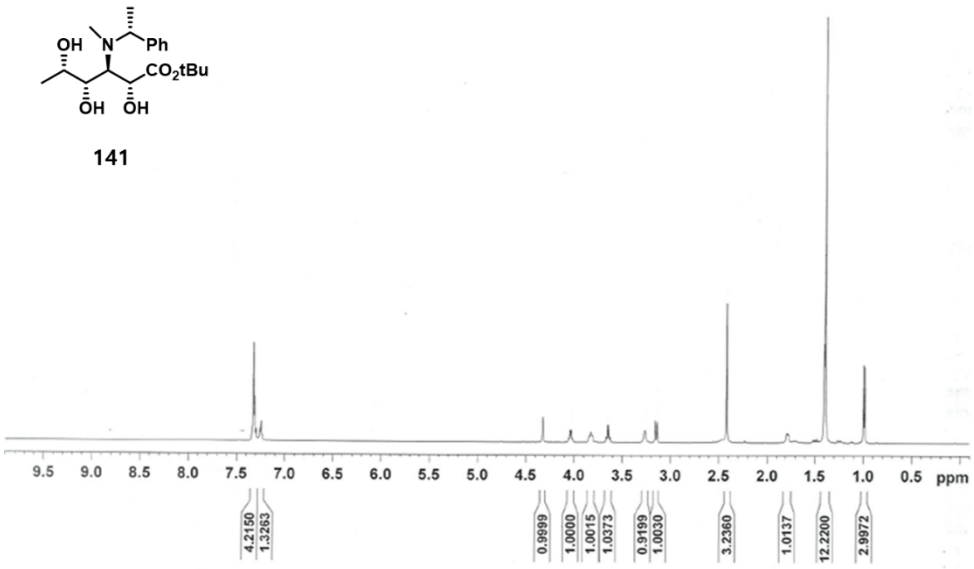

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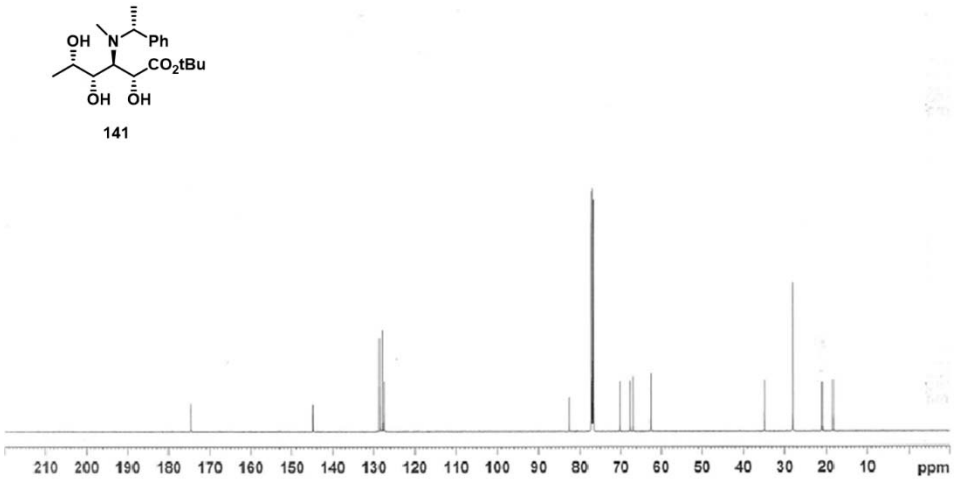

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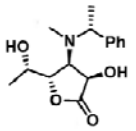

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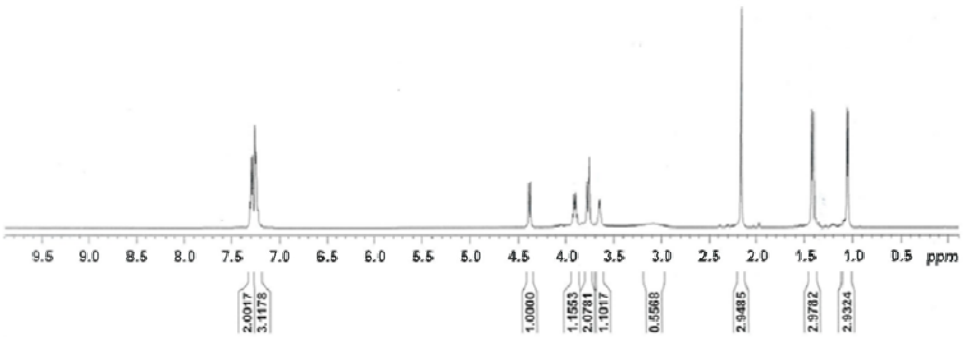

