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DISSERTATION

Asymmetric Total Synthesis of Brasilicardins

(ブラシリカルジン類の不斉全合成)

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Hokkaido University

2019

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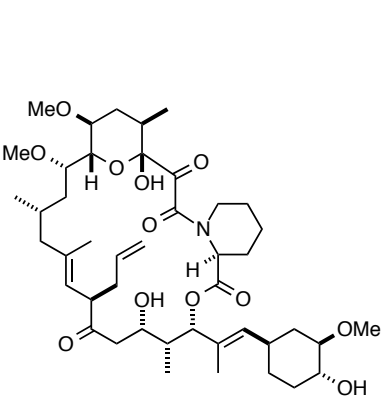
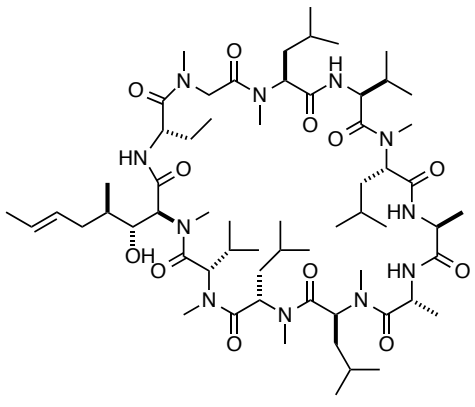
Introduction

Over the past 50 years, the establishment of organ transplantation have provided significant health benefits to hundreds of thousands of patients worldwide. However, the further progress in the development of organ transplantation is eagerly required to overcome incurable diseases that cannot be completely cured by chemotherapy and surgical treatment. To this end, it is indispensable to develop an immunosuppressive drug that prevents organ rejection of transplant recipients during organ transplantation. Immunosuppressive drugs, represented by tacrolimus (FK-506) (**1**) and cyclosporin A (**2**) have been clinically used for suppression of rejection after organ transplantation and control of severe autoimmune disease at present (Figure 1). Tacrolimus (**1**) and cyclosporin A (**2**) bind to the same immunophilin and thus inhibit dephosphorylation of nuclear factor of activated T-cells by acting on calcineurin. Consequently, it inhibits the production of cytokines such as IL-2, and thus shows immunosuppressive action.[1] However, when neural functions of calcineurin are inhibited at the same time, various side effects such as nephrotoxicity and arterial hypertension are observed.[2] Therefore, the development of novel immunosuppressive drugs without such side effects is one of the important clinical and social issues today.



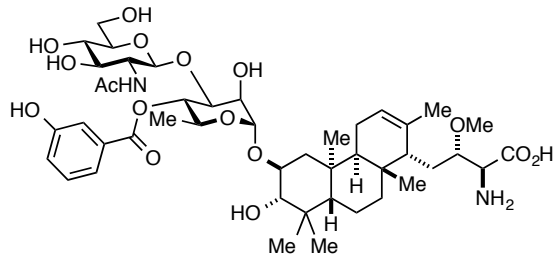
Tacrolimus (FK-506) (**1**)



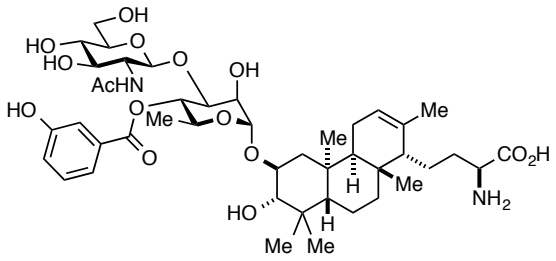
Cyclosporin A (**2**)

Figure 1. Representative immunosuppressive drugs

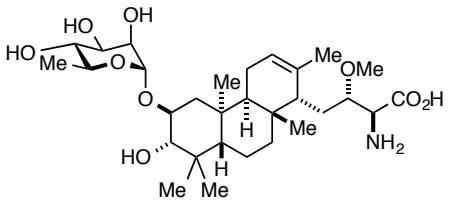
Brasilicardin A (**3**) is a natural product, which was isolated from the cultured broth of the pathogenic actinomycete *Nocardia brasiliensis* IFM-0406, by Kobayashi and co-workers in 1998.[3] Brasilicardin A (**3**) has been shown to exhibit a potent immunosuppressive and cytotoxic activity.[3,4] Particularly, it is reported that the former activity is induced by amino acid deprivation via the inhibition of the neutral amino acid transporter system L, and its active expression by a novel mechanism of action.[5] Therefore, **3** has been received attention as a lead compound for a new immunosuppressive drug with no side effects, because the mode of action of this inhibition process are different from those of known immunosuppressive drugs such as tacrolimus (**1**) and cyclosporin A (**2**). However, further biological and pharmacological studies of **3** have not been explored because of the limited availability of **3** from natural sources; therefore, efficient chemical synthesis of **3** and its derivatives as well as simplified analogues are required to explore further biological studies. Additionally, brasilicardins B–D (**4**–**6**) with same terpenoid framework were isolated from the cultured broth of the same strain in 2004 (Figure 2).[6,7]



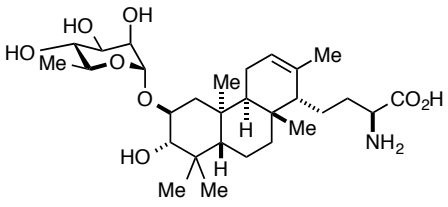
Brasilicardin A (**3**)



Brasilicardin B (**4**)



Brasilicardin C (**5**)



Brasilicardin D (**6**)

Figure 2. Structures of brasilicardins A–D

Structurally, brasilicardins A–D (**3**–**6**) share a unique and highly strained *anti-syn-anti*-fused perhydrophenanthrene skeleton (i.e., the ABC-ring system) containing two angular methyl groups on the B-ring that possesses a thermodynamically unstable boat conformation (Figure 3).[3,6] To this skeleton, different amino acid side chain and a mono- or disaccharide moiety are attached. Brasilicardins A–D has been extremely attractive synthetic targets because of their intriguing molecular architecture and significant biological properties. However, their complex and unique hybrid structure consisting of a terpene, an amino acid, and a sugar, which exhibits characteristic chemical behavior, hampered their synthesis. Especially, construction of the *anti-syn-anti*-fused perhydrophenanthrene skeleton is the greatest obstacle toward the total synthesis. At present, the sole successful total synthesis is the de novo construction of **3** and **5** by Anada, Hashimoto and co-workers in 2017,[8] in spite of considerable synthetic efforts over the last two decades.

