# DISSERTATION

## Total Synthesis of Palau'amine

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# Contents

# Introduction

The pyrrole-imidazole alkaloids comprise a large family of natural products, and they have received a great deal of attention for their potent biological activities and tremendous structural diversity.[1-2] Especially among them, marine-derived natural products such as palau'amine (**1**), axinellamines (**2**), massadine (**3**), ageliferin (**4**), sceptrin (**5**), cyclooroidin (**6**), agelastatin A (**7**), and phakellin (**8**), which were known as members of oroidin (**9**) family, have received much attention from synthetic chemists because of the guanidine containing intriguing molecular architecture, high content rate of nitrogen atom (C/N~2/1), highly functionalized frameworks, contiguous stereogenic centers , and high polarity. In hot pursuit of these natural products, tremendous synthetic efforts have been undertaken over the world. Throughout these synthetic studies, effective methods for the synthesis of complex alkaloids have been remarkably developed.

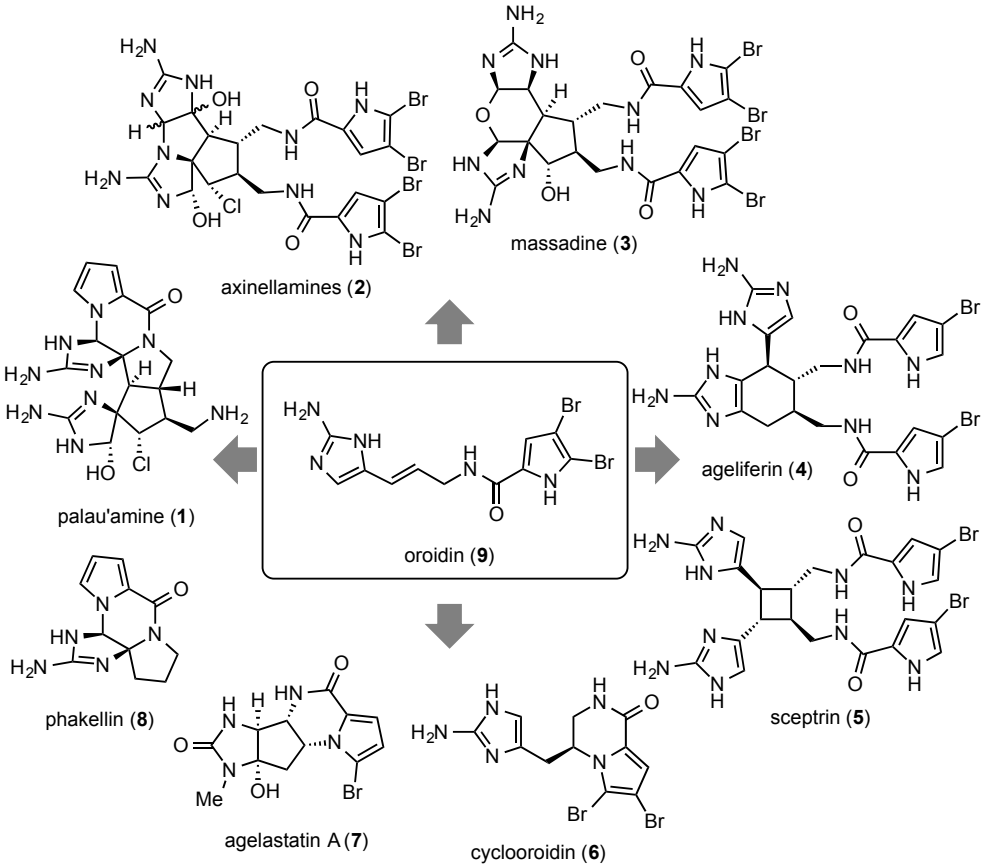



**Figure 1.** The pyrrole-imidazole alkaloids

Palau'amine (**1**) was originally isolated from a sponge, *Stylotella aurantium*, in 1993 by Scheuer and colleagues as a novel class of pyrrole-imidazole alkaloids.[3] Since the initial disclosure of palau'amine (**1**), **1** has received a great deal of attention due to the significant biological properties such as antifungal, antitumor and immunosuppressive activities. In particular, the immunosuppressive activity of **1** reported one of most potent value in class,[3b] and two studies on its mode of action have been reported.[4] Thus, the development of **1** as molecular probes is required for further elucidation of the potential of palau'amine as an immunosuppressive agent. In addition, investigation into the structure-activity relationship also might be needed for the development of novel lead compound of immunosuppressive agent. On the other hand, palau'amine congeners, 4-bromo derivative **10a**, konbu'acidines **11**, styloguanidines **12**, isophakellins **13** have not shown such a comparable activity, even though **10b** was reported as a selective compound against a human melanoma cell line (Figure 2).[3b] Only dibromophakellin **8b** inhibit the proteolytic activity of the human 20S proteasome.[4a]

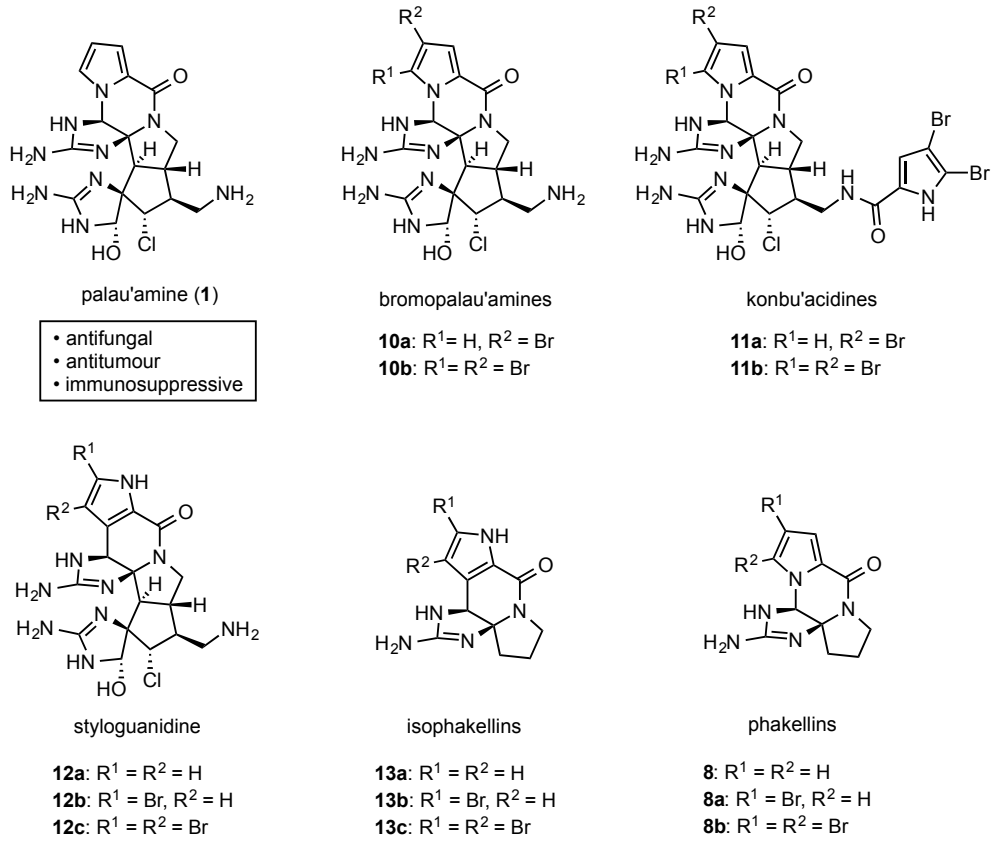



**Figure 2.** Palau'amine and its congeners

The structure of palau'amine was initially proposed as **1'** in Figure 3, indicating two guanidine moieties, eight contiguous stereogenic centres including a nitrogen-substituted quaternary carbon center, hexayclic ring system with a spiro cycle, and a fully substituted complex cyclopentane ring as a structural features. Since the challenging molecular architecture and significant biological properties, palau'amine had been an attractive synthetic target over two decades. Actually, several research groups had been a great interest and many synthetic approaches toward **1'** were reported.[5] However, the total synthesis of originally proposed structure of palau'amine (**1'**) has never thus far been accomplished.

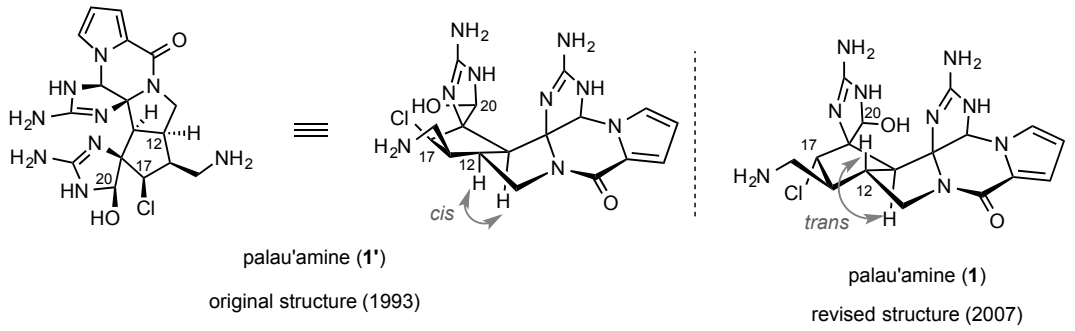


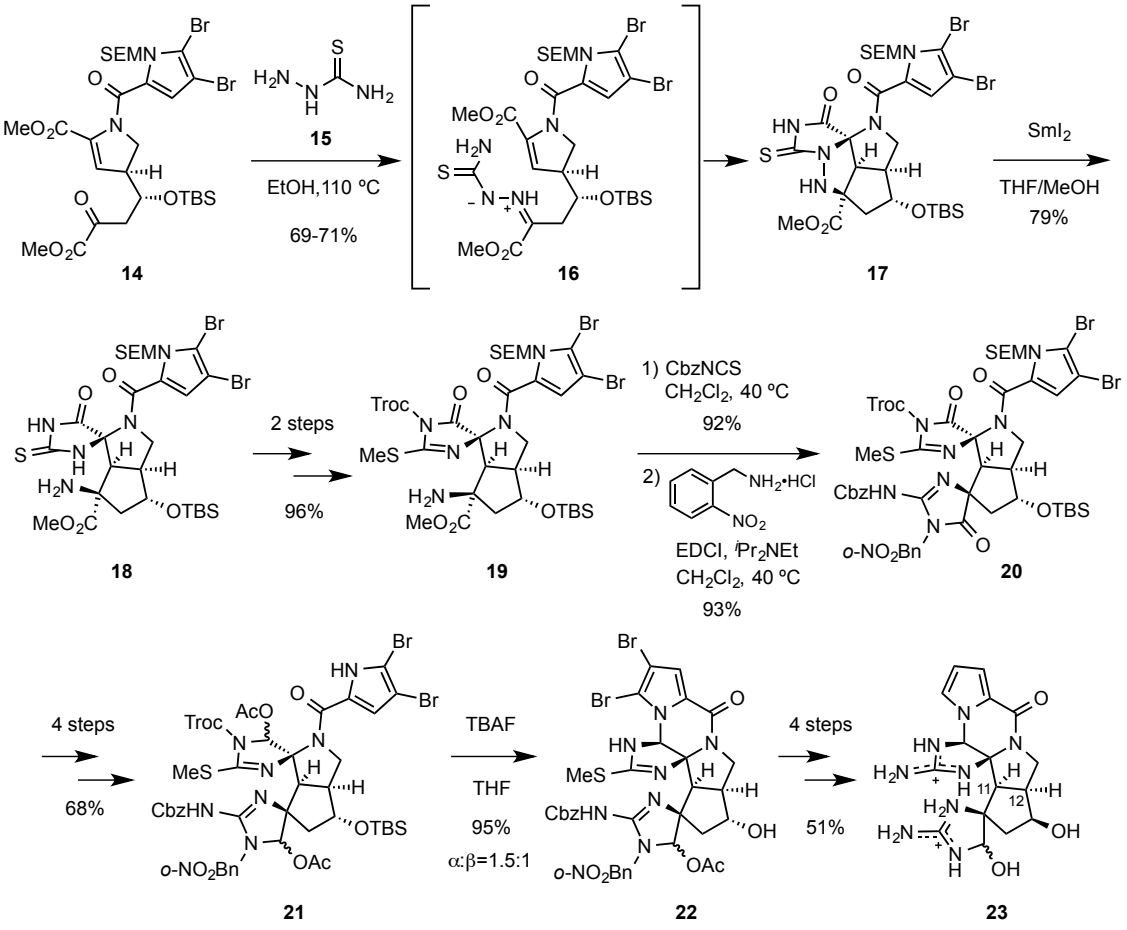

**Figure 3.** Originally proposed structure of palau'amine (**1'**)

On the other hand, according to several groups that include those of Köck[6], Quinn[7], and Matsunaga[8] in 2007, the proposed structure **1'** was revised as **1**, which instead possesses the indicated the *trans*-ring junction at C12, the β-chlorine substituent at C17 and the β-hemiaminal at C20 position. After the revision, palau'amine kept more attentions because of the unprecedented *trans*-bicyclo[3.3.0]octane core. Not surprisingly, many attempts to synthesize revised palau'amine[9] and related natural products[10] have been reported, and numerous reviews of these different approaches[11] have also been published. A part of these studies is introduced in the next section.

## Synthetic studies for originally proposed structure of palau'amne having *cis*-azabicyclo[3.3.0]octane skeleton

Overman and colleagues efficiently achieved the first synthesis of hexacyclic congeners having the originally proposed *cis*-azabicyclo[3.3.0]octane skeleton in 2007 (Scheme 1).[5k] The noteworthy feature of their synthesis is streocontrolled construction of tetracyclic ring core by means of intramolecular 1,3-dipolar cycloaddition reaction of azomethine imines. The reaction of dihydropyrrole **14** with thiohydrazide **15** was accomplished in EtOH at 110 ºC, in which resulting

azomethine imine **16** immediately induced an 1,3-dipolar cycloadditon reaction followed by subsequent condensation reaction of thioamide with ester to afford hexacyclic compound **17**. The N-N bond of **17** was reductively cleaved by the use of $SmI_2$ and sequential two steps gave amine **19**. The introduction of guanidine moiety was accomplished by two steps sequence, consisting of a conversion of **19** into Cbz-protected isothiourea and a condensation reaction using EDCI with *o*-nitrobenzylamine, to afforded spirocyclic **20** in high yield. After the conversion of **20** into acetyl protected hemiaminal **21** in four steps, cyclization reaction was performed through the basic condition using TBAF to give ketopiperadine **22** in excellent yield as an inseparable epimeric mixture of hemiaminal. Finally, synthesis of hexacyclic congener **23**, which had the cis configuration of the azabicyclo[3.3.0]octane skeltone, was achieved in four steps involving convertion of isothiourea to guanidine and deprotections. The $^1$H-NMR spectra of each epimer of **23** revealed that the coupling constant of the ring junction (H11/H12) were particularly different ($J$ = 12.0 and 10.7 Hz, respectively) from that of the natural palau'amine ($J$ = 14.3 Hz), suggesting that the structural revisin as *trans*-azabicyclo[3.30]octane ring system is correct (Table 1).

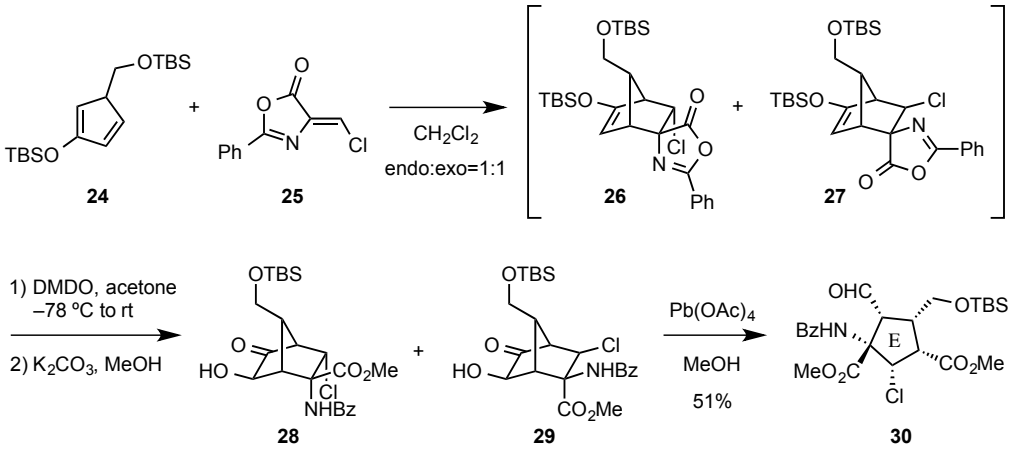



**Scheme 1.** Synthesis of originally proposed palau'amine derivatives **23** by Overman's group

| | Natural (Scheuer)[3] | | **23** (Overman)[5k] | |
|---|---|---|---|---|
| Position | 1H | 13C | 1H | 13C |
| 11 | 3.08 (d, 14.1) | 56.3 | 3.82 (d, 12.0) (α) | 53.1 (α) |
| | | | 3.35 (d, 10.7) (β) | 59.9 (β) |
| 12 | 2.52 (dddd) | 41.8 | 3.07 (dddd, 12.0, 10.1, 6.1, 4.1) (α) | 45.3 (α) |
| | | | 3.15 (dddd, 10.7, 9.9, 5.1, 4.6) (β) | 44.2 (β) |

**Table 1.** Selected $^{1}$H- and $^{13}$C-NMR data for palau'amine, **23(α)** and **23(β)** in $D_2O$

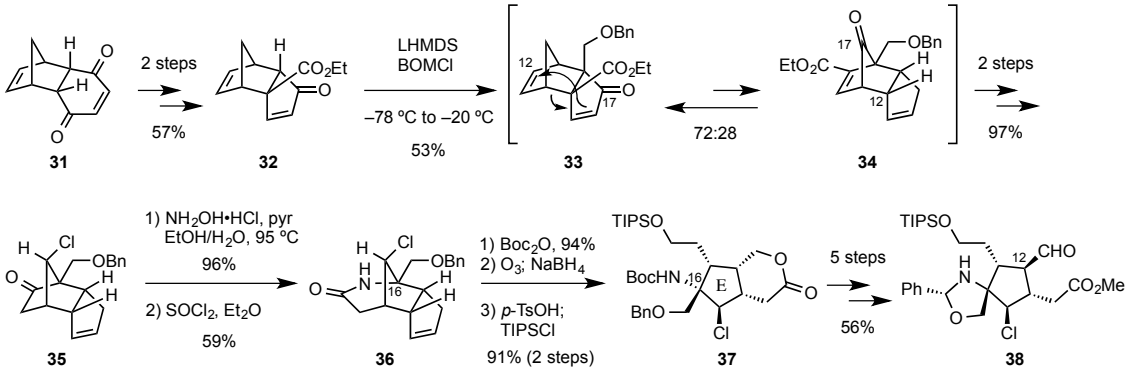
In 2008, Gleason and colleagues reported the synthesis of fully functionalized cyclopentane core with all-*cis* configuration that corresponds to E-ring system of originally proposed palau'amine **1'** (Scheme 2).[5m-n] In their synthesis, the Diels-Alder reaction was adopted to construct the cyclopentane core. The [4+2] cycloaddition reaction of diene **24** with chloromethyleneoxazolone **25** proceeded smoothly to afford cycloadducts **26** and **27**, having the nitrogen-substituted quaternary carbon center, as a 1:1 stereoisomeric mixture. Since the mixture was unstable to column chromatography, they were directly treated with DMDO as a condition of the Rubottom oxidation, and subsequent methanolysis of the oxazolone group gave a mixture of **28** and **29**. Finally, the synthesis of E-ring with all-*cis* configuration (**30**) was achieved by oxidative cleavage of α-hydroxy ketone of the separated **28**.




**Scheme 2.** Construction of E-ring having all-*cis* configuration by Gleason's group

**Synthetic studies for revised structure of palau'amne having *trans*-azabicyclo[3.3.0]octane skeleton**

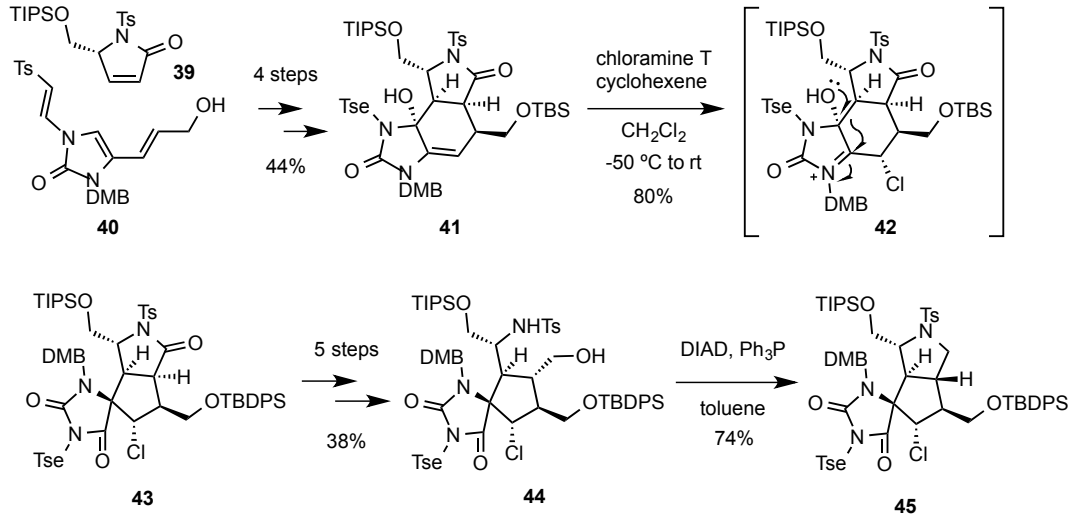
Gin's group reported a flexible approach to the proposed and revised structure of palau'amine employing [3,3]-sigmatropic rearrangement and Beckman rearrangement (Scheme 3).[51] Dihydroxyquinone **31**, which was prepared by the Diels-Alder reaction of cyclopentadiene with benzoquinone, was converted into cyclopentanone **32**. Treatment of **32** with LHMDS and BOMCl afforded benzyloxymethyl ketone **33** which directly underwent a desired [3,3]-sigmatropic rearrangement to provide a 72:28 equilibrium mixture between the ketone **33** and enoate **34** in favor of **33**. After the transformation of functional groups, the Beckman rearrangement of **35** was carried out via oxime formation and subsequent activation using $SOCl_2$ to afford **36** possessing a nitrogen-substituted quaternary carbon center that corresponds to C16 position in modest yield. **36** was converted to cyclopentane **37** by sequential reactions of an introduction of Boc group, ozonolysis followed by $NaBH_4$ reduction, and a protection of resulting primary alcohol. The stereoselective access to all-*trans* E-ring was achieved via epimerization at C12 position to furnished aldehyde **38**. In addition, all-*cis* E-ring could be also obtained from **33**.