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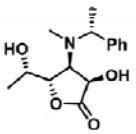

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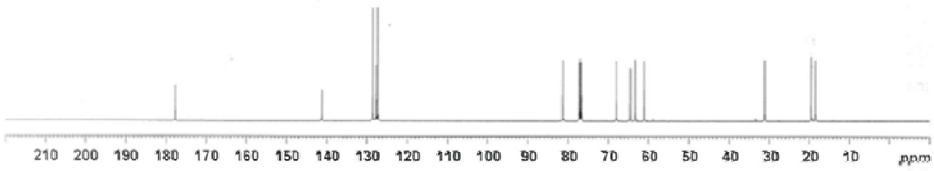

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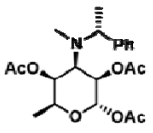
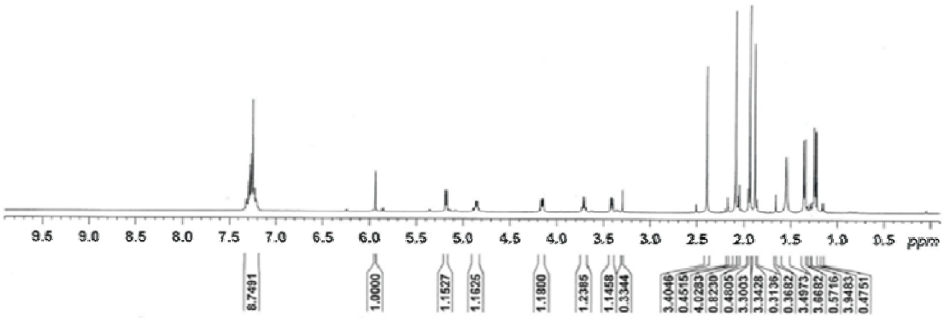
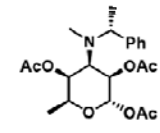


149

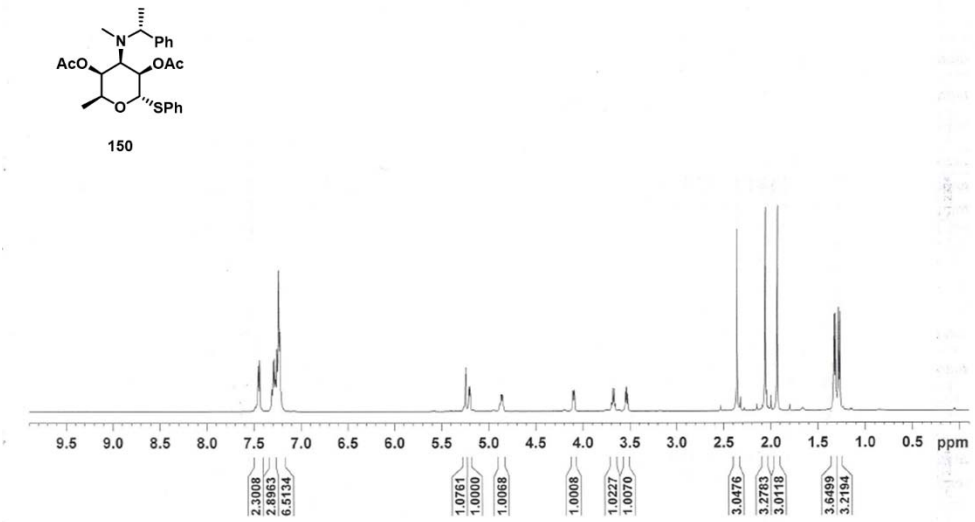


▼ ^{13}C-NMR ($CDCl_3$, 100 MHz)