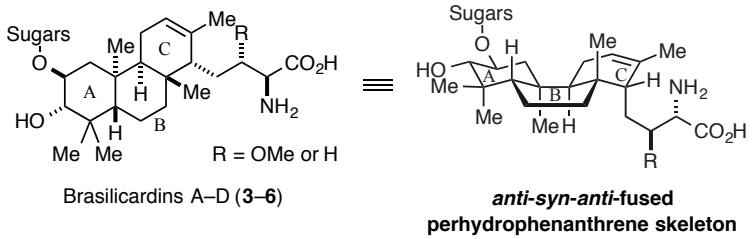
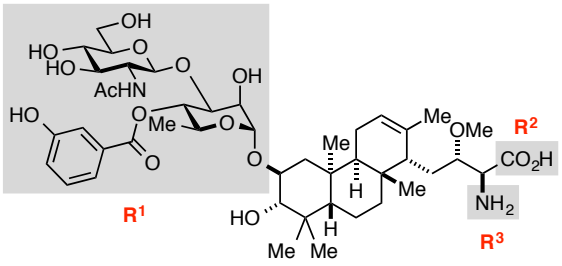


Figure 3. *Anti-syn-anti*-fused perhydrophenanthrene skeleton in brasilicardins A–D

Owing to their unique biological properties, the Kobayashi's group and the Jung's group have independently carried out the structure–activity relationship (SAR) studies of brasilicardins. Their SAR is succinctly described below.

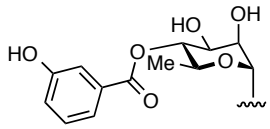
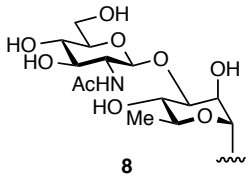
Kobayashi and co-workers have conducted the SAR studies of brasilicardin A (**3**) for immunosuppressive and cytotoxic activities (Table 1).[3,5,6,9] They prepared eleven derivatives (**7**–**17**) from **3** and assayed for their inhibitory effects to the mouse mixed lymphocyte reaction (MLR) and several human tumor cell lines. Three sites, i.e., carboxyl and amino groups in the side chain as well as a sugar unit of these derivatives differed from **3**, while the tricyclic core remained intact. Brasilicardin C (**5**), **7** and **8**, which possess a different sugar unit from **3**, have cytotoxic activity, but

MLR activity was significantly lower than **3**. Although MLR activity was decreased in methyl ester **9**, it showed more potent cytotoxicity against human T-cell acute lymphoblastic leukemia (MOLT4) and human B-cell lymphoblastic leukemia (Ball-1). Interestingly, it was revealed that the *N*-methyl form (**12**) of **3** showed stronger immunosuppressive and cytotoxic activities than **3**, while the *N,N*-dimethyl form (**13**) of **3** resulted in significant decrease of those activities. Although there is no clear correlation between these three sites and their biological activities, protection of carboxylic and amino groups tends to decrease immunosuppressive and cytotoxic activities.



Brasilicardin A (**3**)

	IC$_{50}$ (μg/mL)	
	MLR	L1210
Brasilicardin A (**3**)	0.18	1.2
Brasilicardin B (**4**)	2.5	>10
Brasilicardin C (**5**)	2.5	7.8
Brasilicardin D (**6**)	>10	>10

	IC$_{50}$ (μg/mL)		
R^1	MLR	DLD-1	MOLT4
Brasilicardin A (**3**)	0.18	2.48	29
Brasilicardin C (**5**)	2.5	–	–
 **7**	100	4.26	1.14
 **8**	100	50	7.28

			IC$_{50}$ (μg/mL)		
Compounds	R^2	R^3	MLR	MOLT4	Ball-1
3	CO_2H	NH_2	0.18	29	50
9	CO_2Me	NH_2	1.38	0.24	0.68
10	CO_2Me	NHMe	5.24	4.25	4.25
11	CO_2Me	NMe_2	21.8	9.45	25

		IC$_{50}$ (μg/mL)			
Compounds	R^3	MLR	DLD-1	Lu65	MOLT4
3	NH_2	0.18	2.48	1.25	29
12	NHMe	0.12	0.23	0.85	0.02
13	NMe_2	0.68	50	100	2.46
14	NHAc	16.8	0.89	100	100
15	NHCbz	13.8	100	100	100
16	NHBn	73.2	50	50	0.28
17	NHEt	4.28	50	17.4	1.25

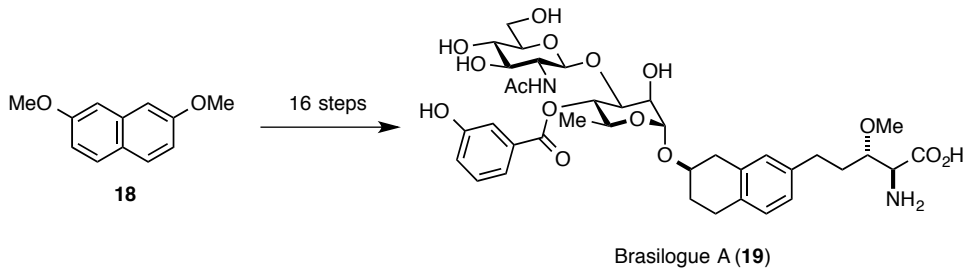
MLR : mouse mixed lymphocyte reaction
DLD-1 : human colon adenocarcinoma
MOLT4 : human T-cell acute lymphoblastic leukemia
L1210 : mouse lymphocytic leukemia
Lu65 : human lung non-small cell carcinoma
Ball-1 : human B-cell lymphoblastic leukemia

Table 1. SAR studied of brasilicardin A for immunosuppressive and cytotoxic activities

Jung and co-workers have synthesized an brasilicardin A analogue (brasilogue A, **19**) in which the natural tricyclic skeleton was replaced with a synthetically more accessible substituted tetrahydronaphthalene core, in 16 steps from commercially available 2,7-dimethoxynaphthalene **18** (Scheme 1).[10] They tested its ability to inhibit the proliferation of human T-cells. Although