**Scheme 3.** Construction of E ring by Gin's group

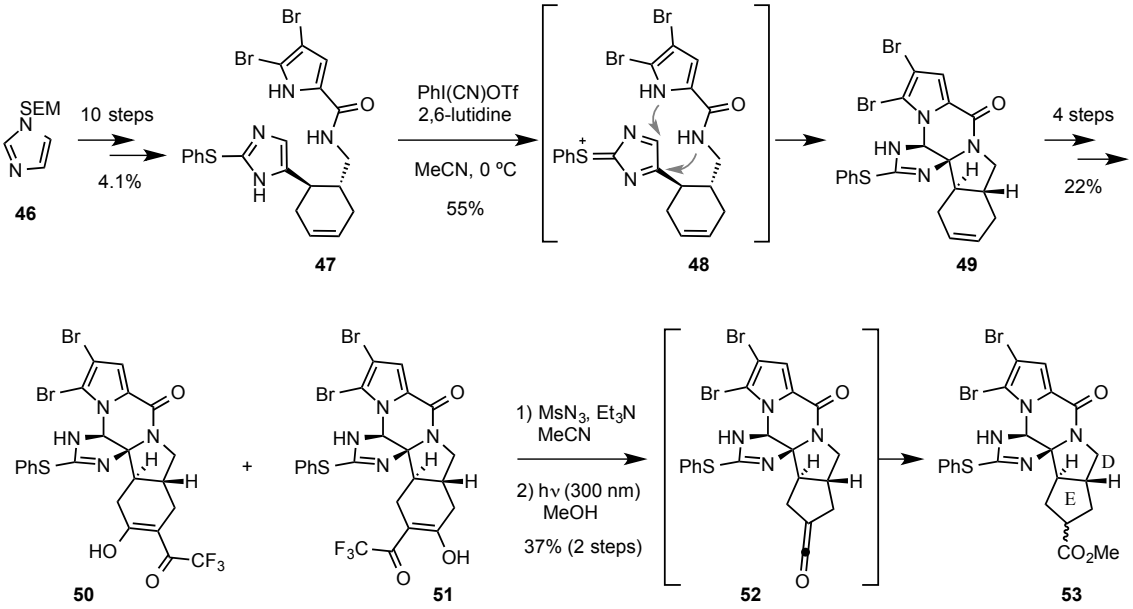
Romo and colleagues successfully synthesized the *trans*-azabibyclo[3.3.0]octane derivative via Mitsunobu reaction in 2008 (Scheme 4).[9a] The Diels–Alder reaction between enone **39** and diene **40** set *cis* configuration exclusively and transformation of functional groups gave cycloadduct **41** in four steps. Treatment of cyclohexene **42** with chloramine T readily took place chlorination of the olefine, in which the resulting iminium **42** immediately induced a semi-pinacol rearrangement to give spirocyclic compound **43** in good yield. After methanolysis of lactam, subsequent epimelization and reduction of resulting ester afforded primary alcohol **44** which was subjected to the Mitsunobu

reaction using DIAD and $Ph_3P$ leading to *trans*-azabibyclo[3.3.0]octane skeltone **45**. The stereochemical outcome of **45** was confirmed by an nOe spectroscopy experiment, and this is the first example of direct construction of the peculiar *trans*-5,5 core of palau'amine.



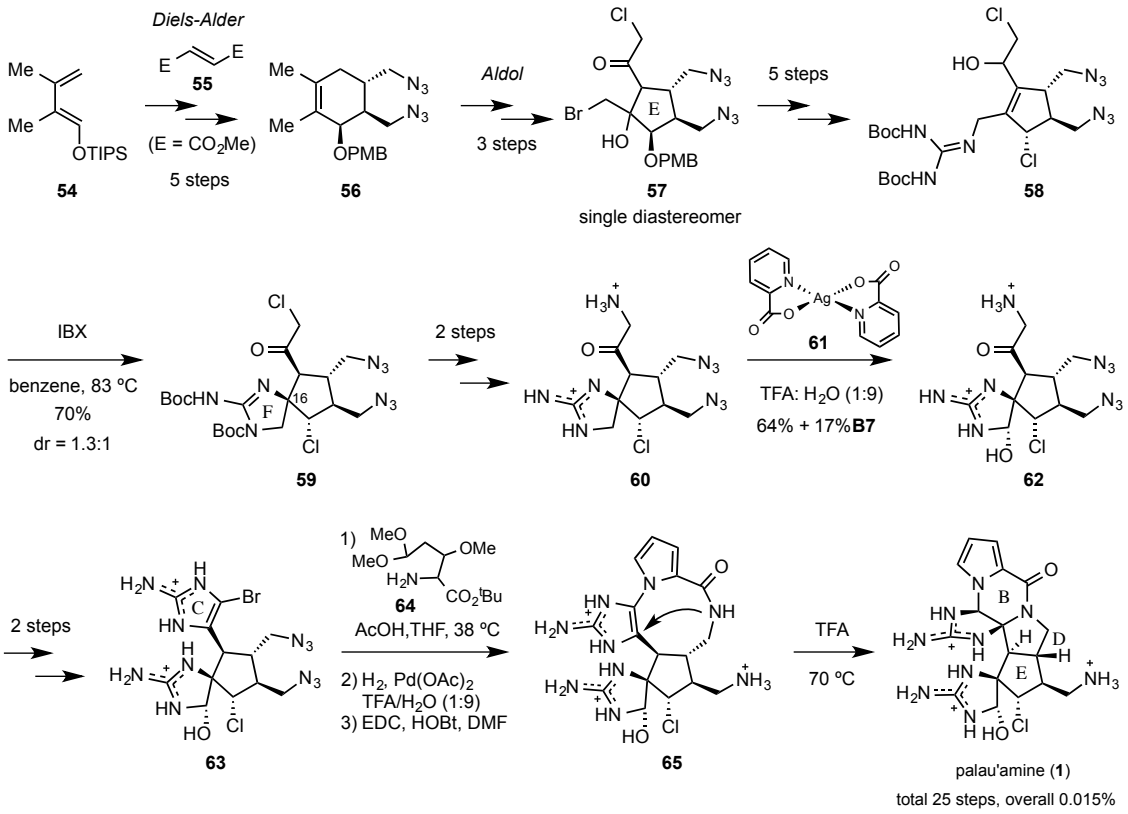

**Scheme 4.** Construction of *trans*-azabicyclo[3.3.0]octane skeleton by Romo's group

Feldman and colleagues reported another strategy for the construction of *trans*-azabibyclo[3.3.0]octane skeleton via the Wolf rearrangement reaction (Scheme 5).[9e] Starting with SEM protected imidazole **46**, isothiiourea **47** was prepared in 10 steps. Treatment of **47** with standard Stang reagent[12] conditions afforded sulfonium **48** and a subsequent double cyclization reaction involving attacking of amido and pyrrole to imines respectively gave raise to *trans*-6/5 ring system **49**. After conversion to **50** via a hydration reaction of the olefin, oxidation of resulting alcohol and introduction of trifluoroacethyl group, two structural isomers **50** and **51** were obtained. Treatment of the mixture of **50** and **51** with the diazotransfer reagent $MsN_3$ afforded α-diazoketone, and subsequent irradiation of light in MeOH gave methylester **53**, via ketene intermediate **52**, as a 1:1 diastereomeric mixture. The ring system of **53** corresponds to the pentacyclic framework of the palau'amine having *trans*-azabicyclo[3.3.0]octane skeltone (D/E ring junction).



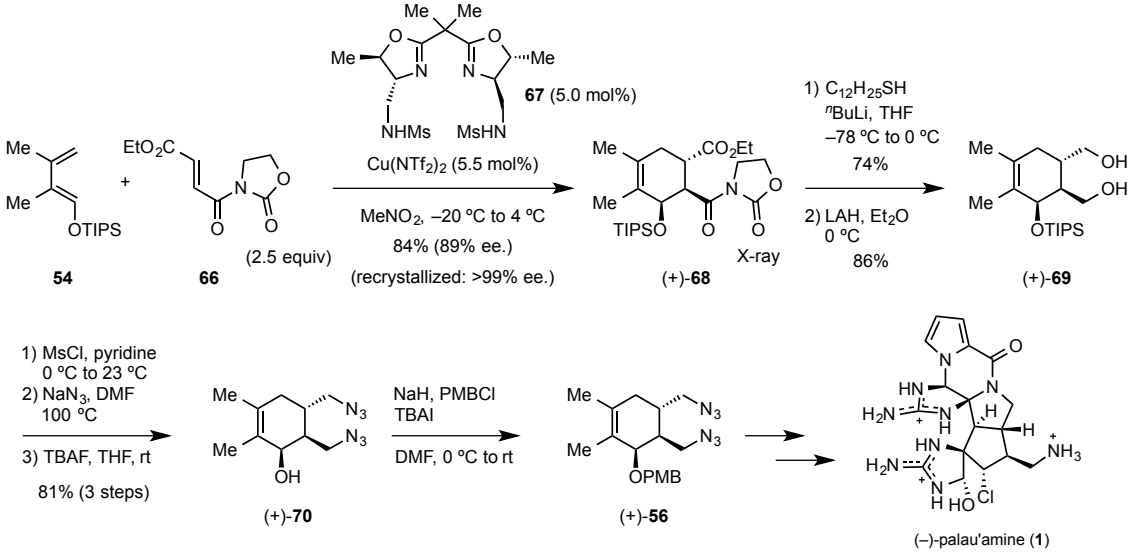

**Scheme 5.** Construction of *trans*-azabicyclo[3.3.0]octane skeleton by Feldman's group

Baran and colleagues achieved first total synthesis of palau'amine in 2010 (Scheme 6).[13] The Diels-Alder reaction of diene **54** with dimethyl fumarate **55** set three of key stereochemical relationships and subsequent transformation of functional groups afforded six membered-ring **56**. The ring contraction reaction was took place via a cleavage of olefin and an aldol reaction to give pentacyclic compound **57** corresponding E-ring system. After introduction of secondary chloride with stereoinversion and Boc-protected guanidino group, the desired spirocyclization reaction was then achieved via oxidation of the secondary hydroxyl group, in which the resulting enone immediately induced the Michael addition reaction, leading to spirocyclic EF ring system **59** as a ratio of 1.3:1 diastereomeric mixture. Following introduction of primary amino group and removal of Boc group, a chemoselective oxidation reaction of **60** was took place using silver picolinate **61**[10b-d], novel C-H oxidation of the guanidine moiety at the α-position. Guanidinylation of primary amine **62** followed by bromination using $Br_2$ afforded **63** that possessed C-ring system with the bromide. Introduction of the pyrrole moiety was accomplished by a coupling of pyrrole surrogate **64** with the bromoimidazole ring (C-ring) of **63**, and a subsequent hydrogenation and condensation reaction gave rise to macro-palau'amine **65**. Then, they achieved the total synthesis of palau'amine (25 from commercially available material, 0.015% overall yield) via a final transannular cyclization reaction, which took place under acidic conditions using heat.




**Scheme 6.** Total synthesis of palau'amine by Baran's group

Furthermore, in 2011, Baran's group achieved an enantioselective total synthesis of palau'amine by expanding the initial Diels-Alder reaction to catalytic asymmetric version (Scheme 7).[14] At the first step of the synthesis, catalytic asymmetric [4+2] cycloaddition reaction of diene **54** with dienophile **66** was successfully proceeded by treatment with copper(II) trifluoromethanesulfonimide and the Ishihara's catalyst **67**[15] , and the enantiomerically pure **68** (>99% *ee*) was obtained after recrystallization. This method was applicable to the gram-scale reaction. Since one-step reduction of **68** was found to be difficult, **68** was converted into thioester and subsequent LAH reduction afforded diol **69**. The introduction of azide groups was accomplished by two steps sequence, mesylation-azidation procedure, and subsequent removal of TIPS group gave secondary alcohol **70**. A PMB protection of hydroxyl group of **70** furnished optically pure **56**. The asymmetric total synthesis of palau'amine was completed from (+)-**56** by following previous racemic route shown in Scheme 6. The optical rotation and circular dichroism spectra of synthetic palau'amine were identical with the isolation data reported by Quinn[7b], indicating that the correct enantiomer corresponding to the natural product was obtained.

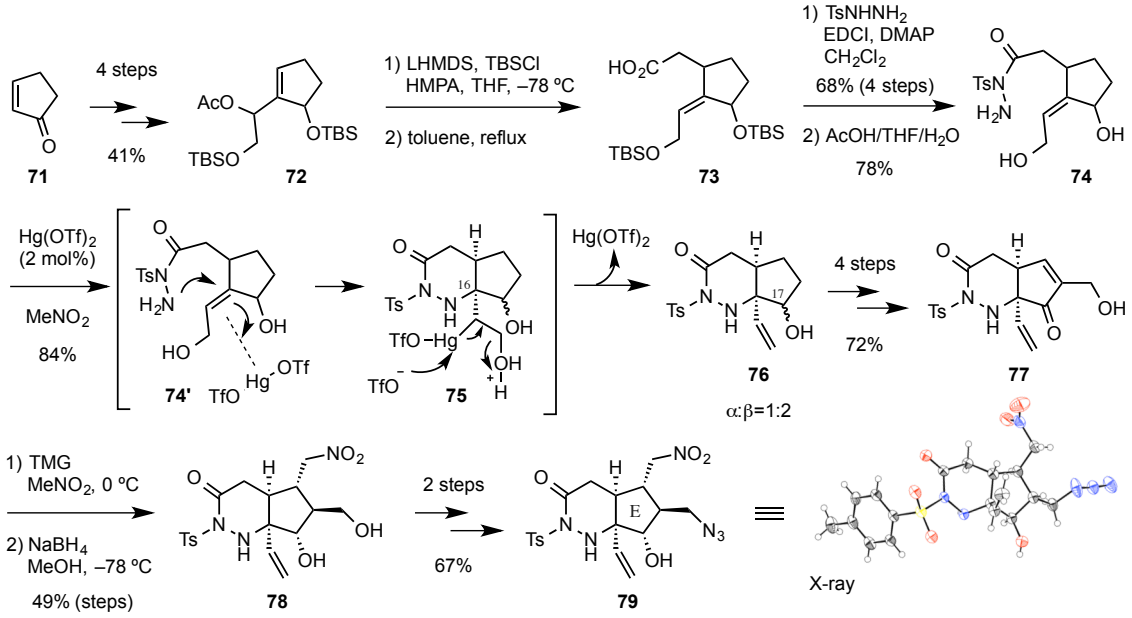



**Scheme 7.** Enantioselective total synthesis of (–)-palau'amine by Baran's group

Although they established short and elegant synthetic route to **1**, the total synthesis of palau'amine is still a challenging undertaking.[14] In particular, there is need of an efficient method for constructing an ABDE tetracyclic ring system that includes a *trans*-bicyclo[3.3.0]octane skeleton as the basic structure of **1**. Although the development of such a system will be extremely difficult, it is also absolutely critical for not only the field of synthetic organic chemistry but also the elucidation of pharmacophores and the development of palau'amine probes.

On the other hand, our group reported an efficient synthesis of the cyclopentane core **79** in 2009 (Scheme 8).[16] The synthesis of **79** began with commercially available cyclopentenone **71**, which was converted into acetate **72** by a sequential reaction of the Morita-Baylis-Hillaman reaction, acetylation, Luche reduction, and TBS protection. After the treatment of **72** with LHMDS, TBSCl and HMPA, refuxing in toluene induced the desired Ireland-Claisen rearrangement to afford carboxylic acid **73**. Next, our group attempted to prepare an acyl tosylhydrazide by the coupling of **73** with *N*-tosylhydrazide by the combined action of EDCI and DMAP in dichloromethane.[17] Surprisingly, the nitrogen atom masked with a tosyl group participated in the condensation to give a 1:2 diastereomeric mixture of coupling product in 68% overall yield after four steps from **72**. The TBS groups were then cleaved under mild acidic conditions to give diol **74**. Treatment of **74** with 2 mol% of Hg $(OTf)_2$[18] in nitromethane at room temperature smoothly initiated an amino–mercuration

reaction to afford an intermediate **75**, which had the nitrogen-substituted quaternary carbon center corresponding to the C16 position. Subsequent protonation-demurcuration then provided the desired cyclization adduct **76** in 84% yield as a separable 1:2 diastereomeric mixture. Stereochemical outcome at the ring junction was completely controlled to be *cis* regardless of the stereochemistry of the secondary alcohol at C17. Oxidation to enone and introduction of a hydroxymethyl group afforded alcohol **77**. Subsequent the Michael addition of nitromethane followed by a reduction of the ketone provided nitrodiol **78**. Since the addition of nitromethane occurred at the convex face and the hydroxymethyl group subsequently avoided steric repulsion with the resulting nitromethyl group, the stereochemical outcome of E-ring intermediate **78** was controlled to the desired configuration. The stereochemistry of **78** was further confirmed by X-ray crystallography after conversion to azide **79**.




**Scheme 8.** $Hg(OTf)_2$-catalyzed synthesis of the cyclopentane core

In this dissertation, the author describes a development of the novel cascade reaction for the construction of the ABDE tetracyclic ring core of palau'amine and a speculation of the reaction mechanism by using a DFT calculation in Chapter 1 (Figure 4). In Chapter 2, the completion of the total synthesis of palau'amine and a biological assay are described.

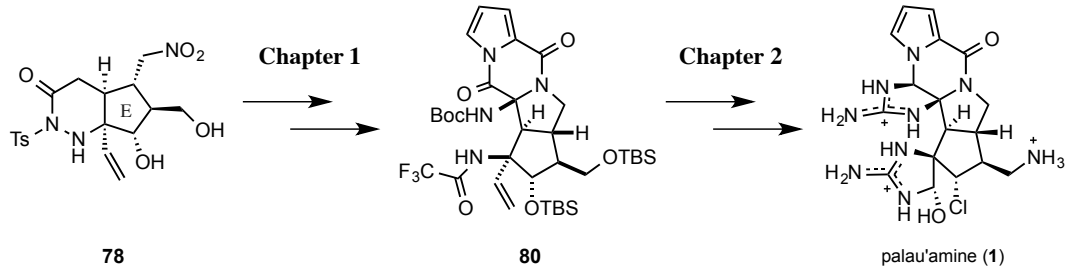



**Figure 4.** Outline of this dissertation

# Chapter 1

## Single Step Construction of the ABDE Tetracyclic Ring Core by a Cascade Reaction

The synthetic plan of **1** from E-ring intermediate **78** toward the ABDE tetracyclic ring system was shown in Figure 5. In this synthesis, palau'amine would be obtained by the transformation of functional groups after the construction of a hexacyclic ring core **81**. The two cyclic guanidines corresponding to the C- and F-rings of **81** would be built on amino and carbonyl groups of ABDE tetracyclic ring core **82**. The B- and D-rings of **82** would be formed by a sequential cyclization reaction of amide and pyrrole nitrogen with the imine and methyl esters of **83** respectively. As the acylimine moiety of **83** is highly electron deficient, the nucleophilic addition of amide anion to the C10 carbon center would occur to form a D-ring over the steric strain of the *trans*-bicyclo[3.3.0]octane skeleton (D/E ring junction). The iminoester moiety of **83** would be generated from hydrazide **84** by an N–N bond cleavage and a formation of imine at the C10 position. The author planned to adopt an E1cB eliminative cleavage of the N–N bond of **84** to obtain iminoester **83** directly, although, unlike in the case of reductive cleavage, there have been very few examples of E1cB eliminative cleavage of N–N bond[19]. The direct formation of **83** under basic conditions was expected to induce further cascade cyclization reactions leading to **82**, that is the ABDE tetracyclic core ring core **83** might be obtained from **84** in a single step. The pyrazolidine ring of **84** would be obtained from previously synthesized **78** by the introduction of an electron-withdrawing group and ring contraction via an intramolecular $S_N2$ reaction.

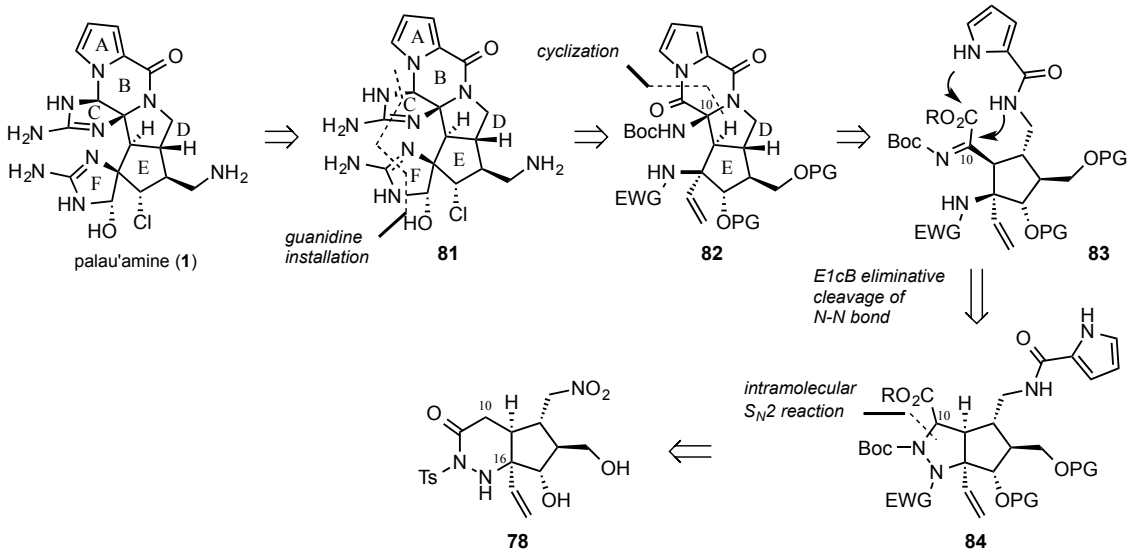
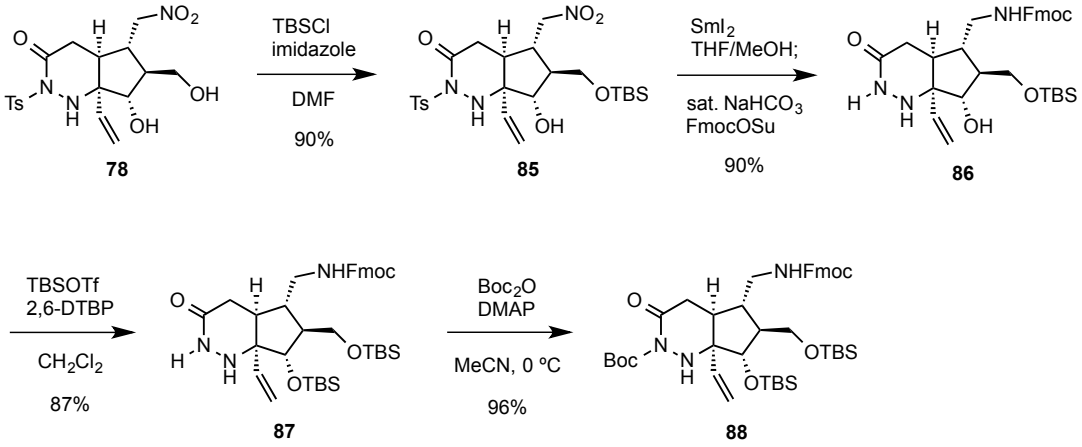



**Figure 5.** Retrosynthetic analysis of palau'amine

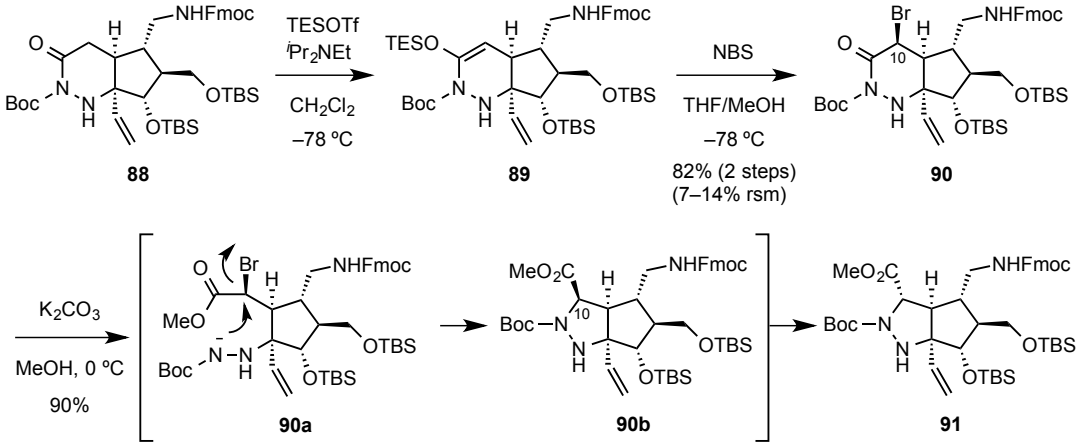
**Synthesis of the E1cB eliminative cleavage precursor.**

Firstly, the author attempted to synthesize the precursor **84** (Scheme 9). After introduction of the TBS group into the primary alcohol of **78** to increase hydrophobicity, the tosyl group was reductively removed and the nitro group was reduced to the amino group by treatment with $SmI_2$. The resulting primary amine was protected by Fmoc group to afford **86**. Further protections of secondary alcohol and acylhydrazide proceeded smoothly to give **88** by treatment with TBSOTf as a silylation reagent followed by $Boc_2O$ in the presence of a catalytic amount of DMAP. As the author expected, Boc protection occurred on the nitrogen possessing the acyl group due to the acidity of NH protons and steric hindrance.



