약학석사학위논문

(−)-Incarvilline, (+)-Incarvine C, (−)-Incarvillateine의 전합성에 관한 연구

Studies on the Total Synthesis of
(−)-Incarvilline, (+)-Incarvine C, and (−)-Incarvillateine

2013년 8월

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약학과 약품제조화학 전공

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지도교수 서 영 거

이 논문을 약학석사 학위논문으로 제출함

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서 효 원의 약학석사 학위논문을 인준함

2013년 8월

위 원 장 _____(印)

부위원장 _____(印)

위 원 _____(印)

국문초록

중국 북동부에 서식하는 식물 *Incarvillea sinensis*의 지상부에서 1990년 새로운 종류의 monoterpene alkaloids인 (-)-Incarvillateine의 분리 보고를 필두로, 1992년, 1995년에 각각 (-)-incarvilline과 (-)-incarvines A-C가 잇달아 분리 보고 되었다. *Incarvillea sinensis*는 중국에서 전통적으로 “Jiaohao”라는 이름으로 류마티즘과 통증 경감을 목적으로 민간약으로 사용되어 왔다. 이 식물에서 분리 보고 된 천연물 중 (-)-incarvilline과 (-)-incarvillateine이 강력한 진통효과를 가짐이 보고되어 있다. 특히 morphine에 필적할만한 강력한 진통효과를 보이는 (-)-incarvillateine의 활성기전이 κ, μ, δ -opiate receptor mechanism을 거치는 morphine과는 달리 κ, μ-opiate receptor와 adenosine receptor mechanism을 거치는 것으로 생각되어지기 때문에 새로운 활성 경로를 가지는 진통제의 개발이 가능할 것으로 보여 주목을 받고 있다.

(-)-Incarvillateine은 생합성적으로 (+)-incarvine C의 dimer로 여겨지고 있다. 이는 *cis-anti cis*-4원환을 중심으로 알칼로이드와 방향족 환이 C_2 대칭으로 연결되어 있다. 특히, 알칼로이드 모핵인 (-)-incarvilline은 5개의 연속된 입체탄소가 bicyclic piperidine 골격에 밀집되어 있다.

본 논문에서는 (-)-incarvilline, (+)-incarvine C, (-)-incarvillateine의 핵심 합성 중간체인 7-*epi*-Incarvilline을 입체선택적으로 합성하였다. 본 합성에서는 (1) 입체 선택적 Pd(0)-catalyzed allylic alkylation, (2) [2.1.2] bridged bicyclic lactone의 *cis*-fused 5,6-bicyclic lactam으로의 효율적인 전환, (3) 반응 기질에 의해 입체 선택성이 조절되는 수소화 반응과 1,4-첨가 반응을 핵심 반응으로 이용하였다.

나아가 (-)-incarvillateine의 전합성을 목표로 *cis-anti cis*-4원환을 입체 선택적으로 합성하고자 하였다. 고리 내부에 두 개의 lactone과 두 개의 olefin을 갖는 12원환의 전구체를 double Ireland-Claisen 전이반응을 통해 고리를 축소시켜 원하는 입체탄소를 갖는 4원환을 합성하고자 하였다.

주요어: Total synthesis, Monoterpene alkaloid, (-)-Incarvilline, (-)-Incarvillateine, Pd(0)-catalyzed allylic alkylation, Ireland-Claisen rearrangement

학 번: 2011-23732

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List of Schemes

Abbriviations

Ac	acetyl
Boc	*tert*-butoxycarbonyl
br	broad resonance
Bu	butyl
calcd	calculated
CM	cross metathesis
coe	cis-cyclooctene
d	doublet
DBU	1,8-diazabicycloundec-7-ene
DEAD	diethylazodicarboxylate
DHP	dihydropyran
DIBAL	diisobutylaluminum hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	*N*,*N*-4-dimethylaminopyridine
DMAPh	4-(dimethylamino)phenyl
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
dppb	1,4-bis(diphenylphosphino)butane
dr	diastereomeric ratio
ED	effective dose
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
eq	equivalent
Et	ethyl
FAB	fast atom bombardment
h	hour
HMPA	hexamethylphosphoramide
HR-MS	high resolution mass spectroscopy
HWE	Horner - Wadsworth - Emmons
Hz	hertz
Im	imidazole

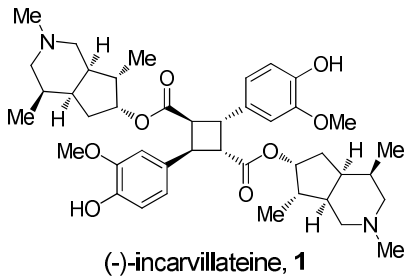
IR	infrared
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LR-MS	low resolution mass spectroscopy
m	multiplet
Me	methyl
min	minute
MOM	methoxymethyl ether
Ms	mesyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
Ns	nosyl
Nuc	nucleophile
PCC	pyridinium chlorochromate
Ph	phenyl
Piv	pivaloyl
PPTS	pyridinium *p*-toluenesulfonate
pyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
pyr	pyridine
q	quartet
quin	quintet
RCM	ring closing metathesis
rt	room temperature
s	singlet
t	triplet
TBAF	tetra-*n*-butylammoniumfluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
tert	tertiary
Tf	triflate
THF	tetrahydrofuran

THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	tosyl

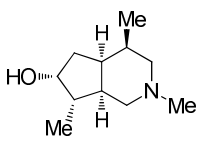
Ⅰ Introduction

1. Biological Activities and Structural Features of Incarvillea Alkaloids

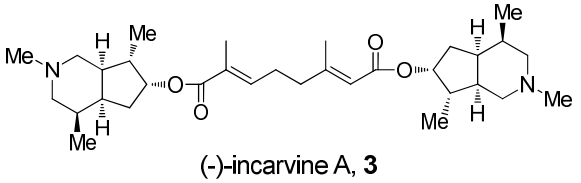
1.1. Isolation



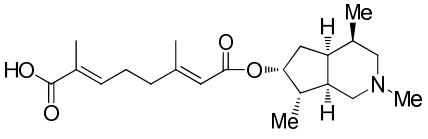
(-)-incarvillateine, **1**



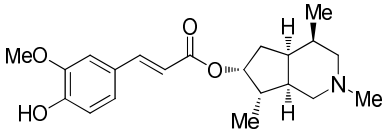
(-)-incarvilline, **2**



(-)-incarvine A, **3**



(+)-incarvine B, **4**



(+)-incarvine C, **5**

Figure 1. Incarvillea Alkaloids

In 1990, a new class of monoterpene alkaloid, (-)-incarvillateine (**1**), was first isolated by Chi and co-workers from the aerial part of the plant *Incarvillea sinensis* which is well known Chinese fork medicine as "Jiaohao".[1] (-)-Incarvilline (**2**) and (+)-incarvines A-C (**3**)-(**5**) were also isolated from the same plant in 1992 and 1995, respectively (Figure 1).

1.2. Biological Activities

The analgesic properties of natural products, (-)-incarvilline (**2**), (+)-incarvine C (**5**), and (-)-incarvillateine (**1**) were investigated by Chi and Nohara groups.[2]

In the formalin-induced pain model in mice, (-)-incarvillateine (**1**) showed a significant antinociceptive effect.[2a] The formalin-induced pain model can be divided into two phases, neurogenic and inflammatory phase. The first neurogenic phase is from 0 to 10 min after the injection of drugs because of its direct stimulation of the nerve fibers. The second inflammatory phase is from 10 to 30 min after the injection due to the inflammatory reaction.

(-)-Incarvillateine (**1**) exhibited significant analgesic properties in both phases.[2a] Its ED_{50} values were 0.0174 mmol/kg (first phase) and 0.0078 mmol/kg (second phase) which are lower than those of morphine. The relative potency is about 1.06 (first phase) and 1.33 (second phase) times stronger than morphine.

In addition, the partial reversion of the first phase of the (-)-incarvillateine (**1**) by pretreatment with naloxone suggested its action is related to the central opioid pathways.[2c] κ-Receptor antagonist, nor-binaltorphimine, and μ-receptor antagonist, β-funaltrexamine, antagonized the effect of

(-)-incarvillateine (**1**), while δ-receptor antagonist, naltrindole, did not block the effect. Interestingly, the antinociceptive effect of (-)-incarvillateine (**1**) was antagonized by adenosine-receptor antagonist, theophylline. These results suggested that the analgesic property of (-)-incarvillateine (**1**) is related to κ, μ-receptors and adenosine-receptor.

Furthermore, the structure-activity relationship test clearly indicated that the presense of a monoterpene alkaloid and a dimeric structure carrying a cyclobutane ring is important factor of the antinociceptive effects of (-)-incarvillateine (**1**).[2b]

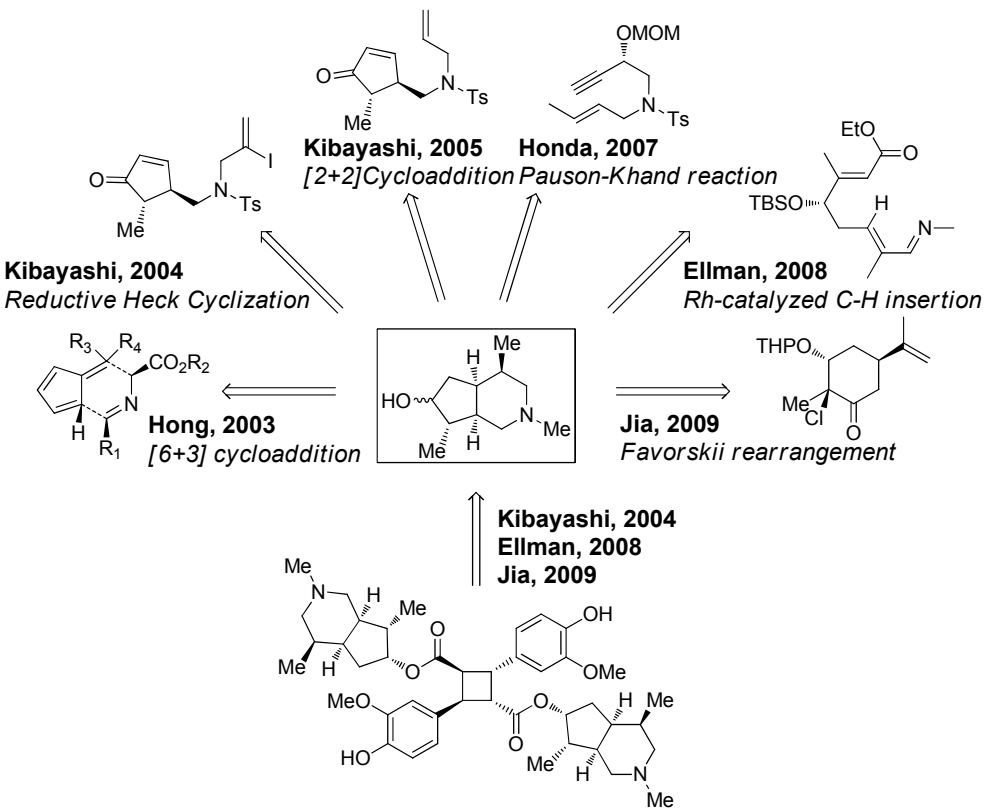
1.3. Structural Features

The alkaloid unit of Incarvillea alkaloids, (-)-incarvilline (**2**), is structurally attractive target. This is because compactly arranged five contiguous stereocenters on the *cis*-fused bicyclic piperidine system.

The *cis-anti cis*-cyclobutane centerpiece structure within (-)-incarvillateine (**1**) is also intriguing target for synthetic chemists. Schmidt and co-workers has extensively investigated the photo-induced [2+2] dimerization.[3] They has demonstrated *cis-anti cis*-cyclobutane could be selectively obtained by [2+2] photodimerization of *trans*-truxinic acids crystallizing in β-crystalline form. While this topochemical [2+2] photodimerization is a powerful tool for the synthesis of symmetrical cyclobutane system, Baran's total synthesis of piperaborenine B showed another remarkable synthetic strategy obtaining aryl-substitued *cis-anti cis*-cyclobutane system employing palladium catalyzed C-H activation.[4] His investigations paved the way for the synthesis of unsymmetrical cyclobutane system.

2. Previous Synthetic Approaches

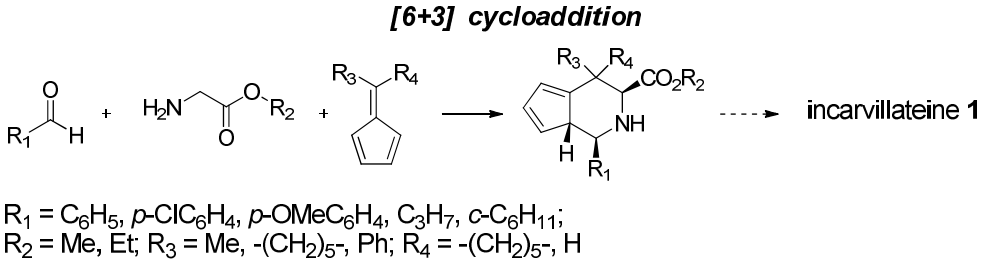
Total six synthetic studies about incarvillea alkaloids had been published (Scheme 1).[5] While one of those studies was about the constructing the framework by Hong and co-workers, five were the enantioselective total synthesis of (-)-incarvillateine (**1**) or (-)-incarvilline (**2**).



Scheme 1. Previous Synthetic Approaches

2.1. Hong's Synthetic Study

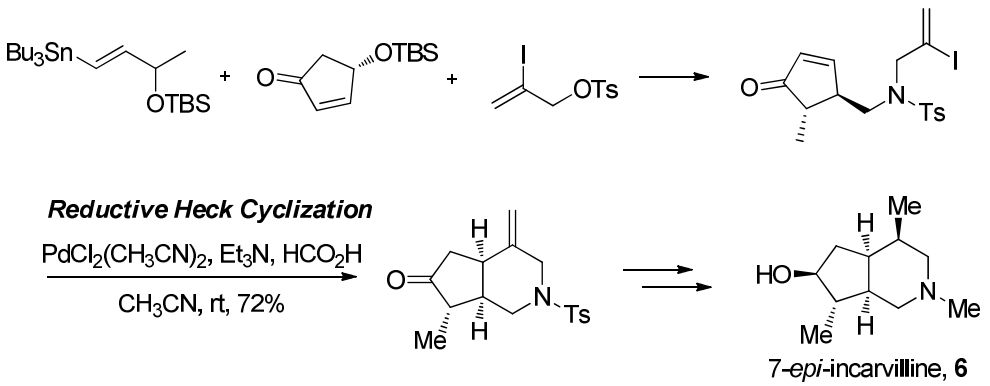
As the first synthetic suggestion about (-)-incarvillateine (**1**), Hong and co-workers developed a novel hetero [6+3] cycloaddition of N-alkylidene glycine esters to fulvenes (Scheme 2).[5a] This methodology can provide [2]pyrindine derivatives.



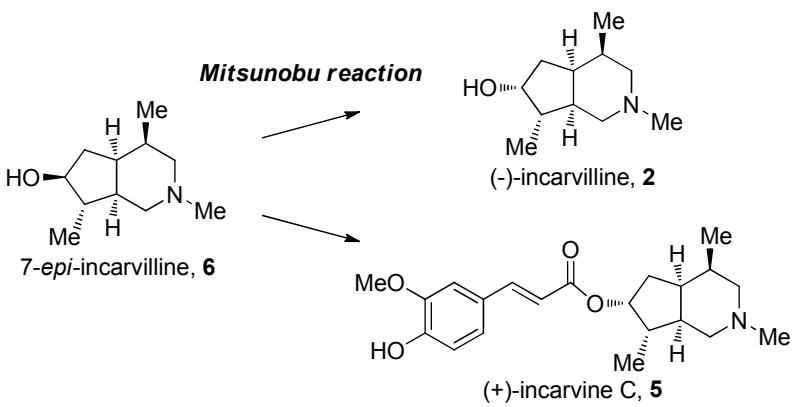
Scheme 2. Hetero [6+3] Cycloaddition Providing (-)-Incarvilline (2) Moiety

2.2. Kibayashi's Total Synthesis of (-)-Incarvilline, (+)-Incarvine C, and (-)-Incarvillateine

The first total syntheses of (-)-incarvilline (**2**), (+)-incarvine C (**5**), and (-)-incarvillateine (**1**) were reported by Kibayashi in 2004.[5b] They used three-component coupling reaction and reductive Heck-type cyclization as the key transformations to 7-*epi*-incarvilline **6** (Scheme 3). (-)-Incarvilline (**2**) and (+)-incarvine C (**5**) were furnished by simple transformations including Mitsunobu type hydroxyl group inversion and Mitsunobu type esterification from the advanced key intermediate, 7-*epi*-incarvilline **6** (Scheme 4).

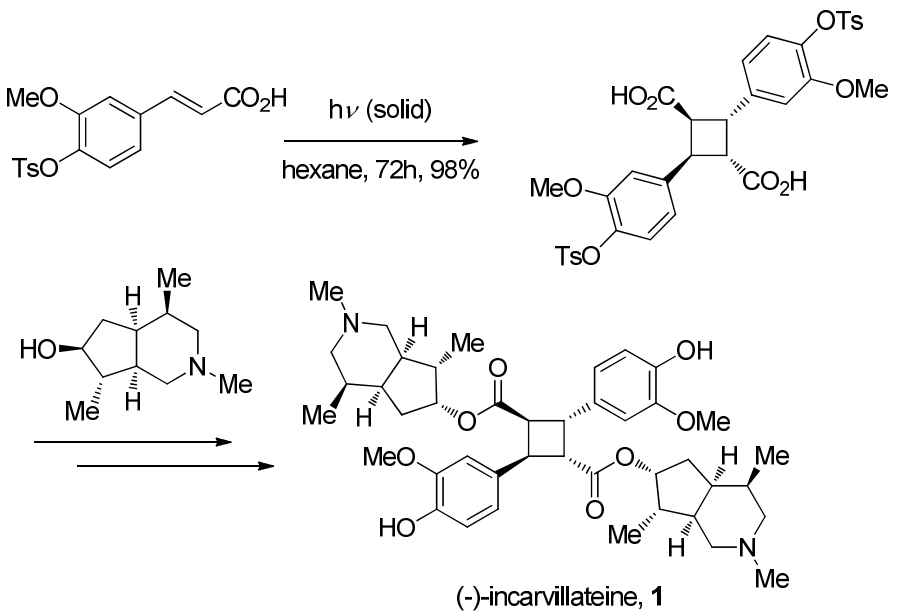


Scheme 3. 7-*epi*-Incarvilline 6 via Three-Component Coupling Reaction and Reductive Heck-type Cyclization



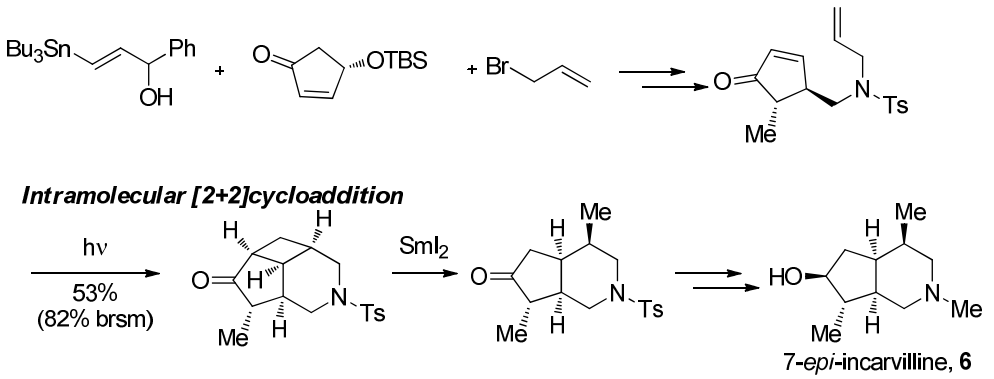
Scheme 4. Completion of (-)-Incarvilline (2) and (+)-Incarvine C (5)

In the course of obtaining (-)-incarvillateine (**1**), they employed solid state [2+2] photodimerization to yield *cis-anti cis*-cyclobutane core unit (Scheme 5).[5b] The importance of topochemistry controlled by the packing arrangement of molecules was demonstrated in this synthesis.



Scheme 5. [2+2] Photodimerization and Completion of the Total Synthesis of (-)-Incarvillateine (1)

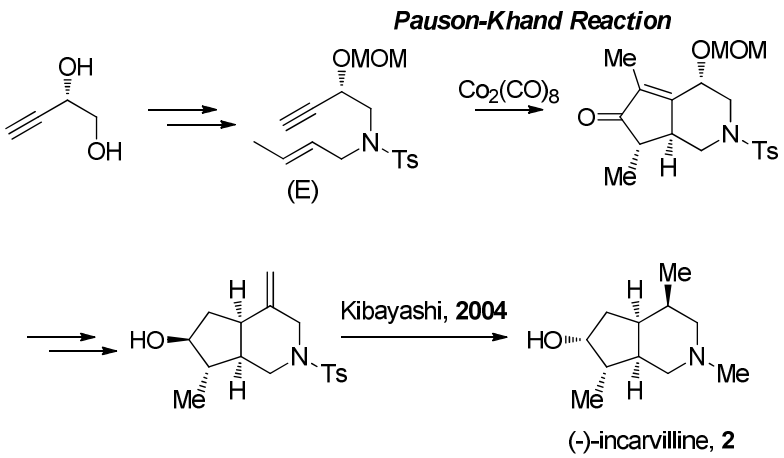
The [2+2] cycloaddition to furnish the (-)-incarvilline (**2**) moiety was also reported by Kibayashi group in 2005 (Scheme 6).[5c] They similarly used three component coupling reaction to get the precursor for [2+2] cycloaddition. The stereoselective [2+2] photocycloaddition between two olefins provided the skeleton of 7-*epi*-incarvilline **6**.



Scheme 6. 7-*epi*-Incarvilline 6 via [2+2] Cycloaddition

2.3. Honda's Formal Synthesis of (-)-Incarvilline

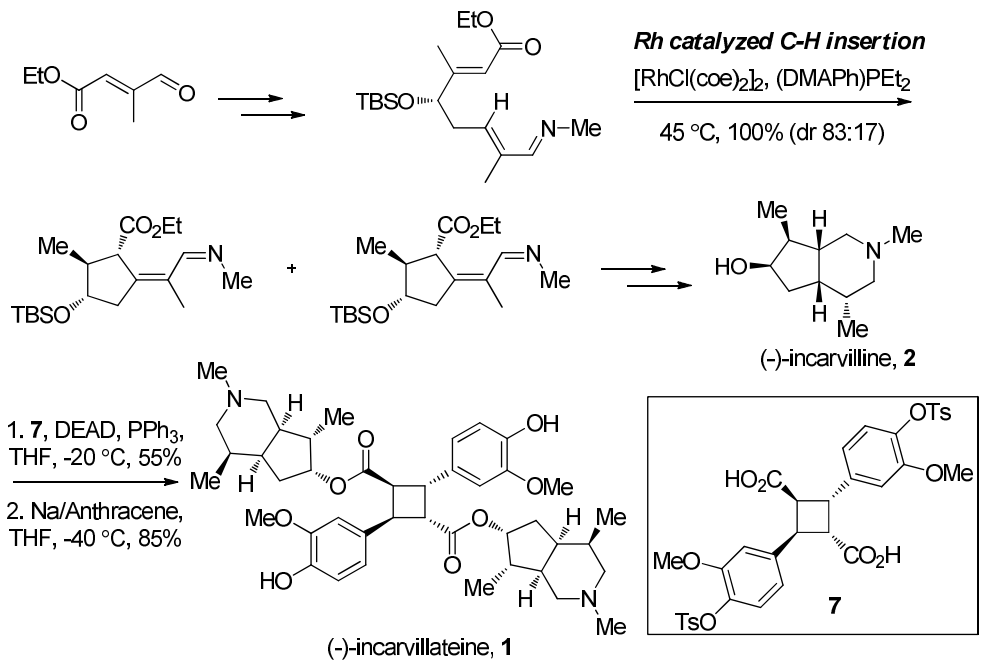
The diastereoselctive formal synthesis of a monoterpene alkaloid, (-)-incarvilline (**2**), was described by Honda group in 2007 (Scheme 7).[5d] Intramolecular Pauson-Khand Reaction of the enyne amide was employed to get the skeleton of (-)-incarvilline (**2**) as the key step.