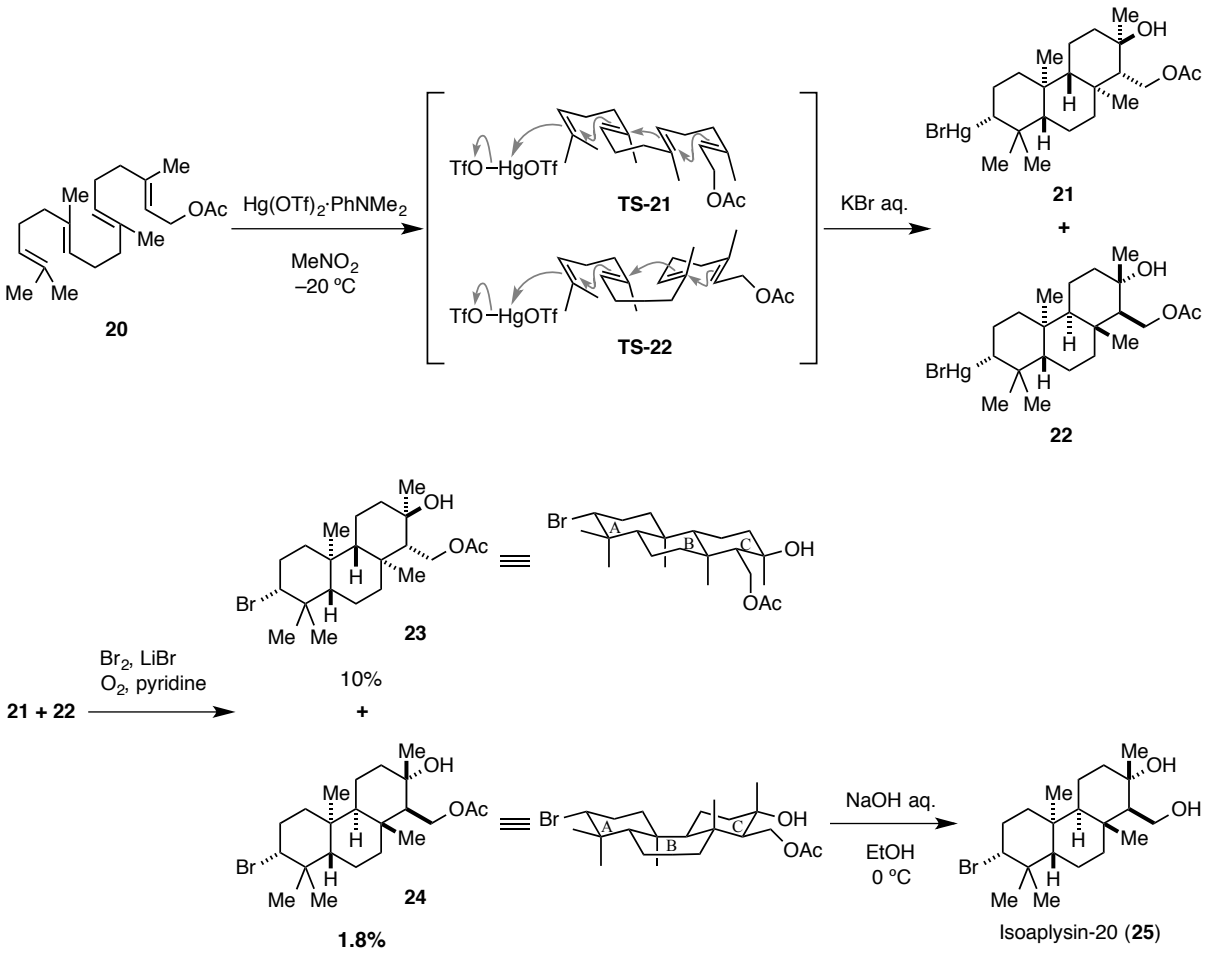
brasilogue A (**19**) possesses the same amino acid and the disaccharide units, this compound did not display the immunosuppressive activity of human T-cells. This result demonstrates that merely approximating the distance between the sugar and the amino acid units of **3** is not sufficient for bioactivity, hence, it seems that the rigid tricyclic skeleton (the ABC-ring system) also impacts its bioactivity.

However, further biological and pharmacological studies of brasilicatrdins, especially brasilicardin A (**3**), have not been explored because of the limited availability of **3** from natural sources; therefore, efficient chemical synthesis of **3** and its derivatives as well as simplified analogues are required to explore further biological studies.



Scheme 1. Synthesis and bioactivity of a brasilicardin A analogue

Recently, biomimetic or bioinspired strategies have been attracted much attention in natural products synthesis because they often provide a shortcut toward synthetic efficiency. In this respect, Nishizawa and co-workers completed the total synthesis of isoaplysin-20 (**25**) by the biomimetic polyene cyclization approach to the *anti*-*syn*-*anti*-fused perhydrophenanthrene skeleton (Scheme 2).[11] Thus, the $Hg(OTf)_2$-mediated cyclization of tetraene **20** afforded tricyclic compounds **21** and **22**, and the subsequent bromination of **21** and **22** gave bromides **23** and **24**. Hydrolysis of **24** afforded isoaplysin-20 (**25**). In this cyclization, the major product **23** was produced via the thermodynamically stable chair transition state at the B-ring (**TS-21**). On the other hand, the minor product **24**, which was produced via the thermodynamically unstable boat transition state at the B-ring (**TS-22**), was extremely low yield. Apparently, development of an alternative strategy to such skeleton is needed for the stereoselective and efficient synthesis.

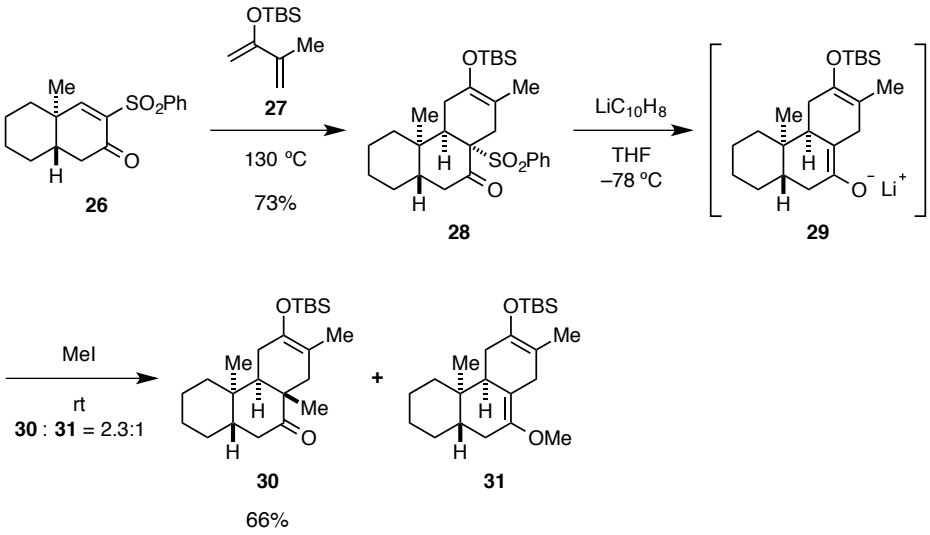


Scheme 2. Approach by the Nishizawa's group

In 2017, after twenty years of isolation, the first total synthesis of brasilicardins A (**3**) and C (**5**) was reported by Anada, Hashimoto, and co-workers.[8] Previous synthetic studies of brasilicardins are summarized in chronological order in the following sections.