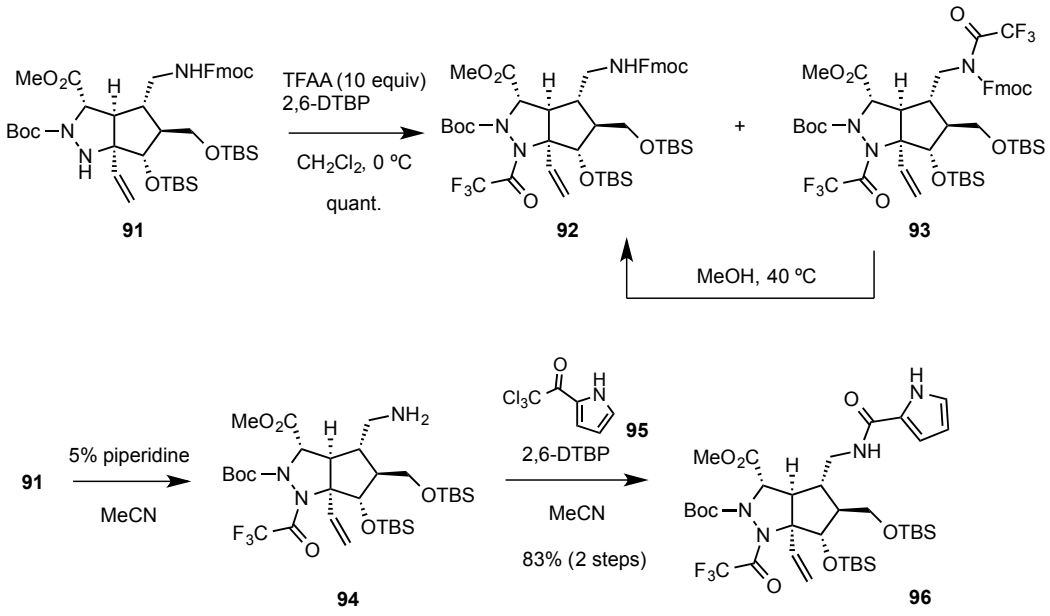

**Scheme 9.** Synthesis of the protected 6/5 ring system **88**

Treatment of **88** with TESOTf and $^{i}Pr_2NEt$ at –78 ºC readily afforded silyl ketene aminal **89**, and the crude product was treated with NBS in a mixed solvent of THF and MeOH to give bromide **90** in an 82% two-step yield along with 7–14% of starting material **88** (Scheme 10). The use of $Et_3N$ instead of $^{i}Pr_2NEt$ showed a decline in yield of the **89** due to the removal of Fmoc group. The stereochemical outcome of **90** was determined by a nuclear Overhauser effect spectroscopy experiment, which indicated the β-configuration of bromide. It is likely to be that the attack of bromide on the concave face was derived from the steric hindrance of the vinyl group. Subsequent methanolysis of **90** afforded an amide anion **90a** that immediately induced an intramolecular $S_N2$ reaction, leading to **90b**. At this stage, **90b** was considered to readily epimerize to **91**, to avoid the steric repulsion of a tighter concave face. The stereochemistry of **91** was determined by a nuclear Overhauser effect spectroscopy experiment.




**Scheme 10.** Synthesis of ring contracted compound **91**

Next, the author attempted to introduce a strong electron-withdrawing group to nitrogen on a tetra-substituted carbon center (Scheme 11). After various examinations, the author found that only a trifluoroacetyl group could be introduced to afford **92** by treatment with an excess amount of trifluoroacetic anhydride. Although overacetylated product **93** was also obtained, the extra trifluoroacetyl group on the carbamate was automatically removed in methanol at 40 °C in a quantitative yield. Finally, removal of the Fmoc group and condensation of the resulting primary amine **94** with pyrrole trichloromethyl ketone **95** afforded **96** as a precursor of the key cascade reaction in an 83% three-step yield.




**Scheme 11.** Synthesis of the cascade cyclization precursor

**Single step construction of the ABDE tetracyclic ring core.**

Having prepared the cleavage precursor **96**, the author next attempted the single step construction of an ABDE tetracyclic ring system (Figure 6). To induce an E1cB eliminative cleavage of the N–N bond, **96** was treated with 3.0 equiv of LHMDS as a strong base at –78 ºC and warmed to room temperature (condition I). The reaction afforded the expected tetracyclic compound **80** that corresponds to the ABDE ring of palau'amine, including the *trans*-bicyclo[3.3.0]octane skeleton, in modest yield. The transfused D/E ring junction and the stereochemistry of **80** were confirmed by a nuclear Overhauser effect experiment (Figure 7) and by comparison of the coupling constant with the natural product (Figure 8). It was noteworthy that the coupling constant at the C11 proton indicated the characteristic value ($J$=14.5 Hz) of a *trans*-bicyclo[3.3.0]octane skeleton. The reaction pathway leading to the ABDE ring system **80** is explained below.

Treatment of **96** with 3.0 equiv of a strong base would abstract two NH protons and hydrogen at the C10 position, thereby inducing a β-elimination of nitrogen possessing an electron-withdrawing group of **96'**. This would lead simultaneously to both the cleavage of the N–N bond and the imine formation at the C10 position to give **96A**. The nucleophilic addition of amide anion to the electron-deficient C10 carbon center would occur immediately to give **96B** possessing a *trans*-bicyclo[3.3.0]octane skeleton (D/E ring junction). Furthermore, the cascade reaction would not stop at **96B** due to the remaining pyrrole anion and subsequent condensation of pyrrole with methyl ester formed a B-ring to give **96C**. The results encouraged us to scale up this reaction from a few milligrams to 100 mg with the goal of completing the total synthesis of palau'amine. However, the reaction was found to suffer from poor reproducibility, often leading to poor to low yields even after a prolonged reaction time.

After careful consideration of the reaction mechanism, the author established an improved method involving the partial protonation of the anionic intermediates with acetic acid (condition II). Upon treatment with 3.0 equiv of LHMDS, substrate **96** undergoes stepwise lithiation of the two NH protons at –78 ºC and then the C10-proton at around 0 ºC. Once the C10 proton is abstracted, the formation of **96A** and the subsequent cyclization of amide anion leading to **96B** would proceed rapidly and completely. Indeed, only **96B** was detected as its protonated form by thin layer chromatography (TLC), indicating the fast conversion of **96A** (within 10 min) to **96B** and the slow formation of **96C** from **96B**. The smaller p$K$a value (in dimethyl sulfoxide) of the pyrrole moiety (should be ~23 of pyrrole) compared with that of methanol (28) predicted that the equilibrium between **96B** and **96C** favored the former, which led us to remove the methoxide ion without quenching the pyrrole anion. Thus, after checking the conversion of **96** into **96B** by TLC (see

supporting experimental section), the mixture was cooled to –78 ºC again and an exact 1.0 equiv of acetic acid was slowly added. On warming to room temperature, the desired product **96** was obtained in up to 74% yield with good reproducibility in acceptable scales for total synthesis.

The mechanism underlying the cascade reaction under 'condition II' is explained as follows. The intermediate **96B** possesses three nitrogen anions of Boc-carbamate (~24), pyrrole (~23) and trifluoroacetoamide (~17), according to the order of basicity by comparison of the p*K*a values of protonated NH functional groups. Thus, an exact 1.0 equiv of acetic acid would protonate only the anion of Boc-carbamate and trianion **96B** would be converted into dianion **96D**. Although the mixture was warming to room temperature, the remaining pyrrole anion induced condensation with methyl ester, simultaneously generating methoxide as in the case with trianion. However, as the condensation product **96E** possesses an active NH proton, unlike in the case with trianion, methoxide does not attack the pyrrole amide but extracts the active Boc-NH proton to give the same dianion **96C** with a quenching methoxide anion. Among various acids, including phenol and imide derivatives, acetic acid was found to be the best protonating reagent. In addition, precise amounts of LHMDS and acetic acid are very important for this p*K*a game reaction. As stated above, the author succeeded in establishing an efficient method for constructing the basic core structure of palau'amine.

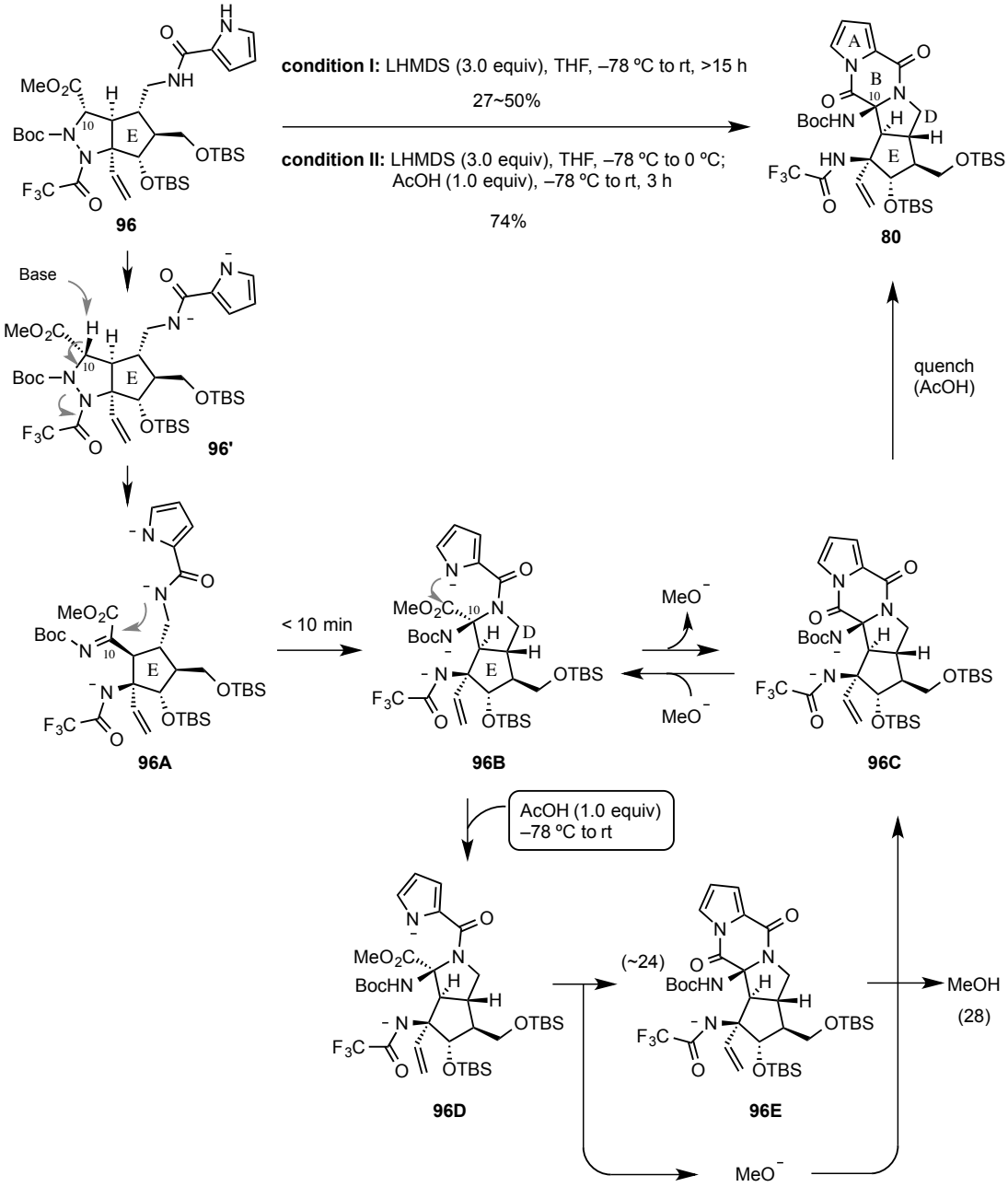



**Figure 6.** Construction of ABDE ring system and comparison of the basicity of nitrogen anions

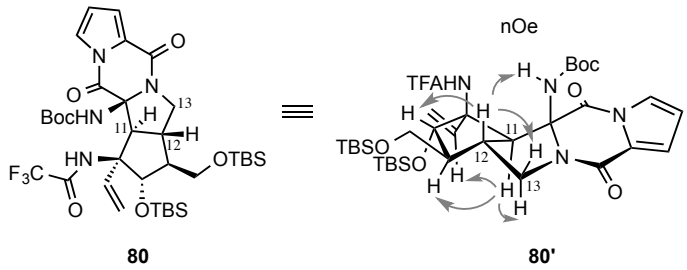



**Figure 7.** Nuclear Overhauser effect experiment of **80**

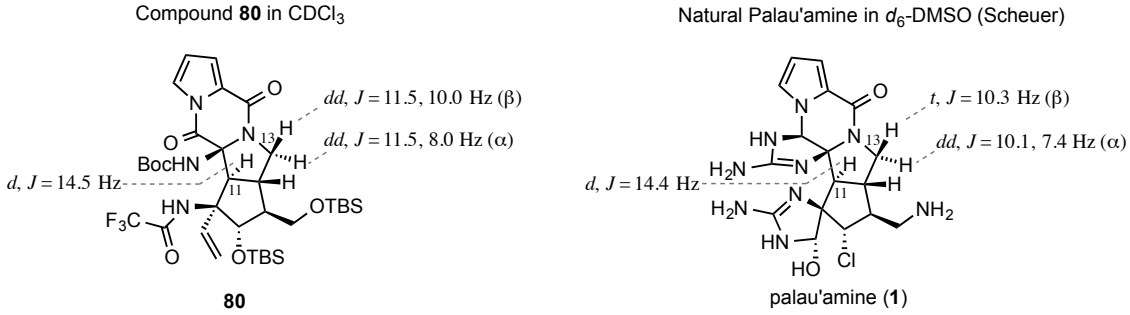



**Figure 8.** Comparison of the coupling constant of **80** with the natural palau'amine[3]

**Theoretical calculations on the coordination effect of lithium.**[20]

The remaining question in this cascade reaction is how the amide anion of **96A** got close to the C10 carbon center, to overcome the steric strain of the *trans*-bicyclo[3.3.0]octane skeleton, although the Boc-imine moiety of **96A** was highly electron deficient. Thus, the author focused on the coordination effect of lithium ion. If the lithium countercation of amide anion formed a coordination bond with the carbonyl group of methyl ester, the amide nitrogen (N14) and the C10 carbon center would be located at transannular positions that are close to each other due to the strain of the eight-membered ring. To investigate this coordination effect, theoretical calculations were carried out by the density functional theory method. The optimized structure of **96A** including lithium ions is shown in Figure 9 (the effect of coordination of solvent THF molecules to lithium ions are discussed in the Supplementary Data; see the Supplementary Discussion and Supplementary Fig. 1-2).

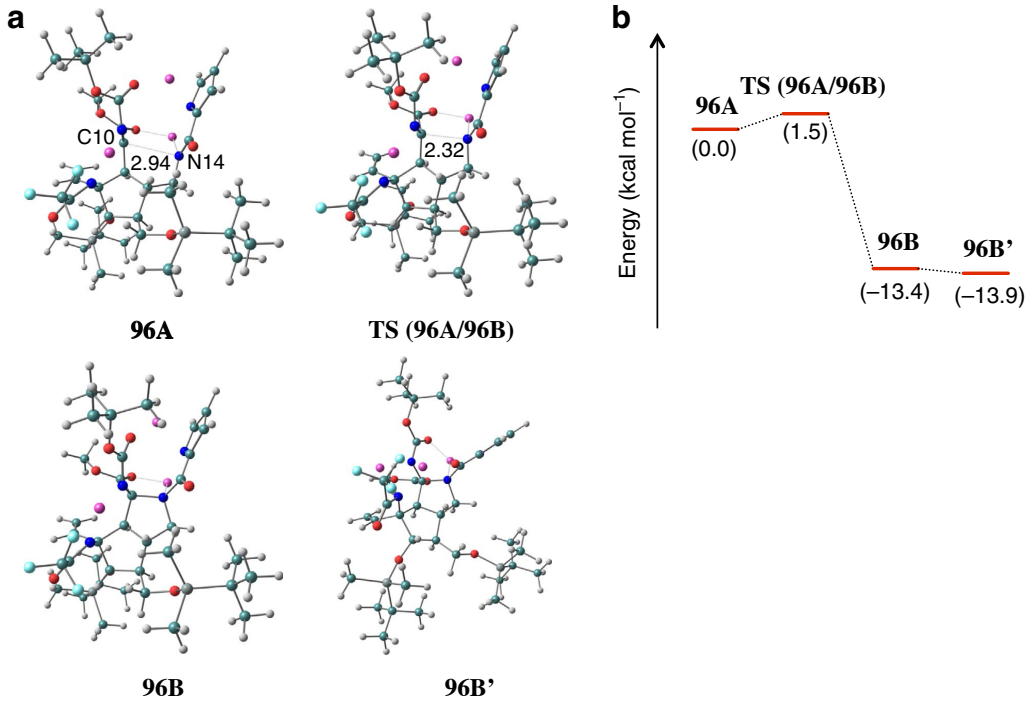
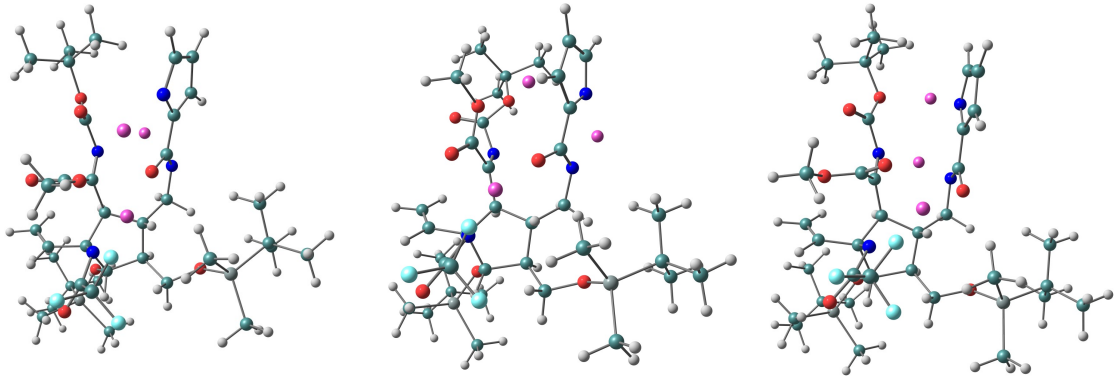



**Figure 9.** Optimized structures and energy diagram of **96**. (a) Optimized structures of **96A**, **96B**, **TS(96A/96B)** and **96B'**. **TS(96A/96B)** is a transition-state structure connecting **96A** and **96B**. **96'** represents a structure after the translocation of a lithium atom. The atoms were colour coded as follows: grey, H; pink, Li; green, C; blue, N; red, O; light blue, F; dark grey, Si. (b) Potential energy profile for the cyclization reaction (18A-18B). Calculations were performed by the density functional theory (DFT) using the modern functionals of M06-2X with the 6-31G* basis set. The solvent effects are taken into account by the self-consistent reaction field (THF). The potential energies (in kcal $mol^{-1}$) relative to **96A** are shown in parentheses. All calculations were performed by the Gaussian 09 package58.

Interestingly, the calculation actually indicated not only the expected coordination of lithium amide to the carbonyl group of methyl ester but also the unpredictable coordination of lithium salt of pyrrole anion to the carbonyl oxygen of the Boc group. Therefore, the two *trans*-oriented side chains were quite close to each other by the chelation to two lithium ions and the distance between N14 and C10 at the transannular positions was calculated to be only 2.94 Å. Owing to the short distance between the two reaction points, the energy barrier of the cyclization reaction (**96A**→**96B**) was estimated to be only 1.5 kcal $mol^{-1}$, allowing the reaction to proceed smoothly (see Figure 9b for the potential energy profile of the cyclization reaction.)

Moreover, the energy of TS(**96A/96B)** was compared with that of **TS1**-**TS3**, in which the C10-C11 bond was rotated so that the nitrogen at C10 position become an α-configuration after the cyclization leading to D-ring. The optimized structures **TS1**-**TS3** including lithium ions were shown in Figure 10. The calculations suggested the coordination of lithium amide (N14) to the imine group, along with another coordination of lithium salt of pyrrole anion to both carbonyl oxygens of methyl ester and Boc group that forms eleven- to thirteen-membered ring. However, even minimum potential energy (**TS1)** among them showed +7.7 kcal/mol higher than that of TS(**96A/96B**). Since the energy barrier of the cyclization reaction (**96A→96B**) through **TS(96A/96B)** was previously calculated to be 1.5 kcal/mol, the conformation of the transition-state should be acceptable as **TS(96A/96B)**.



**TS1** (+7.7 kcal/mol) **TS2** (+10.6 kcal/mol) **TS3** (+30.0 kcal/mol)

**Figure 10.** Optimized structures and energy diagram of **TS1-TS3**

Thus, the nucleophilic addition of the amide anion (N14) occurred before the rotation of the single bond of C10–C11, which was also restricted by the coordination effect of lithium ion, to afford **80** as a single diastereomer possessing the β-configuration of the NHBoc group at the C10 position. From the calculated result, it was concluded that the chelation effect of lithium ion played a significant role in the formation of the *trans*-bicyclo[3.3.0]octane skeleton. In fact, this cascade reaction in the presence of 3.6 equiv of HMPA as a lithium ion scavenger afforded a complex mixture, and the desired cyclized (D/E ring) products and related intermediates were not detected. Furthermore, the use of other bases, such as NaHMDS and KHMDS, also did not give any desired cyclization products. In addition, the yield of tetracyclic **80** was dramatically decreased to 10~20%, when the initial treatment of 3.0 equiv of LHMDS was directly conducted at 0 ºC. This result clearly

suggested that the coordination of lithium ions to the two carbonyl groups must be formed first at –78ºC before the extraction of the C10 proton occurs at 0 ºC.

In conclusion, the author has developed an efficient method for the single-step construction of an ABDE tetracyclic ring system. In the cascade reaction, the chelation effect of lithium salt forming an eight-membered ring was crucial for the construction of a *trans*-bicyclo[3.3.0]octane skeleton (D/E ring junction) by bringing two reaction points close to each other at the transannular position. In the next chapter, the achievement of the total synthesis of palau'amine from **80** is described.

# Chapter 2

## Completion of the Total Synthesis of Palau'amine

Having established an efficient method for constructing an ABDE ring system that overcame the most difficult barrier to the total synthesis of palau'amine in Chaper 1, the author attempted a total synthesis from **80** (Figure 11). The author planed to initially construct a C-ring by using an amino group (N9) on C10 and a carbonyl group at C6 as a foothold, and a F-ring would be later formed by the use of an animo group (N23) and olefin at C16. After the construction of hexacyclic core **97**, the transformation of functional groups, including a substitution of primary alcohol to amine and secondary hydroxyl group to chloride with stereoretention, would lead the target molecule, palau'amine **1**.