Scheme 7. Formal Synthesis of (-)-Incarvilline (2) employing Pauson-Khand Reaction

2.4. Bergman and Ellman's Total Synthesis of (-)-Incarvillateine

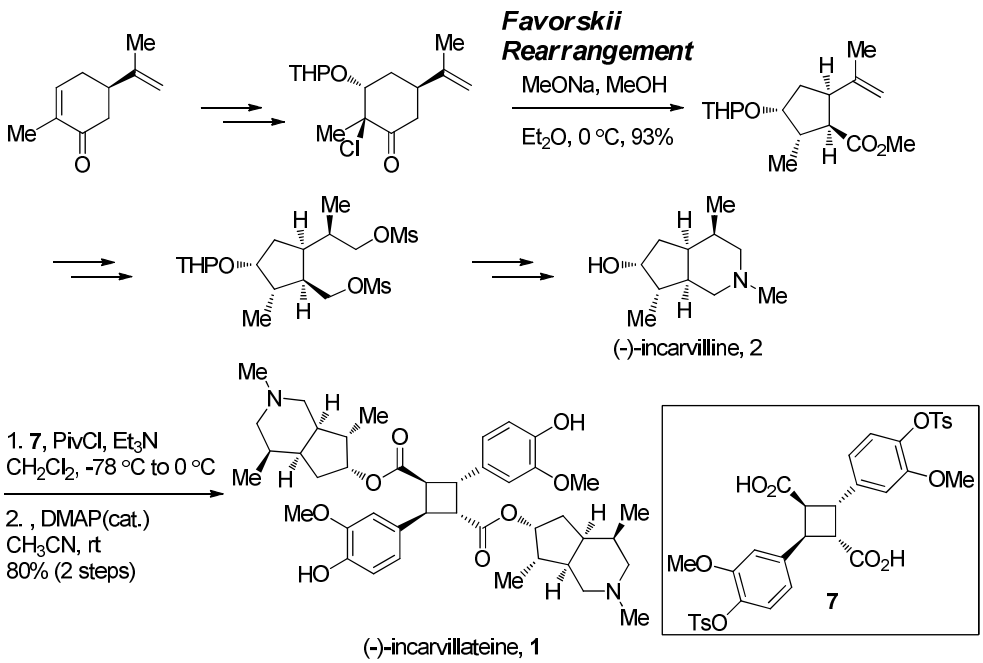
In 2008, the concise asymmetric total synthesis of (-)-incarvillateine (**1**) was published by Bergman and Ellman (Scheme 8).[5e] They employed an intramolecular alkylation via Rh-catalyzed olefinic C-H bond activation to install two of the five necessary stereocenters. They obtained 83:17 ratio of a desired cyclopentane over its diastereo isomer. In addition, Bergman and Ellman group reported the improvement of final Mitsunobu-type esterification reaction from 40% by Kibayashi at 90 ℃ o 55% at low temperture, －20 ℃ An asymmetric synthesis of (-)-incarvillateine (**1**) was accomplished in 11 steps and total 15.4% overall yield.



Scheme 8. Total Synthesis of (-)-Incarvillateine (1) employing Rh-catalyzed C-H Insertion

2.5. Jia's Total Synthesis of (-)-Incarvillateine

Total synthesis of (-)-incarvillateine (**1**) was accomplished by Jia group in 2009 (Scheme 9).[5f] From an abundant chiral source, (-)-carvone, they achived the total synthesis of (-)-incarvilline (**2**) in longest linear 9 steps, 24.3% overall yield via Favorskii rearrangement to construct four of the five necessary stereocenters. Furthermore, final estrification was improved employing direct esterification of acid chloride and (-)-incarvilline (**2**) without the inversion of C7 chiral center.



Scheme 9. Total Synthesis of (-)-Incarvillateine (1) using Favorskii Rearrangement

3. Pd(0)-catalyzed Allylic Alkylation

Palladium catalyzed reaction has renowned for its versitility. Among many types of palladium catalyzed chemistry, Thuji and co-workers first reported π-allylpalladium chloride (I) reacts with ethyl malonate and acetoacetate in 1965 (Scheme 10).[6a] Moreover, Trost and co-workers proposed the ionic complex as an intermediate in Pd(0)-catalyzed allylic alkylation (Figure 2).[6b] While several mechanisms of Pd(0)-catalyzed allylic alkylation has been proposed, the diversity of bond types including C-H, C-O, C-N, C-S, C-P, and most importantly, C-C bonds represent the major benefit of this reaction.

Scheme 10. Pd(0)-catalyzed Allylic Alkylation

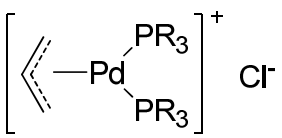


Figure 2. Proposed Intermediate

Suh et al. reported a new variant of Pd(0)-catalyzed stereoselecive cyclization in 1997.[7a] The preparation of [2.1.2] bicyclic lactone the equivalent of the thermodynamically disfavored *cis*-trisubstituted pentane system was achieved in great diastereoselectivity. The total syntheses of brefeldin A, bacillariolide Ⅲ and a natural iridoid,

(+)-6-hydroxy-7-(hydroxymethyl)-4-methylenehexahydrocyclopenta[*c*]pyran-1(3H)-one were accomplished employing diastereoselective Pd(0)-catalyzed allylic alkylation.[7b, 7c, 7d, 7f] The mechanistic investigation was reported in 2010.[7e] The observed excellent diastereoselectivity is supposed to be attributed to π-σ-π isomerization of π-allylpalladium species to be sterically less demanding [2.1.2] bicyclic structure.

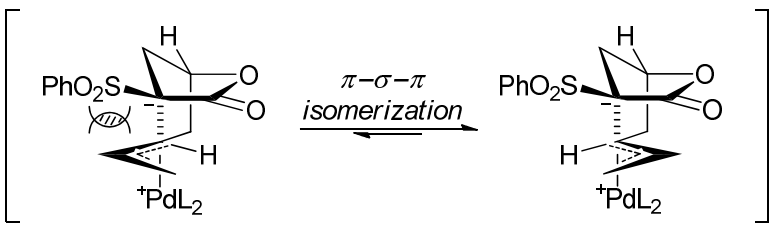
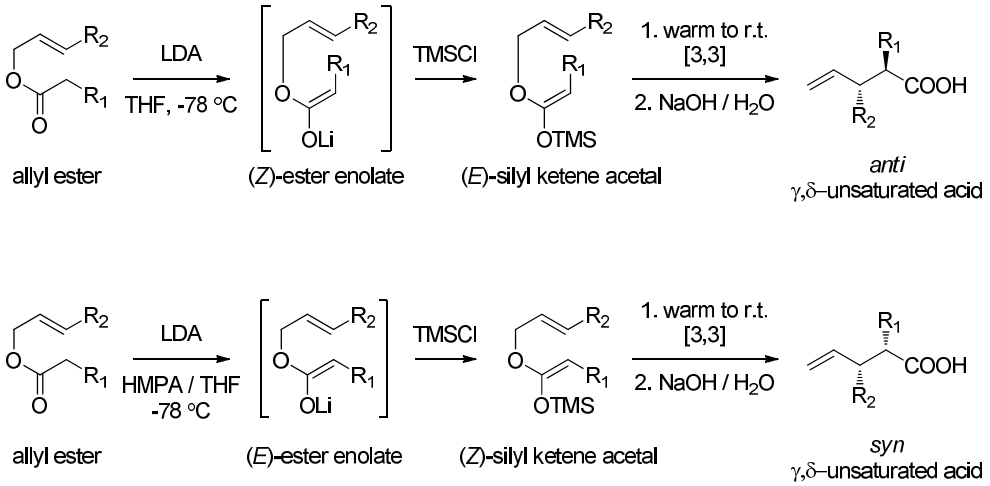


Figure 3. π-σ-π Isomerization of π-Allylpalladium Complex

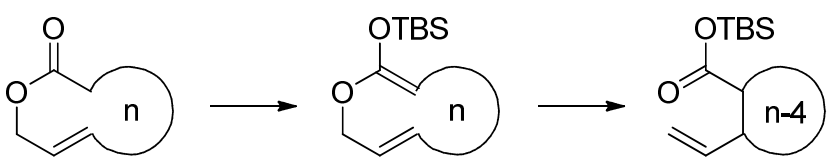
4. Ireland-Claisen Rearrangement

Ireland and co-workers reported the ester enolate version of Claisen rearrangement in 1976 (Scheme 11).[8a] It had a benefit that it can control stereochemistry via stereoselective enolate formation. In spite of this pioneering investigation, there had been rare examples of application in the construction of the carbocyclic ring systems of natural products.



Scheme 11. Ireland-Claisen Rearrangement

Funk and co-workers reported a new variant of Ireland-Claisen rearrangement conceptualized in Scheme 12 in 1982.[8b] He employed Ireland-Claisen Rearrangement for ring contraction using the terminal carbons connected by a carbon chain. The medium- or large-ring lactones were converted to 3- or 5-11-membered ring via ring contraction. The possible transition states for rearrangement of the ketene acetals were rationalized that those prefered boatlike transition state to chairlike transition state.

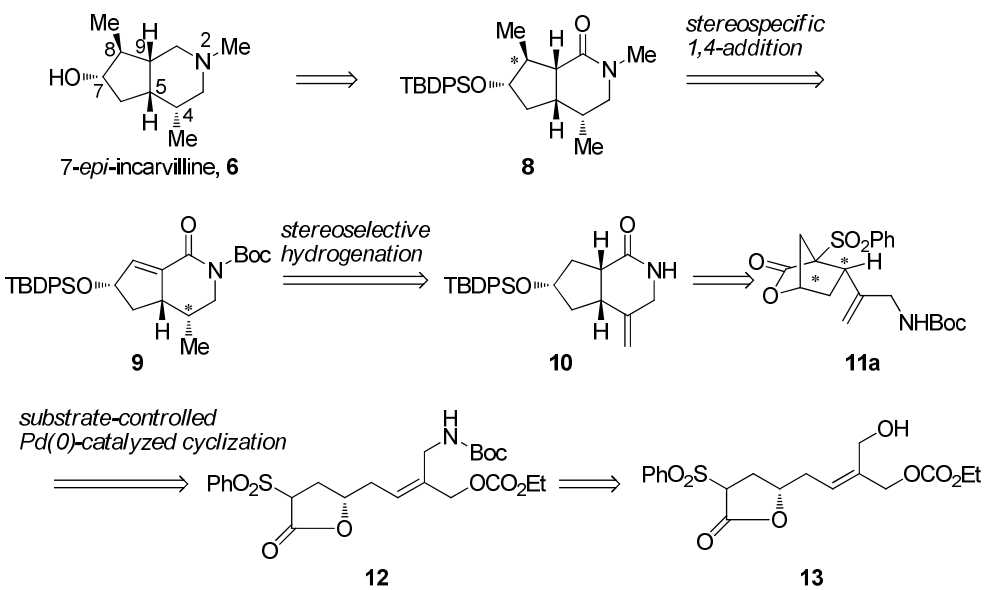


Scheme 12. New Variant of Ireland-Claisen Rearrangement by Funk and co-workers

Ⅱ Result and Discussion

1. Retrosynthetic Analysis of 7-*epi*-Incarvilline

The research primarily aimed to the formal synthesis of incarvillea alkaloids, (-)-incarvilline (**2**), (+)-incarvine C (**5**), and (-)-incarvillateine (**1**) (Scheme 13).



Scheme 13. Retrosynthetic Analysis of 7-*epi*-Incarvilline 6

The retrosynthetic plan toward 7-*epi*-incarvilline **6** is outlined in Scheme 13. The overall strategy was based on the substrate-controlled stereocontrol of the five contiguous stereocenters within the final intermediate **6**. Thus, this synthesis initially focused on the stereoselective construction of the highly functionalized bicyclic lactam **10**, which consists of a *cis*-fused

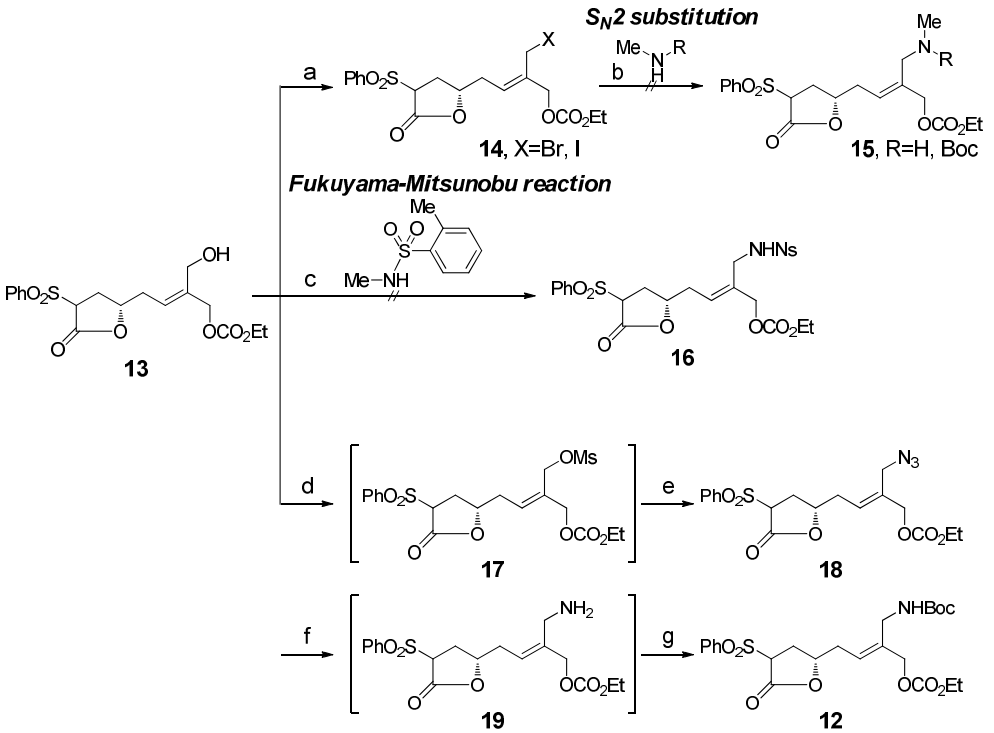
bicyclic skeleton, three stereocenters, and an *exo*-methylene. The two stereocenters with the methyl substituent of **6** could be diastereoselectively elaborated by a stereoselective catalytic hydrogenation and a Michael-addition, respectively. The bicyclic lactam **10** was readily accessible via an isomerization of the bicyclic lactone **11** which would be constructed through the substrate-controlled Pd(0)-catalyzed cyclization of γ-lactone **12** employing the procedure that previously developed in our laboratory.[7] The cyclization precursor **12** was expected to be conveniently prepared from intermediate **13** via an amine substitution.

2. Total synthesis of 7-*epi*-Incarvilline

2.1. Synthesis of the Precursor of Pd(0)-catalyzed Cyclization

Synthesis of **7** commenced with the advanced γ-lactone **13** which was previously reported by our group (Scheme 14).[6f] Initially, we tried Appel reaction with the combination of PPh_3 and NBS or NIS in THF followed by direct S_N2 substitution with methylamine or *tert*-butyl methylcarbamate. However, they did not afford a desired product **15**. Second, Fukuyama-Mitsunobu reaction is the well known process introducing nitrogen. However, this method destroyed γ-lactone **13**, especially the acidic hydrogen within the γ-lactone which is significantly important in Pd(0)-catalyzed cyclization. Eventually, mesylation of **13** and NaN_3 treatment of the resulting mesylate yielded azide **18**. Azide **18** was carefully reduced

under Staudinger conditions, and the resulting primary amine was protected with Boc_2O to give carbamate **12**.[9]



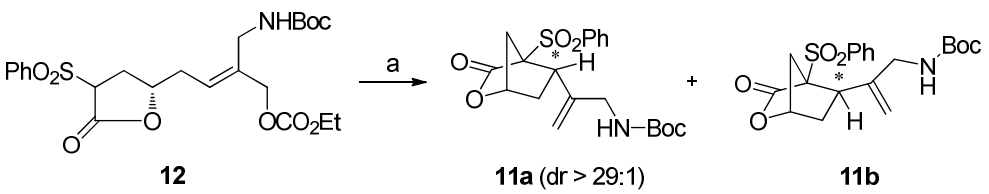
Scheme 14. Synthesis of the Precursor of Pd(0)-catalyzed Cyclization[a]

[a]reagent and conditions : (a) PPh_3, NBS or NIS, THF, rt (b) Methylamine, MeOH, 0 ℃ → rt or *t*-Butyl methylcarbamate, NaH, DMF, 0 ℃ → rt (c) PPh_3, DEAD, N,2-Dimethylbenzenesulfonamide, CH_2Cl_2, rt (d) MsCl, Et_3N, DMF, 0 ℃ e) NaN_3, 96% (f) PPh_3, H_2O, THF, 50 ℃ g) Boc_2O, 77%

2.2. Pd(0)-catalyzed Cyclization

With the desired precursor **12** available, we investigated a diastereoselective Pd(0)-catalyzed cyclization (Scheme 15). The intramolecular allylic alkylation in the presence of $Pd(dppb)_2$ in THF proceeded smoothly

to furnish the desired bicyclic lactone **11a** in 90% yield and with excellent diastereoselectivity (> 29:1). The high diastereoselectivity is likely due to the preference of the π-allylpalladium complex with a less steric repulsion between the benzenesulfonyl group and the amine with Boc protecting group. Cyclization of the azide precursor **18** under the same conditions provided low diastereoselectivity (2:1), which implied a size effect of the R-substituent on the diastereoselectvity (Figure 4).



12 **11a** (dr > 29:1) **11b**

Scheme 15. Pd(0)-catalyzed Cyclization[a]

[a]reagent and conditions : (a) $Pd(dppb)_2$, THF, reflux, 90%

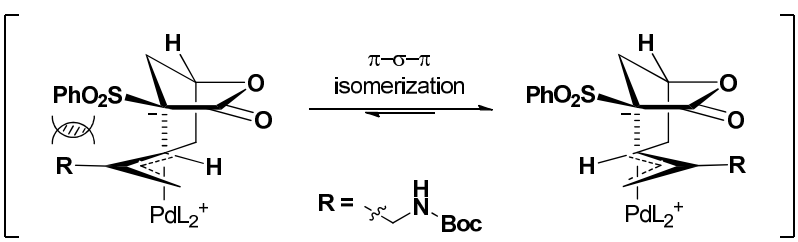
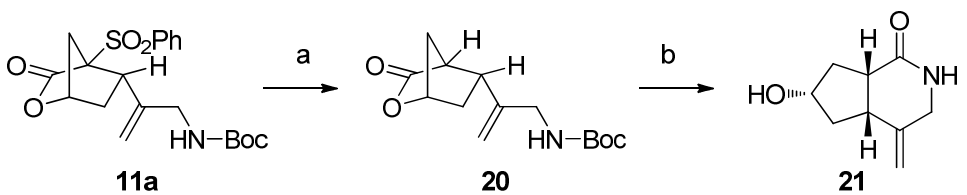


Figure 4. π-σ-π Isomerization of π-Allylpalladium Complex

2.3. Synthesis of Fused Bicyclic Lactam

With the optically active bicyclic lactone **11a** available, we executed construction of the *cis*-fused bicyclic backbone of **6** (Scheme 16). Desulfonylation of **11a** with Na/Hg 6% in the presence of $B(OH)_3$

effectively afforded the bicyclic lactone **20** in 91% yield.[10] Boc-deprotection of **20** with a combination of TMSOTf and 2,6-lutidine and a spontaneous intramolecular amidation produced the *cis*-fused bicyclic lactam **21**.

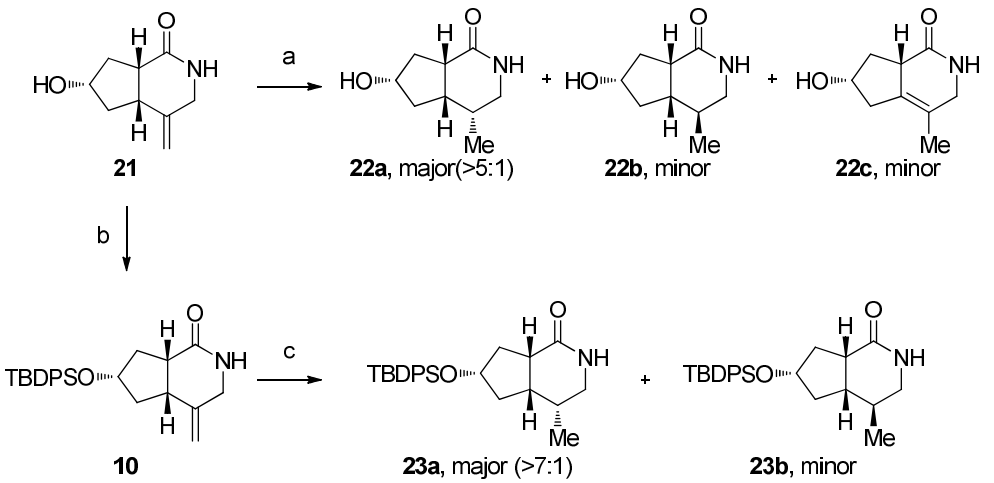


11a **20** **21**

Scheme 16. Intramolecular Amidation of [2.1.2] Bicycle to *cis*-fused 5,6-Bicyclic Lactam[a]

[a]reagent and conditions : (a) Na/Hg 6%, B()H)$_3$, MeOH, 91% (b) TMSOTf, 2,6-Lutidine, CH_2Cl_2, 0 ℃ 85%

Hydrogenation of bicyclic lactam **21** with Pd/C catalyst under H_2 gas afforded desired α-methyl lactam **22a** as major with β-methyl lactam **22b** as minor and trace amounts of olefin isomerized product **22c**. The ratio was moderate (> 5:1), moreover, trace amounts of olefin isomerized product **22c** were not seperable. Hence, we converted the sequence to protect free alcohol **21** to TBDPS ether **10**. Exposure of TBDPS ether **10** to catalytic hydrogenation conditions (Pd/C, H_2) resulted in a stereoselective reduction of *exo*-methylene to afford α-methyl lactam **23a** in 98% yield with a good diastereoselectivity (> 7:1, assigned by ^{1}H NMR). The diastereomeric mixture of **23a** and **23b**, which was inseparable by chromatograpy, was purified after Boc-protection to give an optically pure lactam **24** in 98% yield.[11]



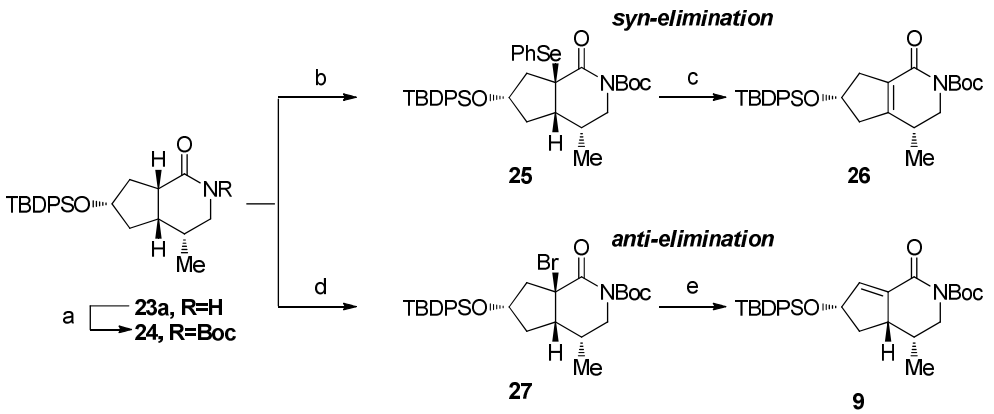
Scheme 17. Hydrogenation of *exo*-Methylene[a]

[a]reagent and conditions : (a) Pd/C 10%, H_2, MeOH (b) TBDPSCl, Im, CH_2Cl_2, 0 ℃ 98% (c) Pd/C 10%, H_2, MeOH, 98%

2.4. Introducing the Site Specific Michael Acceptor

At the conversion stage from bicyclic lactam **23a** to 7-*epi*-incarvilline **6**, we encountered a challenging task for the stereoselective incorporation of the methyl substituent on the C8 stereocenter (Scheme 18). After intensive investigation for an efficient construction of the C8 stereocenter, we focused on the substrate-controlled stereoselective Michael-addition. To generate a requisite Michael acceptor, our initial attempt utilizing a sequence of α-phenylselenylation of Boc-activated lactam **24** and subsequent selenoxide elimination resulted in a *syn*-elimination involving a β-hydrogen at the ring junction. Thus, we turned our attention to an alternative procedure for a selective *anti*-elimination involving the C8 hydrogen. Diastereoselective α-bromination of Boc-activated lactam **24** with LDA and N-bromosuccinimide in THF afforded **27**.[12] Exposure of α-bromolactam **27** to DBU in CH_2Cl_2

successfully afforded the desired Michael acceptor **9** in high yield.[13]

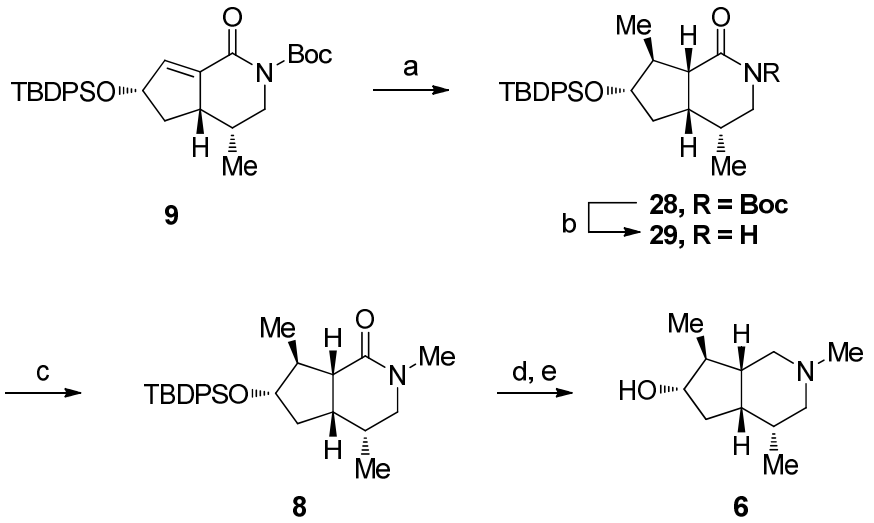


Scheme 18. Introducing the Site Specific Michael Acceptor[a]

[a]reagent and conditions : (a) Boc_2O, DMAP, CH_3CN, 98% (b) PhSeBr, LHMDS, THF, HMPA, − 3 ℃ (c) H_2O_2 (d) NBS, LDA, − 8 ℃ →) ℃ 93% (e) DBU, CH_2Cl_2, 89%

2.5. Completion of the Synthesis of 7-*epi*-Incarvilline

The TMSCl-promoted Michael addition reaction of **9** with Me_2CuLi exclusively produced the desired lactam **28** in 88% yield without the observation of other diastereomer.[14] The excellent stereoselectivity is likely mainly due to an attack of Me_2CuLi on the convex face of the cyclopentene moiety. Careful Boc-deprotection of **28** with TMSOTf and 2,6-lutidine followed by N-methylation of the resultant lactam **29** furnished N-methylated lactam **8**. Sequential TBDPS deprotection of **8** and amide reduction[15] finally provided 7-*epi*-incarvilline **6**, a core and advanced intermediate for syntheses of (-)-incarvilline (**2**), (+)-incarvine C (**5**), and (-)-incarvillateine (**1**).[16] The correct C7 stereochemistries for **1**, **2**, and **5** are provided by Mitsunobu reaction of **6** with the corresponding carboxylic acid.[6]