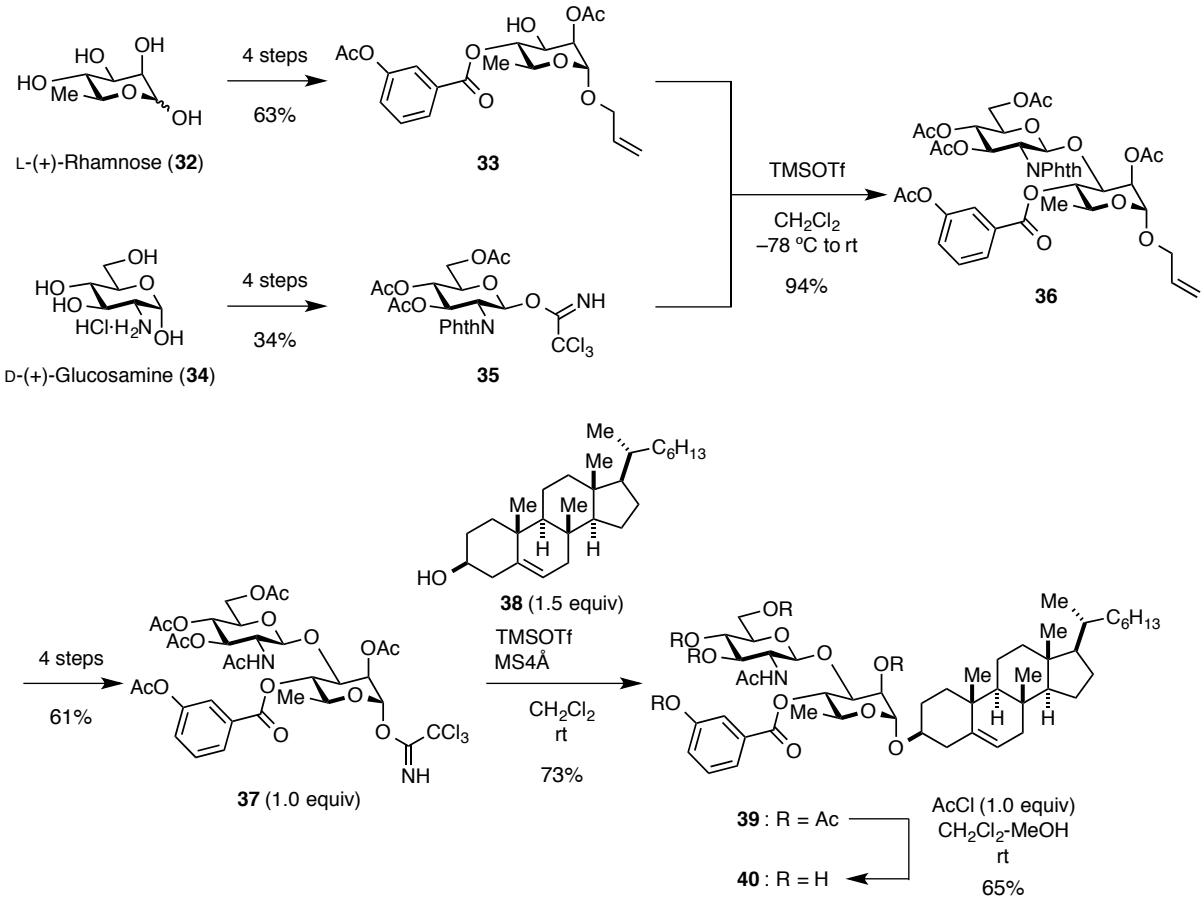
Coltart and Danishefsky reported impressive method for construction of the *anti-syn-anti*-fused perhydrophenanthrene skeleton of **3** by the combination of an intermolecular Diels–Alder reaction and the subsequent reductive angular methylation as the key steps (Scheme 3).[12] Thus, the Diels–Alder reaction of enone **26**, which was prepared from Wieland–Miescher ketone, with silyloxydiene **27** proceeded to give *syn*-cycloadduct **28**. Ketosulfone **28** was treated with lithium naphthalenide to

generate the tetrasubstituted enolate **29**, which was kinetically methylated through the action of MeI. The desired *C*-methylated ketone **30** was chemoselectively obtained in 66% yield along with the *O*-methylated enol ether **31** (**30**:**31** = 2.3:1).



Scheme 3. Approach by Coltart and Danishefsky

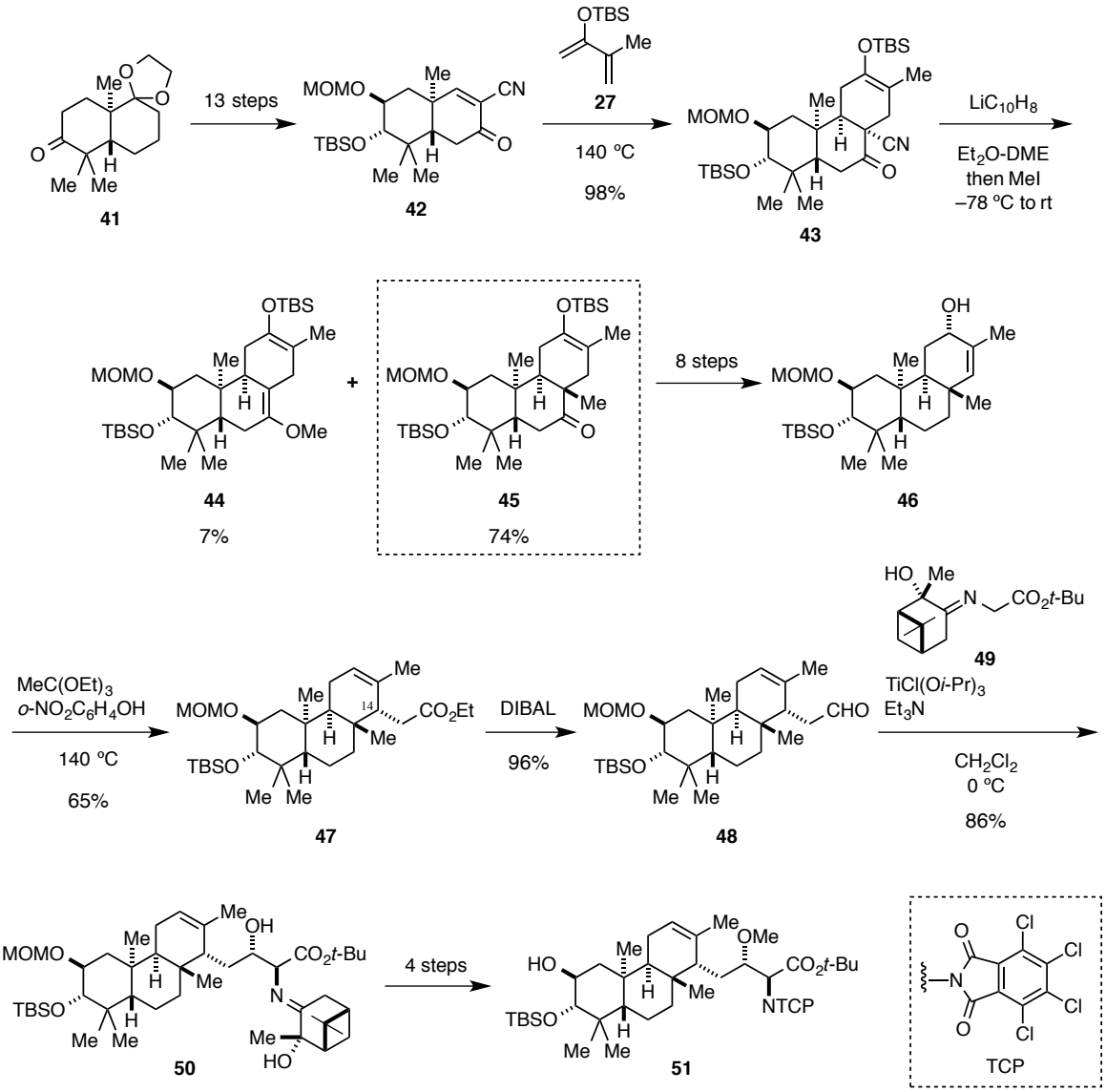
Jung and Koch reported the synthesis of the protected carbohydrate moiety **37** and its glycosylation to cholesterol (**38**) (Scheme 4).[13] Namely, disaccharide **36** was synthesized using a TMSOTf-mediated glycosylation of the glycosyl donor **35** derived from D-(+)-glucosamine (**34**) and the glycosyl acceptor **33** derived from L-(+)-rhamnose (**32**). Coupling of imidate **37**, which was obtained from **36** by four steps, with the model aglycone **38** using TMSOTf as a promoter was achieved in good yield with the desired α-glycoside **39** as the major product (α/β = 9:1). It is also noteworthy that all of the five acetate groups of **39** were selectively cleaved by acidic methanolysis without affecting the benzoate functionality of the disaccharide unit.