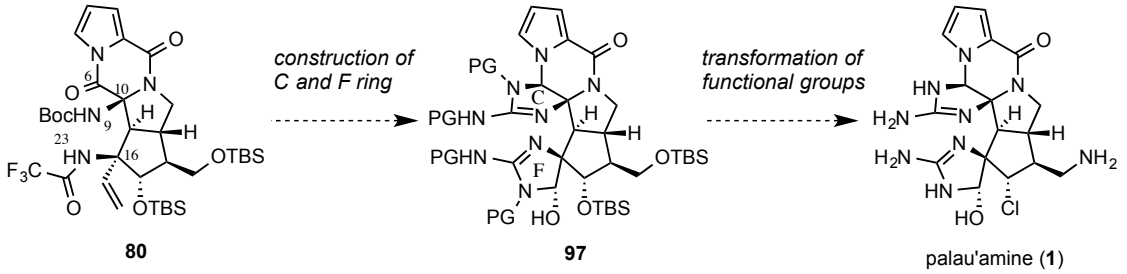
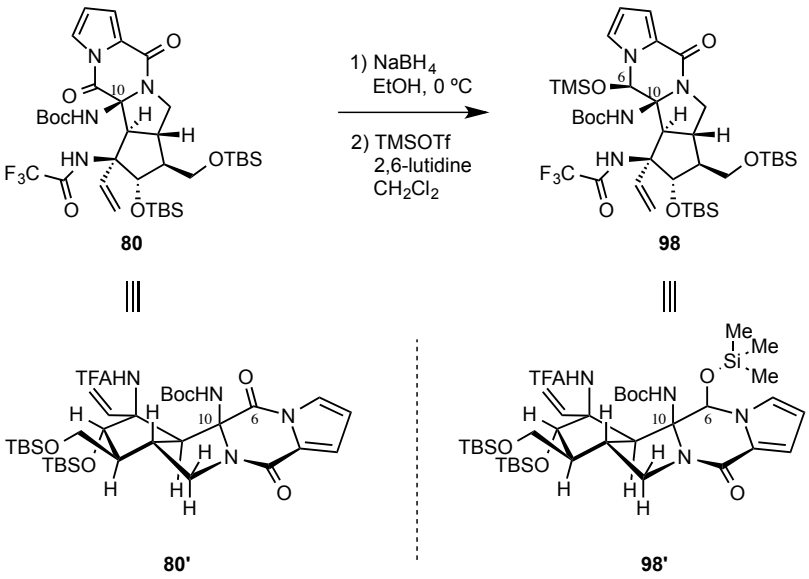



**Figure 11.** Plan for a construction of C- and F-ring and transformation of functional groups

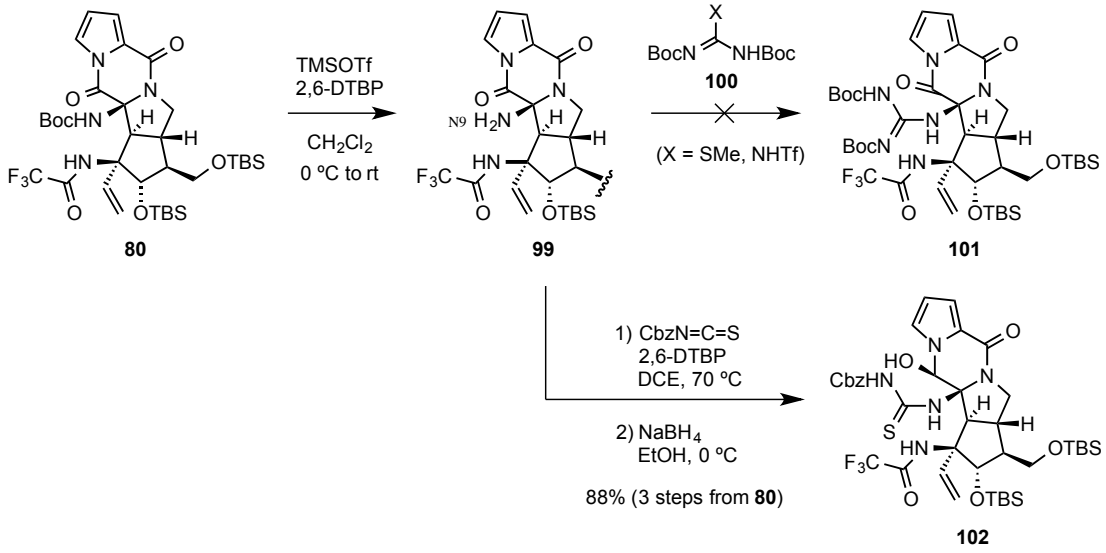
**Total synthesis of palau'amine.**

The reduction of pyrrole carbonyl moiety of **80** and removal of the Boc protecting group according to Ohfune's method[21] was firstly tried (Scheme 12). While the reduction of **80** using $NaBH_4$ smoothly proceeded to give desired hemiaminal, subsequent treatment with TMSOTf could not remove Boc group but afforded only silyloxy compound **98**, indicating that the $sp^3$ carbon center generated by the reduction of carbonyl group increased the steric hindrance around the N9 amino group. Therefore the above reduction-deprotection sequence was switched because the $sp^2$ carbon of the C10 carbonyl of **80** retains planar configuration so that the N9 amino group is less hindered than the $sp^3$ carbon at C6 of **98**.



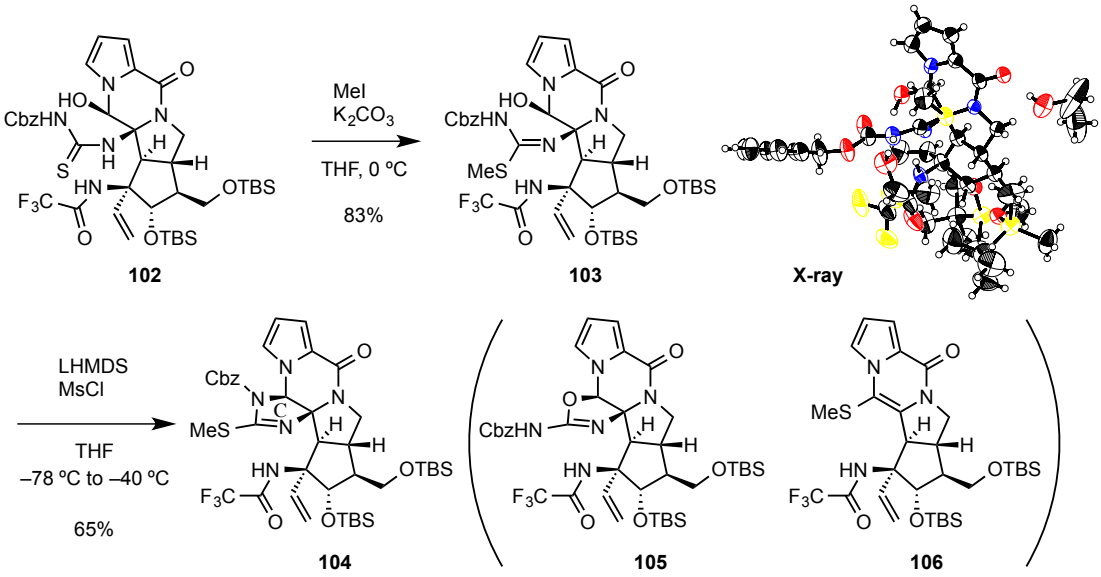

**Scheme 12.** Unsuccessful route for removal of the Boc group

As the author expected, the removal of Boc group of **80** smoothly proceeded to give amine **99** (Scheme 13). However, next direct formation of guanidine using carbodiimide derivatives **100**[22] did not proceed under various conditions. Therefore, the amino group (N9) of **99** was temporarily converted into thiourea by treatment with N-benzyloxycarbonyl isothiocyanate (CbzNCS) and the pyrrole amide at C6 was selectively reduced to hemiaminal **102** as an isolable compound in 88% overall yield after three steps from **80**. Only CbzNCS as a small and reactive reagent reacted with the sterically hindered resulting N9 amine.




**Scheme 13.** Installation of a guanidine precursor to N19

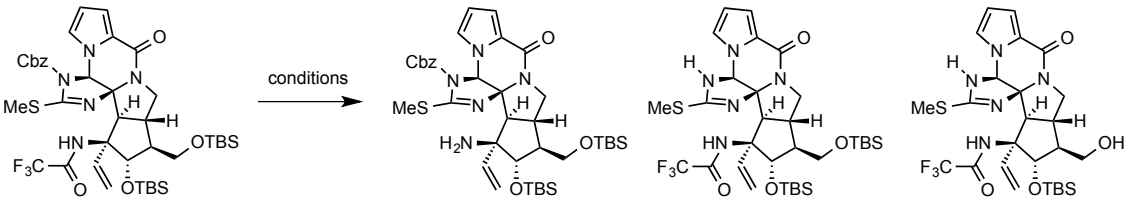
As the thiourea moiety of **102** could not be directly converted into guanidine due to the predominant cyclization from hemiaminal oxygen to activated thiourea to give **105**, the thiourea moiety was converted into isothiourea **103**. At this stage, the structure of the synthetic intermediate including the *trans*-bicyclo[3.3.0]octane skeleton was unambiguously confirmed by an X-ray diffraction study. Treatment of **103** with LHMDS and methanesulfonyl chloride at –78 to –40 ºC induced a sequential reaction of mesylation, the elimination of mesylate and the addition of nitrogen to the isothiourea moiety to give pentacyclic **104** in 65% yield, in a manner similar to that of the synthesis of (–)-dibromophakellstatin reported by Nagasawa and colleagues[23]. In addition, when $Et_3N$ was used instead of the strong base, LHMDS, vinyl sulfide **106** was obtained as a major product.




**Scheme 14.** Construction of a C-ring

Having constructed a C-ring, the author next tried to form an F-ring. At the beginning, the removal of trifluoroacetyl group was investigated (Table 2). A methanolysis and hydrolysis conditions induced a cleavage of Cbz group (entry1) and deprotection of primary TBS group (entry 3). When the methanolysis or ammonolysis conditions were took place under heat, an unknown product was gradually generated after conversion to **109** (entry 2, 4). Even commonly used reductive condition, $NaBH_4$ in EtOH at 50 °C gave the Cbz-cleaved product **108** without reduction of the trifluoroacetyl group (entry 5). After further several investigations, only the strong reductive condition using DIBAL at –78 ºC in toluene (entry 6) was found to be successful for the removal of

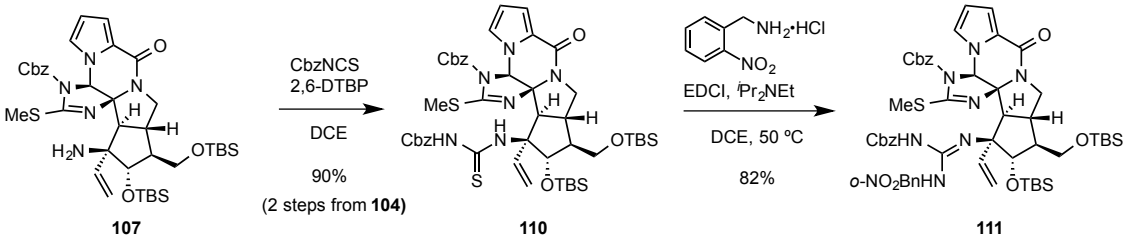
the trifluoroacetyl group, in which minimum necessary amount of DIBAL (2.1 equiv) was demanded to suppress the over-reduction of amido carbonyl group.




| entry | conditions | result |
|---|---|---|
| 1 | $K_2CO_3$, MeOH, rt | **108** |
| 2 | $K_2CO_3$, MeOH, 60 ºC | unknown |
| 3 | 1M NaOH, THF, 40 ºC | **109** |
| 4 | $NH_3$, MeOH, 100 ºC | unknown |
| 5 | $NaBH_4$, EtOH, 50 ºC | **108** |
| 6 | DIBAL (2.1 equiv) toluene, –78 ºC | **107** |

**Table 2.** Investigation for cleavage of the trifuluoroacetyl group

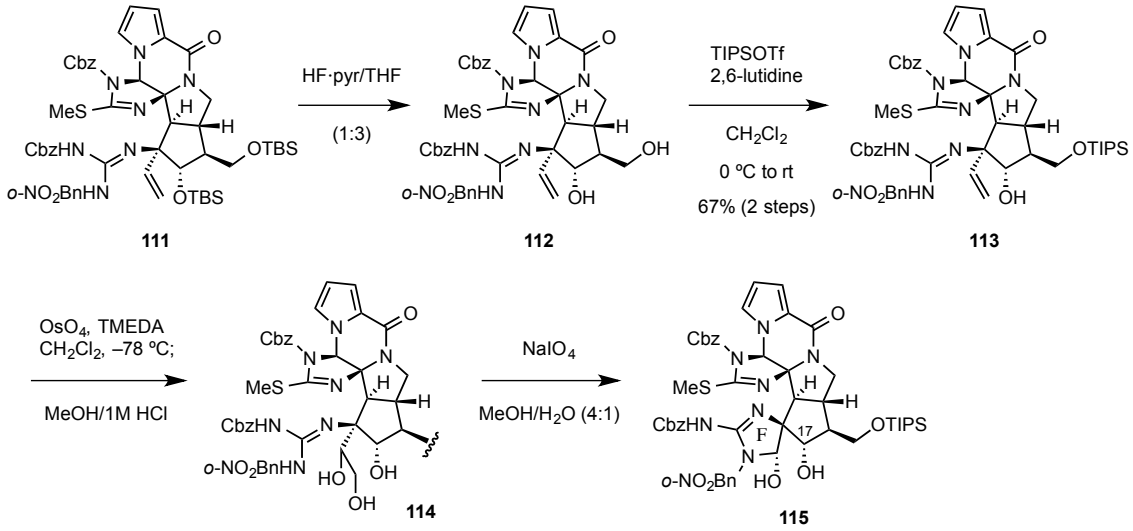
Subsequent treatment of the resulting amine **107** with CbzNCS afforded thiourea **110** in good yield (Scheme 15).[5k] The thiourea moiety was directly converted into guanidine **111** by the condensation reaction using EDCI[24] with *o*-nitrobenzylamine in 82% yield. A direct installation of a guanidine group to the resulting amine of **107** was not also succeeded due to the instability of **107** under a carbodiimide formative conditions[22].




**Scheme 15.** Installation of a guanidine group corresponding to F-ring

Having prepared **111** involving an alkyl- and carbamate-protected guanidine, next challenge was the oxidative cleavage of the vinyl group (Scheme 16). However, the oxidative transformation of vinyl group without the oxidation of pyrrole was difficult, probably due to the steric hindrance of

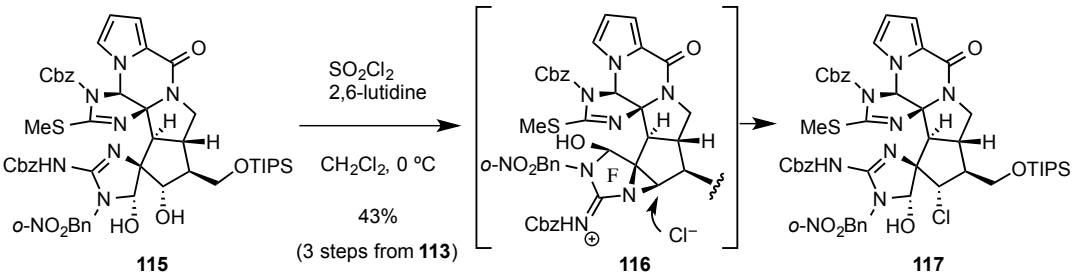
the TBS group at the C17 position.[25] Thus, two TBS groups were removed by HF-pyridine (acidic) and only primary hydroxyl group was protected again by the TIPS group, to give **113** in a 67% two-step yield. On the other hand, the deprotection of secondary TBS group was not successfully performed under TBAF (basic) or TASF (neutral)[26] conditions. In the case of the free secondary hydroxyl group, dihydroxylation using $OsO_4$ and TMDEA in dichloromethane[27], applying an hydrogen bonding interaction with the secondary hydroxy group proceeded smoothly at –78 ºC to give osmate and subsequent hydrolysis in the mixed solution of methanol and 1M HCl afforded the desired diol **114**. In contrast, the use of aqueous solution of $NaHSO_3$ or $Na_2SO_3$ as a reductant of the osmate showed a slow conversion rate and decline in yield. The oxidative cleavage of diol **114** was successful only in the mixed solution of methanol and water (4:1) to give an unstable F-ring product **115**, which gradually decomposed even under the neutral condition, due probably to the retro-aldol reaction at the C17 position. Product **115** was then directly used for the next reaction without purification.




**Scheme 16.** Construction of a spirocyclic F-ring

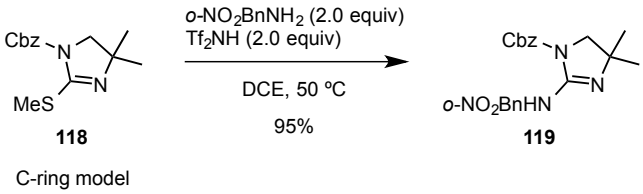
With the construction of an ABCDEF ring system of palau'amine, the conversions of functional groups into **1** were finally attempted (Scheme 17). The substitution of the secondary hydroxyl group to chloride with stereoretention proceeded by the use of the neighbouring-group effect of guanidine on the F-ring. The activation of secondary alcohol by using sulfuryl chloride induced the participation of guanidine depicted as **116** in analogy with 'massadine aziridine'[28] and the subsequent nucleophilic attack of chloride afforded **117** with an α-configuration of chloride, along with a small amount of epimer at the C20 position as an unnatural configuration. On the other

hand, the hydroxyl group of hemiaminal also reacted with excess sulfuryl chloride to give dichloride when more than 1.0 equiv of sulfuryl chloride was used, and the chloride at the C20 position was readily hydrolysed to convert back to **117**. Meanwhile, the use of other chloride source, such as methansulfonyl chloride (MsCl) or thionyl chloride ($SOCl_2$), did not furnish **117**.




**Scheme 17.** Substitution of secondary chloride with stereoretention

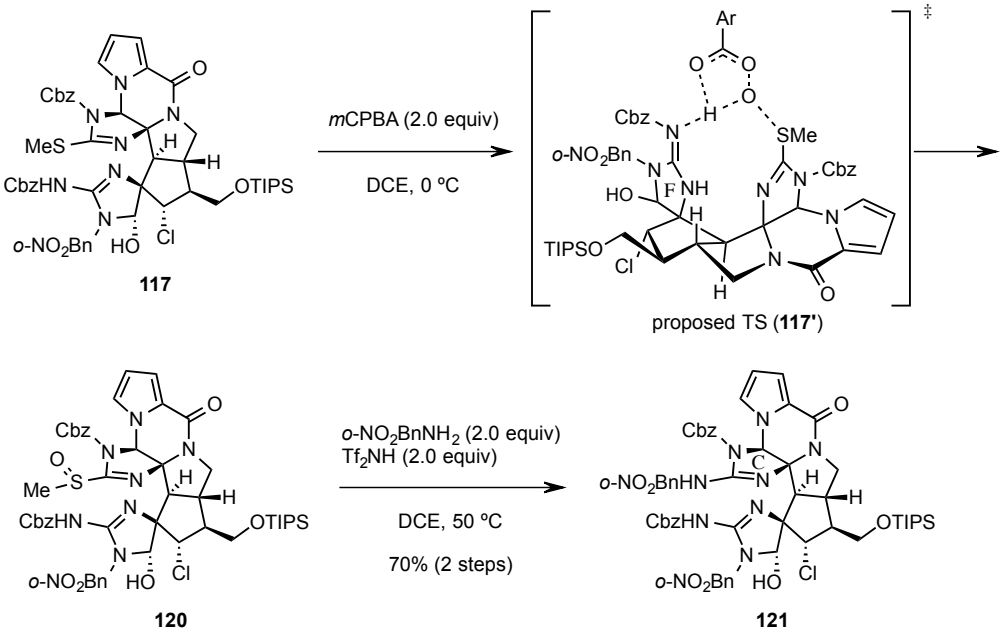
Next, the author had to develop a new method for converting the methylthio group into an amino group, leading to guanidine under acidic conditions[29], because the author found that hexacyclic intermediates were readily decomposed under the basic conditions. After various examinations using C-ring model compound **118**, the author achieved to establish the efficient condition for the conversion of cyclic isothiourea into guanidine under acidic condition, i.e. treatment of **118** with a trifluoromethanesulfonic imide salt of *o*-nitrobenzylamine (as a 1:1 ratio) in 1,2-dichloroethane (DCE) afforded **119** in excellent yield (Scheme 18).




**Scheme 18.** Development of a new guanidinylation method under acidic conditions

However, the above condition was unfortunately not applicable to the advanced palau'amine substrate. Thus, the oxidation state of the thioether was tried to increase for the improvement of its leaving group ability (Scheme 19). The oxidation of methylthio group of **117** without harmful effects to pyrrole moiety was succeeded by only using *m*CPBA, due to the coordination effect of guanidino group on F-ring throuth hydrogen bonding as shown by a proposed transition-state **117'**.

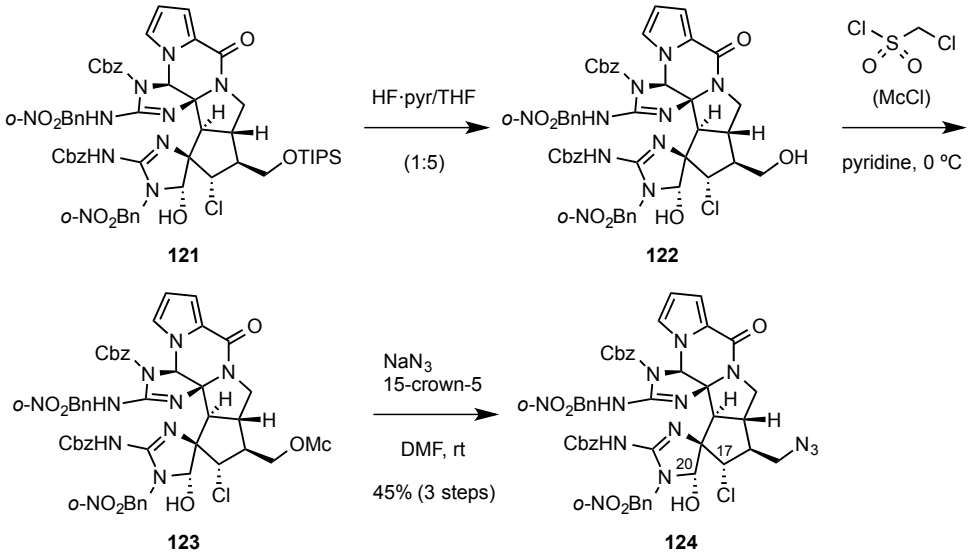
Furthermore, the overoxidation into sulfone and the use of a salt other than trifluoromethanesulfonic imide afforded only a complex mixture. The sulfoxide **120** was then treated again with the originally developed acidic guanidinylation conditions to give **121** in a 70% two-step yield.