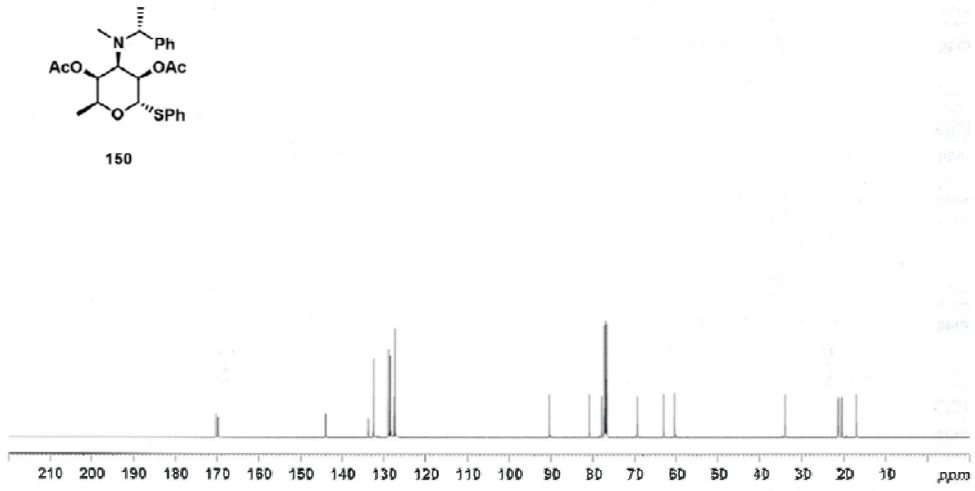


149

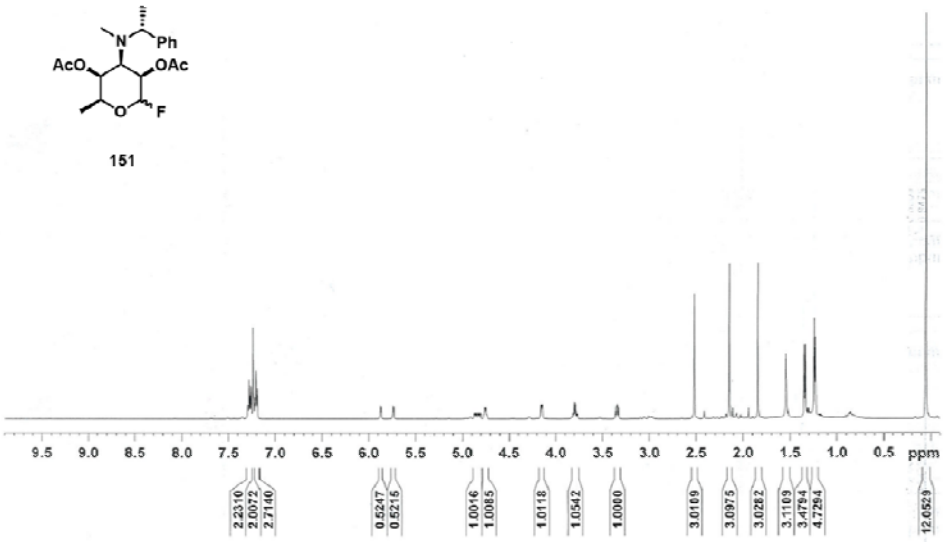
▼ ^{1}H-NMR ($CDCl_3$, 500 MHz)



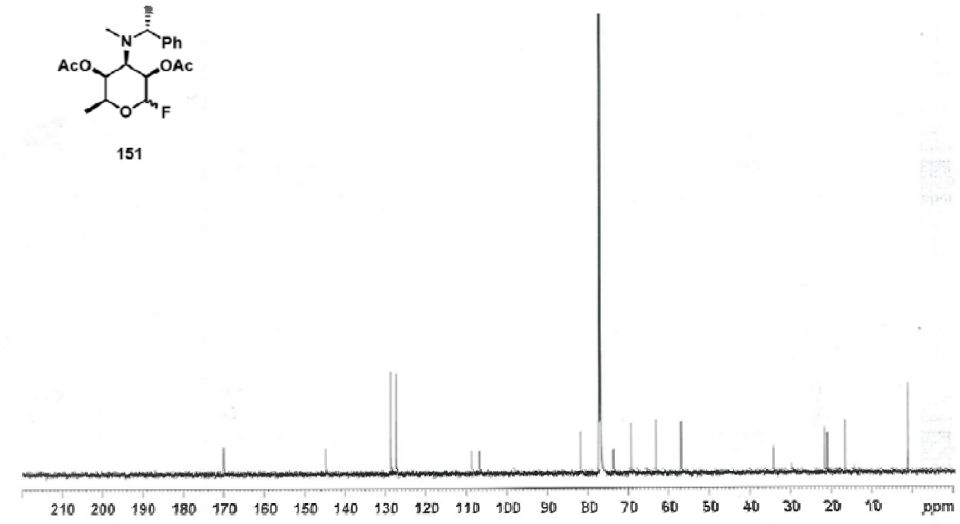
▼ ^{13}C-NMR ($CDCl_3$, 125 MHz)



▼ ^{1}H-NMR ($CDCl_3$, 500 MHz)



▼ ^{13}C-NMR ($CDCl_3$, 125 MHz)



VII. 국문초록

Fluvirucin은 actinomycete에 속하는 토양 미생물로부터 분리된 macrolactam 계 항생물질로서 fluvirucin A_{1-2}, B_{1-5} 등 7종류가 보고되었다. 최근 보고된 천연물로는 *Nonomuraea terkmeniaca* MA7364 및 MA7381로부터 분리된 6-desmethyl-N-methylfluvirucin A_1, N-methylfluvirucin A_1, 그리고 fluvirucin B_0이 있다.