Scheme 4. Glycosylation studies by Jung and Koch

On the other hand, Anada, Hashimoto, and co-workers completed the total synthesis of brasilicardins A (**3**) and C (**5**) by applying the Coltart and Danisfefsky's strategy (Scheme 5).[8,12] Thus, Diels–Alder reaction of cyano enone **42**, which was synthesized from the Wieland–Miescher ketone derivative **41**, with silyloxydiene **27** proceeded smoothly to afford the tricyclic compound **43** as a single isomer. Cyanoketone **43** was treated with lithium naphthalenide to generate the required enolate, which was methylated through the action of MeI. The desired *C*-methylated ketone **45** was obtained in 74% yield along with 7% of the *O*-methylated enol ether **44** (**44**:**45** = 9:91). Note that the use of α-cyanoketone (cf. **43**) as a precursor was of critical importance for the chemoselective and reductive C8 methylation. The C14 tertiary stereogenic center of **47** was constructed by the Johnson–Claisen rearrangement of allyl alcohol **46**. After converted to aldehyde **48**, aldol coupling of **48** with the titanium enolate generated from the chiral glycine derivative **49** led to the formation

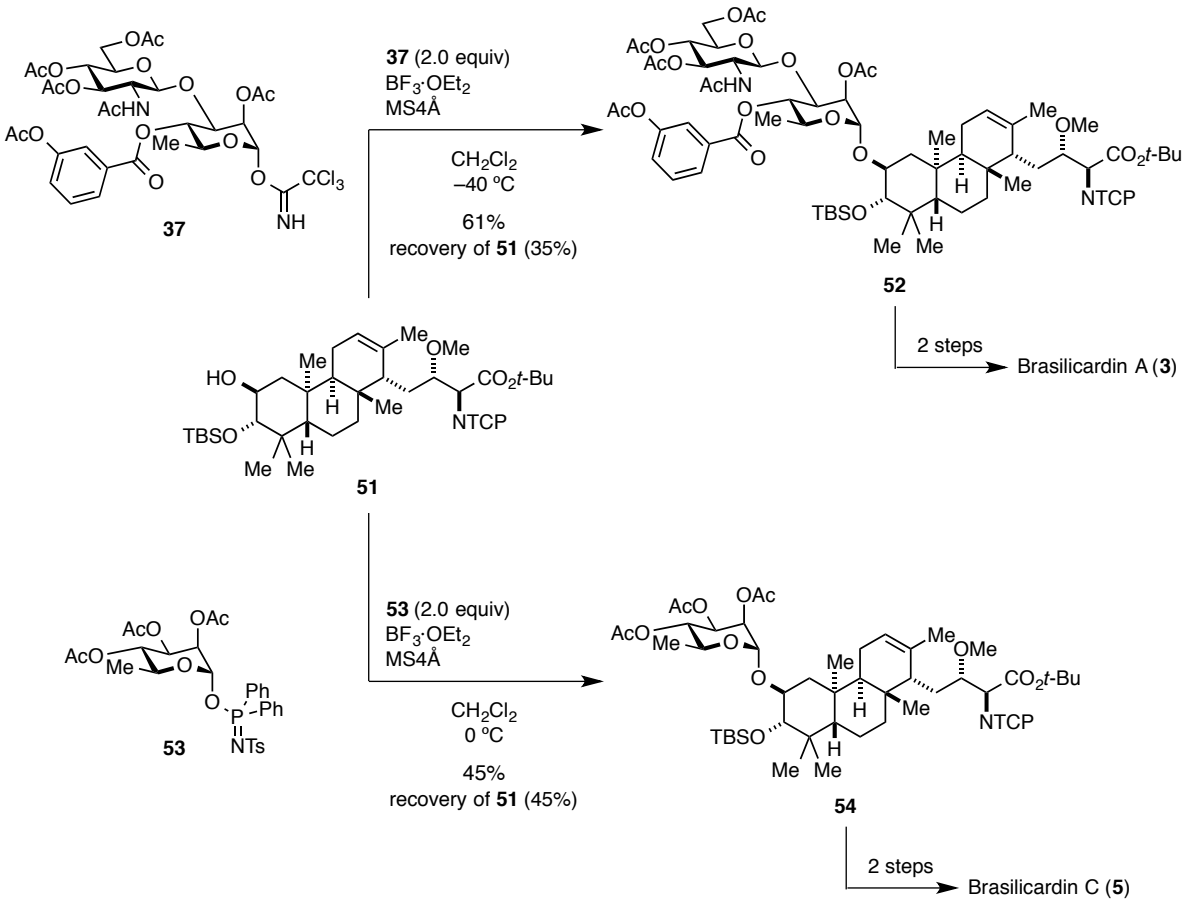
of the *anti*-α-amino aldol product **50** as a single isomer.[14] Subsequently, the glycosyl acceptor **51** was synthesized by a four-step sequence.