**117** **120** **121**

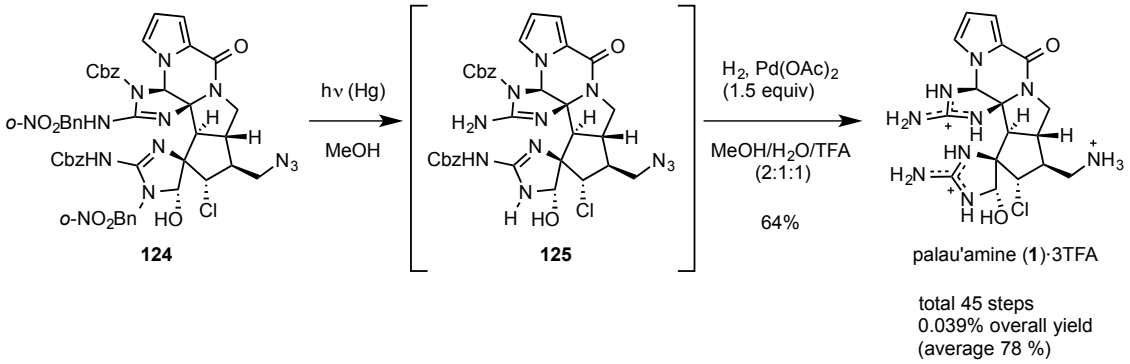
**Scheme 19.** Transformation of cyclic isothiourea to guanidine

In the final transformation of the functional group, the primary alcohol was converted into chloromethanesulfonate **123**[30], after removal of the TIPS group. The azidation reaction of **123** proceeded at room temperature to afford **124** as a protected palau'amine (Scheme 20). When methanesulfonate was adopted as a leaving group, the azidation reaction required a high temperature (50 °C) that also induced azidation at the C17 position via the neighbouring-group effect. Fortunately, the minor epimer of the unnatural configuration at the C20 position disappeared at this stage.




**Scheme 20.** Conversion of the primary alcohol to azide

Finally, Hg-lump irradiation[31] followed by direct hydrogenation as a deprotection of **124** afforded **1** in 64% yield as a 3TFA salt (Scheme 21). Synthetic **1** showed spectral data ($^{1}$H- and $^{13}$C-NMR [3,7], high-resolution mass spectra) completely identical to those of natural palau'amine **1**. Throughout this total synthesis, **1** was obtained in 0.039% overall yield after 45 steps (78% average yield at each step) from commercially available cyclopentenenone **71**. As a result of the 45-step synthesis, many synthetic intermediates as derivatives of **1** possessing various ring core systems were actually obtained for the first time.




**Scheme 21.** Completion of the total synthesis of palau'amine

**Biological test of synthetic palau'amine.**

The immunosuppressive activity of synthetic palau'amine was examined (Figure 12). Lymphocytes derived from a mouse spleen were treated with various concentrations of an aqueous

solution of synthetic **1** for 1 h and then the cells were incubated with phorbol 12-myristate 13-acetate and lectin[32]. After incubation for 5 h, the interleukin-2 (IL-2) in the culture supernatant was measured by using an enzyme-linked immunosorbent assay kit. Thereupon, the synthetic palau'amine•3TFA salt was confirmed to exhibit strong immunosuppressive activity. The $IC_{50}$ value was determined to be 45.3 μM, which is a practical level of activity, as it was for cyclosporine A. Not surprisingly, the synthetic intermediate **121** as a negative control did not exhibit immunosuppressive activities, due to the large hydrophobic protecting groups of all polar functional groups, and it slightly increased the production of IL-2. Therefore, the author confirmed that not only the spectral data but also the biological properties of synthetic **1** were identical to those of natural palau'amine. Recently, Tepe and colleagues[4] reported that palau'amine **1** and its related natural products inhibit IκBα degradation. On the other hand, the author revealed that the synthetic palau'amine•3TFA salt inhibited the release of IL-2 from lymphocytes in the same manner as cyclosporine A, which is known to inhibit the IκBα degradation and nuclear factor-κB[33]. Thus, the synthetic palau'amine•3TFA salt was also expected to exhibit a similar inhibition of IκBα degradation.

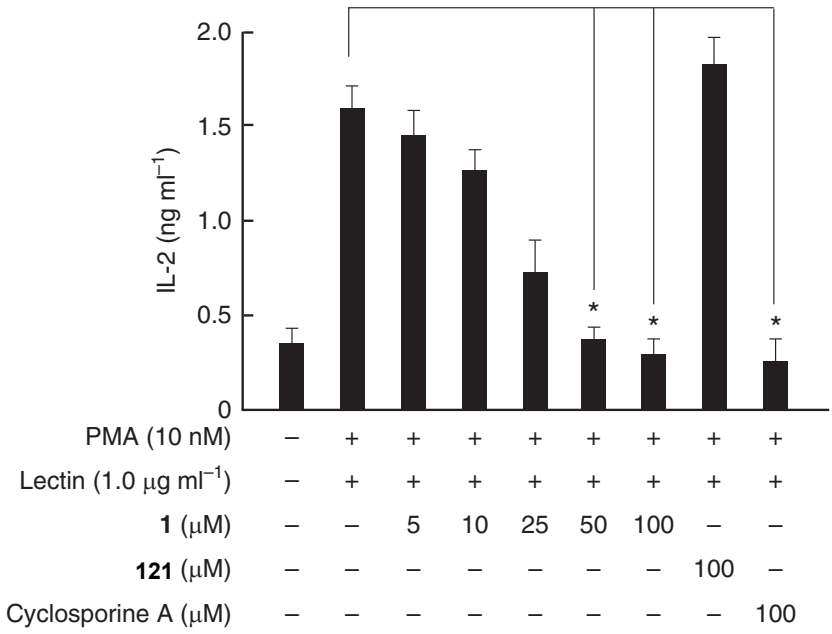



**Figure 12.** Immunosuppressive activity of synthetic palau'amine at various concentrations. Balb/c splenic lymphocytes were treated with various concentrations of an aqueous solution of synthetic **1**, synthetic **121** (100 μM) and cyclosporine A (100 μM) at 37 °C for 1 h, and then the cells were incubated with phorbol 12-myristate 13-acetate (PMA, 10 nM) and lectin (1.0 μg $ml^{-1}$). After incubation for 5 h, the IL-2 in culture supernatant was measured by using an enzyme-linked immunosorbent assay kit (error bars, s.e.m.; *P<0.01).

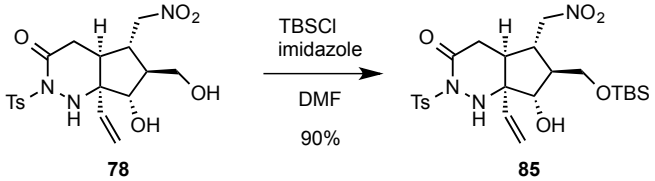
In summary, the author has achieved the total synthesis of palau'amine **1** via the single-step construction of an ABDE tetracyclic ring system. The synthesis of this natural product had led to the development of a new guanidinylation method, which undergoes under acidic condition. With the establishment of an efficient method for constructing a tetracyclic basic structure of palau'amine, various synthetic analogues for structure–activity relationship (SAR) study and chemical probes of palau'amine would be accessible. For example, protected palau'amine **124** might be able to introduce labeling groups at desired spots on a C-ring, F-ring or a primary amine of an E-ring. Therefore, the chemistry described here offers not only a solution to a formidable synthetic challenge but also an alternative synthetic route to elucidate a pharmacophore and the mechanistic details of bioactivities of palau'amine.

# Experimental Section

## General Procedures.

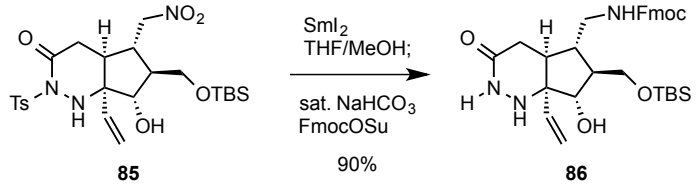
All the reaction were carried out in a round-bottomed flask with an appropriate number of necks and side arms connected to a three-way stopcock and /or a rubber septum cap under an argon atmosphere. All vessels were first evacuated by rotary pump and then flushed with argon prior to use. Solution and solvent were introduced by hypodermic syringe through a rubber septum. During the reaction, the vessel was kept under a positive pressure of argon. Dry THF was freshly prepared by distillation from benzophenone ketyl before use. Anhydrous $CH_2Cl_2$, DMF, ethanol, MeCN, methanol, pyridine and toluene were purchased from Kanto Chemical Co. Inc.

Infrared (IR) spectra were recorded on JASCO FT/IR-4100 spectrophotometer using 5 mm KBr plate. Wavelengths of maximum absorbance are quoted in $cm^{-1}$. $^1$H-NMR spectra were recorded on a JEOL ECA–400 (400 MHz), JEOL ECA-500 (500 MHz), and Bruker AV–500 (500 MHz) in $CDCl_3$, *d*–MeCN and $D_2O$. Chemical shifts are reported in part per million (ppm), and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). $^{13}$C-NMR spectra were recorded on a JEOL ECA–400 (100 MHz), Bruker AV–400N (100 MHz) and Bruker AV–500 (125 MHz) in $CDCl_3$, $C_6D_6$, $CD_3CN$ and $D_2O$. Chemical shifts are reported in part per million (ppm). High resolution mass (HRMS) spectra were recorded on a Thermo Scientific Exactive, Instrumental Analysis Division, Equipment Manager Center Creative Research Institution, Hokkaido University and a Waters SYNAPT-G2 Si HDMS, Tokushima Bunri University. High performance liquid chromatography (HPLC) was recorded on a HITACHI D-2500 Chromato-Integrater. Analytical thin layer chromatography (TLC) was performed using 0.25 mm E. Merck Silica gel (60F-254) plates. Reaction components were visualized phosphomolybdic acid or ninhydrin or *p*-anisaldehyde in 10% sulfuric acid in ethanol. Kanto Chem. Co. Silica Gel 60N (particle size 0.040–0.050 mm) was used for column chromatography.




Compound **85**:

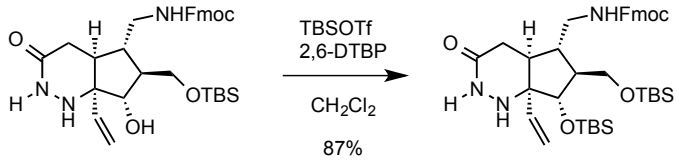
To a solution of alcohol **78** (8.42 g, 19.8 mmol) in DMF (50 mL) were added imidazole (4.04 g, 59.7 mmol) and TBSCl (3.57 g, 23.7 mmol) at 0 ºC. After being stirred at 0 ºC for 1 h, a saturated aqueous $NH_4Cl$ solution (200 mL) was added. The mixture was extracted with EtOAc (200 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1 to 1/1) to afford silyl ether **85** (9.62 g, 17.8 mmol, 90%) as a white amorphous material. IR (KBr): 3479, 3288, 2953, 2928, 2857, 1716, 1597, 1551, 1471, 1433, 1363, 1257, 1171, 1088, 1006, 911, 837, 814 $cm^{-1}$ ; $^1H$-NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.00 (dd, *J* = 17.6, 10.8 Hz, 1H), 5.43 (d, *J* = 10.8 Hz, 1H), 5.34 (d, *J* = 17.6 Hz, 1H), 4.68 (dd, *J* = 12.4, 4.0 Hz, 1H), 4.56 (dd, *J* = 12.0, 7.6 Hz, 1H), 4.40 (s, 1H), 3.93 (dd, *J* = 10.9, 5.2 Hz, 1H), 3.79 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.68 (dd, *J* = 10.8, 5.6 Hz, 1H), 2.70–2.60 (m, 1H), 2.57 (dd, *J* = 15.8, 7.2 Hz, 1H), 2.44 (s, 3H), 2.41 (dt, *J* = 15.6, 4.0 Hz, 1H), 2.22–2.12 (m, 1H), 1.74 (tt, *J* = 10.8, 4.4 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); $^{13}C$-NMR (125 MHz, $CDCl_3$): δ 170.26, 145.43, 136.24, 134.81, 129.54, 128.84, 118.52, 77.09, 75.16, 69.25, 62.18, 46.39, 42.65, 40.99, 36.74, 25.85, 21.66, 18.18, –5.63, –5.70; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd for $C_{24}H_{37}O_7N_3NaSSi$, 562.2014; found, 562.2018.




Compound **86**:

To a solution of $SmI_2$ in THF (0.1 M, 178 mmol, 1.78 L) were added MeOH (89 mL) and a solution of alcohol **85** (9.62 g, 17.8 mmol) in THF (89 mL) at room temperature. After being stirred for 2 h, the mixture was stirred under air atmosphere for 30 min until the color of solution was turned to yellow (ca. 30 min), and then a saturated aqueous

$NaHCO_3$ solution (2 L) was added. After being stirred for 30 min, FmocOSu (9.00 g, 26.7 mmol) was added. The mixture was stirred for 30 min and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 L x 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 2/1 to 0/1) to afford carbamate **86** (9.26 g, 16.0 mmol, 90%) as pare yellow amorphous material. IR (KBr): 8261, 2928, 2857, 2360, 1705, 1673, 1519, 1449, 1252, 1106, 910, 837 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 6.78 (br s, 1H), 5.87 (dd, *J* = 18.2, 10.8 Hz, 1H), 5.40 (d, *J* = 10.8 Hz, 1H), 5.33 (d, *J* = 17.6 Hz, 1H), 5.28 (br s, 1H), 4.42 (qn, *J* = 7.6 Hz, 2H), 4.21 (t, *J* = 7.2 Hz, 1H), 4.04 (br s, 1H), 3.86–3.78 (m, 2H), 3.78–3.70 (m, 1H), 3.45–3.25 (m, 2H), 2.55–2.30 (m, 2H), 2.25–2.10 (m, 1H), 1.75–1.50 (m, 1H), 0.89 (s, 9H), 0.07 (s, 6H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 175.87, 156.83, 143.85, 141.27, 137.58, 127.62, 126.99, 124.96, 119.93, 117.01, 76.32, 68.53, 66.62, 63.61, 48.01, 47.22, 43.94, 43.82, 41.83, 33.63, 25.85, 18.11, –5.58, –5.59; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd for $C_{32}H_{43}O_5N_3NaSi$, 600.2864; found, 600.2868.

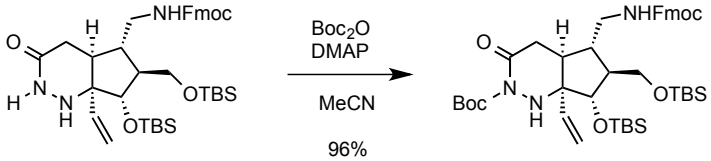



**86** **87**

Compound **87**:

To a solution of carbamate **86** (9.26 g, 16.0 mmol) in $CH_2Cl_2$ (160 mL) were added 2,6-DTBP (20.8 mL, 96.0 mmol) and TBSOTf (11.0 mL, 48.0 mmol) at –78 ºC. After being stirred at –78 ºC for 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (200 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (200 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 5/1 to 1/2) to afford silyl ether **87** (9.63 g, 13.9 mmol, 87%) as a white amorphous material. IR (KBr): 3734, 3271, 2953, 2928, 2856, 2360, 2341, 1714, 1682, 1520, 1471, 1252, 1132, 837 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 6.63 (br s, 1H), 5.90 (dd, *J* = 17.6, 11.2 Hz, 1H),

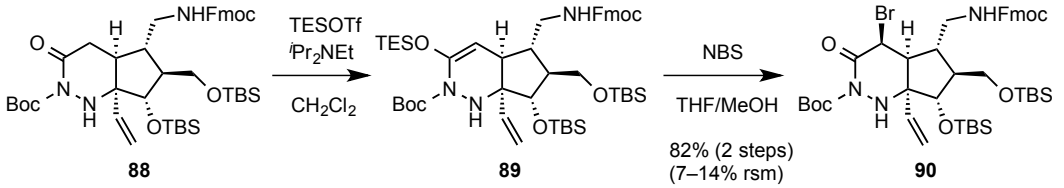
5.48 (br s, 1H), 5.24 (d, $J$ = 11.2 Hz, 1H), 5.17 (d, $J$ = 17.6 Hz, 1H), 4.40 (t, $J$ = 6.8 Hz, 2H), 4.21 (t, $J$ = 6.8 Hz, 1H), 3.98 (s, 1H), 3.84 (d, $J$ = 10.8 Hz, 1H), 3.77 (d, $J$ = 10.0 Hz, 1H), 3.52 (t, $J$ = 10.0 Hz, 1H), 3.48–3.38 (m, 1H), 3.32–3.22 (m, 1H), 2.52–2.38 (m, 2H), 1.72–1.60 (m, 1H), 1.60–1.45 (m, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 6H), 0.03 (s, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 175.66, 157.18, 144.32, 144.28, 141.62, 138.32, 127.93, 127.32, 125.33, 120.25, 115.73, 76.79, 68.50, 66.93, 63.30, 49.28, 47.62, 44.24, 43.50, 41.87, 33.66, 26.21, 26.16, 18.49, 18.35, –3.49, –4.45, –5.23; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd for $C_{38}H_{57}O_5N_3NaSi_2$, 714.3729; found, 714.3734.




**87** **88**

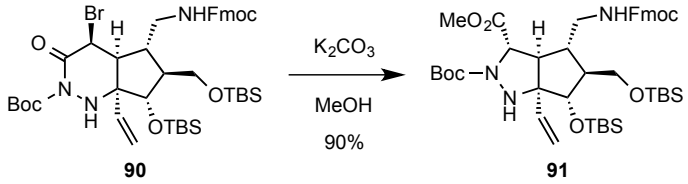
Compound **88**:

To a solution of silyl ether **87** (9.63 g, 13.9 mmol) in MeCN (139 mL) were added $Boc_2O$ (3.64 mL, 16.7 mmol) and DMAP (170 mg, 1.39 mmol) at 0 ºC. After being stirred 0 ºC for 2 h, the reaction was quenched with brine (150 mL). The mixture was extracted with EtOAc (200 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 8/1 to 2/1) to afford **88** (10.5 g, 13.3 mmol, 96%) as a white amorphous material. IR (KBr): 3734, 2929, 2360, 2341, 1771, 1717, 1522, 1472, 1252, 1152, 837 $cm^{-1}$: $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.76 (d, $J$ = 7.6 Hz, 2H), 7.56 (d, $J$ = 7.6 Hz, 2H), 7.39 (t, $J$ = 7.4 Hz, 2H), 7.31 (t, $J$ = 7.4 Hz, 2H), 5.99 (dd, $J$ = 17.6, 11.2 Hz, 1H), 5.45 (br t, 1H), 5.23 (s, 1H), 5.21 (d, $J$ = 11.2 Hz, 1H), 5.18 (d, $J$ = 17.6 Hz, 1H), 4.41 (dd, $J$ = 13.6, 11.2 Hz, 2H), 4.21 (t, $J$ = 11.2 Hz, 1H), 3.79 (d, $J$ = 10.0 Hz, 1H), 3.79 (d, $J$ = 10.0 Hz, 1H), 3.51 (dd, $J$ = 10.0, 6.4 Hz, 1H), 3.45–3.35 (m, 1H), 3.30–3.15 (m, 1H), 2.64 (dd, $J$ = 14.4, 5.6 Hz, 1H), 2.38 (dd, $J$ = 14.4, 8.0 Hz, 1H), 2.24–2.18 (br dd, $J$ = 14.4, 8.0 Hz, 1H), 1.70–1.60 (m, 1H), 1.60–1.50 (m, 1H), 1.54 (s, 9H), 0.92 (s, 9H), 0.89 (s, 9H), 0.19 (s, 3H), 0.07 (s, 3H), 0.06 (s, 6H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 170.16, 156.72, 151.05, 143.91, 141.29, 137.49, 127.61, 127.00, 125.01, 119.93, 115.40, 84.18, 68.51, 66.53, 62.02, 50.04, 47.29, 43.91, 42.28, 41.97, 38.03, 28.01, 25.91, 25.82, 18.19, 18.00, –3.78, –4.97, –5.47, –5.55 (one peak missing in $CDCl_3$); HRMS (ESI, *m/z*): $[M+Na]^+$ calcd for $C_{43}H_{65}O_7N_3NaSi_2$, 814.4253; found, 814.4251.




Compound **90**:

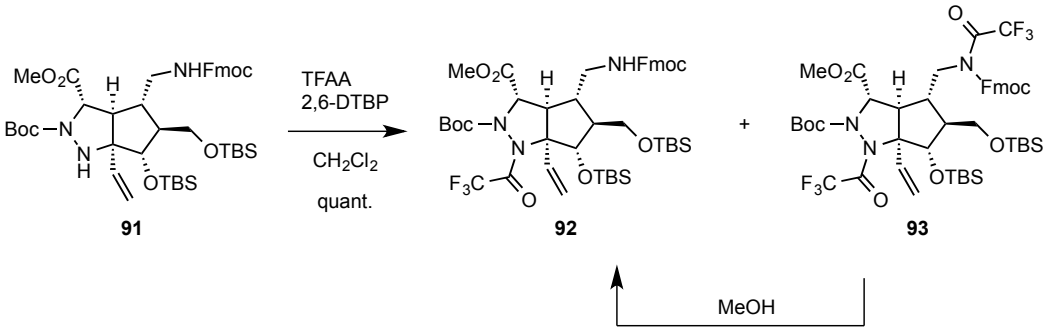
To a solution of **88** (10.5 g, 13.3 mmol) in $CH_2Cl_2$ (132 mL) were added $^iPr_2NEt$ (23.6 mL, 132 mmol) and TESOTf (11.6 mL, 66.0 mmol) at –78 °C. After being stirred at –78 °C for 3 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution (100 mL). The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (150 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude silyl ketene aminal **89**. The crude **89** was used for next step without purification. To a solution of residue in THF (66 mL) were added MeOH (66 mL) and NBS (3.05 mL, 17.2 mmol) at –78 °C. After being stirred at –78 °C for 1 h, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (50 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1 to 4/1) to afford bromide **90** (9.41 g, 10.8 mmol, 82% for 2 steps) as a white amorphous material and recovered **88** (1.46 g, 1.85 mmol, 14%). IR (KBr): 3734, 3649, 3373, 2928, 2856, 2360, 2341, 1770, 1718, 1523, 1472, 1370, 1253, 1150, 835 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.76 (d, $J$ = 7.2 Hz, 2H), 7.59 (dd, $J$ = 7.6, 4.8 Hz, 2H), 7.40 (t, $J$ = 7.6 Hz, 2H), 7.32 (tdd, $J$ = 7.6, 2.8, 1.2 Hz, 2H), 5.91 (dd, $J$ = 18.0, 11.2 Hz, 1H), 5.25 (d, $J$ = 10.8 Hz, 1H), 5.22 (d, $J$ = 18.0 Hz, 1H), 5.14 (br s, 1H), 4.91 (s, 1H), 4.61 (d, $J$ = 4.8 Hz, 1H), 4.44 (d, $J$ = 6.8 Hz, 2H), 4.21 (t, $J$ = 6.8 Hz, 1H), 3.89 (d, $J$ = 10.4 Hz, 1H), 3.77 (br d, $J$ = 10.0 Hz, 1H), 3.62 (dd, $J$ = 10.6, 4.0 Hz, 1H), 3.42–3.28 (m, 2H), 2.68–2.58 (m, 1H), 2.32–2.18 (m, 1H), 1.76–1.62 (m, 1H), 1.52 (s, 9H), 0.91 (s, 9H), 0.90 (s, 9H), 0.21 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 166.13, 156.96, 150.49, 143.95, 143.84, 141.33, 137.34, 127.66, 127.09, 127.07, 124.98, 119.95, 116.57, 84.11, 76.88, 69.17, 66.71, 60.12, 51.06, 48.94, 47.26, 44.64, 41.93, 40.27, 27.96, 25.96, 25.86, 18.22, 18.05, –3.77, –4.85, –5.42, –5.50; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd for $C_{43}H_{64}O_7N_3BrNaSi_2$, 892.3358; found, 892.3360.