Scheme 19. Completion of the Synthesis of 7-*epi*-Incarvilline 6[a]

[a]reagent and conditions : (a) CuBr·Me_2S, MeLi, TMSCl, Et_2O, SMe_2, − 8 ℃ → rt, 88% (b) TMSOTf, 2,6-Lutidine, CH_2Cl_2, 0 ℃ → rt, 97% (c) NaH, MeI, DMF, 92% (d) TBAF, THF, 99% (e) Alane *N*,*N*-dimethylethylamine, THF, 92%

3. Retrosynthetic Analysis of (-)-Incarvillateine

3.1. Initial Approach to *cis-anti cis*-Cyclobutane

To the completion of the total synthesis of (-)-incarvillateine (**1**), stereoselective constructing *cis-anti cis*-cyclobutane core structure was required. The aromatic ring system would be elaborated from cyclobutane **31** by Diels-Alder reaction using corresponding Danishefsky-type diene. Ester linkages could be furnished by the method by Kibayashi, Bergman and Ellman, and Jia groups.[5b, 5e, 5f]

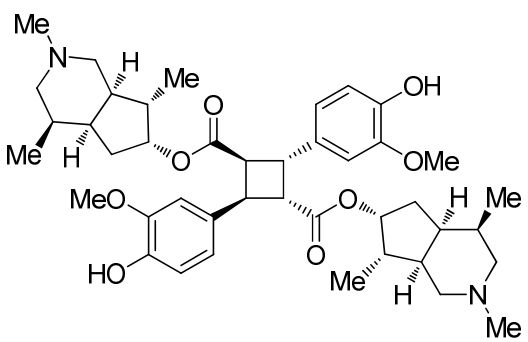
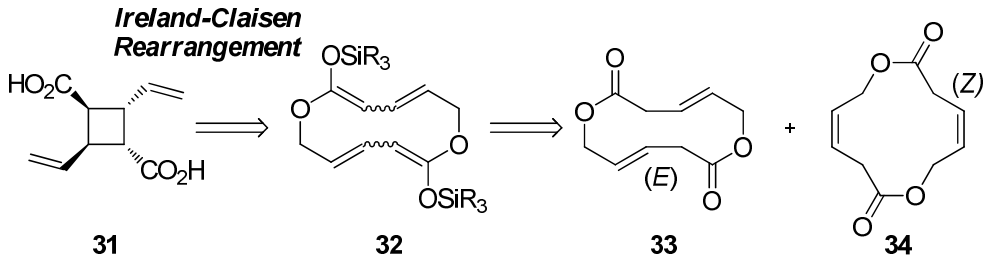


Figure 5. (-)-Incarvillateine (1)

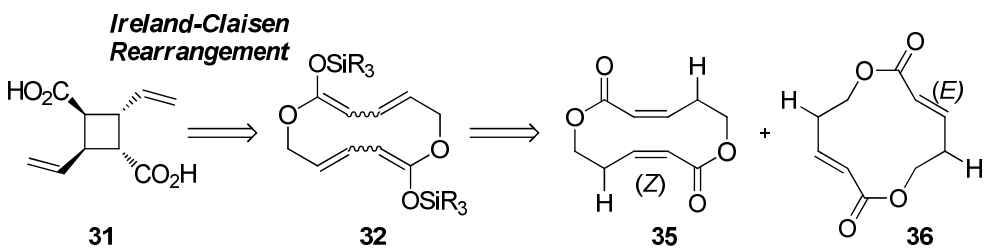
Cyclobutane **31** with four *cis-anti cis*-contiguous stereocenters would be elaborated by double Ireland-Claisen rearrangement via double boatlike transition states. Ketene acetal **32** was designed as Scheme 20.[8] The corresponding bis-lactone **33** or **34** was supposed to be achieved using two times of HWE-olefination or Wittig olefination followed by macrolactonization.



Scheme 20. Initial Retrosynthetic Analysis of the Core Structure of (-)-Incarvillateine (1)

3.2. Revised Approach to *cis-anti cis*-Cyclobutane

Owing to the difficulty for preparing unconjugated bis-lactone **33** or **34**, we turned our attention to conjugated system **35** or **36** (Scheme 21). Two conjugated double bond could be elaborated by Cross Metathesis and Ring Closing Metathesis, respectively.[17] The precursor of Ireland-Claisen rearrangement, bis-ketene acetal **32**, seemed to be afforded via double γ-deprotonation and subsequent silicon trap of bis-conjugated lactone **35** and **36**.

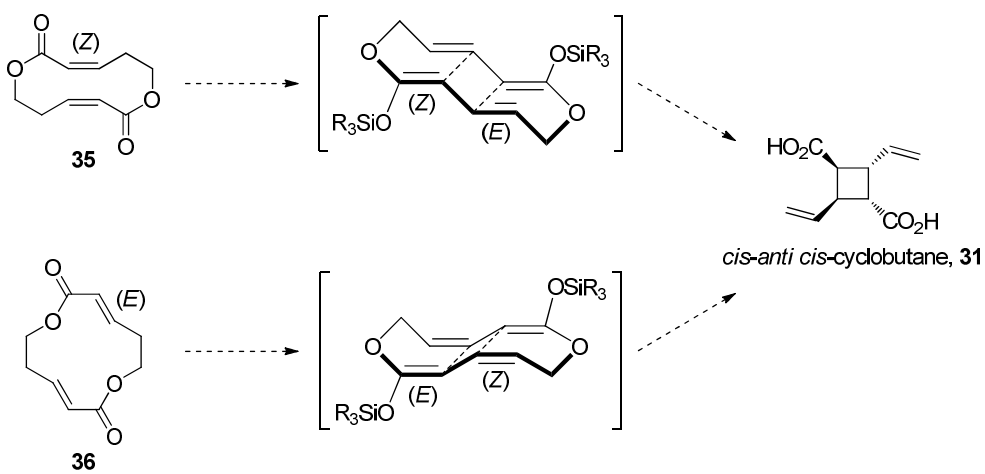


Scheme 21. Revised Retrosynthetic Analysis of the Core Structure of (-)-Incarvillateine (1)

3.3. Plausible Transition State of Double Ireland-Claisen Rearrangement

The centerpiece cyclobutane of (-)-incarvillateine (**1**) seemed to be elaborated from conjugated bis-lactone **35** or **36** via double Ireland-Claisen rearrangement. The plausible transition states could be illustrated in Scheme 22.

Cameron and co-workers have investigated enolization of α,β-unsaturated esters with regio- and geometrical control.[18] He demonstrated that (*Z*)-α,β -unsaturated ester would elaborate (*E*)-β,ɣ-unsaturated (*Z*)-silyl ketene acetal via treatment of LDA/Me_3SiCl. On the other hand, (*E*)-α,β-unsaturated ester would afford (*Z*)-β,ɣ-unsaturated (*E*)-silyl ketene acetal via treatment of LDA/Me_3SiCl and HMPA.



Scheme 22. Plausible Transition State of Double Ireland-Claisen Rearrangement

Hence, we could design two cyclic transition states which can afford

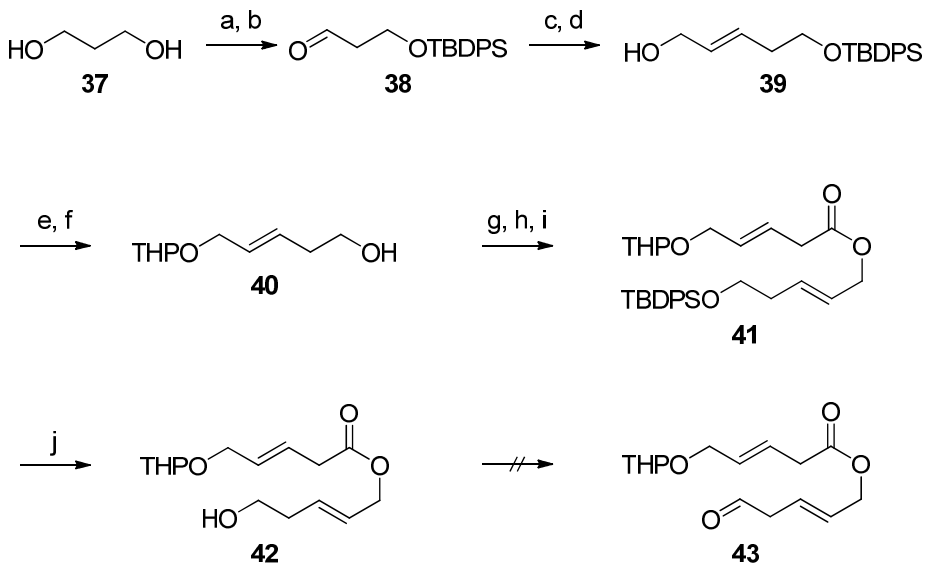
cis-anti cis-cyclobutane system via boatlike transition states. Two (*Z*)-double bonds containing bis-conjugated lactone **35** seemed to be enolized to (*E*)-β,γ-unsaturated (*Z*)-silyl ketene acetal under LDA/Me_3SiCl condition. Otherwise, two (*E*)-double bonds containing bis-conjugated lactone **36** seemed to be enolized to (*Z*)-β,γ-unsaturated (*E*)-silyl ketene acetal under LDA/Me_3SiCl/HMPA condition. Both Ireland-Claisen rearrangement precursors would go through the boatlike transition states to afford two γ,δ-unsaturated acid containing *cis-anti cis*-cyclobutane structure.

4. Synthetic Approach to (-)-Incarvillateine

4.1. Initial Approach to the Precursor of Double Ireland-Claisen Rearrangement

From the commercially available 1,3-propanediol **37**, we protected one of the two hydroxyl group with TBDPSCl and oxidized the other to aldehyde **38** using PCC and NaOAc in 78% for two steps. Aldehyde **38** was converted to two carbon elongated allyl alcohol **38** employing HWE-olefination followed by DIBAL reduction at −40 ℃ in 46% yield. After protecting newly formed free hydroxyl group to THP ether in 72% yield, TBDPS group was removed by TBAF in 67% yield to give homoallyl alcohol **40**. Homoallyl alcohol **40** was oxidized by DMP oxidation follwed by Pinnick oxidation to carboxylic acid. With the carboxylic acid in hand, ester **41** was afforded with allyl alcohol **39** using the combination of EDCI and DMAP in 35% yield for three steps. TBDPS protecting group was

removed under TBAF in 54% yield, though, unconjugated aldehyde **41** was not achieved by oxidation including DMP or Ley oxidation. Only conjugated system via olefin isomerization was achieved.



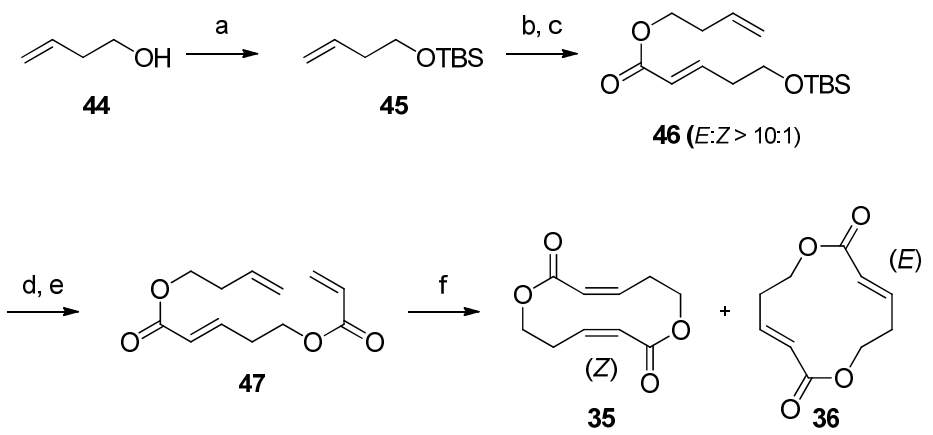
Scheme 23. Initial Approach to the Precursor of Double Ireland-Claisen Rearrangement[a]

[a]reagent and conditions : (a) TBDPSCl, Im, CH_2Cl_2 (b) PCC, NaOAc, CH_2Cl_2, 78% for two steps (c) NaH, Ethyl 2-diethoxyphosphorylacetate, THF, 0℃ 75% (d) DIBAL, THF, − ℃ 46% (e) DHP, PPTS, CH_2Cl_2, rt, 72% (f) TBAF, THF, rt, 67% (g) DMP, CH_2Cl_2, rt (h) $NaClO_2$, NaH_2PO_4, 2-Methyl-2-butene, *t*-BuOH, H_2O, rt (i) **39**, EDCI, DMAP, 35% for three steps (j) TBAF, THF, rt, 54%

4.2. Revised Approach to the Precursor of Double Ireland-Claisen Rearrangement

The synthesis commenced with TBS protection of 3-buten-1-ol **44**. After CM between TBS ether **45** and acrylic acid using Grubbs' 2nd catalyst in

CH_2Cl_2, esterification with 3-buten-1-ol **44** in the presence of pyBOP and DIPEA in CH_2Cl_2 furnished homoallyl ester **46** in 57% yield for two steps. The RCM precursor was afforded by the TBS deprotection followed by esterification with DIPEA and acryloyl chloride in THF in 51% yield for two steps. After RCM of bis-terminal alkene **47** (*E*:*Z* > 10:1 mixture, assigned by ^{1}H NMR) using Hoveyda-Grubbs 2nd catalyst at 70 ℃ in bezene, the resultant was revealed that bis-lactone **35** with two (*Z*)-olefin and bis-lactone **36** with two (*E*)-olefin were furnished in 1.3:1 ratio in total 88% yield. While internal double bond within the RCM precursor **47** had around 10:1 ratio of (*E*)-olefin to (*Z*)-olefin, RCM product revealed very different ratio (Table 1). The ratio of **35** to **36** was increased along the higher reaction temperature and the longer reaction time. In this case, the strain of the medium sized ring might force internal double bond participate to olefin isomerization promoted by olefin metathesis catalyst, thus furnished thermodynamically more stable product. Also, total yield was raised up by higher reaction temperature and the longer reaction time.



Scheme 24. Revised Approach to the Precursor of Double Ireland-Claisen Rearrangement[a]

[a]reagent and conditions : (a) TBSCl, Im, CH_2Cl_2, rt, 75% (b) Grubbs' 2nd catalyst, Acrylic acid, CH_2Cl_2, reflux (c) pyBOP, DIPEA, 3-Buten-1-ol, CH_2Cl_2, rt, 57% for two steps (d) HF·pyr, THF, rt (e) DIPEA, $CH_2CHCOCl$, THF, rt, 51% for two steps (f) Hoveyda-Grubbs 2nd cataylst, benzene, 70 ℃ 88% (**35**:**36** = 1.3:1)

Entry	Condition	Yield (**35** + **36**)	Ratio (**35** : **36**)
1	3.5h at 70 ℃	29%	1 : 3.6
2	5h at 70 ℃→ 6h at rt	60%	1 : 1.5
3	16h at 70 ℃	88%	1.3 : 1

Table 1. Ring Closing Metathesis of bis-Terminal Alkene 47

4.3. Computational Calculations of the Precursors of Double Ireland-Claisen Rearrangement

The energy minimized 3D structures of all four kinds of symmetrical bis-ketene acetals ((*E*)-Ketene Acetal/(*E*)-olefin, (*E*)-Ketene Acetal/(*Z*)-olefin, (*Z*)-Ketene Acetal/(*E*)-olefin, (*Z*)-Ketene Acetal/(*Z*)-olefin) were calculated by Material Studio. However, computational studies did not show favorable results. Contrary to the expected transition states, any kind of precursors was not supposed to give a cyclobutane with four desired stereocenters. As the energy minimized conformations in Figure 6, all kinds might provide all *trans*-cyclobutane system via double Ireland-Claisen rearrangement.

Because of the strain of four double bond containing 12-membered ring, two bulky TBS group posed at the same direction. In the energy minimized structures, (*E*)-Ketene Acetal/(*E*)-olefin and (*Z*)-Ketene Acetal/(*Z*)-olefin system would have two boatlike conformations, but seemed to give all *trans*-cyclobutane after Ireland-Claisen rearrangement. Similarly, (*Z*)-Ketene Acetal/(*E*)-olefin system would provide all *trans*-cyclobutane via double chairlike transition states. (*E*)-Ketene Acetal/(*Z*)-olefin system was not supposed to undergo sigmatropic rearrangement because two carbon centers were too far from each other.

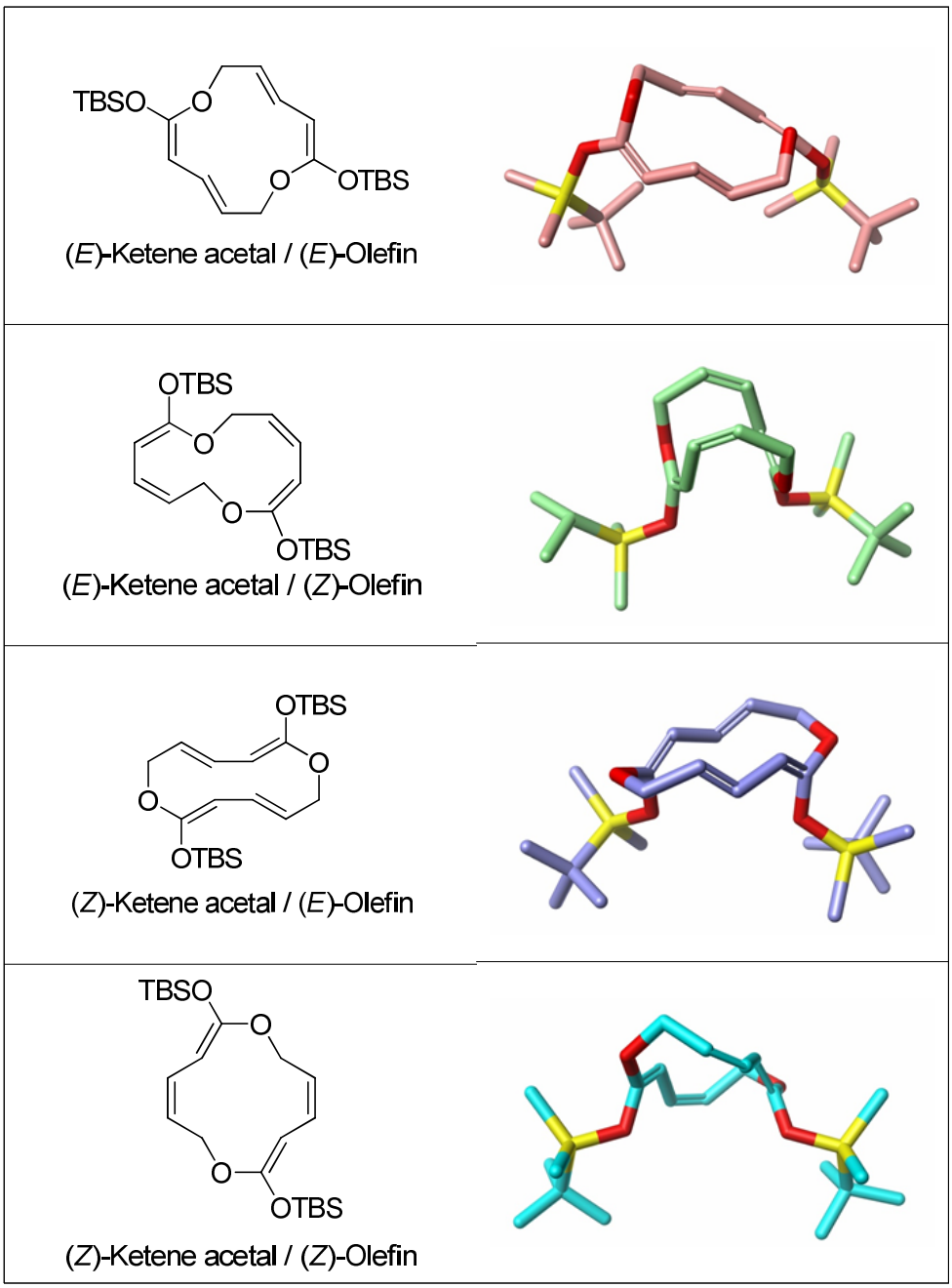


Figure 6. Energy Minimized 3D Structure of bis-Ketene acetals[a]

[a]Calculated by Material Studio

Ⅲ Conclusion

In conclusion, we have accomplished the substrate-controlled asymmetric synthesis of 7-*epi*-incarvilline **6** for the formal synthesis of (-)-incarvilline (**2**), (+)-incarvine C (**5**), and (-)-incarvillateine (**1**) via a high-yielding sequence from the known intermediate **13**. The key features of our synthesis include diastereoselective construction of the [2.1.2] bicyclic lactone **11a** using a stereoselective Pd(0)-catalyzed cyclization, isomerization of the bridged bicyclic lactone **20** to the *cis*-fused 5,6-bicyclic lactam **21** and elaboration of two stereocenters via stereoselective catalytic hydrogenation and Michael addition.

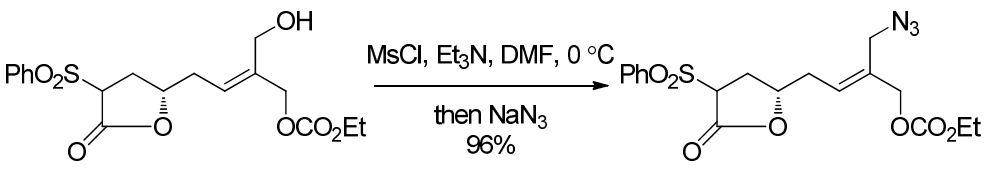
Furthermore, we attempted to stereoselectively synthesize *cis-anti cis*-cyclobutane core structure of (-)-incarvillateine (**1**) via double Ireland-Claisen rearrangement. The precursors of Ireland-Claisen rearrangement, bis-lactone **35** and **36,** were achieved employing Cross Metathesis and Ring Closing Metathesis as the key transformations. We anticipated corresponding bis-ketene acetal **32** might afford *cis-anti cis*-cyclobutane core structure of (-)-incarvillateine (**1**) through a variant of Ireland-Claisen rearrangement by Funk and co-workers via double boatlike transition states.

Ⅳ Experimental

General Experimental

Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran and Et_2O were distilled from sodium benzophenone ketyl. Dichloromethane, chloroform, triethylamine, acetonitrile and pyridine were freshly distilled from calcium hydride. All solvents used for routine isolation of products and chromatography were reagent grade and glass distilled. Reaction flasks were dried at 100°C. Air and moisture sensitive reactions were performed under argon atmosphere. Flash column chromatography was performed using silica gel 60 (230-400mesh, Merck) with the indicated solvents. Thin-layer chromatography was performed using 0.25mm silicagel plates (Merck). Optical rotations were measured with JASCODIP-1000 digital polarimeter at ambient temperature using 100mm cell of 2mL capacity. Infrared spectra were recorded on a Perkin-Elmer 1710 FT-IR spectrometer. Mass spectra were obtained with VG Trio-2 GC-MS instrument. High resolution mass spectra were obtained with JEOL JMS-AX 505WA instrument. ^1H and ^{13}C NMR spectra were recorded on either JEOL JNM-GCX400, Bruker FT-NMR 500MHz Avance 500 or JEOL ECA-600 spectrometer as solutions in deuteriochloroform ($CDCl_3$). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent ($CHCl_3$). ^{1}HNMR data were reported

in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; br, broad and/or multiple resonance), number of protons and coupling constant in hertz (Hz).

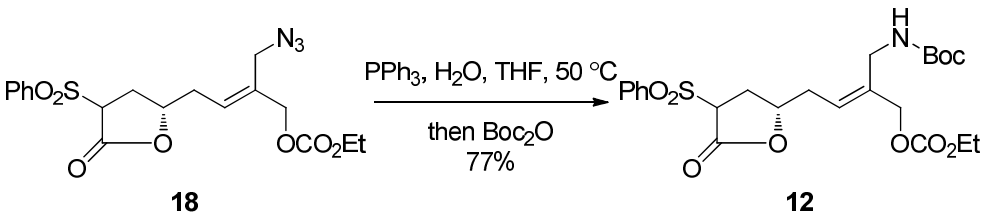


13 **18**

(*E*)-2-(Azidomethyl)-4-((*2S*)-5-oxo-4-(phenylsulfonyl)tetrahydrofuran-2-yl)but-2-en-1-yl ethyl carbonate (18).

To a mixture of the allyl alcohol **13** (4.20 g, 10.6 mmol) and Et_3N (1.47 mL, 10.6 mmol) in anhydrous DMF (50 mL) under argon was slowly added MsCl (0.820 mL, 10.6 mmol) at 0 ℃ After stirring for 1 h at 0 ℃ NaN_3 (3.50 g, 52.8 mmol) was added. The reaction mixture was stirred at room temperature for 5 min, the reaction mixture was quenched with aq. NH_4Cl, and then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 2) to afford 4.30 g (96%) of the allyl azide **18** as a colorless oil: FT-IR (thin film, neat) ν_{max} 3636, 3546, 3066, 2983, 2465, 2103, 1778, 1745, 1584, 1448, 1401, 1374, 1354, 1324, 1311 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz, mixture of diastereomers) δ 7.96－ － 56 (m, 2H), 5.80 (m, 1H), 4.80 (m, 0.7H), 4.62－ 59 (m, 2H), 4.51 (m, 0.3H), 4.23－ － 84 (m, 2H), 3.07 (ddd, 0.7H, *J* = 14.6,

6.9, 3.3 Hz), 2.79 (m, 0.3H), 2.69 (m, 0.3H), 2.64－ 50 (m, 2H), 2.34 (ddd, 0.7H, *J* = 18.6, 10.0, 8.5 Hz), 1.30－ .25 (dt, 3H, *J* = 12.3, 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.3, 167.0, 154.7, 154.7, 136.6, 136.6, 134.8, 134.7, 133.2, 132.8, 129.5, 129.3, 129.3, 129.2, 128.4, 127.8, 78.3, 69.4, 69.4, 64.8, 64.3, 63.9, 47.5, 47.4, 33.6, 33.1, 29.0, 28.1, 14.2, 14.1; LR-MS (FAB$^+$) *m/z* 424 (M + H$^+$); HR-MS (FAB+) calcd for $C_{18}H_{22}N_3O_7S$ (M + H$^+$) 424.1178; found 424.1175.