Scheme 5. Synthesis of brasilicardins A and C aglycon by the Anada and Hashimoto's group

Brasilicardins A (**3**) and C (**5**) could be synthesized from the common intermediate **51** (Scheme 6). Thus, on the basis of the Jung's glycosylation studies,[13] coupling of trichloroacetimidate **37** with the glycosyl donor **51** using boron trifluoride diethyl ether complex ($BF_3 \cdot OEt_2$) as a promoter was achieved in 61% yield (94% brsm) with the desired α-glycoside **52** as a single isomer. Finally,

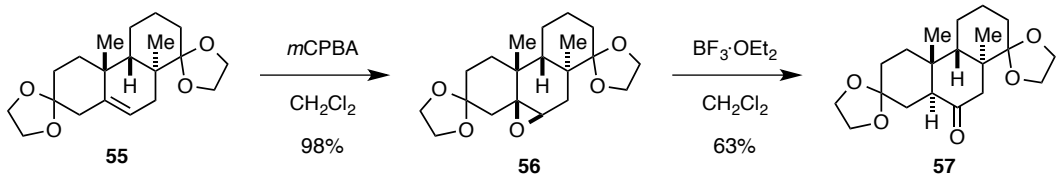
removal of the *tert*-butyl ester, the TCP group,[15] and the five acetyl groups completed the synthesis of brasilicardin A (**3**) by the two steps. Also, total synthesis of brasilicardin C (**5**) was achieved by carrying out a similar conversion using diphenylphosphinimidate (**53**).[16]



Scheme 6. Total synthesis of brasilicardins A and C by the Anada and Hashimoto's group

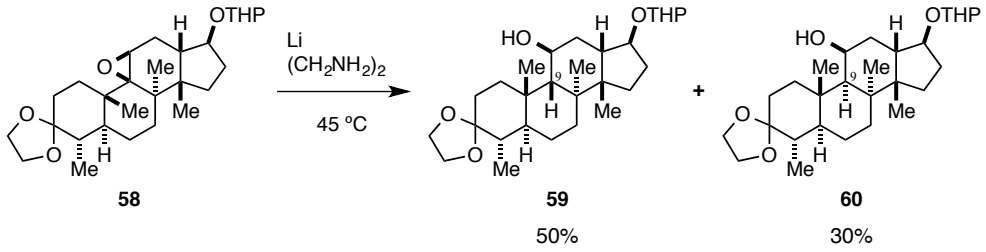
Anti-syn-anti-fused perhydrophenanthrene skeleton was also found in several natural products, thus alternative approaches to such skeleton have been reported in the literature. In the following section, the representative examples in the previous approaches are shown, and the author will also discuss them. Additional studies are cited in the references.[17]

Ireland and co-workers succeeded in the first chemical synthesis of the *anti-syn-anti*-fused perhydrophenanthrene in their studies directed toward the total synthesis of fusidic acid (Scheme 7).[18] Thus, alkene **55**, which was prepared via Robinson annulation, was oxidized with meta-chloroperoxybenzoic acid (*m*CPBA) to give epoxide **56**. Subsequently, epoxide **56** was converted to the desired ketone **57** via the ring opening of epoxide induced by $BF_3 \cdot OEt_2$ followed by hydride shift.



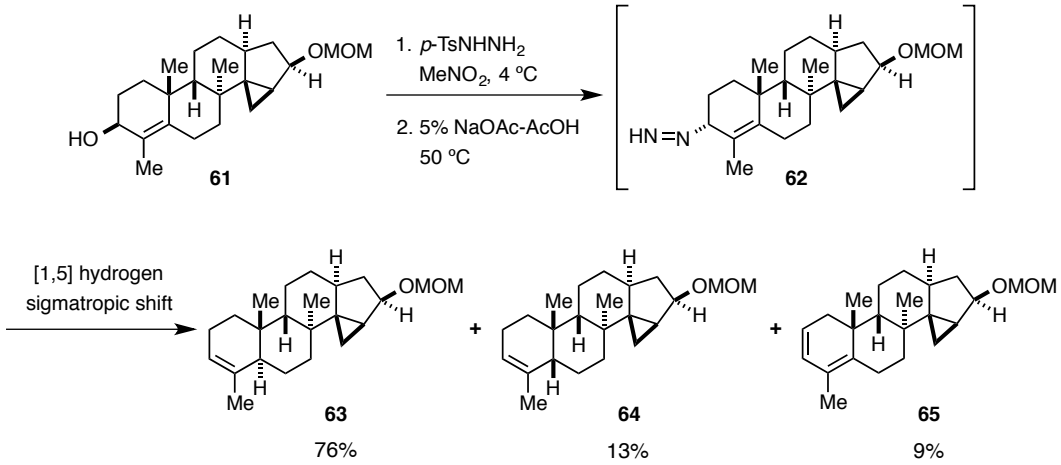
Scheme 7. Approach by the Ireland's group

Dauben and co-workers constructed the *anti-syn-anti*-fused perhydrophenanthrene skeleton which was highlighted by the reductive opening of epoxide (Scheme 8).[19] Thus, treatment of tetracyclic epoxide **58** with lithium in ethylenediamine afforded the desired 9β-H derivative **59** in 50% yield along with the undesired 9β-H derivative **60** in 30% yield.



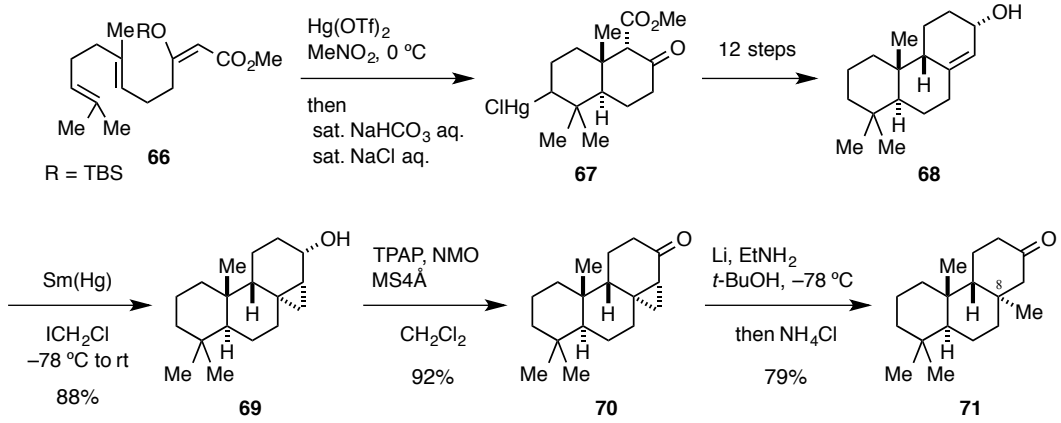
Scheme 8. Approach by the Dauben's group

Corey and Virgil have synthesized alkene **63** containing the *anti-syn-anti*-fused perhydrophenanthrene skeleton using a [1,5] hydrogen sigmatropic shift of the hydrodiazene intermediate **62** prepared from allyl alcohol **61** (Scheme 9).[20]