**90** **91**

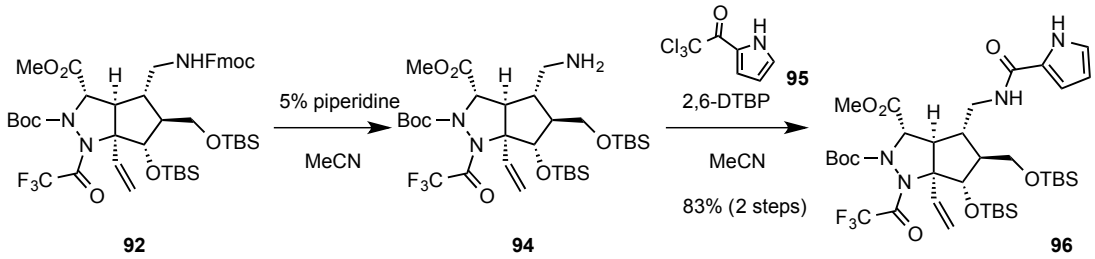
Compound **91**:

To a solution of bromide **90** (9.41 g, 10.8 mmol) in MeOH (108 mL) was added $K_2CO_3$ (1.64 g, 11.9 mmol) at 0 ºC. After being stirred at 0 °C for 10 min, the reaction was quenched with a saturated aqueous $NH_4Cl$ solution (100 mL) was added. The mixture was extracted with EtOAc (100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1 to 4/1) to afford ester **91** (7.99 g, 9.72 mmol, 90%) as a white amorphous material. IR (KBr): 3724, 3343, 2953, 2929, 2895, 2857, 2360, 2341, 1698, 1521, 1472, 1389, 1366, 1252, 1136, 1005, 938, 837 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 6.10 (d, *J* = 18.0, 11.2 Hz, 1H), 5.61 (br s, 1H), 5.27 (d, *J* = 11.2 Hz, 1H), 5.20 (d, *J* = 18.0 Hz, 1H), 4.50–4.38 (m, 1H), 4.45 (dd, *J* = 10.4, 6.8 Hz, 1H), 4.40 (dd, *J* = 10.4, 6.8 Hz, 1H), 4.21 (m, 1H), 4.21 (s, 1H), 3.75 (dd, *J* = 10.4, 2.4 Hz, 1H), 3.67 (d, *J* = 11.6 Hz, 1H), 3.65 (s, 3H), 3.52 (dd, *J* = 10.4, 6.4 Hz, 1H), 3.45–3.20 (m, 2H), 2.43 (dd, *J* = 6.4, 2.8 Hz, 1H), 1.90–1.75 (m, 1H), 1.65–1.59 (m, 1H), 1.48 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.22 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$): δ 171.99, 156.58, 144.07, 143.93, 141.32, 141.29, 135.55, 127.62, 127.00, 125.00, 119.91, 116.39, 80.88, 76.32, 66.50, 61.95, 56.58, 52.28, 50.70, 47.31, 44.34, 44.22, 28.30, 25.93, 25.88, 18.23, 17.99, –3.58, –5.26, –5.47, –5.55; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd for $C_{44}H_{67}O_8N_3NaSi_2$, 844.4359; found, 844.4368.



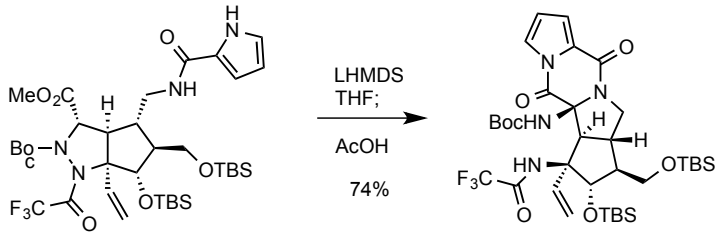

Compound **92**;

To a solution of ester **91** (7.99 g, 9.72 mmol) in $CH_2Cl_2$ (97 mL) were added 2,6-DTBP (31.5 mL, 145.8 mmol) and TFAA (13.6 mL, 97.2 mmol) at 0 ºC. After being stirred 0 °C for 1 h, a saturated aqueous $NaHCO_3$ solution (100 mL) was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (100 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1 to 4/1) to afford a mixture of trifluoroacetamide **92** and di-trifluoroacetamide **93**. The mixture of **92** and **93** in MeOH (200 mL) was heated to 40 ºC for 3 h and concentrated under reduced pressure to afford trifluoroacetamide **92** (8.93 g, 9.72 mmol, quant.) as a white amorphous material. IR (KBr): 3734, 2929, 2857, 2360, 2342, 1717, 1508, 1472, 1371, 1253, 1205, 1155, 838 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$, 60 ºC): δ 7.76 (d, *J* = 7.6 Hz, 2H), 7.58 (dd, *J* = 7.2, 4.0 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 6.48 (dd, *J* = 17.6, 11.2 Hz, 1H), 5.65 (br s, 1H), 5.24 (d, *J* = 11.2 Hz, 1H), 5.16 (d, *J* = 17.6 Hz, 1H), 4.83 (br s, 1H), 4.45 (dd, *J* = 17.2, 6.8 Hz, 1H), 4.38 (dd, *J* = 17.2, 7.2 Hz, 1H), 4.22 (t, *J* = 7.2 Hz, 1H), 3.98 (d, *J* = 10.0 Hz, 1H), 3.92 (dd, *J* = 10.4, 2.8 Hz, 1H), 3.69 (s, 3H), 3.52–3.33 (m, 3H), 3.07 (d, *J* = 10.0 Hz, 1H), 1.78–1.65 (m, 1H), 1.55–1.45 (m, 1H), 1.50 (s, 9H), 0.95 (s, 9H), 0.91 (s, 9H), 0.19 (s, 3H), 0.08 (s, 9H); $^{13}$C-NMR (125 MHz, $CDCl_3$, 60 ºC): δ 169.14, 156.58, 156.28, 155.02 (q, *J* = 35.6 Hz), 144.19, 144.10, 141.48, 141.45, 132.41, 127.72, 127.06, 125.05, 124.98, 120.01, 116.40, 116.01 (q, *J* = 286.9 Hz), 85.00, 79.45, 79.30, 67.01, 65.42, 63.82, 55.89, 53.13, 52.46, 47.50, 44.74, 43.24, 27.89, 26.11, 26.00, 18.33, 18.25, –4.08, –4.58, –5.35, –5.36; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd for $C_{46}H_{66}O_9N_3F_3NaSi_2$, 940.4182; found, 940.4187.




Compound **96**;

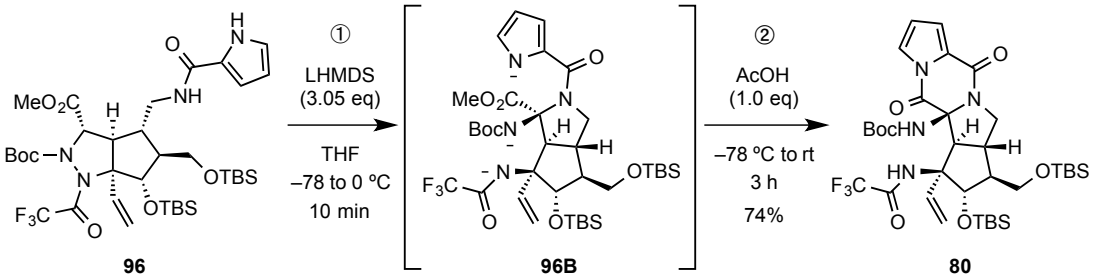
To a solution of 5% piperidine in MeCN (194 mL) was added trifluoroacetamide **92** (8.93 g, 9.72 mmol) at room temperature. After being stirred for 10 min, water (200 mL) was added. The mixture was extracted with EtOAc (200 mL x3). The combined organic layers were washed with brine (300 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **94**. To a solution of crude **94** in MeCN (49 mL) were added 2,6-DTBP (5.45 mL, 25.2 mmol) and 2-(trichloroacetyl)pyrrole **95** (2.67 g, 12.6 mmol) at room temperature. The mixture was stirred for 48 h and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1 to 1/1) to afford pyrrole **96** (6.37 g, 8.07 mmol, 83% for 2 steps) as a white solid material. IR (KBr): 3734, 3257, 2954, 2930, 2858, 2360, 2342, 1743, 1636, 1559, 1520, 1472, 1437, 1372, 1254, 1205, 1155, 838 $cm^{-1}$; $^1$H-NMR (400 MHz, $CDCl_3$, 60 ºC): δ 9.23 (br s, 1H), 6.90 (s, 1H), 6.51 (s, 2H), 6.54 (dd, $J$ = 17.6, 11.2 Hz, 1H), 6.23 (br d, $J$ = 2.3 Hz, 1H), 5.26 (d, $J$ = 11.2 Hz, 1H), 5.19 (d, $J$ = 17.6 Hz, 1H), 4.85 (br s, 1H), 3.99 (d, $J$ = 9.6 Hz, 1H), 3.93 (d, $J$ = 10.8 Hz, 1H), 3.85–3.75 (m, 1H), 3.71(s, 3H), 3.51 (dd, $J$ = 10.8, 6.8 Hz, 1H), 3.44 (dd, $J$ = 12.8, 6.0 Hz, 1H), 3.14 (d, $J$ = 8.4 Hz, 1H), 1.75–1.60 (m, 2H), 1.49 (s, 9H), 0.94 (s, 9H), 0.93 (s, 9H), 0.19 (s, 3H), 0.12 (s, 6H), 0.08 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$, 60 ºC): δ 169.63, 161.32, 156.14, 155.00 (q, $J$ = 37.1 Hz), 132.46, 126.06, 121.50, 116.49, 115.99 (q, $J$ = 287.5 Hz), 109.81, 108.98, 84.97, 79.57, 78.85, 65.65, 63.36, 56.12, 52.54, 52.40, 44.16, 41.31, 27.98, 26.08, 26.07, 18.41, 18.22, –4.15, –4.54, –5.24, –5.28; HRMS (ESI, *m/z*): $[M+Na]^+$ calcd for $C_{36}H_{59}O_8N_4F_3NaSi_2$, 811.3716; found, 811.3714.

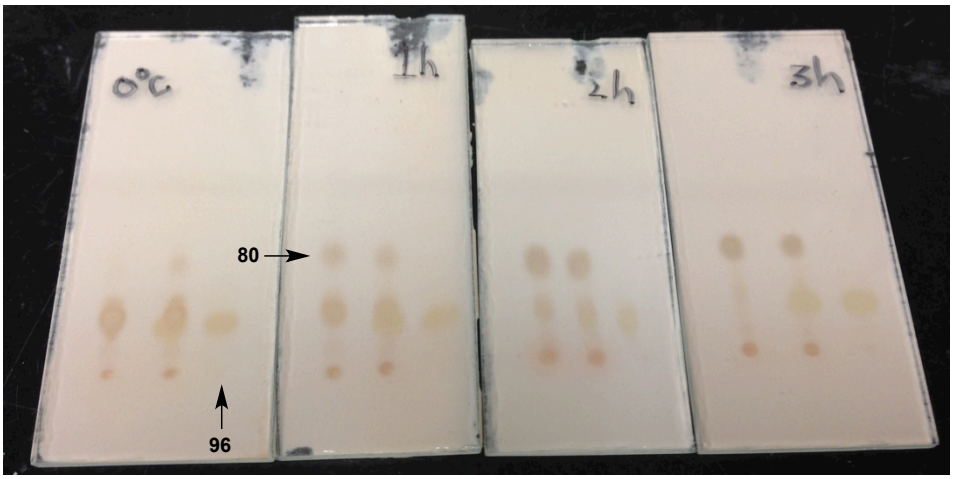



Compound **80**:

To a solution of pyrrole **96** (120 mg, 0.152 mmol) in THF (7.6 mL) was added 1.0 M THF solution of LHMDS (464 μL, 0.464 mmol) at –78 °C. The mixture was warmed up to 0 °C and the resulting yellow solution was further stirred at this temperature for 10 min. After the mixture was cooled to –78 °C, 1.0 M THF solution of AcOH (152 μL, 0.152 mmol) was slowly added. The mixture was stirred at room temperature for 3 h. The reaction was quenched with 1.0 M THF solution of AcOH (319 μL, 0.319 mmol), and to the mixture was added brine (10 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL x3). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1 to 2/1) to afford tetracyclic compound **80** (85.1 mg, 0.112 mmol, 74%) as a white amorphous material. IR (KBr): 3372, 2954, 2930, 2858, 2360, 2342, 1734, 1653, 1472, 1419, 1369, 1254, 1158, 1108, 1107, 837 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$): δ 7.43 (dd, *J* =3.0, 1.5 Hz, 1H), 7.29 (br s, 1H), 7.08 (dd, *J* = 3.0, 1.5 Hz, 1H), 6.48 (t, *J* = 3.0 Hz, 1H), 5.91 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.56 (br s, 1H), 5.31 (d, *J* = 11.0 Hz, 1H), 5.08 (d, *J* = 17.5 Hz, 1H), 4.98 (d, *J* = 7.5 Hz, 1H), 3.88 (dd, *J* = 11.5, 8.0 Hz, 1H), 3.88 (dd, *J* = 10.3, 7.5 Hz, 1H), 3.61 (dd, *J* = 10.3, 7.5 Hz, 1H), 3.45 (dd, *J* = 11.5, 10.0 Hz, 1H), 2.87-2.75 (m, 1H), 2.45 (d, *J* = 14.5 Hz, 1H), 1.88 (dtd, *J* = 11.0, 7.5, 3.5 Hz, 1H), 1.30 (s, 9H), 0.91 (s, 9H), 0.86 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 161.85, 157.47 (q, *J* = 36.4 Hz), 156.61, 153.21, 136.43, 126.34, 120.02, 118.72, 115.73 (q, *J* = 287.4 Hz), 115.67, 113.89, 83.01, 82.23, 74.16, 65.16, 62.99, 60.86, 52.89, 46.54, 40.82, 27.76, 25.82, 25.75, 18.22, 17.97, –4.04, –5.20, –5.45, –5.54; HRMS (ESI, *m/z*): [M–H] calcd for $C_{35}H_{54}O_7N_4F_3Si_2$, 755.3489; found, 755.3499.

**TLC analysis in the conversion of compound 96 to 80**



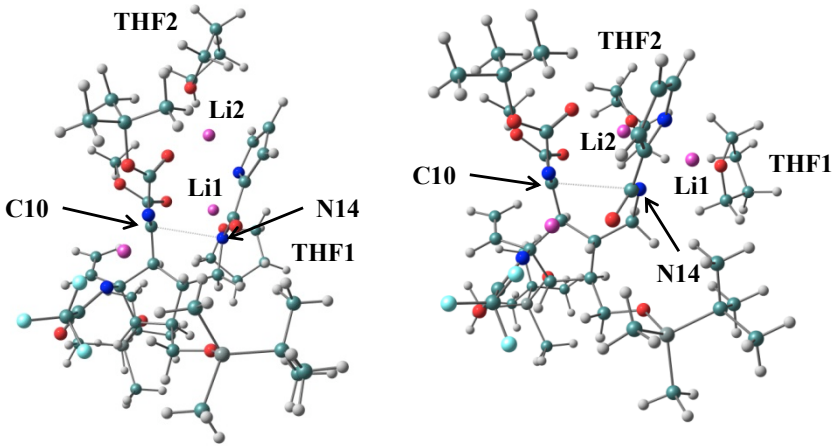

TLC (hexane/EtOAc = 3:1)

## Supplementary Discussion

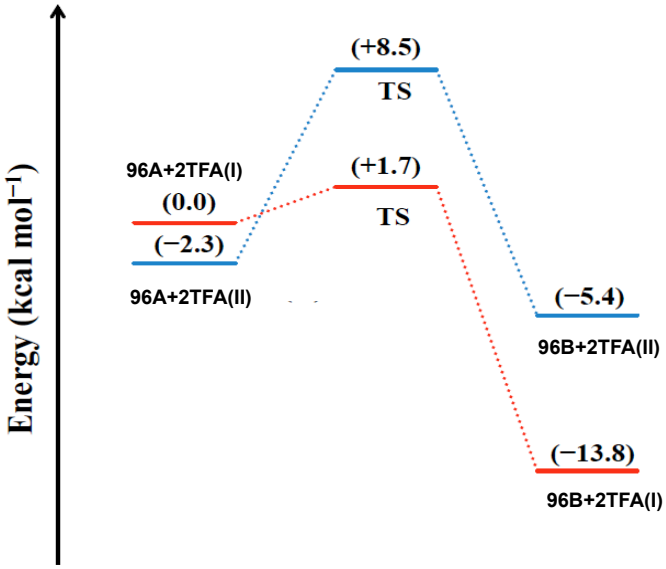
### Investigation of the solvent effects on chelate formation

The effects of solvent molecules (THF) on the chelate formation are examined by adding explicitly two THF molecules to **96A** in the DFT calculations. This system is immersed in the self-consistent reaction field (continuous) model. The author placed two THF molecules around the two lithium ions that are close to the amide and pyrrole anions and optimized the whole structure without any geometrical constraints. The optimized two lowest energy structures, which are denoted as **96A+2THF(I)** and **96A+2THF(II)**, are given in Supplementary Figure 1. **96A+2THF(II)** is slightly more stable than **96A+2THF(I)** by 2.3 kcal/mol.

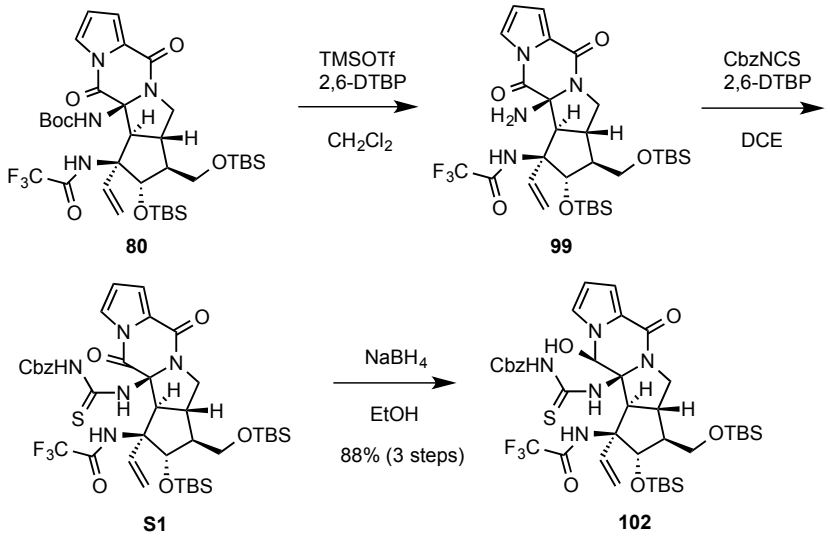
The structure of **96A** moiety in **96A+2THF(I)** is essentially similar to **96A** without any explicit solvent molecules, where one of the lithium ions (Li1) forms a coordination to the carbonyl group of methyl ester and the other (Li2) to the carbonyl group of the Boc group. The oxygen atoms of the two THF molecules, O(THF1) and O(THF2), are coordinates to Li1 and Li2, respectively, and the distance between the oxygen atoms of THF and lithium ions are around 1.94 Å. On the other hand, the structure of **96A+2THF(II)** does not exhibit a coordination of the lithium ion to the carbonyl group of methyl ester, and only the coordination to the carbonyl group of the Boc group is seen. As a result, the distance between C10 and N14 (3.21 Å) is longer than that of **96A+2THF(I)** (2.84 Å). From these two structures, the potential energy profiles to **96B+2THF(I)** or **96B+2THF(II)** are investigated, and the results are shown in Supplementary Figure 2. As seen in the figure, the energy barrier from **96A+2THF(I)** to **96B+2THF(I)** is only 1.7 kcal/mol and it is quite close to those of **96A** →**96B** (1.5 kcal/mol). On the other hand, the energy barrier from **96A+2THF(II)** to **96B+2THF(II)** is appreciably higher. Considering that the energy difference between **96A+2THF(I)** and **96A+2THF(II)** is only 2.3 kcal/mol, the coordination of lithium ions to both the carbonyl group of methyl ester and the Boc group is a key intermediate step to the facile formation of the *trans*-bicyclo[3.3.0]octane skeleton




**Supplementary Figure 1.** Optimized structure of **96A+2THF (I)** and **96A+2THF(II)**



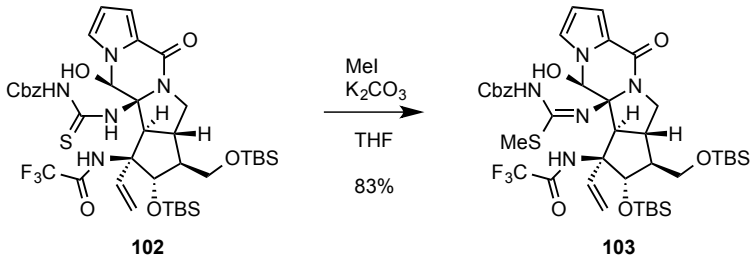

**Supplementary Figure 2.** Potential energy profiles for the cyclization of **96A+2THF (I)→ 96B+2THF(I)** and **96A+2THF(II)→96A+2THF (II)**. The potential energies (in kcal/mol) relative to **96A+2THF(I)** are shown in parenthesis.




Compound **102**:

To a solution of tetracyclic compound **80** (681 mg, 0.900 mmol) in $CH_2Cl_2$ (18 mL) were added 2,6-DTBP (1.17 mL, 5.40 mmol) and TMSOTf (812 μL, 4.50 mmol) at 0 ºC. After being stirred for 30 min at room temperature, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (20 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **99**. The crude amine **99** was used for the next step without purification due to its instability. To a solution of amine **99** in DCE (18 mL) were added 2,6-DTBP (389 μL, 1.8 mmol) and CbzNCS (869 mg, 4.50 mmol) at room temperature. The mixture was heated to 70 ºC for 12 h and concentrated under reduced pressure to give crude **S1**. The crude thiourea **S1** was also used for the next step without purification. A solution of thiourea **S1** in EtOH (18 mL) was stirred at room temperature until remaining excess CbzNCS disappeared. The mixture was cooled to 0 ºC and $NaBH_4$ (37.0 mg, 0.990 mmol) was added. After being stirred for 30 min, brine (20 mL) was added. The mixture was extracted with EtOAc (20 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography ($CHCl_3$/EtOAc = 1/0 to 4/1) to afford alcohol **102** (675 mg, 0.792 mmol, 88%) as a white amorphous material. IR (KBr): 3734, 2930, 2857, 2360, 2341, 1732, 1623, 1541, 1471, 1417, 1210, 835 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$): δ 10.80 (s, 1H), 7.89 (s, 1H), 7.39–7.34 (m, 3H), 7.32–7.26 (m, 2H), 7.17 (s,

1H), 7.02 (dd, *J* = 2.5, 1.5 Hz, 1H), 6.92 (dd, *J* = 3.5, 1.5 Hz, 1H), 6.26 (dd, *J* = 17.5, 11.0 Hz, 1H), 6.24 (dd, *J* = 3.5, 2.5 Hz, 1H), 5.70 (d, *J* = 2.5 Hz, 1H), 5.53 (d, *J* = 11.0 Hz, 1H), 5.25 (d, *J* = 17.5 Hz, 1H), 5.15 (d, *J* = 12.0 Hz, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 4.5 Hz, 1H), 4.23 (dd, *J* = 10.0, 8.0 Hz, 1H), 4.13 (br s, 1H), 3.74 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.63 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.40–3.20 (m, 1H), 3.13 (t, *J* = 10.0 Hz, 1H), 2.69 (d, *J* = 14.0 Hz, 1H), 1.90–1.83 (m, 1H), 0.91 (s, 9H), 0.87 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 178.39, 157.17, 155.94 (q, *J* = 35.1 Hz), 152.24, 135.84, 133.96, 128.88, 128.71, 128.69, 128.21, 122.28, 121.57, 121.55, 115.51 (q, *J* = 116.3 Hz), 110.71, 85.19, 82.94, 77.62, 68.44, 66.02, 63.94, 61.46, 53.38, 47.49, 40.65, 25.85, 25.84, 18.32, 17.94, –4.03, –5.17, –5.60, –5.61; HRMS (APCI, *m/z*): [M–H] calcd for $C_{39}H_{55}O_7N_5F_3SSi_2$, 850.3318; found, 850.3335.