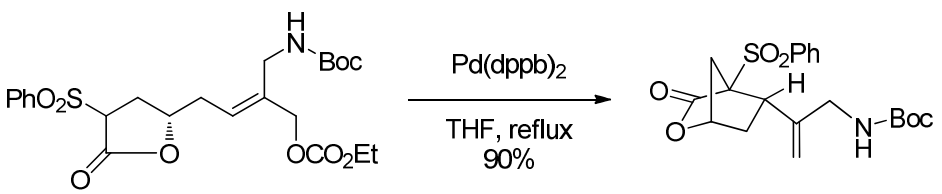


18 **12**

***tert*-Butyl ((*E*)-2-(((ethoxycarbonyl)oxy)methyl)-4-((2*S*)-5-oxo-4-(phenylsulfonyl)tetrahydrofuran-2-yl)but-2-en-1-yl)carbamate (12).**

To a solution of the allyl azide **18** (270 mg, 0.638 mmol) in THF (8 mL) were added Ph_3P (184 mg, 0.702 mmol) and water (46.0 μL, 2.55 mmol). The resulting solution was heated to 50 ℃ and stirred for 14 h. The solution was then cooled down to room temperature, Boc anhydride (0.150 mL, 0.638 mmol) was added. After stirring for 5 min at ambient temperature, the solvent was removed and the residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 2) to afford 241 mg (77%) of the allyl carbamate **12** as colorless foamy solid: FT-IR (thin film, neat) ν_{max} 3403, 3067, 2979, 2936, 1779, 1745, 1709, 1584, 1513, 1479, 1449, 1392, 1367, 1325, 1311 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500

MHz, mixture of diastereomers) δ 7.94－ 89 (m, 2H), 7.68 (t, 1H, *J* = 7.5 Hz), 7.57－ .54 (m, 2H), 5.59 (t, 1H, *J*= 7.4 Hz), 4.90 (brs, 1H), 4.76 (quin, 0.7H, *J* = 6.7 Hz), 4.59－ － － 3.67 (m, 2H), 3.00 (ddd, 0.7H, *J* = 14.2, 6.6, 4.0 Hz), 2.75 (ddd, 0.3H, *J* = 14.2, 10.1, 7.1 Hz), 2.65－ － 37 (s, 9H), 1.28－ 22 (dt, 3H, *J* = 8.8, 7.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.5, 167.2, 155.7, 154.9, 136.7, 135.5, 135.3, 134.6, 134.6, 129.5, 129.3, 129.2, 129.1, 126.0, 125.8, 79.5, 79.4, 69.8, 64.7, 64.1, 64.1, 63.9, 37.5, 32.9, 28.7, 28.3, 14.2, 14.1; LR-MS (FAB+) *m/z* 498 (M + H^+); HR-MS (FAB+) calcd for $C_{23}H_{32}NO_9S$ (M + H^+) 498.1798; found 498.1799.



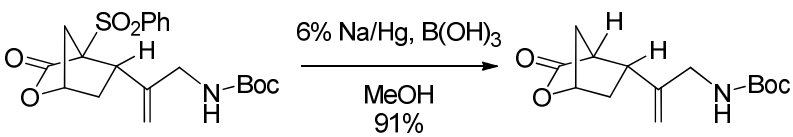
12 **11a**

***tert*-Butyl(2-((1*S*,4*R*,5*S*)-3-oxo-4-(phenylsulfonyl)-2-oxabicyclo[2.2.1]heptan-5-yl) allyl)carbamate (11a).**

To a refluxing solution of the allyl carbamate **12** (162 mg, 0.326 mmol) in THF (2 mL) were added $Pd(OAc)_2$ (15.0 mg, 65.0 μmol) and dppb (63.0 mg, 0.147 mmol). After stirring for 1 h, the reaction

mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 2) to afford 120 mg (90%) of the bicyclic lactone **11a** as colorless foamy solid: $[\alpha]_D^{24}$ － 0.5 (c 0.933, $CHCl_3$); FT-IR (thin film, neat)

ν_{max} 3403, 3067, 3006, 2978, 2931, 1786, 1707, 1584, 1513, 1448, 1391, 1366, 1326, 1312 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, 2H, J = 7.5 Hz), 7.66 (t, 1H, J = 7.5 Hz), 7.54 (t, 2H, J = 7.8 Hz), 5.20 (s, 1H), 5.11 (s, 1H), 4.90 (brs, 1H), 4.81 (s, 1H), 3.87 (d, 2H, J = 5.8 Hz), 3.66 (m, 1H), 2.56 (m, 1H), 2.25 (m, 2H), 2.07 (m, 1H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 167.8, 156.0, 143.7, 136.7, 134.6, 130.1, 129.1, 114.2, 79.4, 75.7, 45.9, 45.1, 40.8, 38.6, 28.4, 28.4, 28.4; LR-MS (FAB+) *m*/*z* 408 (M + H^+); HR-MS (FAB+) calcd for $C_{20}H_{26}NO_6S$ (M + H^+) 408.1481; found 408.1494.

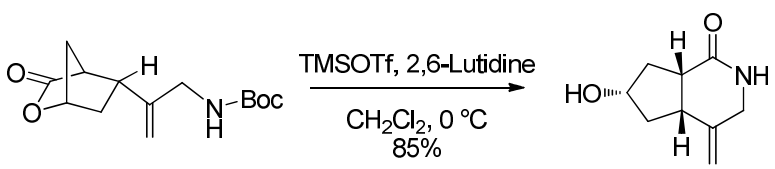


11a **20**

***tert*-Butyl(2-((1*S*,4*S*,5*R*)-3-oxo-2-oxabicyclo[2.2.1]heptan-5-yl)allyl)carbamate (20).**

To a solution of the bicyclic lactone **11a** (2.02 g, 4.96 mmol) in MeOH (30 mL) were added Na/Hg 6% (7.60 g, 19.9 mmol) and $B(OH)_3$ (1.53 g, 24.8 mmol) at ambient temperature. After stirring for 4 h at the same temperature, the reaction mixture was decanted with Et_2O and then quenched with aq. NH_4Cl. After extraction with Et_2O, the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 2) to afford 1.20 g (91%) of the desulfonylated bicycle **20** as white solid: mp

108 - 110 ℃ $[\alpha]_D^{24}$ − 9.2 (c 0.300, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3357, 3090, 2977, 2927, 1786, 1773, 1707, 1656, 1518, 1451, 1391, 1366, 1334 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.07 (s, 1H), 5.02 (s, 1H), 4.87 (s, 1H), 4.72 (brs, 1H), 3.80 (dd, 1H, *J* = 15.5, 6.3 Hz), 3.70 (dd, 1H, *J* = 15.6, 5.8 Hz), 3.05 (s, 1H), 2.96 (m, 1H), 2.26 (dd, 1H, *J* = 10.5, 1.8 Hz), 2.10 (ddd, 1H, *J* = 13.7, 10.4, 1.9 Hz), 1.91 (ddd, 1H, *J* = 13.8, 5.4, 2.5 Hz), 1.76 (d, 1H, *J* = 10.4 Hz) 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.8, 155.9, 144.5, 112.2, 80.2, 79.6, 47.3, 45.7, 41.2, 40.0, 32.6, 28.4, 28.4, 28.4; LR-MS (FAB+) *m/z* 268 (M + H^+); HR-MS (FAB+) calcd for $C_{14}H_{22}NO_4$ (M + H^+) 268.1549; found 268.1545.

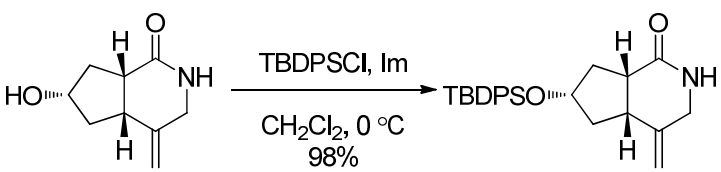


20 **21**

(4a*R*,6*S*,7a*S*)-6-Hydroxy-4-methyleneoctahydro-1*H*-cyclopenta[*c*]pyridin-1-one (21).

To a solution of the desulfonylated bicycle **20** (206 mg, 0.771 mmol) in CH_2Cl_2 (6 mL) were added 2,6-lutidine (0.360 mL, 3.08 mmol) and TMSOTf (0.420 mL, 2.31 mmol) at 0 ℃ After stirring for 2 h at the same temperature, the reaction mixture was quenched with aq. NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2 : MeOH = 20 : 1)

to afford 109 mg (85%) of the hydroxyl lactam **21** as white solid: mp 122 – 4 ℃ $[\alpha]_D^{24}$ – 0.1 (c 0.700, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3348, 3290, 3076, 2934, 2912, 2877, 1798, 1734, 1656, 1595, 1488, 1442, 1408, 1339, 1316 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.73 (brs, 1H), 4.92 (s, 2H), 4.30 (m, 1H), 4.05 (d, 1H, *J* = 13.7 Hz), 3.72 (dd, 1H, *J* = 13.7, 3.0 Hz), 2.93 (q, 1H, *J* = 8.8 Hz), 2.89 (brs, 1H), 2.73 (td, 1H, *J* = 8.5, 4.1 Hz), 2.25– 2.15 (m, 2H), 2.09 (m, 1H), 1.60 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.3, 141.6, 111.4, 72.3, 45.6, 43.8, 42.3, 40.3, 39.6; LR-MS (FAB+) *m*/*z* 168 ($M + H^+$); HR-MS (FAB+) calcd for $C_9H_{14}NO_2$ ($M + H^+$) 168.1025; found 168.1023.

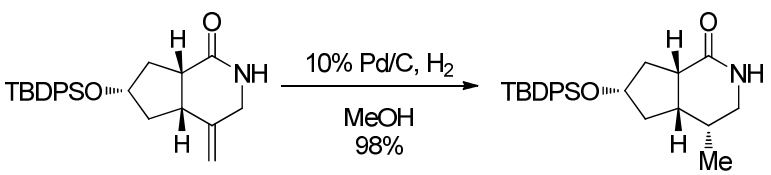


21 **10**

(4a*R*,6*S*,7a*S*)-6-((*tert*-Butyldiphenylsilyl)oxy)-4-methyleneoctahydro-1*H*-cyclopent a[*c*]pyridin-1-one (10).

To a solution of hydroxyl lactam **21** (270 mg, 1.61 mmol) in CH_2Cl_2 (1 mL) were added TBDPSCl (500 μL, 1.94 mmol) and imidazole (130 mg, 1.94 mmol). After stirring for 14 h at room temperature, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 2 : 1) to afford 640 mg (98%) of the TBDPS ether **10** as

white solid: mp 147– 49 ℃ $[\alpha]_D^{24}$ – .18 (c 0.680, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3286, 3196, 3071, 3048, 2958, 2931, 2893, 2857, 1962, 1891, 1823, 1664, 1589, 1488, 1472, 1427, 1390, 1375, 1323 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.67– – .39 (m, 2H), 7.37 – .34 (m, 4H), 6.72 (brs, 1H), 4.92 (s, 1H), 4.89 (s, 1H), 4.20 (quin, 1H, *J* = 6.1 Hz), 4.06 (d, 1H, *J* = 13.3 Hz), 3.73 (dd, 1H, *J* = 13.3, 3.2 Hz), 2.79 (q, 1H, *J* = 8.7 Hz), 2.67 (dd, 1H, *J* = 16.5, 7.8 Hz), 2.11 (m, 2H), 2.04 (m, 1H), 1.73 (m, 1H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 174.7, 141.6, 135.8, 135.7, 134.1, 133.8, 129.6, 129.6, 127.6, 127.6, 111.3, 73.7, 45.8, 43.2, 41.4, 40.7, 39.4, 26.8, 19.0; LR-MS (FAB+) *m*/*z* 406 (M + H^+); HR-MS (FAB+) calcd for $C_{25}H_{32}NO_2Si$ (M + H^+) 406.2202; found 406.2201.

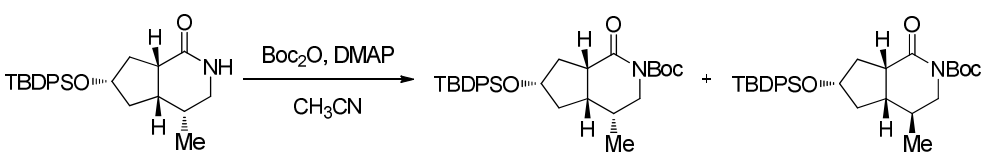


10 **23a** (>7:1)

(4*R*,4a*S*,6*S*,7a*S*)-6-((*tert*-Butyldiphenylsilyl)oxy)-4-methyloctahydro-1*H*-cyclopenta[*c*]pyridin-1-one (23a).

To a solution of the TBDPS ether **10** (376 mg, 0.928 mmol) in MeOH (30 mL) was added Pd/C 10% (380 mg). The reaction was placed under H_2 balloon and stirred for 8 h at room temperature. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel

(EtOAc : *n*-hexane = 2 : 1) to afford 376 mg (98%) of the saturated lactam **23a** (dr > 7:1) as a colorless oil: FT-IR (thin film, neat) ν_{max} 3289, 3201, 3071, 3048, 2958, 2930, 2891, 2857, 2738, 1960, 1891, 1826, 1664, 1589, 1491, 1472, 1461, 1427, 1377 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, mixture of diastereomers) δ 7.66－ － 33 (m, 6H), 6.17 (brs, 1H), 4.16 (quin, 1H, *J* = 6.0 Hz), 3.18 (t, 1H, *J* =11.6 Hz), 3.06 (m, 1H), 2.62 (m, 1H), 2.17－ 05 (m, 3H), 1.98 (m, 1H), 1.79 (m, 1H), 1.47 (m, 1H), 1.01 (s, 9H), 0.88 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, mixture of diastereomers) δ 175.3, 135.8, 135.7, 135.7, 134.3, 133.9, 129.6, 129.5, 127.6, 127.5, 73.7, 73.5, 47.8, 44.2, 42.3, 41.9, 41.3, 40.3, 39.8, 39.7, 39.0, 34.5, 33.6, 29.8, 26.8, 19.0, 17.0, 16.4; LRMS (FAB+) *m*/*z* 408 (M + H^+); HR-MS (FAB+) calcd for $C_{25}H_{34}NO_2Si$ (M + H^+) 408.2359; found 408.2358.



23 (>7:1) **24a** (85%) **24b** (12%)

(4*R*/4*S*,4a*S*,6*S*,7a*S*)-*tert*-Butyl 6-((*tert*-butyldiphenylsilyl)oxy)-4 -methyl-1-oxohexahydro-1*H*cyclopenta[*c*]pyridine-2(3*H*)-carboxylate (24a and 24b).

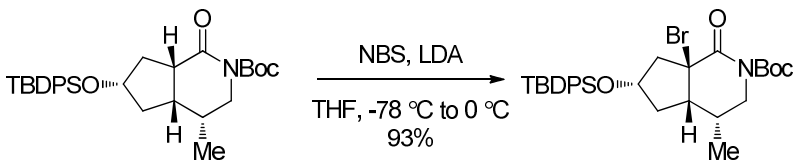
To a mixture of the saturated lactam **23** (dr > 7:1, 253 mg, 0.622 mmol) in CH_3CN (20 mL) were added Boc anhydride (0.430 mL, 1.87 mmol) and DMAP (38.0 mg, 0.311 mmol). After stirring for 24 h at ambient

temperature, the reaction mixture was quenched with H_2O, and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by

flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 50 to 1 : 10) to afford 270 mg (85%) of the Boc activated lactam **24a** as foamy solid: $[\alpha]_D^{25}$ 22.3 (c 1.03, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3071, 3049, 2960, 2932, 2896, 2858, 1898, 1768, 1713, 1589, 1474, 1428, 1392, 1367, 1331 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.65－ － 34 (m, 6H), 4.12 (quin, 1H, *J* = 5.9 Hz), 3.70 (ddd, 1H, *J* = 12.7, 3.7, 1.4 Hz), 3.39 (dd, 1H, *J* = 12.8, 11.5 Hz), 2.76 (dd, 1H, *J* = 17.0, 7.8 Hz), 2.22 (m, 1H), 2.10 (m, 1H), 2.01 (m, 2H), 1.77 (m, 1H), 1.52 (s, 9H), 1.49 (m, 1H), 1.00 (s, 9H), 0.90 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 173.6, 152.9, 135.8, 135.7, 134.1, 133.7, 129.7, 129.6, 127.6, 82.7, 73.5, 47.4, 45.6, 40.3, 39.3, 34.8, 30.3, 28.1, 26.9, 19.0, 16.0; LR-MS (FAB+) *m/z* 508 (M + H^+); HR-MS (FAB+) calcd for $C_{30}H_{42}NO_4Si$ (M + H^+) 508.2883; found 508.2877.

Further elution afforded **24b** (38.0 mg, 12%) as foamy solid: $[\alpha]_D^{25}$ － 3.7 (c 1.46, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3071, 3049, 2958, 2931, 2893, 2858, 1893, 1769, 1714, 1589, 1473, 1460, 1428, 1390, 1367, 1338, 1303 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.66－ － 33 (m, 6H), 4.12 (quin,1H, *J* = 6.4 Hz), 3.96 (dd, 1H, *J* = 13.0, 3.2 Hz), 3.02 (dd, 1H, *J* = 12.9, 10.7 Hz), 2.74 (dd, 1H, *J* = 18.5, 8.9 Hz), 2.21 (m, 1H), 2.04 (m, 1H), 1.92 (m, 1H), 1.82 (m, 1H), 1.74 (m, 1H), 1.51 (s, 9H), 1.44 (m, 1H), 1.00 (s, 9H), 0.96 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 173.4, 152.6, 135.8, 135.7, 134.3, 133.8, 129.6, 129.6,

127.6, 127.6, 82.8, 73.6, 51.3, 44.5, 42.8, 40.5, 37.8, 35.3, 28.1, 26.8, 19.0, 17.4; LR-MS (FAB+) *m/z* 508 (M + H^+); HR-MS (FAB+) calcd for $C_{30}H_{42}NO_4Si$ (M + H^+) 508.2883; found 508.2877.

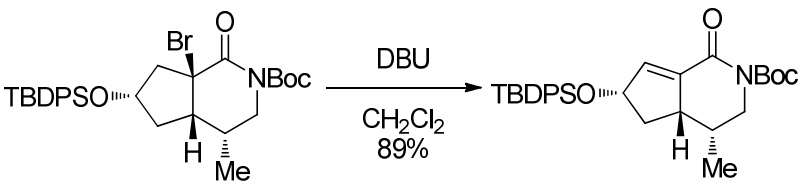


24a **27**

(4*R*,4a*S*,6*S*,7a*R*)-*tert*-Butyl7a-bromo-6-((*tert*-butyldiphenylsilyl) oxy)-4-methyl-1-oxohexahydro-1*H*-cyclopenta[*c*]pyridine-2(3*H*)-carboxylate (27).

To a solution of diisopropylamine (29.0 μL, 0.205 mmol) in THF (1 mL) was added *n*-BuLi (79.0 μL, 0.197 mmol) at − 8 ℃ After stirring for 30 min at − 8 ℃ the Boc activated lactam **24a** (40.0 mg, 78.9μmol) was added. After stirring for 30 min at − 8 ℃ NBS (15.0 mg, 86.8 μmol) was added and then the solution was warmed to 0 ℃ After stirring for 30 min, the reaction mixture was quenched with aq. NH_4Cl, and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 50 to 1 : 10) to afford 43.0 mg (93%) of the α-bromo lactam **27** as white solid: mp 67− 9 ℃ $[\alpha]_D^{25}$ − 0.8 (c 0.207, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3071, 3049, 2961, 2932, 2897, 2858, 1774, 1721, 1589, 1474, 1460, 1427, 1392, 1367, 1326 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.65− − 35

(m, 6H), 4.28 (m, 1H), 3.76 (m, 1H), 3.41 (m, 1H), 2.98 (m, 1H), 2.58 (m, 2H), 2.17 (dd, 1H, *J* = 13.9, 5.8 Hz), 1.92 (m, 1H), 1.52 (s, 9H), 1.49 (m, 1H), 0.98 (s, 9H), 0.92 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.5, 153.4, 135.9, 135.7, 133.7, 133.2, 129.8, 129.7, 127.7, 127.7, 83.2, 71.6, 62.8, 52.1, 49.9, 48.2, 34.7, 28.0, 26.8, 26.1, 18.9, 15.9; LR-MS (FAB+) *m*/*z* 608 (M + Na^+); HR-MS (FAB+) calcd for $C_{30}H_{40}BrNO_4SiNa$ (M + Na^+) 608.1808; found 608.1813.

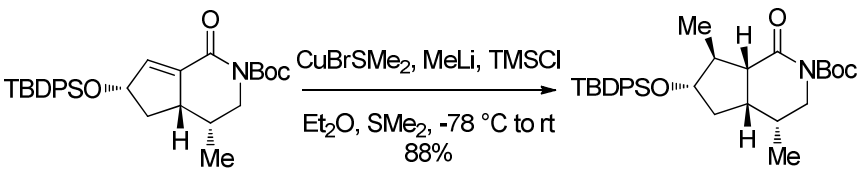


27 **9**

(4*R*,4a*S*,6*S*)-*tert*-Butyl 6-((*tert*-butyldiphenylsilyl)oxy)-4-methyl -1-oxo-4,4a,5,6-tetrahydro-1*H*cyclopenta[*c*]pyridine-2(3*H*)-carboxylate (9).

To a solution of the α-bromo lactam **27** (35 mg, 60 μmol) in CH_2Cl_2 (0.2 mL) was added DBU (10 μL, 600 μmol) at ambient temperature. After stirring for 48 h at the same temperature, the reaction mixture was quenched with aq. NH_4Cl, and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 50 to 1 : 10) to afford 27 mg (89%) of the α,β-unsaturated lactam **9** as a colorless oil; $[\alpha]_D^{25}$ − 0.2 (c 0.467, $CDCl_3$); FT-IR (thin film, neat) ν_{max} 3071, 3049, 2963, 2932, 2897,2857, 1961, 1891, 1824, 1766, 1715, 1637, 1473, 1428, 1393, 1367, 1337 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500

MHz) δ 7.64 (d, 4H, *J* = 7.6 Hz), 7.43－ .34 (m, 6H), 6.73 (s, 1H), 4.88 (tt, 1H, *J* = 7.2, 1.9 Hz), 3.78 (dd, 1H, *J* = 13.1, 3.1 Hz), 3.55 (dd, 1H, *J* = 13.0, 3.3 Hz), 2.84 (m, 1H), 2.24 (td, 1H, *J* = 12.7, 7.1 Hz), 2.07 (m, 1H), 1.71 (m, 1H), 1.51 (s, 9H), 1.03 (s, 9H), 0.96 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.3, 153.4, 145.2, 137.2, 135.7, 135.7, 133.9, 133.6, 129.8, 129.7, 127.7, 127.7, 83.1, 77.6, 53.2, 44.7, 39.0, 29.0, 28.0, 26.8, 19.1, 11.7; LR-MS (FAB+) *m/z* 506 (M + H^+); HR-MS (FAB+) calcd for $C_{30}H_{40}NO_4Si$ (M + H^+) 506.2727; found 506.2715.

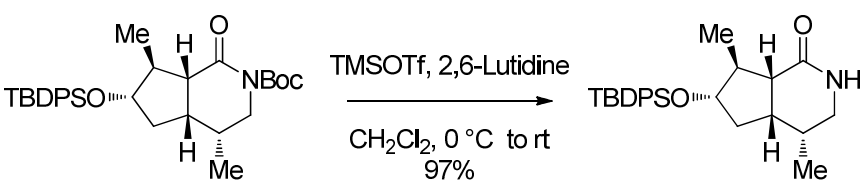


9 **28**

(4*R*,4a*S*,6*S*,7*S*,7a*R*)-*tert*-Butyl 6-((*tert*-butyldiphenylsilyl)oxy)-4, 7-dimethyl-1-oxohexahydro-1*H*cyclopenta[*c*]pyridine-2(3*H*)-carboxylate (28).