이 천연물들은 14원환의 macrolactam의 2,6-dialkyl-10-ethyl-3(or 9)-hydroxy-13-trodecanelactam핵을 가지고 있으며 이 핵을 fluvirucinine이라고 한다. Fluvirucinine은 2번, 3번 (혹은 9번), (6번) 그리고 10번 탄소에 비대칭 탄소가 존재하고 있으며, 3번 또는 9번의 hydroxyl 기에 carbohydrate가 glycosidic linkage로 연결되어 있다. Fluvirucin $B_{2,4}$ 를 제외한 모든 fluvirucins의 carbohydrate는 3'번 탄소에 amine group이 존재하고 모든 치환기가 한 방향으로 위치하는 독특하고 매우 congested된 구조를 가지고 있다.

6-Desmethyl-N-methyl Fluvirucin A_1, N-methyl Fluvirucin A_1 그리고 Fluvirucin B_0, B_1, B_3 의 경우에는 *Haemonchus contortus* larvae 에 대한 *in vitro*에서의 강력한 항구충효과가 보고된 바 있고, *in vivo*에서 다소 약한 활성을 보여 이를 극복하기 위한 다양한 유도체들의 합성 및 최적화 과정이 필요할 것으로 보인다. 따라서 본 연구자는 선행 연구를 통해 확립된 두 번의 ACR 반응을 통한 ring expansion 전략을 응용하여, 6-Desmethyl-N-methyl Fluvirucin A_1 의 aglycone인 fluvirucinine을 합성하고, 한편 3,6-Dideoxy-3-methylamino-*L*-talose 을 최초로 합성한 뒤 성공적인 glycosylation을 통한 전합성을 완결하고자 하였으며, 의약화학적 유도체 합성 및 개발에 용이한 합성법 또한 확립하고자 하였다.

Acyl vinylpiperidine **82**으로부터 첫 번째 ACR을 통해 10원환의 *E* olefin lactam

83을 합성하였다. Medium-sized ring 본래의 strain만을 이용하여 높은 선택성으로 알킬화반응을 성공시킨 다음 두 번째 ACR을 통해 원하는 비대칭 치환기를 가지는 14원환의 fluvirucinine 구조를 확립하였다. 이후 macrolactam의 amine 기에 Cbz로 보호하여 glycosylation을 위한 용해도를 높였다.

현재까지 보고된 fluvirucin A series은 그의 aglycone인 fluvirucinine만을 합성 보고하였으며, 완전체의 합성은 Hoveyda 연구팀에 의한 Fluvirucin B_1이 유일하다. 또한 목적하는 천연물 6-Desmethyl-N-methylfluvirucin A_1의 carbohydrate는 기존의 fluvirucin series의 그것에 N-methyl 기가 존재하는 구조적 특징이 있으며 아직 합성된 예가 없다. 특히 glycoside의 모든 치환기가 한 방향으로 존재하는 구조적 congestion으로 인해 합성하기 어려운 화합물로 인식되어 왔다.

본 연구자는 methylamine **149**의 입체선택적 aminohydroxylation 및 dihydroxylation을 통해 치환기들의 비대칭성을 확립하였고, hemiacetal의 furanoside에서 pyranoside로의 변환을 유도하였다. 2,4번 alcohol를 acetylation한 다음 일련의 반응을 통해 fluoroglycoside **163**을 효과적으로 합성 완료하였다. 이미 합성 완료한 6-desmethyl-N-methylfluvirucinine A_1과 glycosylation 반응을 수행하여 6-Desmethyl-N-methylfluvirucin A_1 의 합성을 완결하고자 현재 연구를 계속 진행 중이다.

주요어: 6-desmethyl-N-methylfluvirucin A1, N-methylfluvirucin A1, 3,6-dideoxy-3-methylamino-$_L$-talose, glycosylation, ring expansion, aza-Claisen rearrangement

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