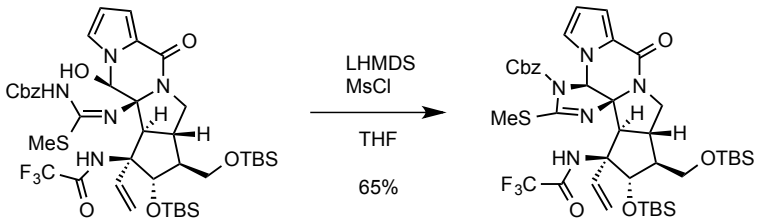



**102** **103**

Compound **103**;

To a solution of **102** (675 mg, 0.792 mmol) in THF (7.9 mL) were added MeI (297 μL, 4.75 mmol) and $K_2CO_3$ (656 mg, 4.75 mmol) at 0 ºC. After being stirred for 1 h, the reaction was quenched with brine (10 mL). The mixture was extracted with EtOAc (10 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 5/1 to 1/1) to afford isothiourea **103** (569 mg, 0.657 mmol, 83%) as a white crystal. m.p. (from ethanol): 151–153 ºC; IR (KBr): 3220, 2953, 2857, 2360, 2410, 1732, 1645, 1542, 1472, 1416, 1387, 1222, 1005, 835 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$): δ 8.51 (br s, 1H), 7.45–7.30 (m, 5H), 7.08 (dd, *J* = 3.0, 1.5 Hz, 1H), 6.88 (dd, *J* = 3.5, 1.5 Hz, 1H), 6.81 (br s, 1H), 6.21 (dd, *J* = 3.5, 3.0 Hz, 1H), 5.99 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.57 (d, *J* = 12.5 Hz, 1H), 5.53 (d, *J* = 12.5 Hz, 1H), 5.34 (d, *J* = 11.0 Hz, 1H), 5.13 (d, *J* = 1.5 Hz, 1H), 5.08 (d, *J* = 17.5 Hz, 1H), 4.77 (d, *J* = 5.0 Hz, 1H), 3.85 (dd, *J* = 11.0, 8.0 Hz, 1H), 3.77 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.58 (dd, *J* =10.0, 5.5 Hz, 1H), 3.23 (t, *J* = 11.0 Hz, 1H), 2.56 (d, *J* = 14.0 Hz, 1H), 2.48–2.35 (m, 1H), 2.29 (s, 3H), 1.87 (dddd, *J* = 10.5, 5.5, 5.0, 3.5 Hz, 1H), 0.89 (s, 9H), 0.86 (s, 9H), 0.15 (s, 3H), 0.07 (s,

3H), 0.03 (s, 6H); $^{13}$C-NMR (125 MHz, $CDCl_3$): δ 157.72, 155.97 (q, *J* = 36.0 Hz), 151.54, 151.13, 134.21, 134.15, 128.99, 128.84, 128.74, 122.98, 121.75, 115.83 (q, *J* = 288.0 Hz), 114.52, 114.14, 110.43, 84.76, 83.37, 80.65, 68.54, 66.19, 62.61, 61.79, 53.44, 46.17, 40.19, 25.82, 25.68, 18.13, 17.99, 14.61, –3.95, –5.41, –5.53, –5.69; HRMS (ESI, *m/z*): $[M+H]^+$ calcd for $C_{40}H_{58}O_7N_5F_3NaSSi_2$, 888.3440; found, 888.3446.

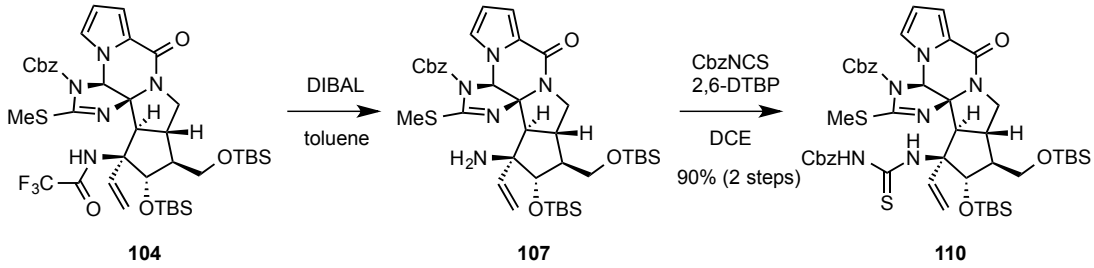



**103** **104**

Compound **104**;

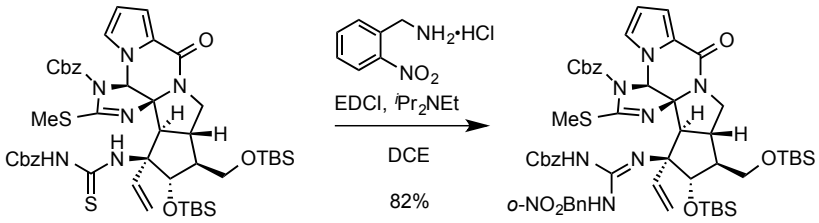
To a solution of isothiourea **103** (569 mg, 0.657 mmol) in THF (6.6 mL) was added 1.0 M THF solution of LHMDS (2.63 mL, 2.63 mmol) at –78 ºC. After being stirred for 30 min, MsCl (236 μL, 2.63 mmol) was added. After being stirred for 1 h at –40 ºC, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution (10 mL). The mixture was extracted with EtOAc (10 mL x3). The combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1 to 2/1) to afford pentacyclic **104** (362 mg, 0.427 mmol, 65%) as a white amorphous material. IR (KBr): 2930, 2360, 2342, 1733, 1654, 1559, 1472, 1421, 1388, 1287, 1158, 837 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$, 60 ºC, as a mixture of romater): δ 7.48–7.38 (m, 5H), 7.36 (s, 1H), 6.94 (br s, 1H), 6.92 (dd, *J* = 3.5 1.5 Hz, 1H), 6.25 (t, *J* = 3.5 Hz, 1H), 6.15 (s, 1H), 5.90 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.35 (d, *J* = 12.0 Hz, 1H), 5.29 (d, *J* = 12.0 Hz, 1H), 4.77 (d, *J* = 10.5 Hz, 1H), 4.76 (d, *J* = 18.0 Hz, 1H), 4.58 (d, *J* = 3.0 Hz, 1H), 4.19 (dd, *J* = 11.0, 8.5 Hz, 1H), 3.83 (dd, *J* =10.5, 4.5 Hz, 1H), 3.52 (dd, *J* = 10.0, 7.5 Hz, 1H), 3.31 (t, *J* = 11.0 Hz, 1H), 3.01–2.89 (m, 1H), 2.72 (d, *J* = 14.0 Hz, 1H), 2.41 (s, 3H), 1.93–1.85 (m, 1H), 0.92 (s, 9H), 0.90 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$, 60 ºC, as a mixture of rotamer): δ 163.23, 156.27, 155.94 (q, *J* = 36.4 Hz), 149.78, 134.16, 133.01, 129.25, 128.92, 128.85, 124.15, 122.64, 115.71 (q, *J* = 287.9 Hz), 114.13, 113.61, 112.36, 87.41, 84.52, 71.91, 69.52, 66.20, 63.77, 63.33, 54.08, 46.88, 41.30, 25.92, 25.82, 18.37, 17.89, 15.19, –4.27, –4.96, –5.50, –5.54 (some peaks are broadened due to the rotamer.); HRMS (ESI, *m/z*): $[M+Na]^+$ calcd

for $C_{40}H_{56}O_6N_5F_3NaSSi_2$, 870.3334; found, 870.3348.




Compound **110**;

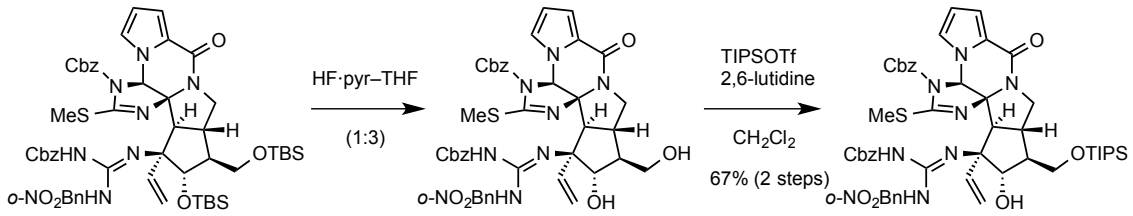
To a solution of pentacyclic **104** (362 mg, 0.427 mmol) in toluene (8.5 mL) was added 1.0 M toluene solution of DIBAL (897 μL, 0.897 mmol) at –78 °C. After being stirred for 10 min, a saturated aqueous $NH_4Cl$ solution (900 μL) and ether (20 mL) were added. After being stirred at room temperature for 1 h, to the mixture was added anhydrous $MgSO_4$. The mixture was vigorously stirred for 1 h, filtered, and concentrated under reduced pressure to give a crude **107**, which was used for the next step without purification. To a solution of crude **107** in DCE (8.5 mL) were added CbzNCS (165 mg, 0.854 mmol) and 2,6-DTBP (92 μL, 0.427 mmol) at room temperature. The mixture was stirred for 2 h and concentrated under reduced pressure. The residue was purified by silica gel, previously treated with *N,N*-dimethylaniline, column chromatography (hexane/EtOAc = 10/1 to 2/1) to afford thiourea **110** (363 mg, 0.384 mmol, 90% for 2 steps) as a yellow amorphous material. The thioura **110** was needed to immediately use for the next step due to its instability. IR (KBr): 3734, 3628, 2929, 2360, 2341, 1732, 1646, 1591, 1558, 1522, 1388, 1348, 1286, 1103, 837 $cm^{-1}$; $^1H$-NMR (500 MHz, $C_6D_6$, 60 °C, as a mixture of romater): δ 9.78 (s, 1H), 7.50 (s, 1H), 7.32–6.95 (m, 12H), 6.17 (dd, *J* = 18.0, 11.5 Hz, 1H), 6.13 (t, *J* = 3.0 Hz, 1H), 5.29 (d, *J* = 2.5 Hz, 1H), 5.14 (d, *J* = 18.0 Hz, 1H), 5.05–4.92 (m, 4H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.71 (d, *J* = 12.5 Hz, 1H), 4.38 (dd, *J* =10.5, 8.0 Hz, 1H), 3.85 (dd, *J* = 9.5, 5.0 Hz, 1H), 3.62 (dd, *J* = 9.5, 8.5 Hz, 1H), 3.30 (t, *J* = 10.5 Hz, 1H), 3.28–3.15 (m, 1H), 2.55 (d, *J* = 14.0 Hz, 1H), 1.95 (s, 3H), 1.04 (s, 9H), 0.92 (s, 9H), 0.37 (s, 3H), 0.28 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); HRMS (ESI, *m/z*): [M–H] calcd for $C_{47}H_{63}O_7N_6S_2Si_2$, 943.3744; found, 943.3763. Since thiourea **110** was gradually decomposed during the NMR experiment at 60 °C, the spectra of time-consuming $^{13}C$-NMR was difficult to obtain. Thus, we added a direct chart of HRMS.




**110** **111**

Compound **111**;

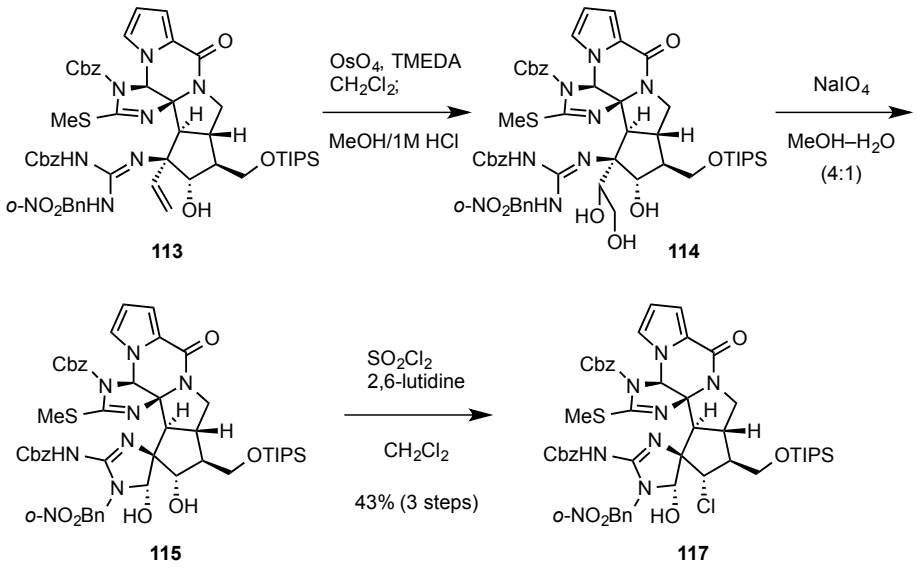
To a solution of thiourea **110** (363 mg, 0.384 mmol) in DCE (7.7 mL) were added $^{i}Pr_2NEt$ (336 μL, 2.30 mmol), *o*-nitrobenzylaminehydrochloride (350 mg, 2.30 mmol) and EDCI (440 mg, 2.30 mmol) in this order at room temperature. After being stirred at 50 °C for 12 h, the reaction was cooled to room temperature and quenched with a saturated aqueous $NH_4Cl$ solution (10 mL). The mixture was extracted with EtOAc (10 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10/1 to 1/1) to afford guanidine **111** (335 mg, 0.315 mmol, 82%) as a white amorphous material. IR (KBr): 3734, 3628, 2929, 2360, 2341, 1732, 1646, 1591, 1558, 1522, 1388, 1348, 1286, 1103, 837 $cm^{-1}$; $^1$H-NMR (500 MHz, $CDCl_3$, 60 °C, as a mixture of rotamer): δ 9.26 (br s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.0 Hz, 1H), 7.45–7.35 (m, 7H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.26 (t, *J* = 7.5 Hz, 1H), 6.93–6.87 (m, 2H), 6.21 (t, *J* = 3.5 Hz, 1H), 6.18 (dd, *J* = 18.0, 11.0 Hz, 1H), 6.02 (s, 1H), 5.30 (d, *J* = 13.0 Hz, 1H), 5.27 (d, *J* = 12.0 Hz, 1H), 5.19 (d, *J* = 13.0 Hz, 1H), 5.11 (d, *J* = 11.0 Hz, 1H), 5.09 (d, *J* = 13.0 Hz, 1H), 5.02 (d, *J* = 18.0 Hz, 1H), 4.93 (br d, *J* = 10.5 Hz, 1H), 4.82 (dd, *J* = 14.5, 7.0 Hz, 1H), 4.66 (dd, *J* = 14.5, 5.0 Hz, 1H), 4.30–4.20 (m, 2H), 3.64 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.56 (dd, *J* = 10.0, 8.5 Hz, 1H), 3.28 (t, *J* = 10.5 Hz, 1H), 3.24–3.14 (m, 1H), 2.73 (d, *J* = 14.0 Hz, 1H), 2.33 (s, 3H), 1.98–1.89 (m, 1H), 0.92 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); $^{13}$C-NMR (125 MHz, $CDCl_3$, 60 °C, as a mixture of rotamer): δ 163.61, 159.44, 156.40, 150.10, 148.99, 137.89, 134.66, 134.44, 133.89, 133.72, 133.46, 129.21, 129.07, 128.99, 128.93, 128.89, 128.34, 127.67, 127.55, 124.94, 124.44, 122.56, 117.78, 113.35, 112.14, 87.11, 85.70, 72.04, 69.23, 66.42, 66.40, 65.60, 64.60, 53.31, 47.41, 42.61, 41.85, 26.16, 25.86, 18.52, 17.94, 14.95, –4.20, –4.97, –5.25, –5.35 (some peaks are broadened due to the rotamer.); HRMS (ESI, *m/z*): $[M+H]^+$ calcd for $C_{54}H_{71}O_9N_8SSi_2$, 1063.4598; found, 1063.4606.




**111** **112** **113**

Compound **113**;

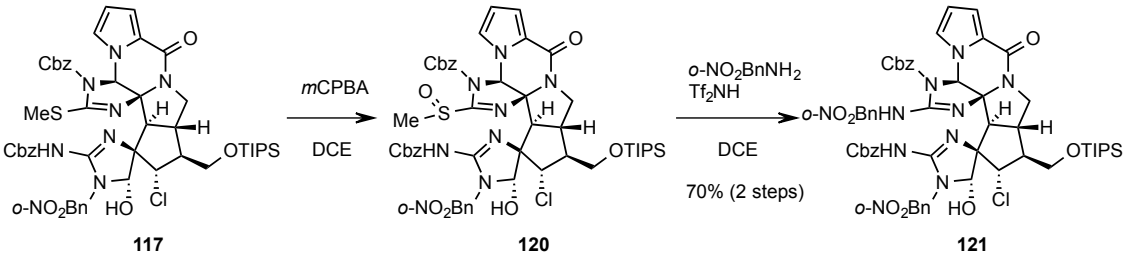
To a mixture of HF·pyr–THF (1:3, 6.3 mL) was added guanidine **111** (335 mg, 0.315 mmol) at room temperature. The mixture was stirred for 50 h and cooled to 0 °C. After the addition of TMSOMe (12 mL), the mixture was concentrated under reduced pressure. The crude diol **112** was used for the next step without purification. To the solution of crude **112** in $CH_2Cl_2$ (6.3 mL) were added 2,6-lutidine (142 μL, 1.26 mmol) and TIPSOTf (169 μL, 0.630 mmol) at 0 °C. After being stirred at room temperature for 1 h, a saturated aqueous $NaHCO_3$ solution (10 mL) was added. The mixture was extracted with EtOAc (10 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 4/1 to 1/2) to afford silyl ether **113** (209 mg, 0.211 mmol, 67% for 2 steps) as a yellow amorphous material. IR (KBr): 3734, 3628, 2942, 2360, 2342, 1733, 1646, 1590, 1558, 1523, 1388, 1348, 1288, 1093 $cm^{-1}$; $^1$H-NMR (500 MHz, $CD_3CN$): δ 9.20 (s, 1H), 8.04 (d, $J$ = 8.0 Hz, 1H), 7.66 (t, $J$ = 7.5 Hz, 1H), 7.57–7.47 (m, 4H), 7.48–7.38 (m, 3H), 7.37–7.26 (m, 5H), 6.95 (br s, 1H), 6.71 (dd, $J$ = 4.0, 1.5 Hz, 1H), 6.23 (br s, 1H), 6.18–6.05 (m, 1H), 6.14 (s, 1H), 5.51 (t, $J$ = 6.0 Hz, 1H), 5.33 (d, $J$ = 12.0 Hz, 1H), 5.29 (d, $J$ = 12.0 Hz, 1H), 5.02 (d, $J$ = 13.0 Hz, 1H), 4.99 (d, $J$ = 13.0 Hz, 1H), 5.02–4.95 (m, 2H), 4.80 (dd, $J$ = 15.5, 7.0 Hz, 1H), 4.62 (dd, $J$ = 15.5, 5.0 Hz, 1H), 4.07 (t, $J$ = 4.0 Hz, 1H), 3.97 (dd, $J$ = 10.5, 8.0 Hz, 1H), 3.80–3.75 (m, 2H), 3.58 (t, $J$ = 9.5 Hz, 1H), 3.25 (t, $J$ = 10.5 Hz, 1H), 3.07–2.95 (m, 1H), 2.84 (d, $J$ = 14.5 Hz, 1H), 2.30 (s, 3H), 1.93–1.85 (m, 1H), 1.12–1.03 (m, 21H); $^{13}$C-NMR (125 MHz, $CD_3CN$): δ 164.00, 160.09, 156.71, 148.94, 138.67, 135.53, 135.33, 134.91, 134.37, 131.72, 129.81, 129.60, 129.39, 129.20, 129.03, 128.21, 128.16, 125.54, 124.86, 123.34, 118.32, 117.51, 112.94, 112.43, 88.05, 86.48, 72.32, 69.68, 66.62, 66.03, 65.47, 64.29, 53.63, 47.47, 42.80, 41.48, 18.17, 14.93, 12.39 (one peak missing in $CD_3CN$) (some peaks are broadened due to the rotamer); HRMS (ESI, *m/z*): $[M+H]^+$ calcd for $C_{51}H_{63}O_9N_8SSi$, 991.4203; found, 991.4212.




Compound **117**;

To a solution of silyl ether **113** (44.0 mg, 44.4 μmol) were added 0.40 M $CH_2Cl_2$ solution of $OsO_4$ (121 μL, 48.4 μmol) and TMEDA (7.2 μL, 48.4 μmol) at –78 ºC. The mixture was stirred for 10 min and warmed to room temperature. To the mixture were added MeOH (1 mL) and 1M HCl (0.2 mL). The mixture was stirred, in the flask wrapped with foil, for 3 h. To the mixture was added 1M solution of $Na_2SO_3$, and the mixture was extracted with EtOAc (2 mL x3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude triol **114**, which was used for the next step without purification. To a solution of crude **114** in MeOH (2.0 mL) and $H_2O$ (0.5 mL) was added $NaIO_4$ (47.5 mg, 222 μmol) at room temperature. After being stirred under dark condition for 1 h, a saturated aqueous $NaHCO_3$ solution (2 mL) was added. The mixture was extracted with EtOAc (2 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Azeotropic treatment with hexane provided crude cyclic hemi-aminal **115** (35.2 mg) and it was used for the next step without purification. To a solution of cyclic hemi-aminal **115** in $CH_2Cl_2$ (1.8 mL) were slowly added 2,6-lutidine (12.3 μL, 106 μmol) and 0.50 M of solution of $SO_2Cl_2$ (78.0 μL, 39.0 μmol) at 0 ºC, successively. After being stirred for 10 min, a saturated aqueous $NaHCO_3$ solution (2 mL) was added. The mixture was extracted with EtOAc (2 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel, previously treated with *N,N*-dimethylaniline, flash column

chromatography (hexane/EtOAc = 4/1 to 1/2) to afford chloride **117** (18.9 mg, 18.6 μmol, 42% for 3 steps) along with inseparable minor diastereomer at C20 position as a pale yellow amorphous material. IR (KBr): 3734, 3628, 3383, 2961, 2865, 2360, 2342, 1717, 1636, 1577, 1556, 1523, 1427, 1395, 1351, 1289, 11367, 1099, 1023, 881, 801 $cm^{-1}$; $^1H$-NMR (500 MHz, $CD_3CN$, 60 ºC): δ 7.99 (d, *J* = 8.0 Hz, 1H), 7.62–7.25 (m, 13H), 6.99 (brs, 1H), 6.94 (br s, 1H), 6.67 (dd, *J* = 3.5, 1.5 Hz, 1H), 6.60 (s,1H), 6.19 (t, *J* = 3.5 Hz, 1H), 5.95 (s,1H), 5.35 (d, *J* = 12.5 Hz, 1H), 5.26 (d, *J* = 12.5 Hz, 1H), 5.24–4.95 (m, 4H), 4.49 (br d, *J* = 13.5 Hz, 1H), 4.02–3.78 (m, 3H), 3.74 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.25–3.12 (m, 2H), 2.75 (d, *J* = 13.5 Hz, 1H), 2.32 (s, 3H), 2.10–2.05 (m, 1H), 1.12–0.98 (s, 21H); HRMS (ESI, *m/z*): $[M+H]^+$ calcd for $C_{50}H_{60}O_9N_8ClSSi$, 1011.3656; found, 1011.3664. Since nitrobenzyl group of **117** was readily removed during the NMR experiment at 60 °C, the spectra of time-consuming $^{13}C$-NMR was difficult to obtain. Thus, we added a chart of HRMS.