To a solution of CuBr • e_2S (80.0 mg, 0.389 mmol) in a mixture of Et_2O (0.3 mL) and SMe_2 (0.3 mL) was added MeLi (1.5 M MeLi·LiBr complex solution in Et_2O, 520 μL, 0.778 mmol) at 0 ℃ and the resulting solution was stirred at 0 ℃ for 1 h. The solution was cooled to － 3 ℃ and a solution of **9** (9.8 mg, 19 μmol) and TMSCl (50 μL, 0.40 mmol) was added dropwise. The resulting solution was allowed to warm to ambient temperature and was stirred for 15 min. The reaction mixture was quenched with aq. NH_4Cl, and extracted with EtOAc . The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The residue was

purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 50 to 1 : 10) to afford 8.9 mg (88%) of the β-methyl lactam **28** as colorless oil: $[\alpha]_D^{27}$ 37.0 (c 0.107, $CHCl_3$); FT-IR (thin film, neat) ν_{max} 3071, 3049, 2961, 2931, 2893, 2858, 1769, 1714, 1589, 1474, 1459, 1428, 1391, 1367, 1327 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.65 (td, 4H, *J* = 7.8, 1.3 Hz), 7.42－ .34 (m, 6H), 3.69 (m, 1H), 3.64 (m, 1H), 3.28 (m, 1H), 2.31 (m, 1H), 2.21 (m, 1H), 2.07 (q, 1H, *J* = 7.3 Hz), 2.00 (m, 1H), 1.63 (m, 1H), 1.51 (s, 9H), 1.41 (m, 1H), 1.02 (s, 9H), 0.96 (d, 3H, *J* = 6.7 Hz),0.81 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 173.3, 152.7, 136.0, 135.9, 134.3, 133.7, 129.7, 129.6, 127.6, 127.5, 82.7, 79.0, 52.2, 47.8, 47.1, 37.2, 33.7, 30.8, 28.1, 27.0, 19.2, 17.1, 15.5; LR-MS (FAB+) *m*/*z* 522 (M + H^+); HR-MS (FAB+) calcd for $C_{31}H_{44}NO_4Si$ (M + H^+) 522.3040; found 522.3042.

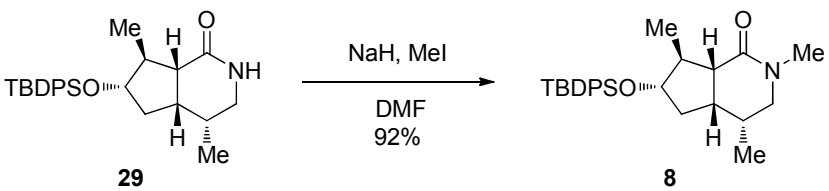


28 **29**

(4*R*,4a*S*,6*S*,7*S*,7a*R*)-6-((*tert*-Butyldiphenylsilyl)oxy)-4,7-dimethyloctahydro-1*H*cyclopenta[*c*]pyridin-1-one (29).

To a solution of the β-methyl lactam **28** (23 mg, 44 μmol) in CH_2Cl_2 (1 mL) were added 2,6-lutidine (10 μL, 88 μmol) and TMSOTf (12 μL, 66 μ

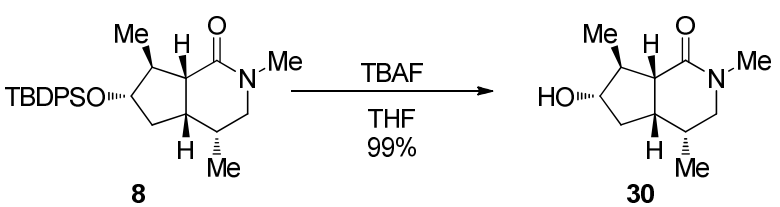
mol) at 0 ℃ The resulting solution was allowed to warm to ambient temperature and was stirred for 2 h. The reaction mixture was quenched with aq. NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 1) to afford 18 mg (97%) of the δ-lactam **29** as a colorless oil: $[\alpha]_D^{27}$ 12.7 (c 0.100, $CDCl_3$); FT-IR (thin film, neat) ν_{max} 3287, 3199, 3071, 3049, 2958, 2930, 2890, 2858, 1960, 1894, 1825, 1664, 1589, 1489, 1460, 1427, 1378 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.67 (dd, 4H, *J* = 11.9, 7.3 Hz), 7.44－ .36 (m, 6H), 5.77 (d, 1H, *J* = 4.6 Hz), 3.71 (dd, 1H, *J* = 12.8, 6.0 Hz), 3.16 (t, 1H, *J* = 11.7 Hz), 3.01 (m, 1H), 2.23 (m, 2H), 2.17 (quin, 1H, *J* = 6.4 Hz), 2.04 (m, 1H), 1.70 (m, 1H), 1.43 (m, 1H), 1.04 (s, 9H), 0.99 (d, 3H, *J* = 6.9 Hz), 0.83 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.9, 135.9, 135.8, 134.4, 133.9, 129.6, 129.6, 127.6, 127.5, 79.4, 48.9, 47.9, 44.1, 37.6, 33.6, 30.3, 26.9, 19.2, 18.0, 16.0; LR-MS (FAB+) *m*/*z* 422 (M + H^+); HR-MS (FAB+) calcd for $C_{26}H_{36}NO_2Si$ (M + H^+) 422.2515; found 422.2511.



29 **8**

(4*R*,4a*S*,6*S*,7*S*,7a*R*)-6-((*tert*-Butyldiphenylsilyl)oxy)-2,4,7-trimethyloctahydro-1*H*cyclopenta[*c*]pyridin-1-one (8).

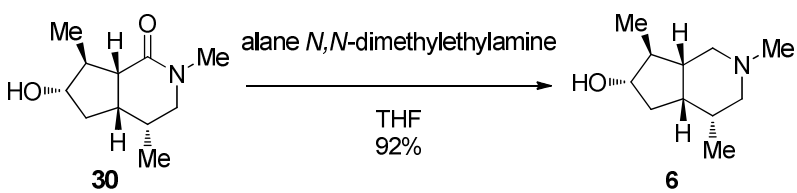
To a solution of the δ-lactam **29** (18 mg, 43 μmol) in DMF (1 mL) was added 60% NaH (1.8 mg, 47 μmol) at 0 ℃ After stirring for 30 min, the resulting solution was added MeI (8.0 μL, 130 μmol). The resulting solution was allowed to warm to ambient temperature and was stirred for 14 h. The reaction mixture was quenched with aq. NH_4Cl. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 3) to afford 17 mg (92%) of the *N*-methyl lactam **8** as a colorless oil: $[\alpha]_D^{27}$ 39.7 (c 0.053, $CDCl_3$); FT-IR (thin film, neat) νmax 3070, 3048, 2957, 2929, 2858, 1644, 1589, 1498, 1460, 1428, 1378, 1333 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.66－ － 33 (m, 6H), 3.66 (dd, 1H, *J* = 13.6, 6.2 Hz), 3.24 (t, 1H, *J* = 11.9 Hz), 2.93 (s, 3H), 2.90 (dd, 1H, *J* = 12.5, 4.4 Hz), 2.23－ 14 (m, 2H), 2.06 (m, 2H), 1.66 (m, 1H), 1.39 (m, 1H), 1.02 (s, 9H), 0.98 (d, 3H, *J* = 6.9 Hz), 0.80 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7, 135.9, 135.9, 134.5, 133.9, 129.6, 129.5, 127.5, 127.5, 79.6, 51.7, 49.4, 48.3, 38.1, 35.4, 33.7, 30.1, 27.0, 19.2, 18.3, 16.0; LR-MS (FAB+) *m/z* 436 (M + H^+); HR-MS (FAB+) calcd for $C_{27}H_{38}NO_2Si$ (M + H^+) 436.2672; found 436.2675.



8 **30**

(4*R*,4a*S*,6*S*,7*S*,7a*R*)-6-Hydroxy-2,4,7-trimethyloctahydro-1*H*-cyclopenta[*c*]pyridin-1-one (30).

To a solution of the *N*-methyl lactam **8** (12 mg, 28 μmol) in THF (0.5 mL) was added TBAF (1.0 M solution in THF, 0.28 mL, 280 μmol) at ambient temperature. After stirring for 3 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : MeOH = 10 : 1) to afford 5.4 mg (99%) of the hydroxyl lactam **19** as a colorless oil: $[\alpha]_D^{24}$ 16.7 (c 0.220, $CDCl_3$); FT-IR (thin film, neat) ν_{max} 3397, 2958, 2929, 2876, 1619, 1504, 1452, 1402, 1381 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.75 (m, 1H), 3.23 (t, 1H, *J* = 12.0 Hz), 2.94 (dd, 1H, *J* = 12.8, 4.4 Hz), 2.91 (s, 3H), 2.37 (m, 2H), 2.14 (m, 1H), 2.02 (m, 1H), 1.94 (m, 1H), 1.40 (m, 1H), 1.14 (d, 3H, *J* = 6.9 Hz), 0.91 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 172.8, 78.4, 51.7, 49.8, 48.4, 38.2, 35.4,32.9, 29.8, 18.0, 16.1; LR-MS (FAB+) *m*/*z* 198 (M + H^+); HR-MS (FAB+) calcd for $C_{11}H_{20}NO_2$ (M + H^+) 198.1494; found 198.1492.

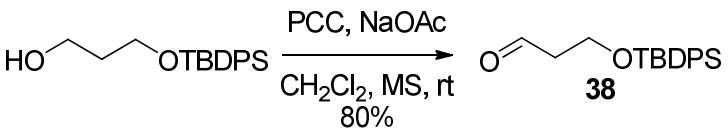


30 **6**

7-*epi*-Incarvilline (6).

To a solution of the hydroxyl lactam **30** (1.5 mg, 7.6 μmol) in THF (0.3 mL) was added alane *N*,*N*-dimethylethylamine (0.5M solution in toluene, 150

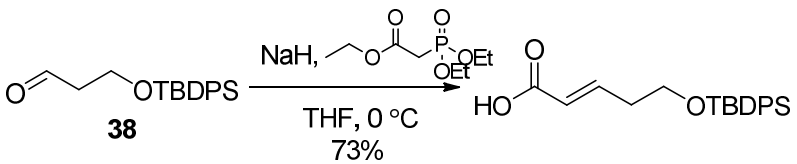
μL, 76 μmol) at ambient temperature. After stirring for 8 h, the reaction mixture was quenched with H_2O. The mixture was filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2 : MeOH : Et_3N = 100 : 10 : 1) to afford 1.3 mg (92%) of the 7-*epi*-incarvilline **6** as a colorless oil: $[\alpha]_D^{23}$ 20.1 (c 0.080, $CDCl_3$); FT-IR (thin film, neat) ν_{max} 3385, 2958, 2925, 2872, 2855, 2798, 2727, 1737, 1656, 1468, 1375 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.80 (td, 1H, *J* = 6.9, 3.2 Hz), 2.67 (q, 1H, *J* = 5.6 Hz), 2.51 (dd, 1H, *J* = 10.8, 3.9 Hz), 2.27 (s, 3H), 2.13 (m, 1H), 2.07－ －90 (m, 2H), 1.85 (m, 1H), 1.74 (brs, 1H), 1.56－51 (m, 2H), 1.02 (d, 3H, *J* = 7.3 Hz), 0.84 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 80.4, 57.7, 57.3, 47.4, 46.0, 45.4, 38.4, 33.0, 30.4, 19.9, 17.6; LR-MS (FAB+) *m*/*z* 184 ($M + H^+$); HR-MS (FAB+) calcd for $C_{11}H_{22}NO$ ($M + H^+$) 184.1701; found 184.1699.



3-((*tert*-Butyldiphenylsilyl)oxy)propanal

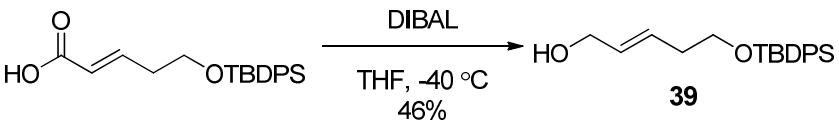
To a solution of 3-TBDPSoxypropan-1-ol (3.39 g, 10.8 mmol) in CH_2Cl_2 (60 mL) were added NaOAc (265 mg, 3.23 mmol), 4Å Molecular Sieve (7 g) and PCC (3.50 g, 16.2 mmol). After stirring for 1 h at room temperature, the reaction mixture was quenched with H_2O, filtered and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$

and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 10) to afford 2.70 g (80%) of the aldehyde **38** as clear oil



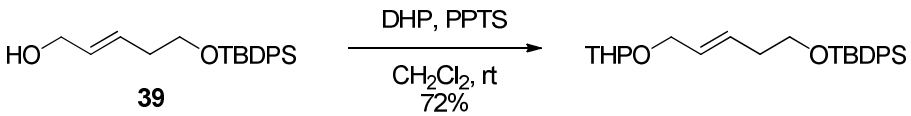
(*E*)-5-((*tert*-Butyldiphenylsilyl)oxy)pent-2-enoic acid

To a solution of the ethyl 2-(diethoxyphosphoryl)acetate (0.24 mL, 1.21 mmol) in THF (6 mL) was added 60% NaH (53.2 mg, 1.33 mmol) at 0 ℃ After stirring for 30 min, the resulting solution was added the aldehyde **38** (190 mg, 0.609 mmol). The resulting solution was stirred for 10 min. The reaction mixture was quenched with H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 20) to afford 175 mg (75%) of the corresponding ester as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72－ － 34 (m, 6H), 6.97 (td, 1H, *J* = 15.5, 7.1 Hz), 5.84 (td, 1H, *J* = 15.6, 1.5 Hz), 4.19 (q, 2H, *J* = 7.0 Hz), 3.75 (t, 2H, *J* = 6.4 Hz), 2.42 (qd, 2H, *J* = 6.4, 1.5 Hz), 1.27 (t, 3H, *J* = 7.1 Hz), 1.03 (s, 9H)



(*E*)-5-((*tert*-Butyldiphenylsilyl)oxy)pent-2-en-1-ol

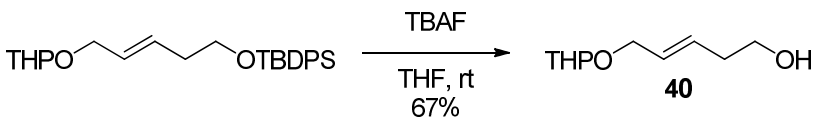
To a solution of the conjugated ester (168 mL, 0.440 mmol) in THF (3 mL) was added DIBAL (1M in THF solution, 0.88 mL, 0.88 mmol) at － 40 ℃ The resulting solution was stirred for 30 min. The reaction mixture was allowed to warm up to room temperature and quenched with H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 10) to afford 69 mg (46%) of the allyl alcohol **39** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61－ － 28 (m, 6H), 5.60 (m, 2H), 3.99 (m, 2H), 3.64 (t, 2H, *J* = 6.8 Hz), 2.23 (m, 2H), 0.98 (s, 9H)



(*E*)-*tert*-Butyldiphenyl((5-((tetrahydro-2H-pyran-2-yl)oxy)pent-3-en-1-yl)oxy)silane

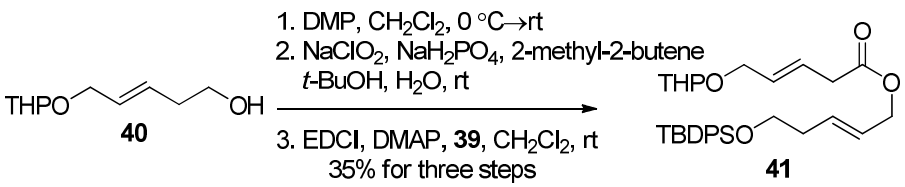
To a solution of the allyl alcohol **39** (72 mL, 0.212 mmol) in CH_2Cl_2 (3 mL) were added PPTS (5.00 mg, 21.2 μmol) and DHP (0.06mL, 0.635 mmol) at room temperature. The resulting solution was stirred for 4 h. The reaction mixture was quenched with Na_2CO_3. The aqueous layer was

extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 10) to afford 65 mg (72%) of the allyl tetrahydropyranoxy product as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66－ －.32 (m, 6H), 5.65 (m, 2H), 4.61 (t, 1H, *J* = 2.7 Hz), 4.16 (m, 1H), 3.92－ 81 (m, 2H), 3.68 (t, 2H, *J* = 6.8 Hz), 3.40 (m, 1H), 2.30 (q, 2H, *J* = 6.6 Hz), 1.81－ 50 (m, 6H), 1.02 (s, 9H)



(*E*)-5-((Tetrahydro-2H-pyran-2-yl)oxy)pent-3-en-1-ol

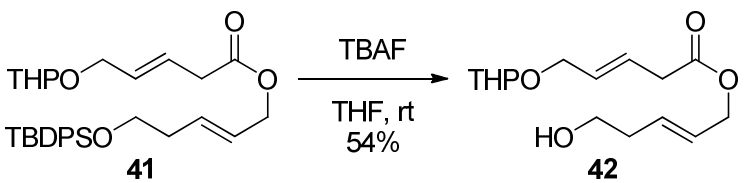
To a solution of the allyl tetrahydropyranoxy compound (65 mL, 0.15 mmol) in THF (1.5 mL) was added TBAF (1M solution in THF, 2 mL, 2 mmol) at room temperature. The resulting solution was stirred for 14 h. The reaction mixture was quenched with H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 5) to afford 19 mg (67%) of the homoallyl alcohol **40** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.70 (quin, 2H, *J* = 1.8 Hz), 4.62 (t, 1H, *J* = 2.9 Hz), 4.22－ .16 (m, 1H), 3.98－ 92 (m, 1H), 3.93 (m, 1H), 3.66 (t, 2H, *J* = 6.2 Hz), 3.49 (m, 1H), 2.32 (m, 1H), 1.84－ 51 (m, 6H)



(*E*)-(*E*)-5-((*tert*-Butyldiphenylsilyl)oxy)pent-2-en-1-yl 5-((tetrahydro-2H-pyran-2-yl)oxy)pent-3-enoate

To a solution of the homoallyl alcohol **40** (50.0 mg, 0.269 mmol) in CH_2Cl_2 (2 mL) was added DMP (500 mg, 1.18 mmol) at 0 ℃ The resulting solution was allowed to warm up to the ambient temperature and stirred for 1 h. The reaction mixture was quenched with Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. To a solution of the resultant in *t*-BuOH (1.5 mL), H_2O (0.5 mL), and 2-methyl-2-butene (0.7 mL) were added $NaClO_2$ (160 mg, 1.77 mmol) and NaH_2PO_4 (150 mg, 1.25 mmol) in H_2O (1 mL) at room temperature. After stirring for 10 min, the reaction mixture was acidified with 2N HCl and evaporated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. To a solution of the carboxylic acid in CH_2Cl_2 (6 mL) were added allyl alcohol **39** (66 mg, 0.19 mmol), EDCI (60 mg, 0.39 mmol), and DMAP (47 mg, 0.39 mmol) at room temperature. After stirring for 16 h, the reaction mixture was quenched with H_2O. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 20)

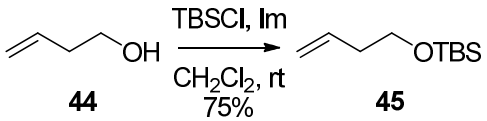
to afford 53 mg (35% for three steps) of the ester **41** as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64－ － .34 (m, 6H), 5.85 － .67 (m, 2H), 5.58 (m, 1H), 4.61 (t, 1H, *J* = 3.8 Hz), 4.50 (d, 2H, *J* = 6.4 Hz), 4.21 (m, 1H), 3.94 (m, 1H), 3.83 (m, 1H), 3.68 (t, 2H, *J* = 6.6 Hz), 3.48 (m, 1H), 3.08 (dd, 2H, *J* = 6.8, 0.7 Hz), 2.29 (q, 2H, *J* = 6.6 Hz), 2.11－ .48 (m, 6H)



41 **42**

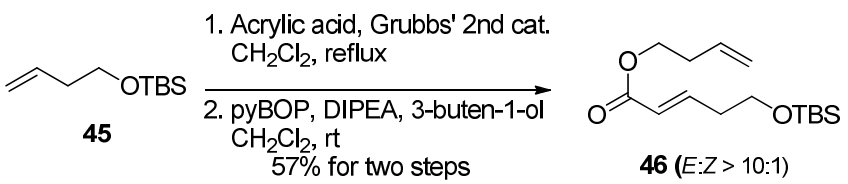
(*E*)-(*E*)-5-Hydroxypent-2-en-1-yl 5-((tetrahydro-2H-pyran-2-yl)oxy)pent-3-enoate

To a solution of the ester **41** (53.0 mL, 0.101 mmol) in THF (0.5 mL) was added TBAF (1M solution in THF, 0.51 mL, 0.51 mmol) at room temperature. The resulting solution was stirred for 30 min. The reaction mixture was quenched with H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 3) to afford 15 mg (54%) of the homoallyl alcohol **42** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.88－ － 51 (m, 2H), 4.22 (m, 1H), 3.95 (qd, 1H, *J* = 6.2, 1.1 Hz), 3.83 (m, 1H), 3.67 (t, 2H, *J* = 6.2 Hz), 3.46 (m, 1H), 3.09 (dd, 2H, *J* = 6.6, 0.9 H), 2.31 (m, 2H), 1.88－ 50 (m, 6H)



(But-3-en-1-yloxy)(*tert*-butyl)dimethylsilane

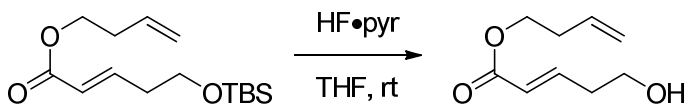
To a solution of the homoallyl alcohol **44** (0.500 mL, 5.81 mmol) in CH_2Cl_2 (10 mL) were added TBSCl (1.05 g, 6.97 mmol) and imidazole (475 mg, 6.97 mmol) at room temperature. The resulting solution was stirred for 2 h. The reaction mixture was filtered with *n*-hexane dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 10) to afford 811 mg (75%) of the TBS ether **45** as a colorless oil



(*E*)-But-3-en-1-yl 5-((*tert*-butyldimethylsilyl)oxy)pent-2-enoate

To a solution of the TBS ether **45** (700 mg, 3.76 mmol) in CH_2Cl_2 (30 mL) were added acrylic acid (0.40 mL, 5.65 mmol) and Grubbs' 2nd catalyst (160 mg, 0.188 mmol) at room temperature. The resulting solution was refluxed for 3 h. The reaction mixture was cooled down to room temperature and concentrated *in vacuo*. To a solution of the resultant in

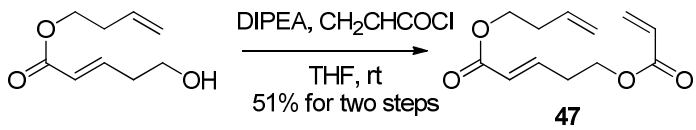
CH_2Cl_2 (30 mL) were added 3-buten-1-ol (0.50 mL, 5.64 mmol), pyBOP (3.91 g, 7.52 mmol) and DIPEA (6 mL) at room temperature. The resulting solution was stirred for 16 h. The reaction mixture was quenched with aq. NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 20) to afford 609 mg (57% for two steps) of the ester **46** as a colorless oil



46 (*E*:*Z* > 10:1)

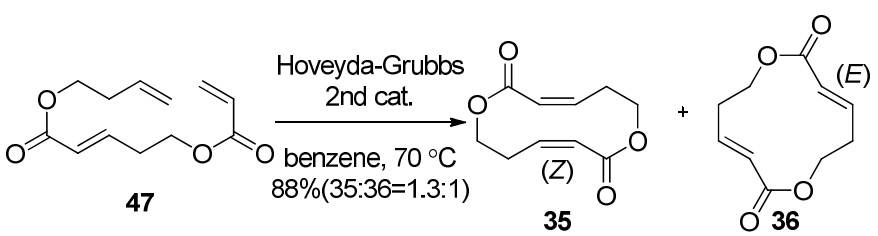
(*E*)-But-3-en-1-yl 5-hydroxypent-2-enoate

To a solution of the ester **46** (299 mg, 1.05 mmol) in THF (5 mL) was added HF·pyr (70%, 0.12 mL, 4.21 mmol) at room temperature. The resulting solution was stirred for 2 h. The reaction mixture was quenched with H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 3) to afford the homoallyl alcohol product as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.94 (m, 1H), 5.91 (d, 1H, *J* = 15.7 Hz), 5.79 (m, 1H), 5.09 (m, 2H), 4.17 (t, 2H, *J* = 6.8 Hz), 4.10 (q, 2H, *J* = 7.2 Hz), 3.76 (t, 2H, *J* = 6.2 Hz), 2.46 (q, 2H, *J* = 6.5 Hz), 2.40 (q, 2H, *J* = 6.6 Hz)



(*E*)-But-3-en-1-yl 5-(acryloyloxy)pent-2-enoate

To a solution of the homoallylalcohol (103 mg, 0.605 mmol) in CH_2Cl_2 (3 mL) were added acryloyl chloride (0.06 mL, 0.727 mmol) and DIPEA (3 mL) at room temperature. The resulting solution was stirred for 2 h. The reaction mixture was quenched with aq. NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 20) to afford 69 mg (51% for two steps) of the bis-terminal alkene **47** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.91 (td, 1H, *J* = 15.8, 7.0 Hz), 6.38 (dd, 1H, *J* = 17.2, 1.4 Hz), 6.09 (m, 1H), 5.92－ － .03 (m, 2H), 5.13－ .03 (m, 2H), 4.24 (t, 2H, *J* = 6.4 Hz), 4.16 (t, 2H, *J* = 6.6 Hz), 2.56 (qd, 2H, *J* = 6.6, 1.7 Hz), 2.39 (qt, 2H, *J* = 6.6, 1.3 Hz)



(3*Z*,9*Z*)-1,7-dioxacyclododeca-3,9-diene-2,8-dione

To a solution of the bis-terminal alkene **47** (61.0 mg, 0.272 mmol) in CH_2Cl_2 (27 mL) was added Hoveyda-Grubbs 2nd catalyst (17.0 mg, 27.2 μ mol) at room temperature. The resulting solution was warmed to 70 ℃ for 16 h. The reaction mixture was cooled down to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc : *n*-hexane = 1 : 10) to afford 25 mg (47%) of the bis-(*Z*)-α,β-unsaturated lactone **35** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.93 (td, 2H, *J* = 9.69 Hz), 6.02 (td, 2H, *J* = 9.69 Hz), 4.41 (t, 4H, *J* = 6.2 Hz), 2.44 (m, 4H)