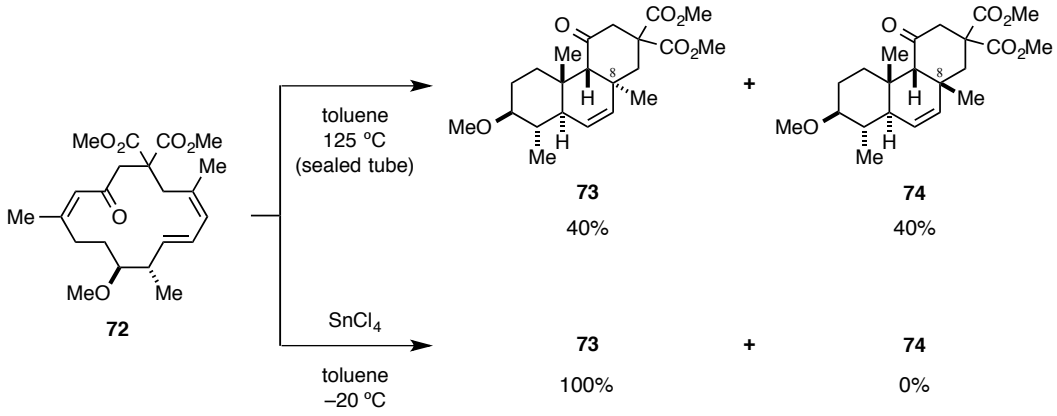
Scheme 9. Approach by Corey and Virgil

Weibel and Heisslar established the new approach to the *anti-syn-anti*-fused perhydrophenanthrene skeleton by the combination of polyene cyclization and cyclopropanation (Scheme 10).[21] Initially, the *trans*-decalin skeleton **67** was constructed by polyene cyclization using stoichiometric use of $Hg(OTf)_2$ for unsaturated ester **66**. Second, forming the C-ring by the intramolecular Horner–Wadsworth–Emmons reaction. Lastly, the hydroxyl group-directed stereoselective cyclopropanation, followed by reductive cleavage of it, resulted in the introduction of methyl group at the C8 position to form the tricyclic compound **71**.



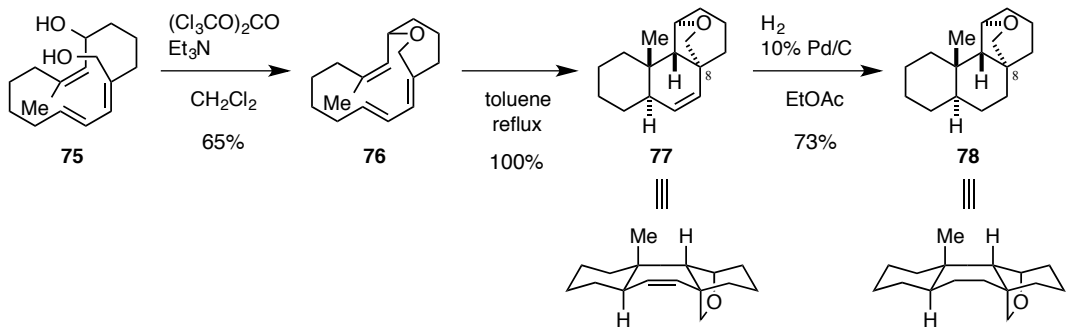
Scheme 10. Approach by Weibel and Heisslar

Deslongchamps and co-workers have synthesized tricycle **73** containing the *anti-syn-anti*-fused perhydrophenanthrene skeleton through the transannular Diels–Alder reaction of *trans–trans–cis* 14-membered ring triene **72** (Scheme 11).[22] They found that the product distribution was dependent on the reaction conditions, i.e., thermal conditions or Lewis caid-catalyzed conditions. Thus, when trienes **72** was heated at 125 ºC in toluene, the two possible *anti-syn-anti* and *syn-syn-syn* transannular Diels–Alder adducts **73** and **74** were obtained as a 1:1 mixture. On the other hand, the transannular Diels–Alder reaction under catalytic condition using tin(IV) chloride, the *anti-syn-anti* transannular Diels–Alder adducts **73** was obtained exclusively in 100% yield.



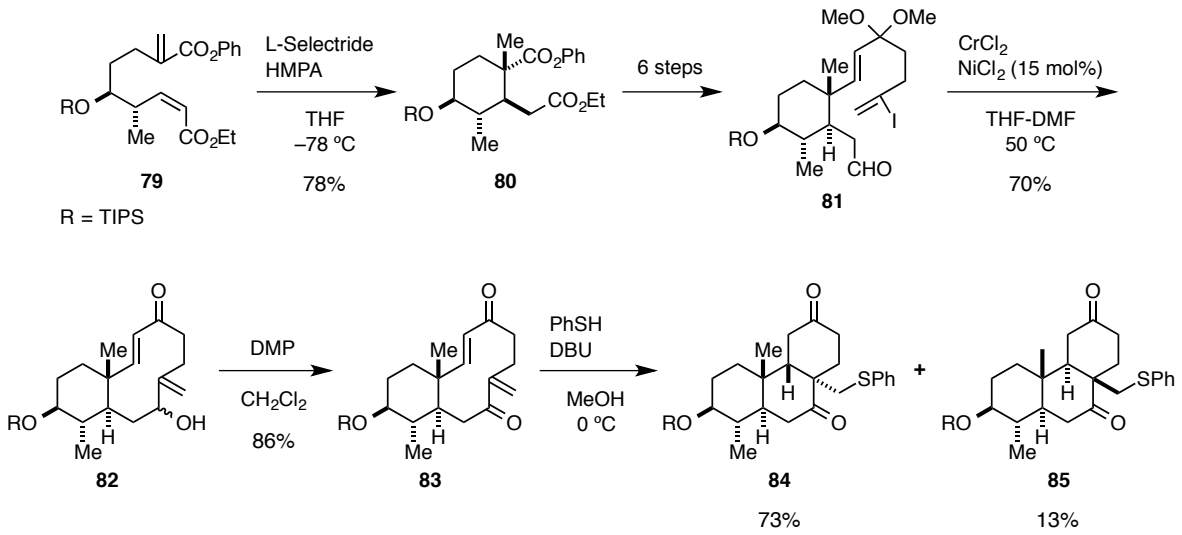
Scheme 11. Approach by the Deslongchamps's group

Jung, Houk and co-workers constructed the *anti-syn-anti*-fused perhydrophenanthrene skeleton via a bicyclic transannular Diels–Alder reaction (Scheme 12).[23] The Diels–Alder precursor **76** was prepared from diol **75**. Upon refluxing in toluene, triene **76** underwent a bicyclic transannular Diels–Alder reaction to form tetracyclic compound **77**. This compound was converted to the ABC-ring system **78** by catalytic hydrogenation. Deoxygenation to generate C8 methyl group from **78** remains a challenge for the total synthesis.