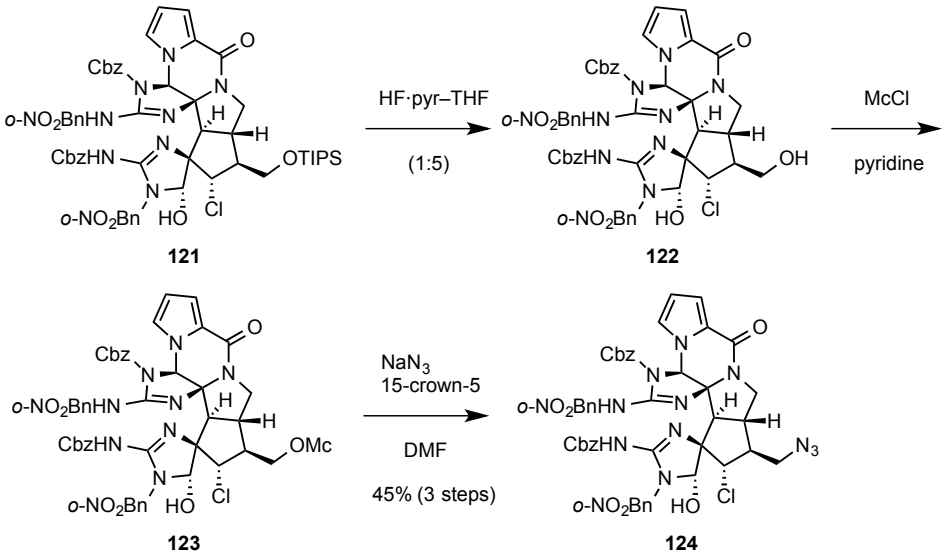



**117** **120** **121**

Compound **121**;

To a solution of chloride **117** (18.9 mg, 18.6 μmol) in DCE (370 μL) was added 0.50 M $CH_2Cl_2$ solution of *m*CPBA (washed with phosphate buffer, 74.4 μL, 37.2 μmol) at 0 ºC. The reaction flask was wrapped with foil to protect nitrobenzyl group. After being stirred at 0 ºC for 3 h, 1M solution of $Na_2SO_3$ (3 drops) was added. After being stirred for 10 min, a saturated aqueous $NaHCO_3$ solution (1 mL) was added. The mixture was extracted with EtOAc (1 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude sulfoxide **120** was used for the next step without purification. To a solution of crude **120** in DCE (0.9 mL) were slowly added a 0.5 M DCE solution of *o*-$NO_2BnNH_2$ (112 μL, 55.8 μmol) and a 0.5 M DCE solution of $Tf_2NH$ (112 μL, 55.8 mmol) at 0 ºC. The reaction flask was wrapped with foil to exclude light. After being stirred at 50 ºC for 2 h, a saturated aqueous $NaHCO_3$ solution (1 mL) was added. The mixture was extracted with EtOAc (1 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$,

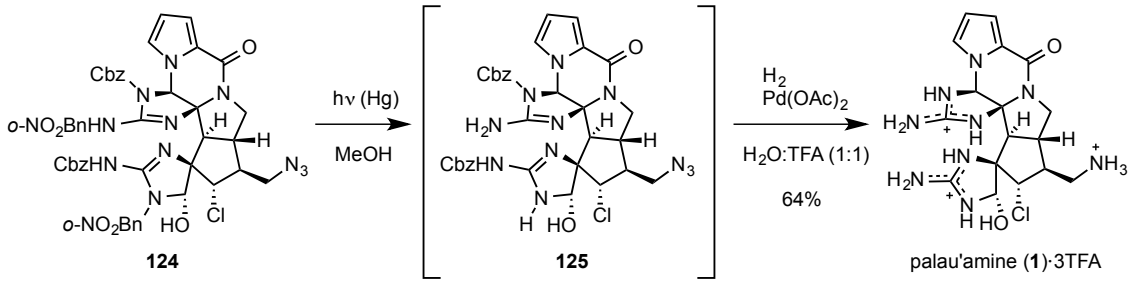
filtered, and concentrated under reduced pressure. The residue was purified by silica gel, previously treated with *N,N*-dimethylaniline, flash column chromatography (hexane/EtOAc = 4/1 to 1/2) afforded guanidine **121** (14.5 mg, 13.0 μmol, 70%) along with inseparable minor diastereomer at C20 position as a pale yellow amorphous material. IR (KBr): 3734, 3638, 3383, 2961, 2865, 2360, 2342, 1730, 1635, 1523, 1396, 1339, 1289, 1261, 1101, 1017, 800 $cm^{-1}$; $^1H$-NMR (500 MHz, $CD_3CN$, 60 °C): δ 7.97 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.65–7.30 (m, 16H), 7.00 (brs, 1H), 6.89 (br s, 1H), 6.61 (dd, *J* = 4.0, 1.5 Hz, 1H), 6.57 (s, 1H), 6.17 (t, *J* = 3.0 Hz, 1H), 5.91 (d, *J* = 5.0 Hz, 1H), 5.38–5.20 (m, 2H), 5.35 (d, *J* = 12.5 Hz, 1H), 5.24 (d, *J* = 12.5 Hz, 1H), 5.16–5.08 (m, 2H), 5.00–4.89 (m, 2H), 4.86 (dd, *J* = 16.0, 6.5 Hz, 1H), 4.56 (dd, *J* = 16.5, 5.5 Hz, 1H), 3.93–3.88 (m, 2H), 3.83 (d, *J* = 3.0 Hz, 1H), 3.79 (d, *J* = 10.0, 6.0 Hz, 1H), 3.22–3.12 (m, 2H), 2.70 (d, *J* = 13.0 Hz, 1H), 2.10–1.90 (m, 1H), 1.14–1.05 (m, 21H); HRMS (ESI, *m/z*): $[M+H]^+$ calcd for $C_{56}H_{64}O_{11}N_{10}ClSi$, 1115.4208; found, 1115.4208. Since nitrobenzyl group of **121** was readily removed during the NMR experiment at 60 °C, the spectra of time-consuming $^{13}C$-NMR was difficult to obtain. Thus, we added a chart of HRMS.




Compound **124**;

Guanidine **121** (14.5 mg, 13.0 μmol) was added HF·pyr–THF (1:5, 260 μL) at room temperature. The reaction flask was rapped with foil to protect nitrobenzyl group. The mixture was stirred for 3 h and cooled to 0 °C. After the addition of TMSOMe (1 mL), the mixture was concentrated under reduced pressure. The crude alcohol **122** was used for the next step without purification. To a solution of crude **122** in pyridine (260 μL) was

slowly added chloromethylsulfonyl chloride (2.3 μL, 26.0 μmol) at 0 ºC. After being stirred at 0 ºC for 10 min, a saturated aqueous $NaHCO_3$ solution (1 mL) was added. The mixture was extracted with EtOAc (1 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude chloromethanesulfonylate **123** was used for the next step without purification. To a solution of crude **123** in DMF (260 μL) were slowly added a 1.0 M DMSO solution of $NaN_3$ (52.0 μL, 26.0 μmol) and 15-crown-5 (5.1 μL, 26.0 μmol) at room temperature. The reaction flask was wrapped with foil to exclude light. After being stirred for 15 h, a saturated aqueous $NaHCO_3$ solution (1 mL) was added. The mixture was extracted with EtOAc (1 mL x3). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by PTLC (hexane/EtOAc = 1/4) to afforded azide **124** (5.7 mg, 58.5 μmol, 45% for 3 steps) as a pale yellow amorphous material. IR (KBr): 3380, 2920, 2360, 2102, 1727, 1633, 1523, 1323, 1397, 1352, 1289, 1192, 1136 $cm^{-1}$; $^1H$-NMR (500 MHz, $CD_3CN$, 60 ºC): δ 7.99 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 7.5 Hz, 1H), 7.73–7.60 (m, 2H), 7.60–7.32 (m, 14H), 7.09 (br s, 1H), 6.92 (br s, 1H), 6.65 (d, *J* = 2.0 Hz, 1H), 6.57 (s, 1H), 6.19 (s, 1H), 5.90 (d, *J* = 4.5 Hz, 1H), 5.45–5.25 (m, 2H), 5.37 (d, *J* = 12.5 Hz, 1H), 5.27 (d, *J* = 12.5 Hz, 1H), 5.20–5.05 (m, 2H), 5.02 (br s, 1H), 4.98–4.85 (m, 2H), 4.60 (dd, *J* = 16.0, 4.0 Hz, 1H), 3.92 (dd, *J* = 10.0, 7.5 Hz, 1H), 3.71 (d, *J* = 6.5 Hz, 1H), 3.56 (dd, *J* = 12.5, 6.0 Hz, 1H), 3.47 (dd, *J* = 12.0, 7.5 Hz, 1H), 3.18 (t, *J* = 10.5 Hz, 1H), 3.15–3.02 (m, 1H), 2.75 (d, *J* = 13.5 Hz, 1H), 2.28–2.18 (m, 1H); HRMS (ESI, *m/z*): $[M+H]^+$ calcd for $C_{47}H_{43}O_{10}N_{13}Cl$, 984.2939; found, 984.2948. Since nitrobenzyl group of **124** was readily removed during the NMR experiment at 60 °C, the spectra of time-consuming $^{13}C$-NMR was difficult to obtain. Thus, we added a chart of HRMS.



**124** **125** palau'amine (**1**)·3TFA

Palau'amine **1**;

A solution of azide **124** (2.5 mg, 2.5 μmol) in MeOH (1.0 mL) was irradiated by Hg-lamp

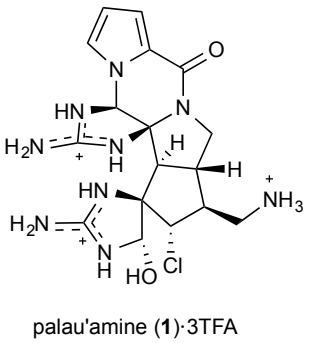
(400 W) at room temperature. After being stirred for 1.5 h, to the reaction mixture were added $H_2O$ (0.5 mL), TFA (0.5 mL) and $Pd(OAc)_2$ (0.9 mg, 3.8 μmol). Then hydrogen gas was bubbled through the mixture for 10 min. After being stirred under hydrogen atmosphere (balloon) at room temperature for 1.5 h, the reaction mixture was filtered through a Cosmonice Filter S (pore size: 0.45 μm, filter diameter 13 mm). The filtrate was concentrated under reduced pressure. The residue was purified by semi-preparative HPLC (Atlantis dC18, 5 μm, 250 x 4.6 mm, 100% $H_2O$ (0.1% $HCO_2H$), 1 mL/min, $R_T$ = 5.0 min) to give pure palau'amine (**1**) as a formate salt. Azeotropic treatment with TFA provided pure palau'amine (**1**)·3TFA (1.2 mg, 1.6 μmol, 64%) as a off-white solid. $^1$H-NMR (500 MHz, $D_2O$): δ 7.01 (dd, *J* = 2.5, 1.5 Hz, 1H), 6.87 (dd, *J* = 4.0, 1.5 Hz, 1H), 6.37 (dd, *J* = 4.0, 2.5 Hz, 1H), 6.36 (s, 1H), 5.96 (s, 1H), 4.33 (d, *J* = 7.5 Hz, 1H), 3.95 (dd, *J* = 10.0, 7.0 Hz, 1H), 3.31 (dd, *J* = 13.2, 6.5 Hz, 1H), 3.29 (t, *J* = 10.2 Hz, 1H), 3.26 (dd, *J* = 13.2, 6.5 Hz, 1H), 3.09 (d, *J* = 14.0 Hz, 1H), 2.49 (m, 1H), 2.47 (m, 1H); $^{13}$C-NMR (125 MHz, $D_2O$): δ 159.57, 157.94, 157.83, 125.21, 122.50, 115.70, 113.89, 83.76, 80.77, 74.03, 72.06, 69.02, 56.35, 48.58, 46.03, 41.87, 41.87; HRMS (ESI–TOF, *m/z*): $[M+H]^+$ calcd for $C_{17}H_{23}O_2N_9Cl$, 420.1663; found, 420.1663.

**HPLC analysis of synthetic palau'amine (1)**

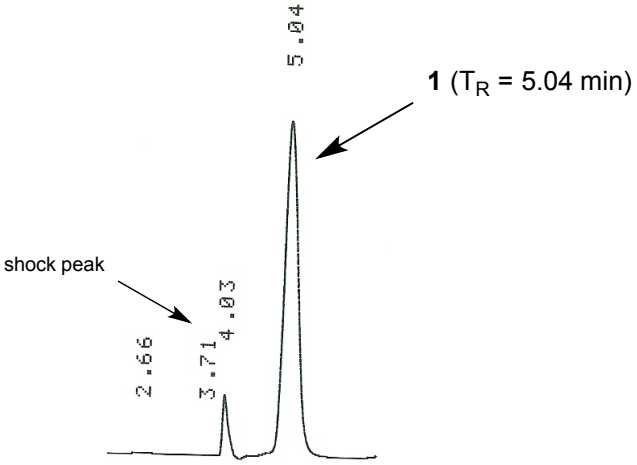
Reverse–Phase HPLC

(Atlantis dC18, 5 μm, 250 x 4.6 mm, 100% $H_2O$ (0.1% $HCO_2H$), 1 mL/min)

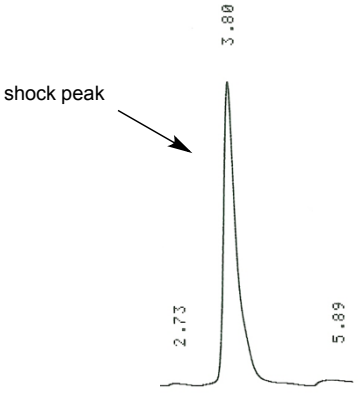
Synthetic Palau'amine (**1**)




palau'amine (**1**)·3TFA




Blank (100% $H_2O$ (0.1% $HCO_2H$))



# References


1. Forte, B.; Malgesini, B.; Piutti, C.; Quartieri, F.; Scolaro, A.; Paeo, G. *Mar. Drugs*. **2009**, *7*, 705-753.
2. Mourabit, A. Al.; Potier, P. *Eur. J. Org. Chem*. **2001**, *2001*, 237-243.
3. (a) Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc*. **1993**, *115*, 3376-3377. (b) Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem*. **1998**, *63*, 3281-3286.
4. a) Lansdell, T. A.; Hewlett, N. M.; Skoumbourdis, A. P.; Fodor, M. D.; Seiple, I. B.; Su, S.; Baran, P. S.; Feldman, K. S.; Tepe, J. J. *J. Nat. Prod*. **2012**, *75*, 980–985. b) Beck, P., Lansdell, T. A., Hewlett, N. M., Tepe, J. J. Groll, M. *Angew. Chem. Int. Ed*. **2015**, *54*, 2830–2833.
5. (a) Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Am. Chem. Soc*. **1997**, *119*, 7159-7160. (b) Dilley, A. S.; Romo, D. *Org. Lett*. **2001**, *3*, 1535-1538. (c) Belanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellew, J. E.; Trenkle, W. C. *J. Org. Chem*. **2002**, *67*, 7880-7883. (d) Poullennec, K. G.; Kelly, A. T.; Romo, D. *Org. Lett*. **2002**, *4*, 2645-2648. (e) Poullennec, K. G.; Romo, D. *J. Am. Chem. Soc*. **2003**, *125*, 6344-6345. (f) Katz, J. D.; Overman, L. E. *Tetrahedron* **2004**, *60*, 9559-9568. (g) Garrido-Hernandez, H.; Nakadai, M.; Vimolratana, M.; Li, Q.; Doundoulakis, T.; Harran, P. G. *Angew. Chem. Int. Ed*. **2005**, *44*, 765-769. (h) Dransield, P. J.; Dilley, A. S.; Wang, S.; Romo, D. *Tetrahedron* **2006**, *62*, 5223-5247. (i) Lanman, B. A.; Overman, L. E. *Heterocycles* **2006**, *70*, 557-570. (j) Nakadai, M.; Harran, P. G. *Tetrahedron Lett*. **2006**, *47*, 3933-3935. (k) Lanman, B. A.; Overman, L. E.; Paulini, R.; White, N. S. *J. Am. Chem. Soc*. **2007**, *129*, 12896-12900. (l) Bultman, M. S.; Ma, J.; Gin, D. Y. *Angew. Chem. Int. Ed*. **2008**, *47*, 6821-6824. (m) Cernak, T. A.; Gleason, J. L. *J. Org. Chem*. **2008**, *73*, 102-110. (n) Hudon, J.; Cernak, T. A.; Ashenhurst, J. A.; Gleason, J. L. *Angew. Chem. Int. Ed*. **2008**, *47*, 8885-8888.
6. Grube, A.; Köck, M. *Angew. Chem. Int. Ed*. **2007**, *46*, 2320-2324.
7. (a) Buchanan, M. S.; Carroll, A. R.; Addelpalli, R.; Avery, V. M.; Hooper, J. N.; Quinn, R. J. *J. Org. Chem*. **2007**, *72*, 2309-2317. (b) Buchanan, M. S.; Carroll, A. R.; Quinn, R. J. *Tetrahedron Lett*. **2007**, *48*, 4573-4574.
8. Kobayashi, H.; Kitamura, K.; Nagai, K.; Nakao, Y.; Fusetani, N.; Van Soest, R. W. M.; Matsunaga, S. *Tetrahedron Lett*. **2007**, *48*, 2127-2129.
9. (a) Wang, S.; Romo, D. *Angew. Chem. Int. Ed*. **2008**, *47*, 1284-1286. (b) Li, Q.; Hurley, P.; Ding, H.; Roberts, A. G.; Akella, R.; Harran, P. G. *J. Org. Chem*. **2009**, *74*, 5909-5919. (c)

Sivappa, R.; Mukherjee, S.; Dias, H. V. R.; Lovely, C. J. *Org. Biomol. Chem.* **2009**, *7*, 3215-3218. (d) Namba, K.; Inai, M.; Sundermeier, U.; Greshock, T. J.; Williams, R. M. *Tetrahedron Lett.* **2010**, *51*, 6557-6559. (e) Feldman, K. S.; Nuriye, A. Y.; Li, J. *J. Org. Chem.* **2011**, *76*, 5042-5060. (d) Ma, Z.; Lu, J.; Wang, X.; Chen, C. *Chem. Commun.* **2011**, *47*, 427-429.

10. (a) Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793-8794. (b) Yamaguchi, J.; Seiple, I. B.; Young, I. B.; O'Malley, D. P.; Maue, M.; Baran, P. S. *Angew. Chem. Int. Ed.* **2008**, *47*, 3578-3580. (c) O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem. Int. Ed.* **2008**, *47*, 3581-3583. (d) Su, S.; Seiple, I. B.; Young, I. S.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 16490-16491. (e) Ding, H., Roberts, A. G.; Harran, P. G. *Angew. Chem. Int. Ed.* **2012**, *51*, 4340–4343. (f) Ma, Z.; Wang, X.; Wang, X.; Rodriguez, R. A.; Moore, C. E.; Gao, S.; Tan, X.; Ma, Y.; Rheingold, A. L.; Baran, P. S.; Chen, C. *Science*, **2014**, *346*, 219-224. (g) Wang, X.; Chen, C. *Tetrahedron*, **2015**, *71*, 3690-3693.
11. (a) Jacquot, D. E. N.; Lindel, T. *Curr. Org. Chem.* **2005**, *9*, 1551-1565. (b) Köck, M.; Grube, A.; Seiple, I. B.; Baran, P. S. *Angew. Chem. Int. Ed.* **2007**, *46*, 6586-6594. (c) Moris, J. C.; Phillips, A. J. *Nat. Prod. Rep.* **2011**, *28*, 269-289. (d) Wang, X.; Ma, Z.; Wang, X.; De, S.; Ma, Y.; Chen, C. *Chem. Commun.* **2014**, *5*0, 8628-8639. (e) Ma, Y.; De S.; Chen, D. C. *Tetrahedron* **2015**, *71*, 1145-1173. (e)
12. Stang, P. J.; Williamson, B. L.; Zhdankin, V. V. *J. Am. Chem. Soc.* **1991**, *113*, 5870–5871.
13. Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem. Int. Ed.* **2010**, *49*, 1095-1098.
14. Seiple, I. B.; Su, S.; Young, I. S.; Nakamura, A.; Yamaguchi, J.; Jørgensen, L.; Rodriguez, R. A.; O'Malley, D. P.; Gaich, T.; Köck, M.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 14710-14726.
15. Sakakura, A.; Kondo, R.;Matsumura, Y.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2009**, *131*, 7762–17764.
16. Namba, K.; Kaihara, Y.; Yamamoto, H.; Imagawa, H.; Tanino, K.; Williams, R. N.; Nishizawa, M. *Chem. Eur. J.* **2009**, *15*, 6560-6563.
17. Namba, K.; Shoji, I.; Nishizawa, M.; Tanino, K. *Org. Lett.* **2009**, *11*, 4970-4973.
18. Namba, K.; Nakagawa, Y.; Yamamoto, H.; Imagawa, H.; Nishizawa, M. *Synlett* **2008** *11*, 1719-1723.
19. Magnus, P.; Garlzt, N.; Selbert, K. A.; Ornholt, A. *Org. Lett.* **2009**, *11*, 5646-5648.
20. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B, et al.; Gaussian 09, revision D.01, Gaussian,

Inc.;Wallingford, CT, **2009**.

21. Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett*. **1985**, *26*, 5543-5546.
22. a) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem*. **1998**, *63*, 3804-3805. b) Gers, T.; Kunce, D.; Markowski, P.; Izdebski, J. *Synthesis* **2004**, *1*, 37-42.
23. Imaoka, T.; Akimoto, T.; Iwamoto, O.; Nagasawa, K. *Chem. Asian J*. **2010**, *5*, 1810-1816.
24. Shinada, T.; Umezawa, T.; Ando, T.; Kozuma, H.; Ohfune, Y. *Tetrahedron Lett*. **2006**, *47*, 1945-1947.
25. Ray, R.; Matterson, D. *Tetrahedron Lett*. **1980**, *21*, 449-450.
26. Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem*. **1998**, *63*, 6436-6437.
27. Donohoe, T. J.; Blades, K.; Moore, P. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N. J.; Stemp, G. *J. Org. Chem*. **2002**, *67*, 7946-7956.
28. Grube, A; Immel, S.; Baran, P. S.; Köck, M. *Angew. Chem. Int. Ed*. **2007**, *46*, 6721-6724.
29. Wena, W.-H.; Wang, S.-Y.; Tsai, K.-C.; Cheng, Y.-S. E.; Yang, A.-S.; Fang, J.-M., Wong, C.-H. *Bioorg. Med. Chem*. **2010**, *18*, 4074-4084.
30. Shimizu, T.; Hiranuma, S.; Nakata, T. *Tetrahedron Lett*. **1996**, *37*, 6145-6148.
31. Nicolaou, K. C.; Winssinger, N.; Pastor, J.; DeRoose, F. *J. Am. Chem. Soc*. **1997**, *119*, 449-450.
32. Granelli-Pipemo, A.; Nolan, P. *J. Immunol*. **1991**, *147*, 2734-2739.
33. Steffan, N. M.; Bren, G.D.; Frantz, B.; Tocci, M. J.; O'Neill, E. A.; Paya, C. V. *J. Immunol*. **1995**, *155*, 4685–4691.

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