(3*E*,9*E*)-1,7-dioxacyclododeca-3,9-diene-2,8-dione

The reaction mixture was purified to afforded 22 mg (41%) of the bis-(*E*)-α,β-unsaturated lactone **36** as white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.88 (td, 2H, *J* = 15.7, 7.1 Hz), 5.85 (td, 2H, *J* = 15.8, 1.5 Hz), 4.27 (t, 4H, *J* = 5.1 Hz), 2.56 (q, 4H, *J* = 6.4 Hz)

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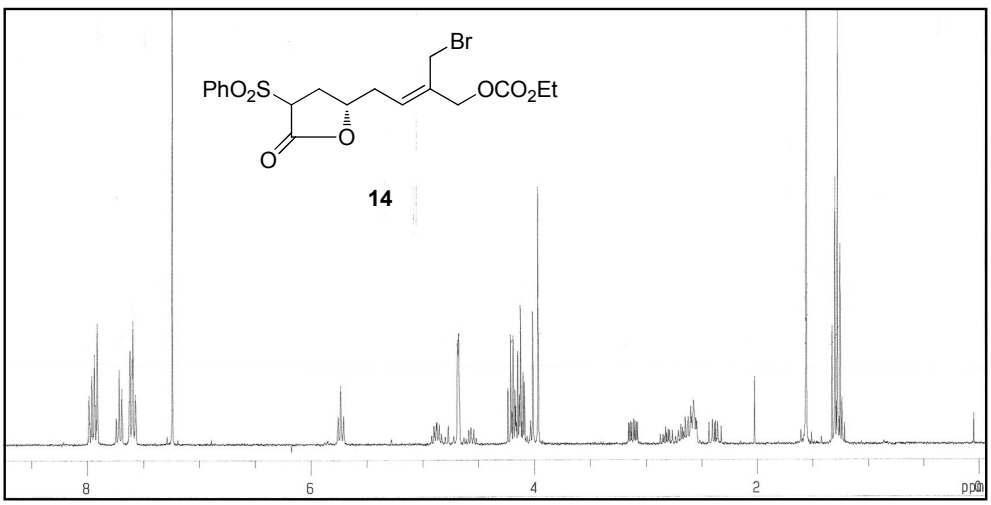
Ⅵ Appendix

▼ ^{1}H NMR ($CDCl_3$, 300MHz)



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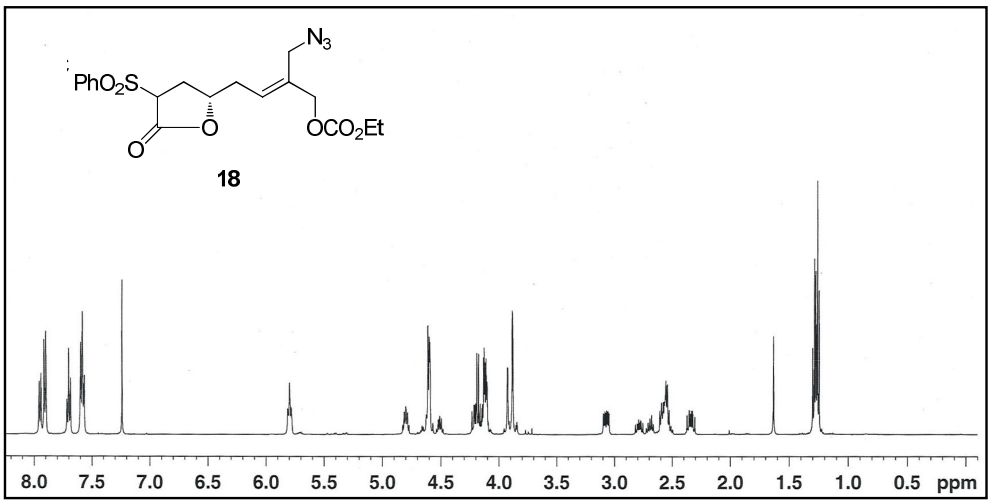

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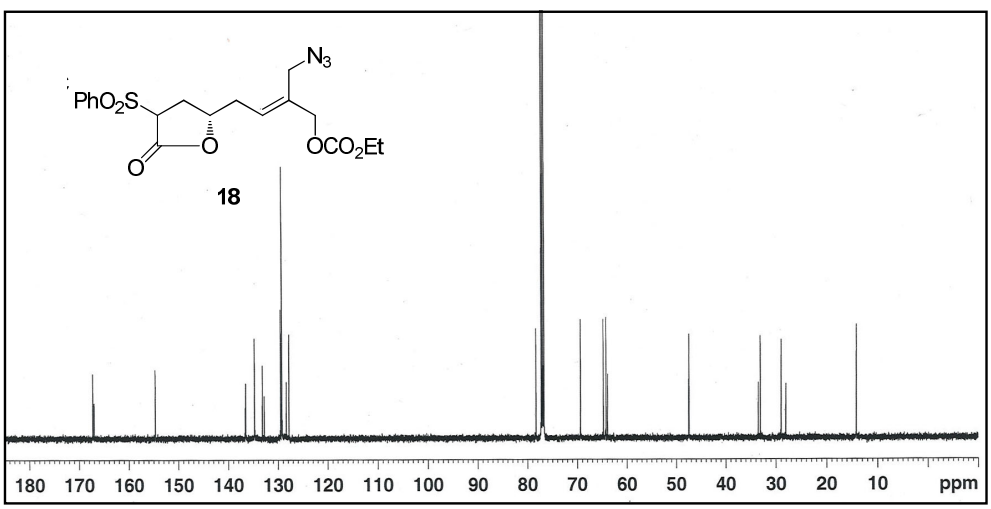

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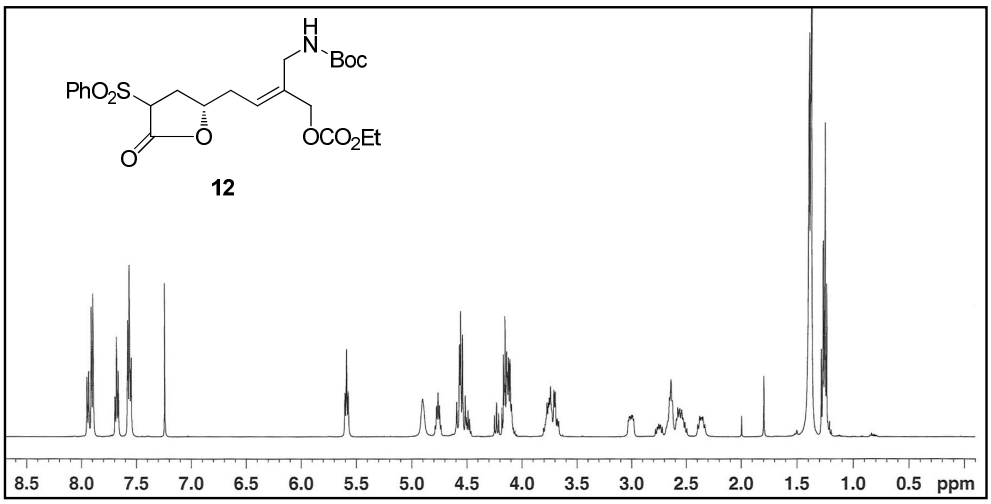

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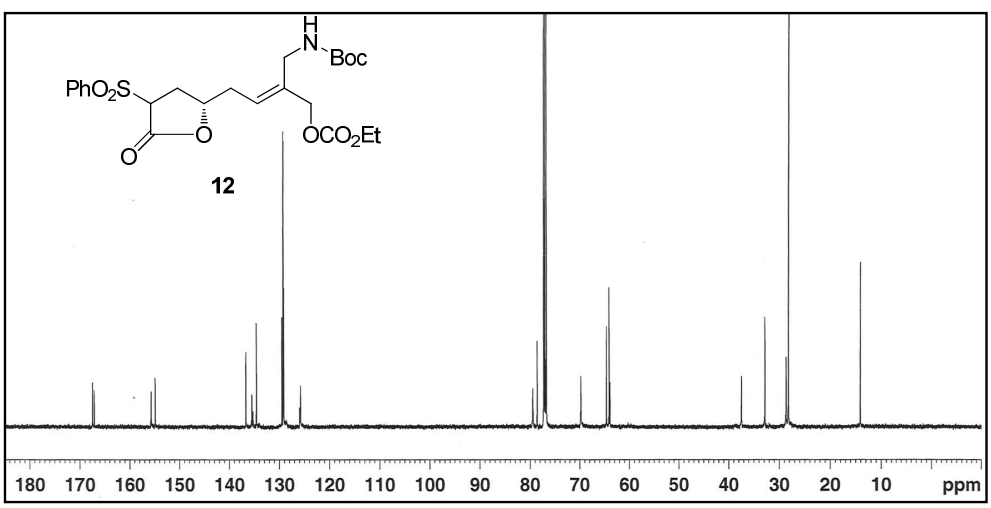

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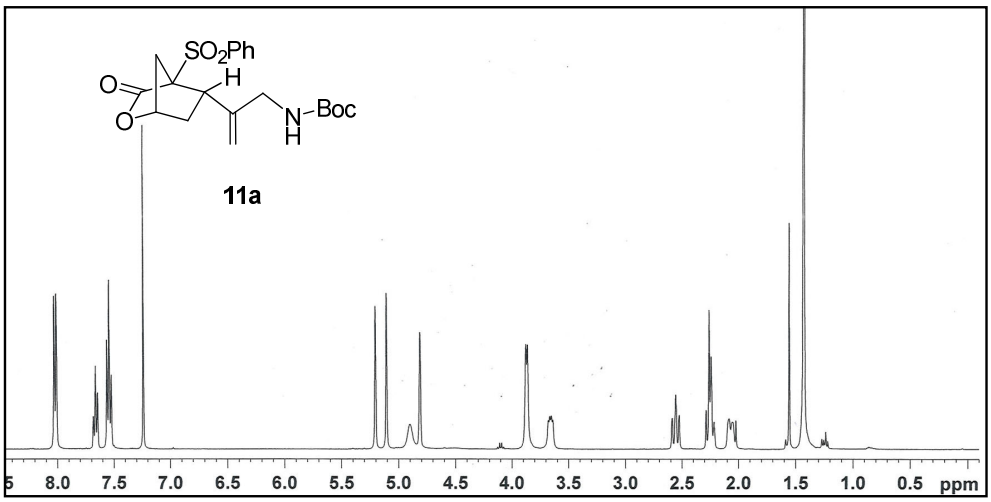

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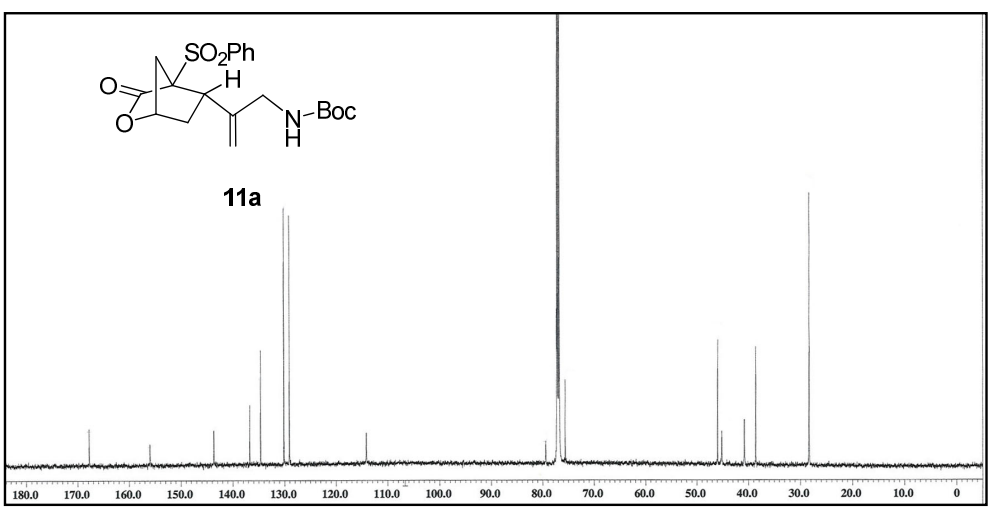

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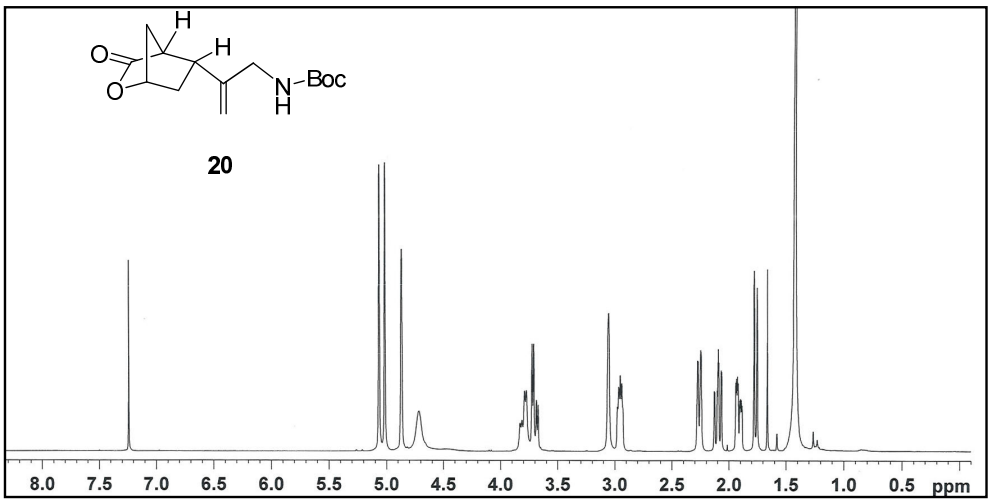

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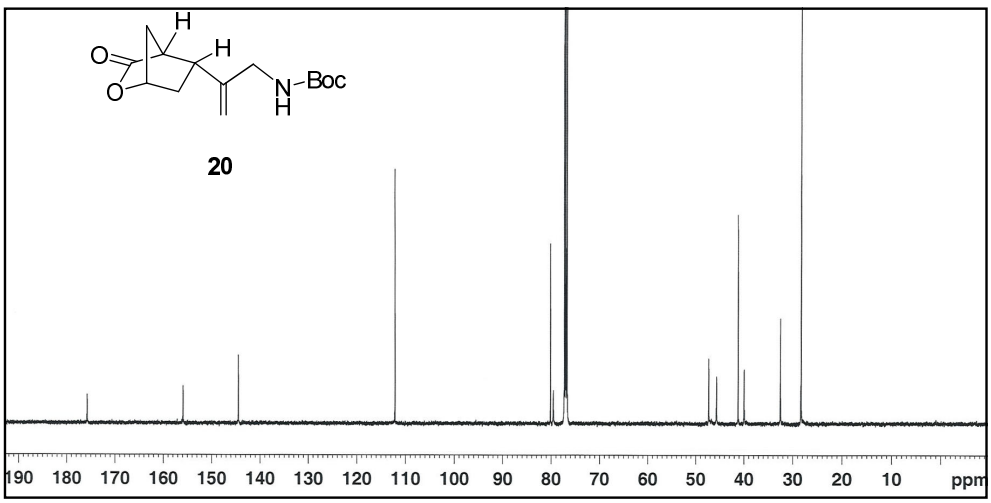

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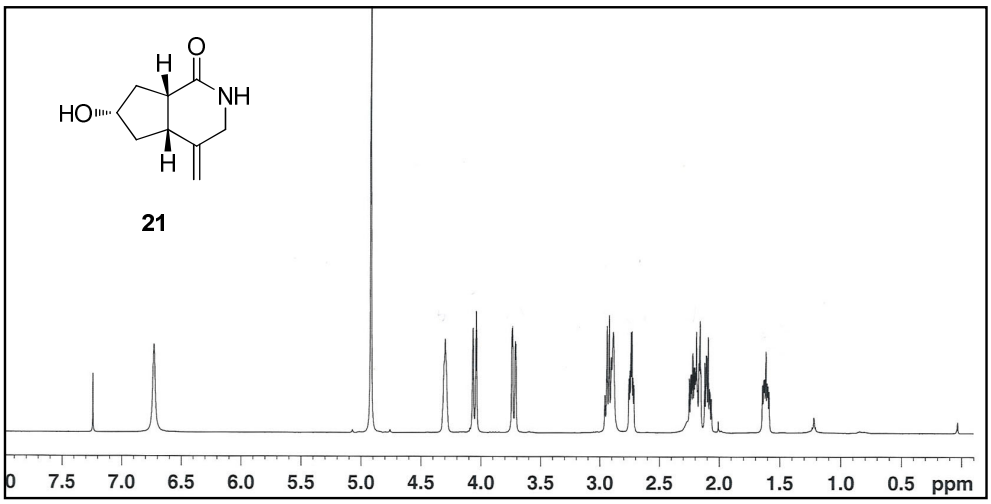

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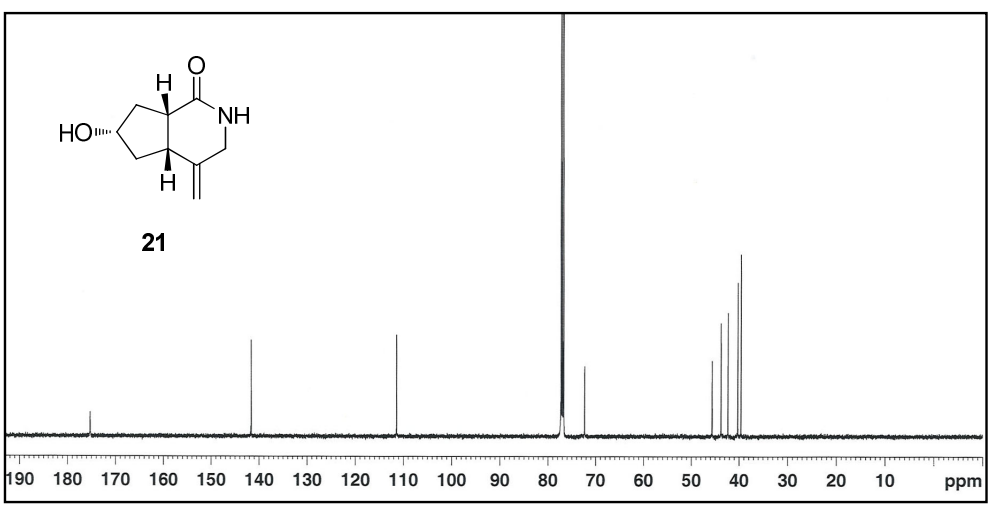

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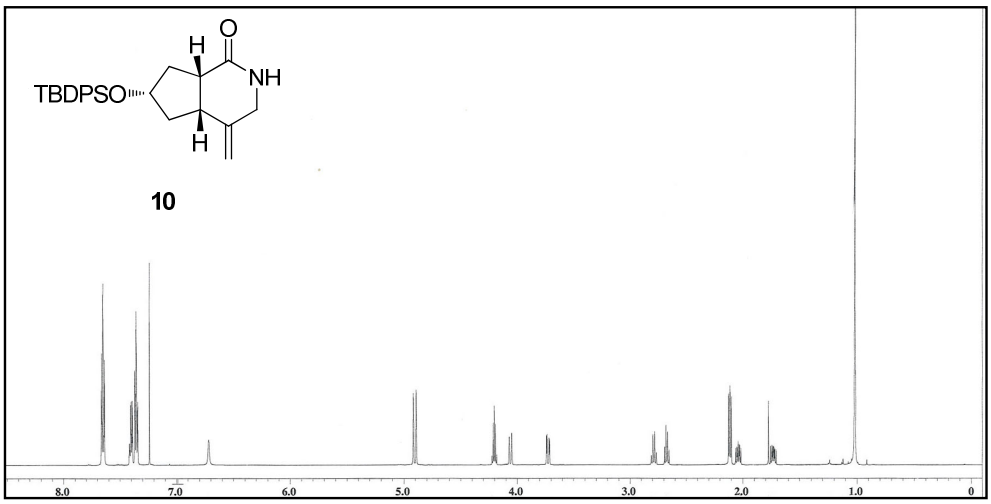

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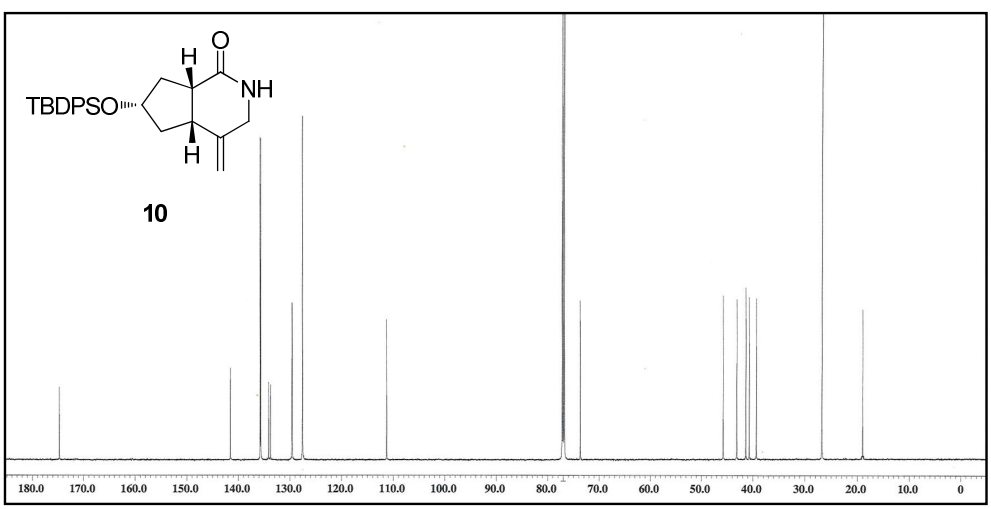

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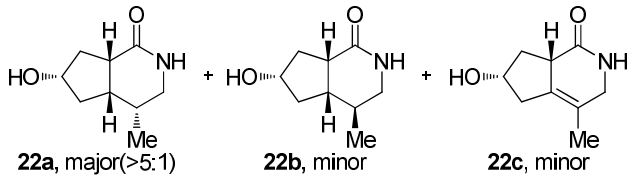

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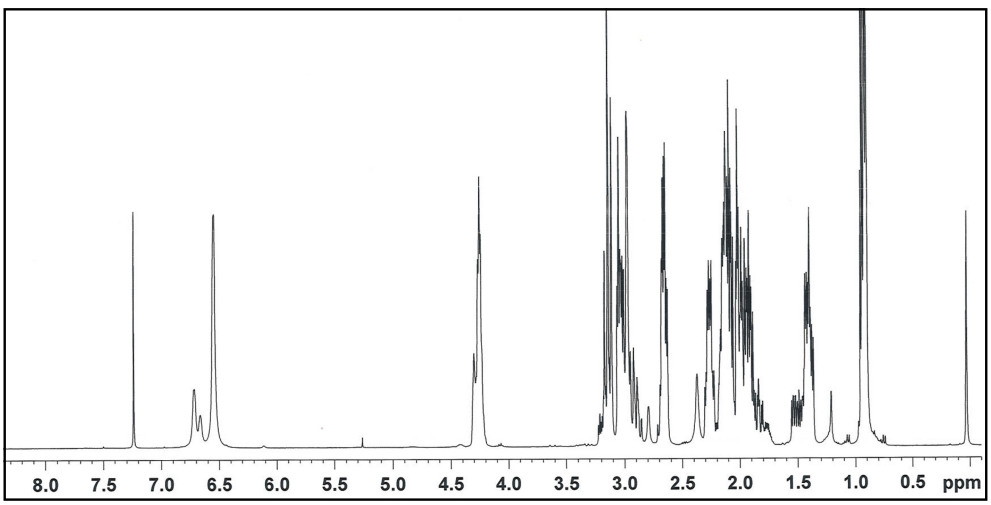

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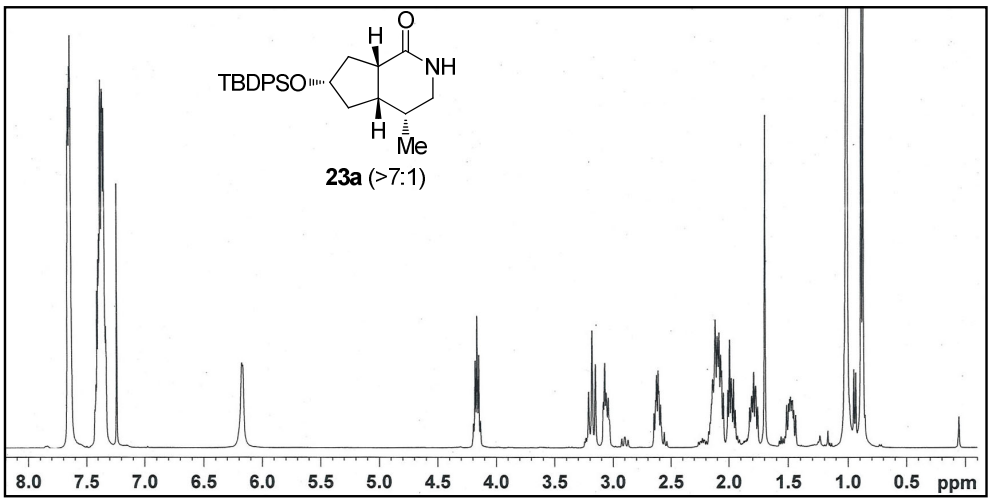

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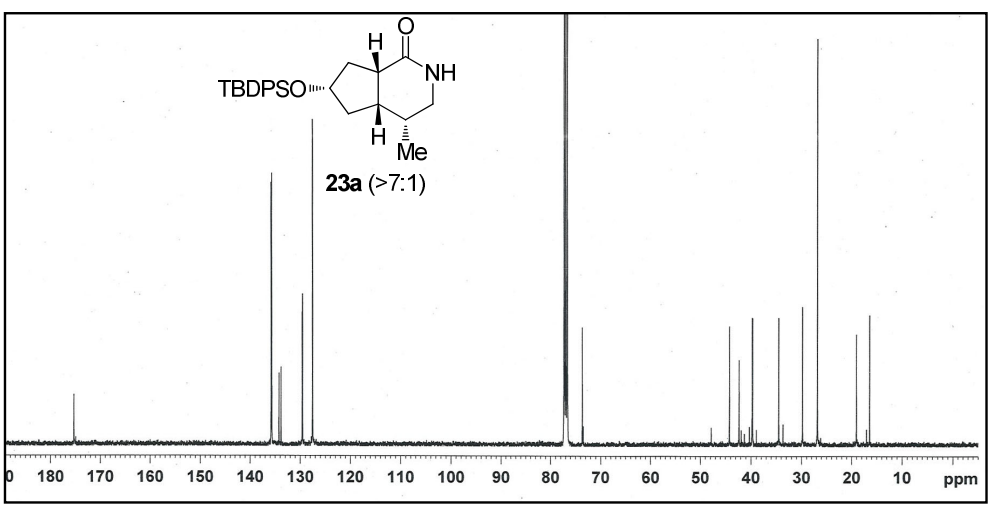

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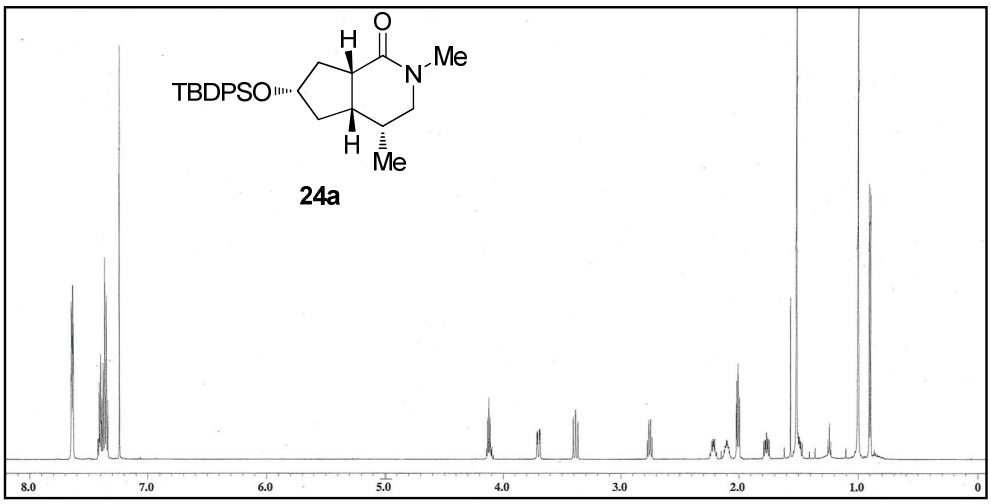

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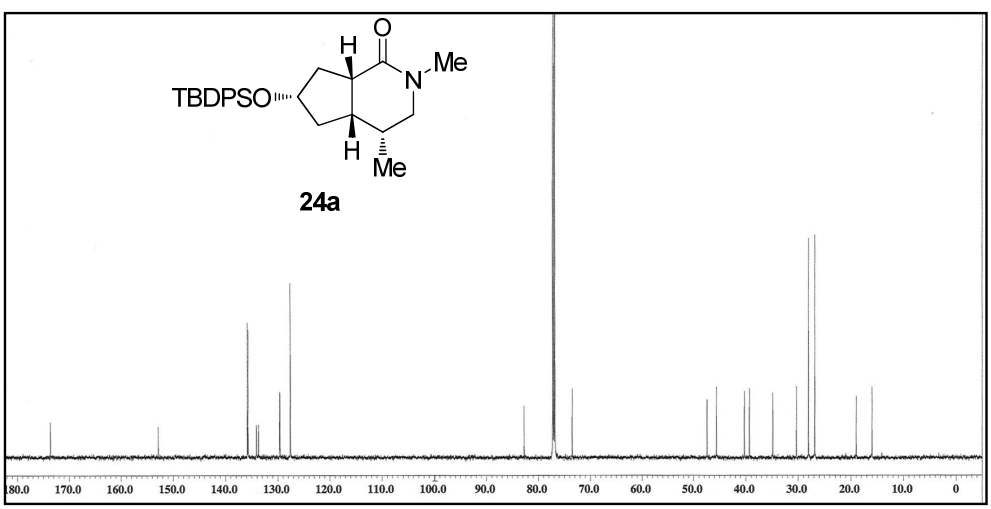

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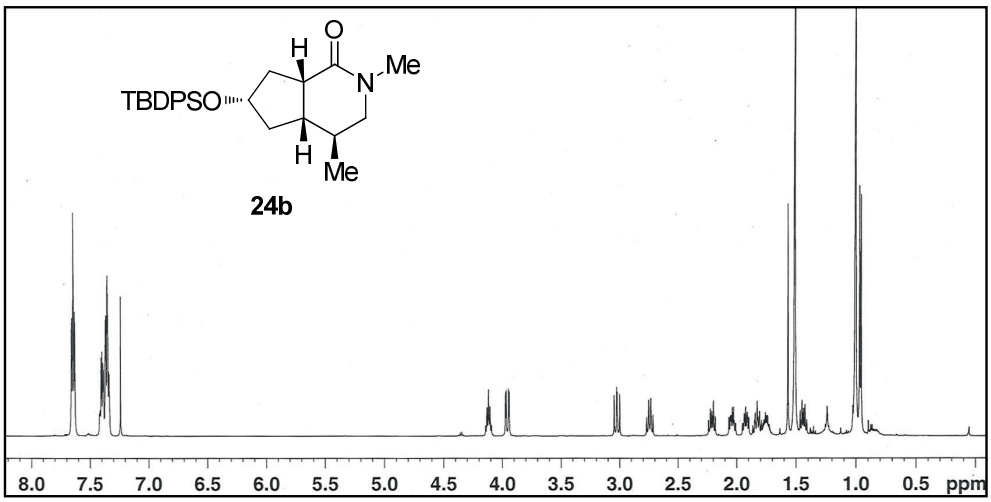

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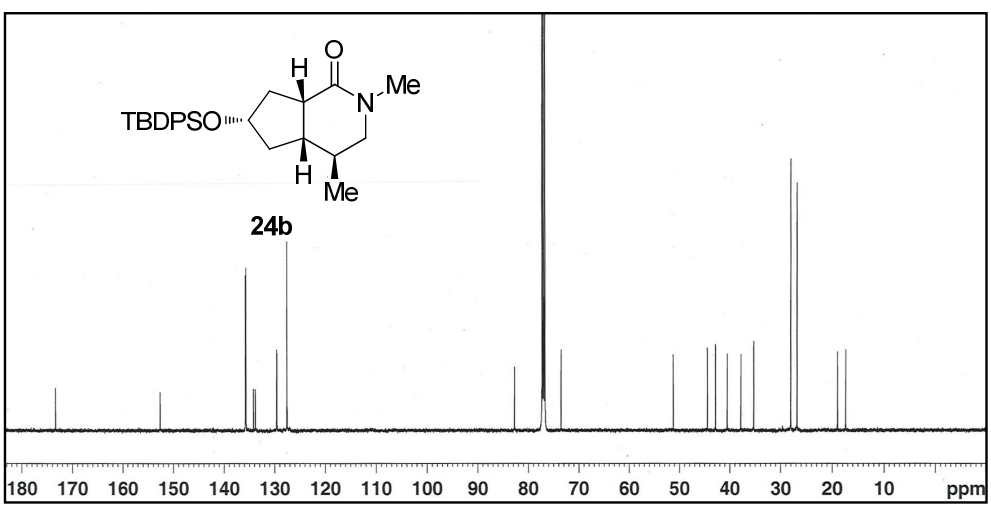

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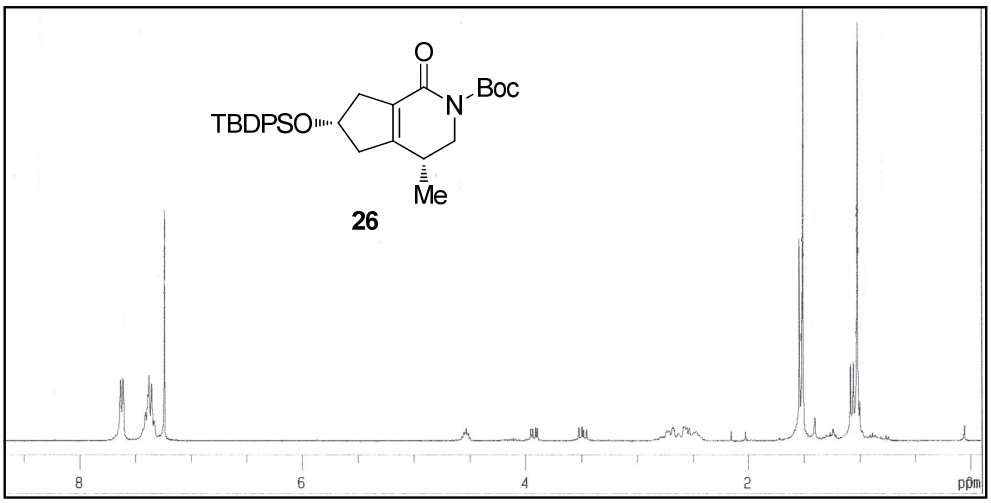

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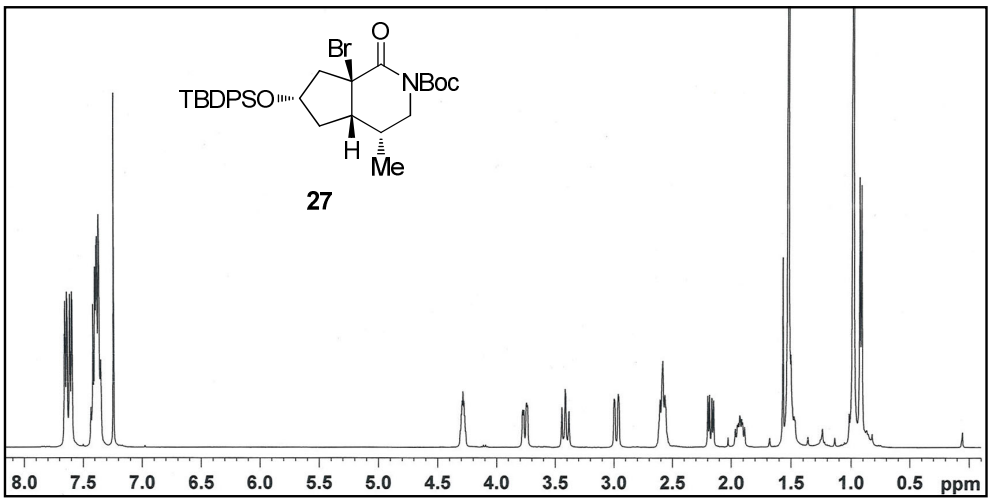
▼ ^{1}H NMR ($CDCl_3$, 400MHz)



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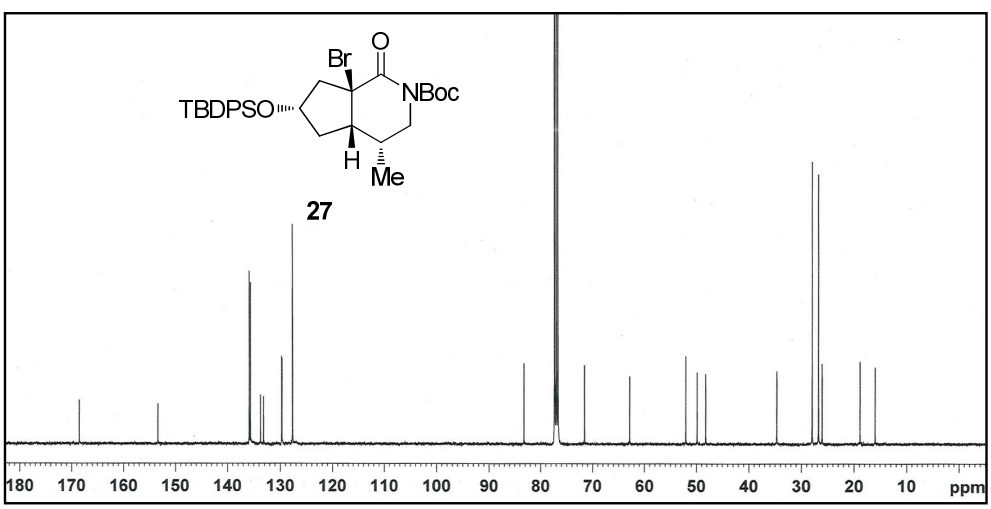

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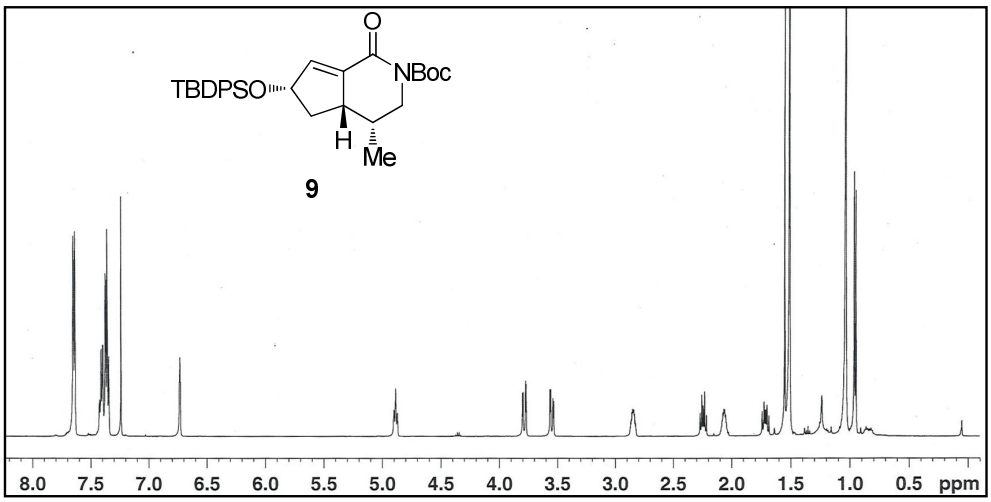

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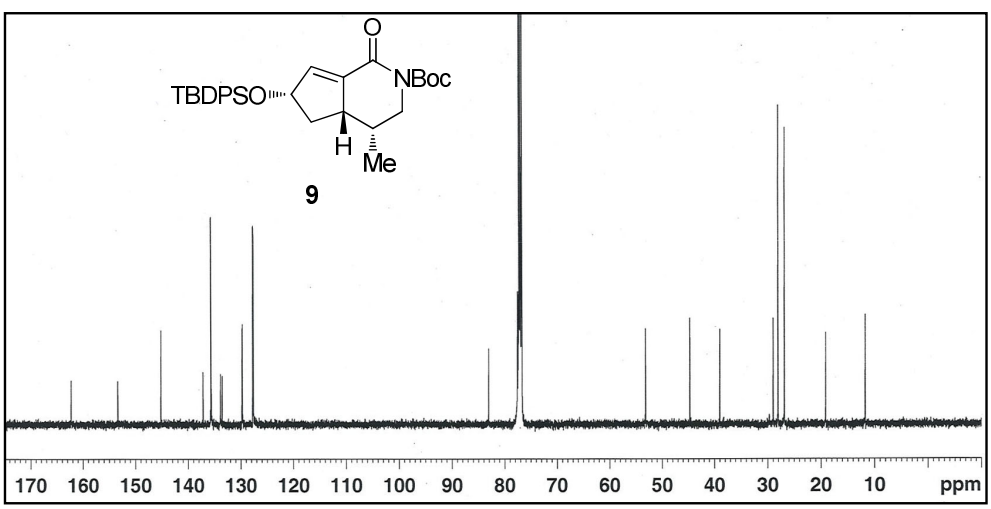

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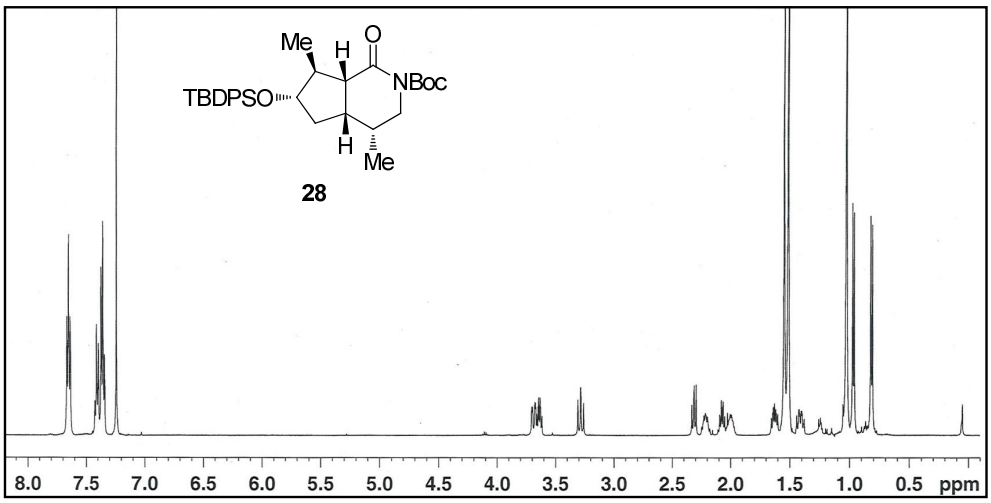

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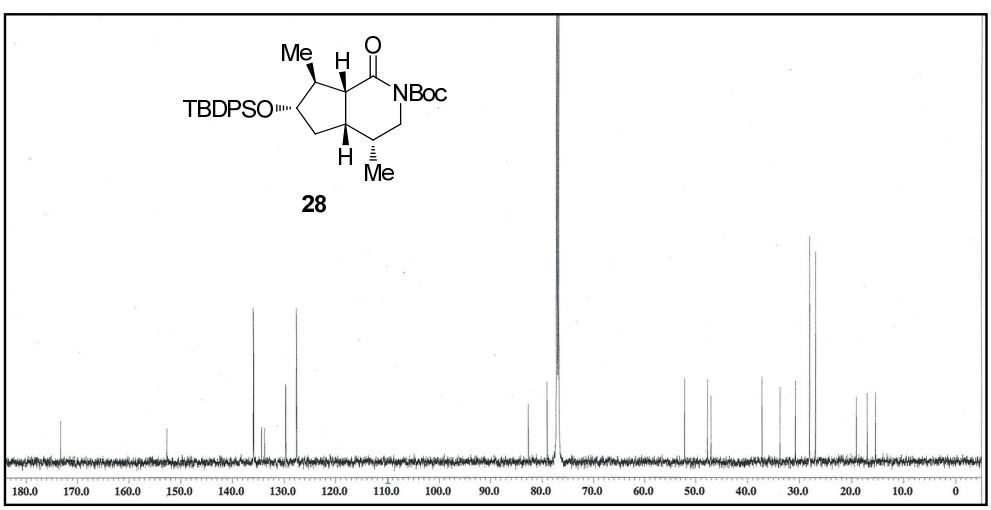

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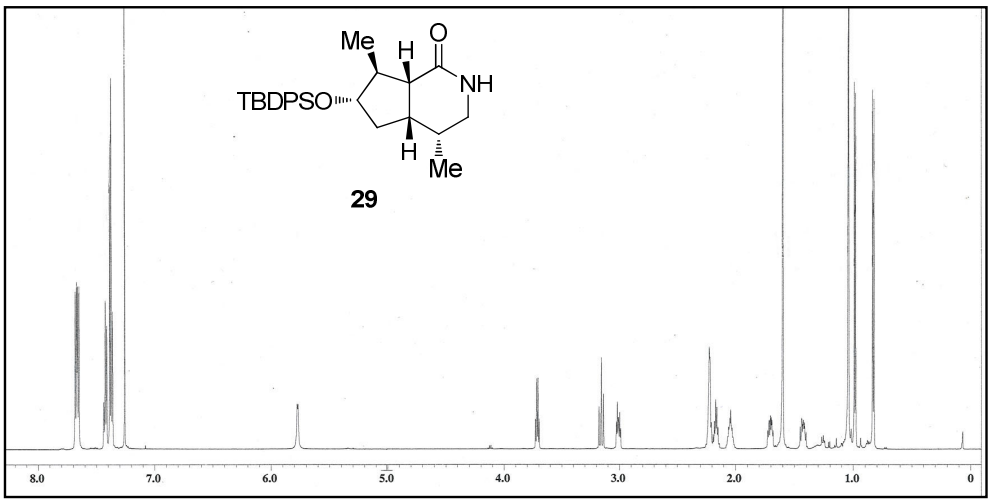

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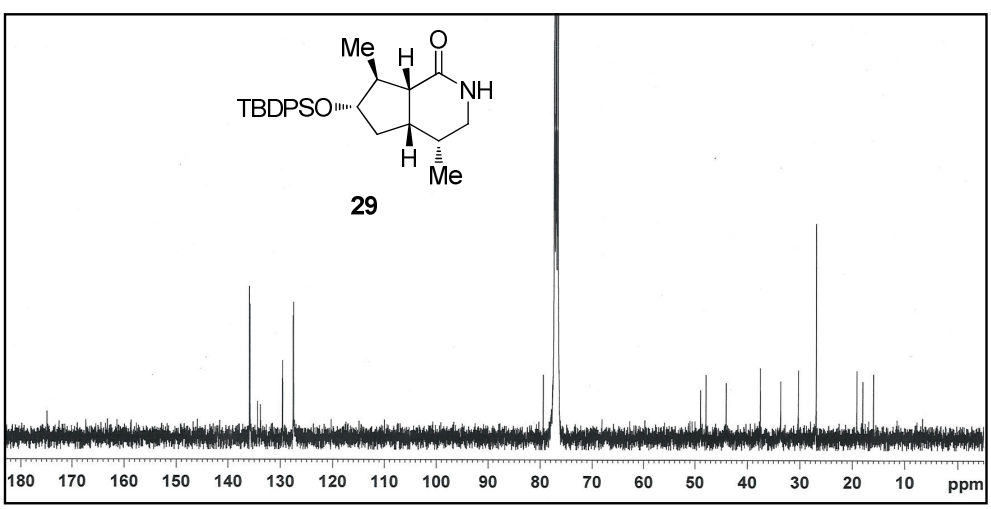
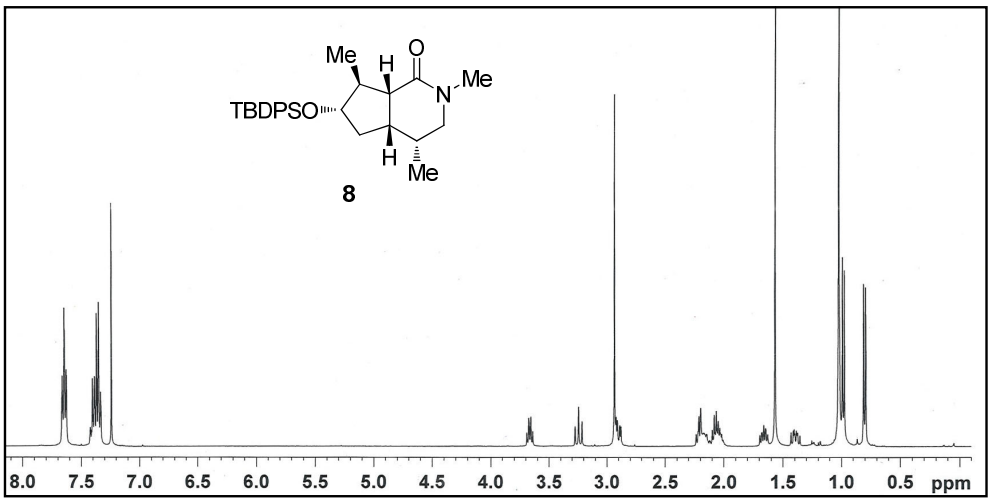
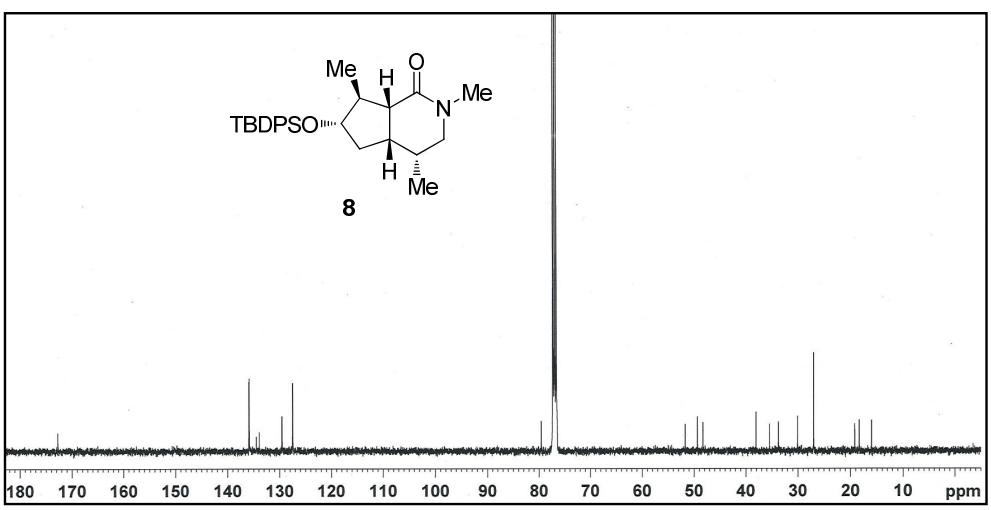


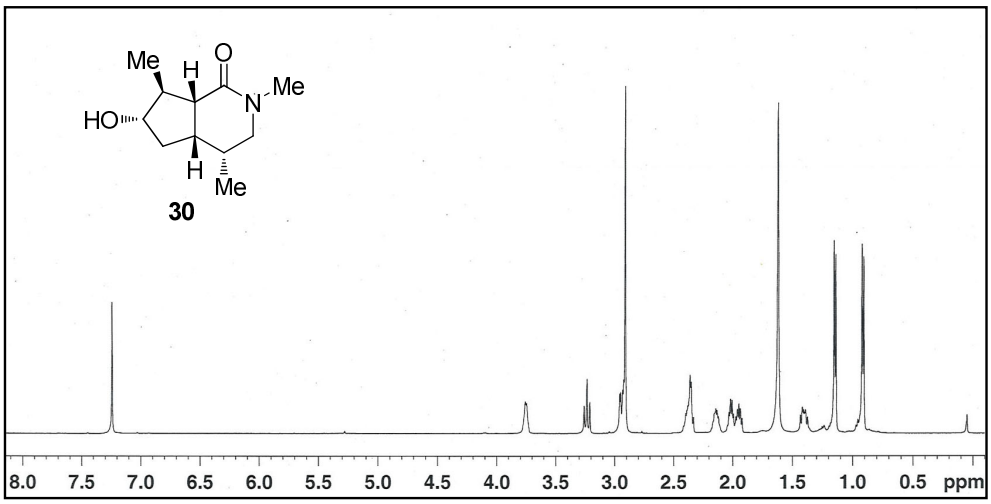
▼ ^{1}H NMR ($CDCl_3$, 400MHz)



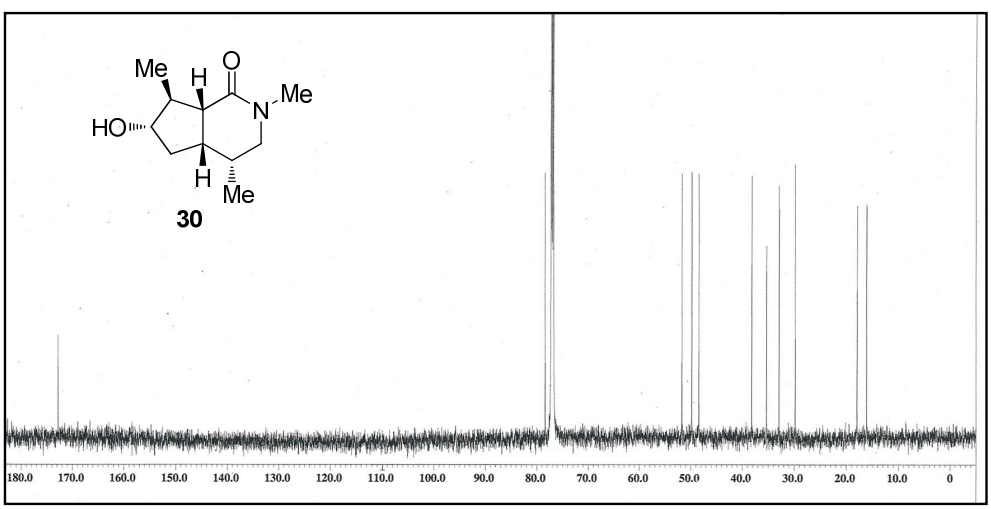
▼ ^{13}C NMR ($CDCl_3$, 100MHz)



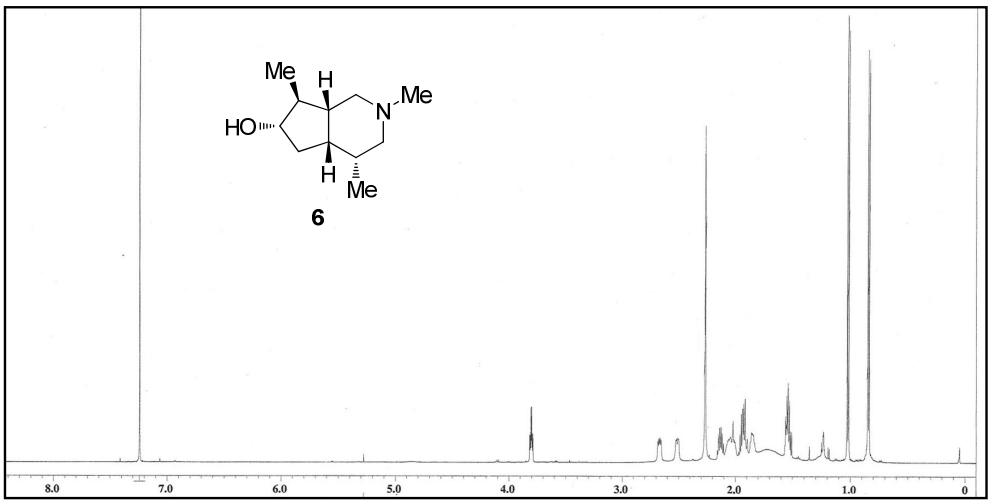
▼ ^{1}H NMR ($CDCl_3$, 500MHz)



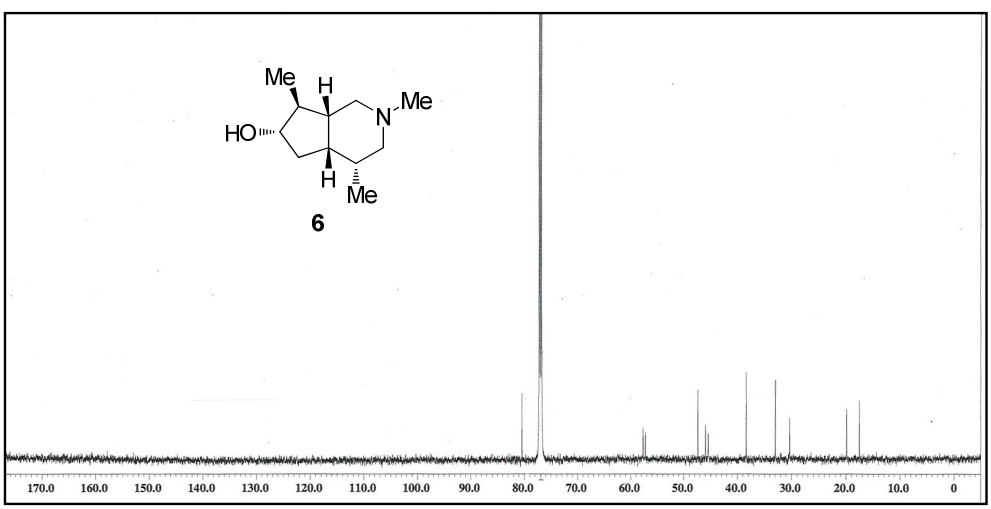
▼ ^{13}C NMR ($CDCl_3$, 150MHz)



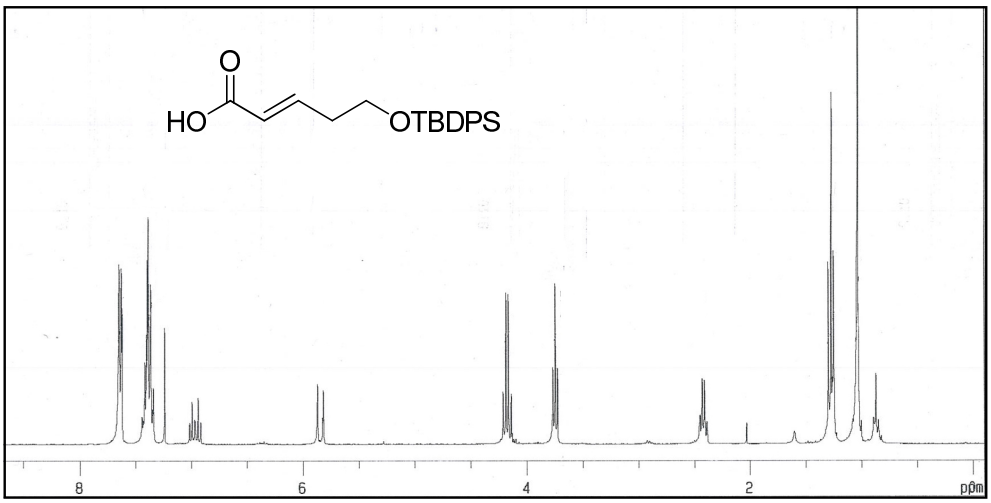
▼ ^{1}H NMR ($CDCl_3$, 600MHz)



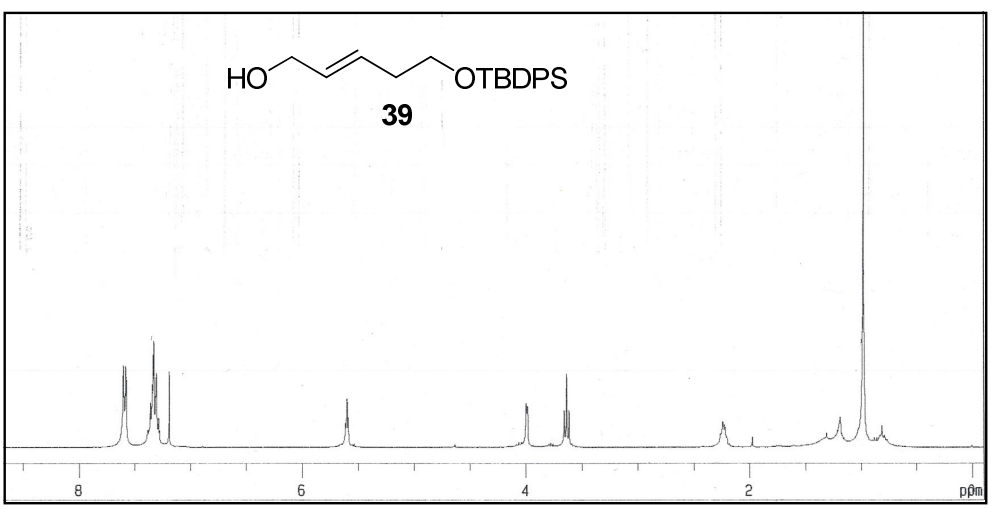
▼ ^{13}C NMR ($CDCl_3$, 150MHz)



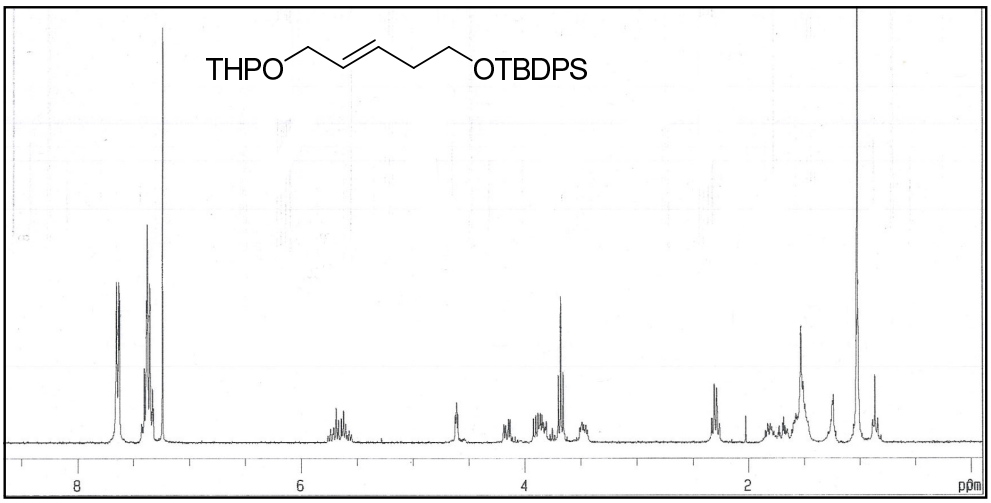
▼ ^{1}H NMR ($CDCl_3$, 300MHz)



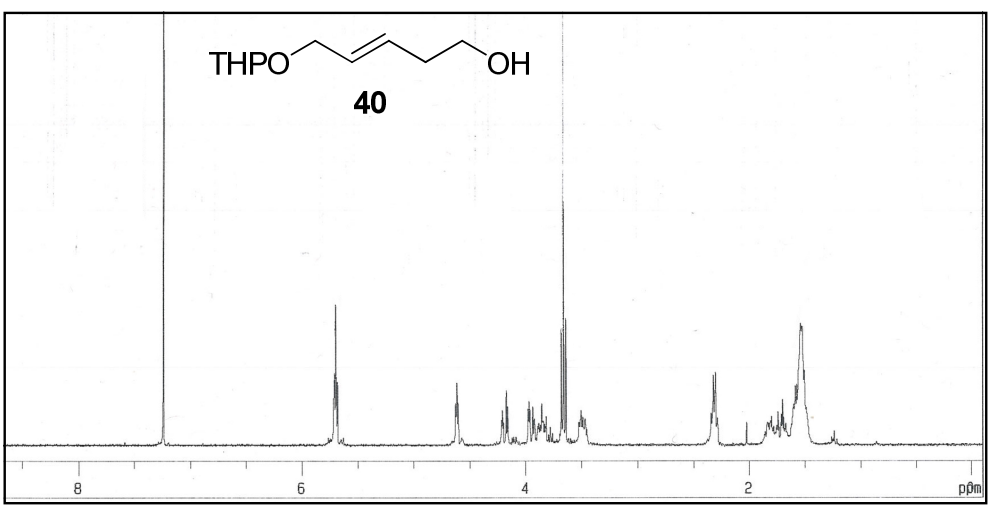
▼ ^{1}H NMR ($CDCl_3$, 300MHz)



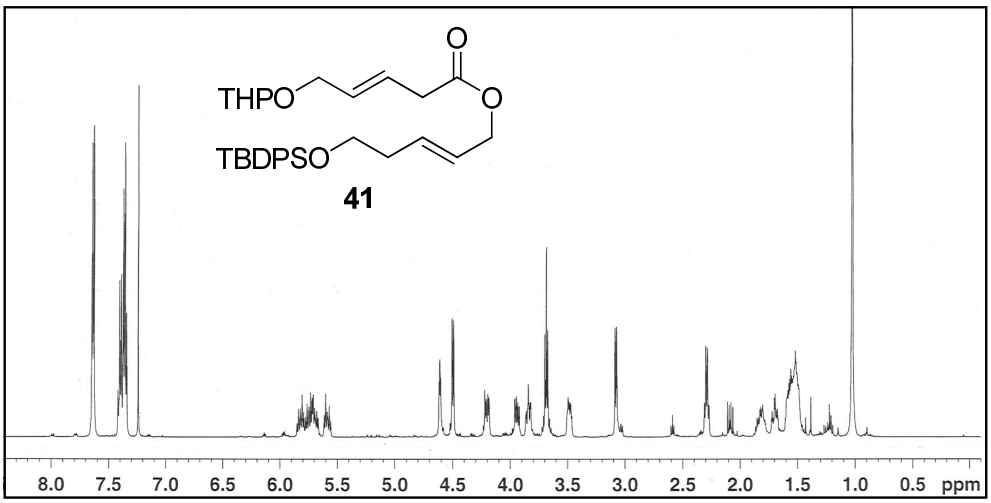
▼ ^{1}H NMR ($CDCl_3$, 300MHz)



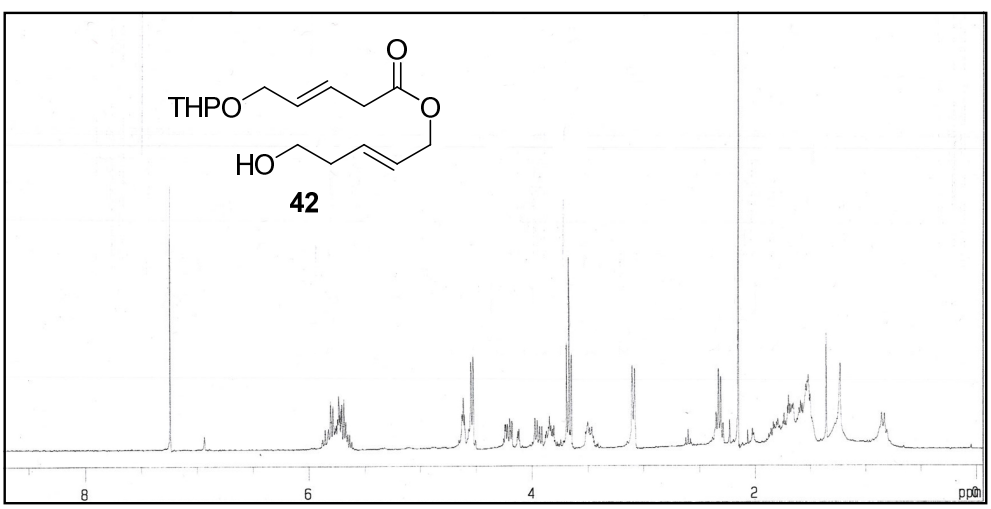
▼ ^{1}H NMR ($CDCl_3$, 300MHz)



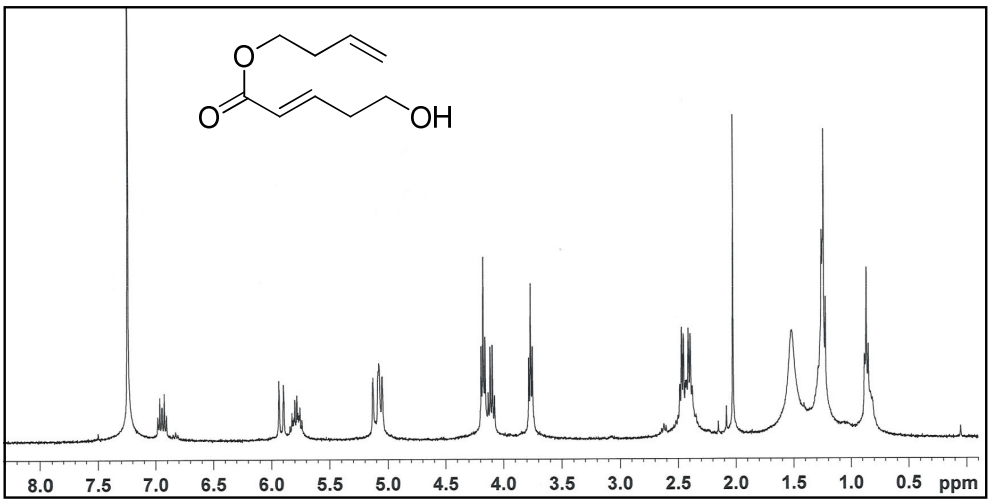
▼ ^{1}H NMR ($CDCl_3$, 500MHz)



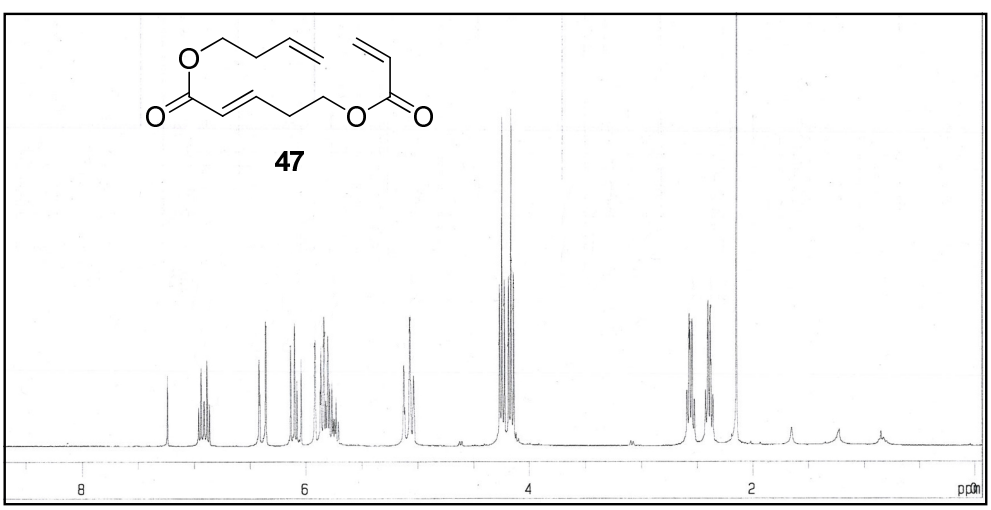
▼ ^{1}H NMR ($CDCl_3$, 300MHz)



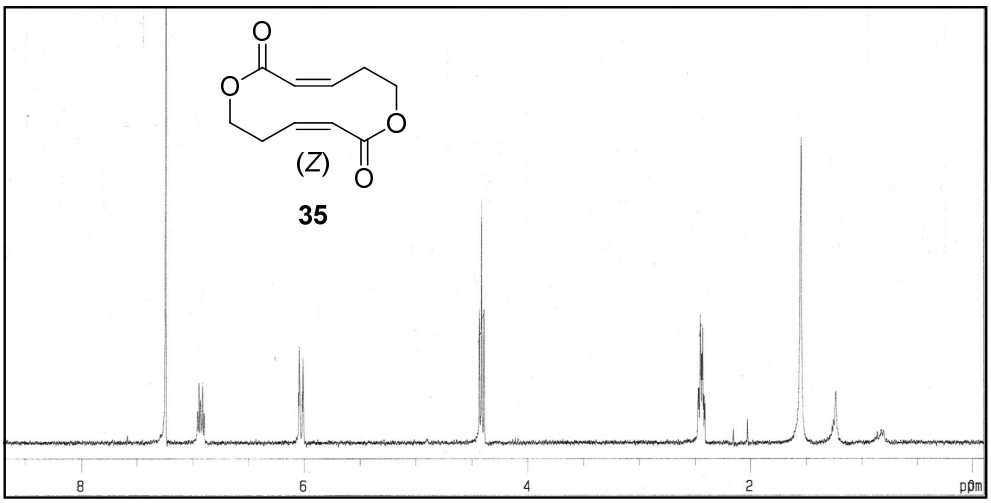
▼ ^{1}H NMR ($CDCl_3$, 400MHz)



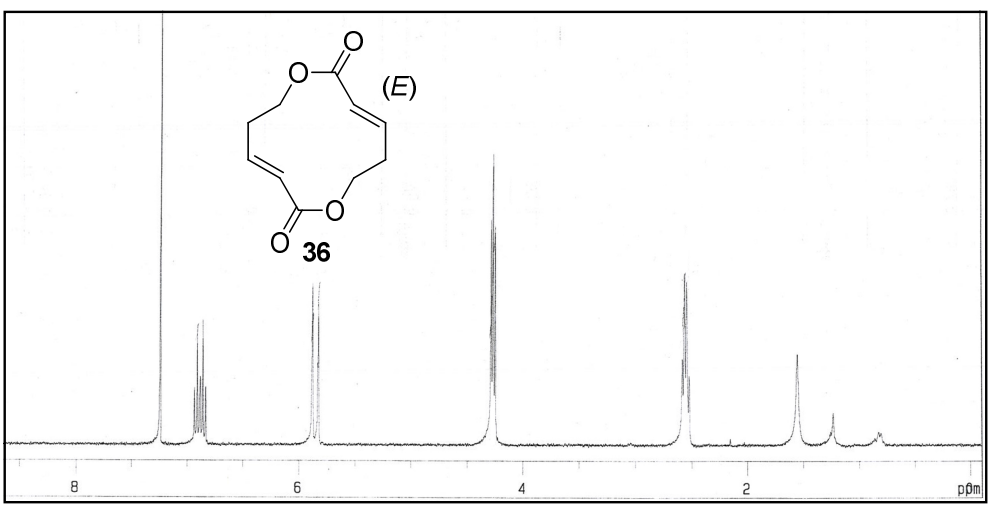
▼ ^{1}H NMR ($CDCl_3$, 300MHz)



▼ ^{1}H NMR ($CDCl_3$, 300MHz)



▼ ^{1}H NMR ($CDCl_3$, 300MHz)



Ⅶ Abstract

Studies on the Total Synthesis of (-)-Incarvilline, (+)-Incarvine C, and (-)-Incarvillateine

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In 1990, a new class of monoterpene alkaloid, (-)-incarvillateine, was isolated from the aerial part of Chinese plant *Incarvillea sinensis*. (-)-Incarvilline and (+)-incarvines A-C were isolated from the same plant. *Incarvillea sinensis* has been used as a Chinese folk medicine as "Jiaohao" for rheumatism or relieving pain. (-)-Incarvilline and (-)-incarvillateine showed strong analgesic effects. Especially, significant antinociceptive property of (-)-incarvillateine has received the attention due to its different mechanism compared to morphine. While morphine has κ, μ, δ-opiate receptor mechanism, (-)-incarvillateine is considered interacting with κ, μ -opiate receptor and adenosine receptor mechanism.

Structurally, (-)-incarvillateine is the dimer of (+)-incarvine C. It has *cis*-*anti* *cis*-cyclobutane core structure and C_2-symmetric alkaloid units and aromatic parts. Moreover, (-)-incarvilline as the alkaloid part of incarvillea alkaloids has five contiguous stereocenters within bicyclic piperidine system.

Herein, we have accomplished the substrate-controlled asymmetric synthesis of 7-*epi*-incarvilline for the formal synthesis of (-)-incarvilline, (+)-incarvine C, and (-)-incarvillateine. The key features of our synthesis include (1) diastereoselective construction of the [2.1.2] bicyclic lactone using a stereoselective Pd(0)-catalyzed cyclization, (2) isomerization of the [2.1.2] bicyclic lactone to the *cis*-fused 5,6-bicyclic lactam and (3) elaboration of two stereocenters via stereoselective catalytic hydrogenation and Michael addition.

Furthermore, we attempted to stereoselectively synthesize *cis*-*anti* *cis*-cyclobutane core structure of (-)-incarvillateine via double Ireland-Claisen rearrangement. We anticipated bis-ketene acetal precursor might afford *cis*-*anti* *cis*-cyclobutane core structure of (-)-incarvillateine through Ireland-Claisen rearrangement via double boatlike transition states.

Key words: Total synthesis, Monoterpene alkaloid, (-)-Incarvilline, (-)-Incarvillateine, Pd(0)-catalyzed allylic alkylation, Ireland-Claisen rearrangement

Student number: 2011-23732