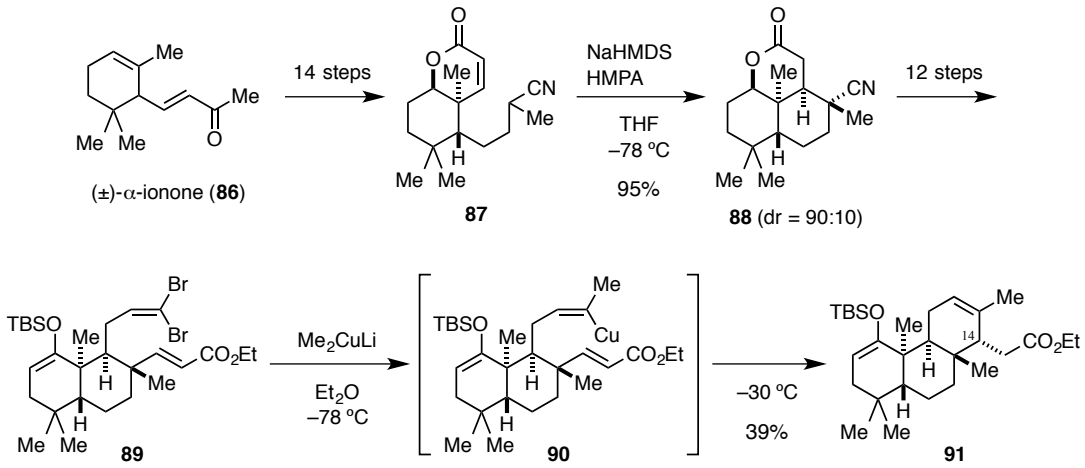
Scheme 12. Approach by the Jung and Houk's group

Fujii and Nakada constructed the *anti-syn-anti*-fused perhydrophenanthrene skeleton via intermolecular/transannular Michael reaction cascade (Scheme 13).[24] Thus, the Michael reduction/intramolecular Michael reaction cascade of α-methylidene ester **79** with lithium tri-*sec*-butylborohydride (L-Selectride®) in the presence of HMPA at –78 ºC in THF afforded the six-menbered carbocyclic compound **80** as a sole product. Then, the intramolecular Cr-mediated reaction of vinyl iodide **81**, which was obtained from **80** by six steps, was carried out in a THF/DMF mixture to afford the ten-menbered carbocyclic alcohol **82**. When the bis-enone **83**, which was prepared from **82** using Dess–Martin oxidation, was treated with thiophenol and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 0 ºC in MeOH, **83** underwent the intermolecular/transannular Michael addition to give the desired tricyclic compound **84** in 73% yield along with the undesired tricyclic compound **85** in 13% yield.



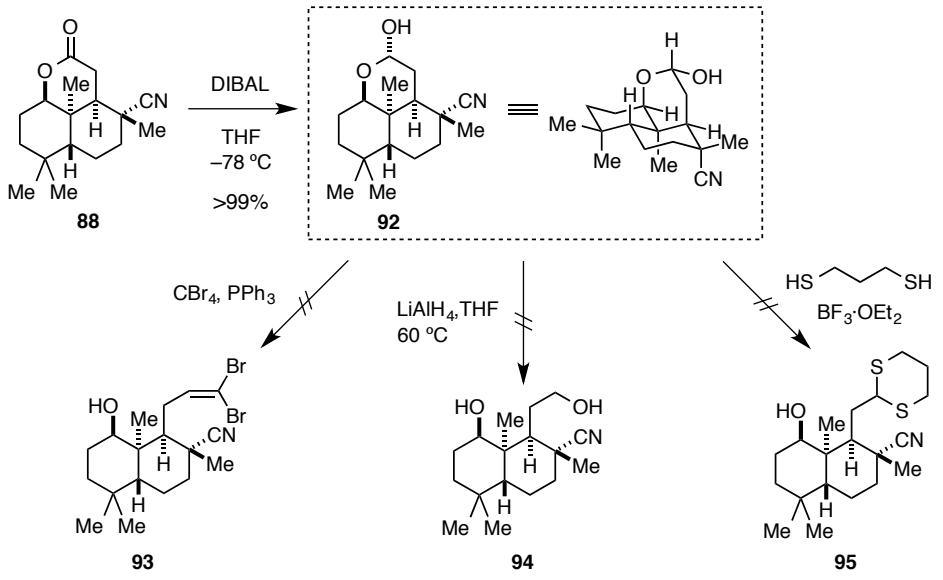
Scheme 13. Approach by Fujii and Nakada

In this connection, Mr. Mori in the author's laboratory independently conducted the studies directed toward the total synthesis of brasilicardin A (**3**). He developed the novel strategy for constructing the *anti-syn-anti*-fused perhydrophenanthrene skeleton by using double intramolecular Michael additions developed by author's laboratory (Scheme 14).[25] Thus, α,β-unsaturated lactone **87** possessing an alkanenitrile side chain, was prepared from (±)-α-ionone (**86**). When **87** was treated with NaHMDS in the presence of HMPA at –78 ºC in THF, **87** underwent the intramolecular Michael addition to give **88** having a quaternary carbon atom.[26] Then, lactone **88** was converted to the α,β-unsaturated ester **89** possessing exocyclic dibromoalkene. When **89** was treated with Me_2CuLi, the C-ring formation stereoselectively occurred to afford the tricyclic compound **91** in 39% yield.[27] This reaction appeared to proceed through the formation of (*Z*)-vinyl copper intermediate **90** followed by an intramolecular Michael addition of **90** to give **91**. In this way, he accomplished the construction of the *anti-syn-anti*-fused perhydrophenanthrene skeleton by using double intramolecular Michael additions as the key steps.



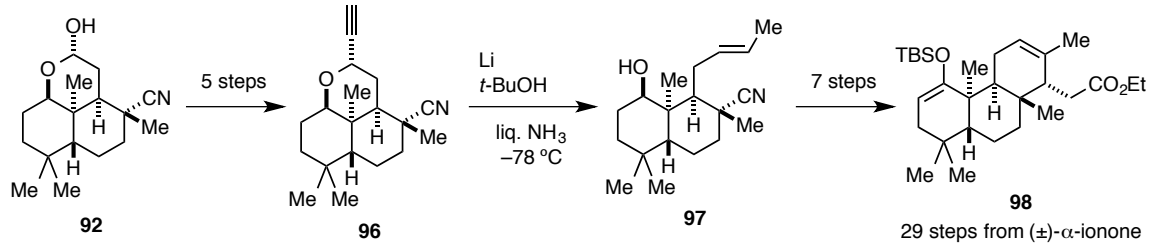
Scheme 14. Synthesis of the ABC-ring model compound **91** by Mori

However, the following synthetic issues remained in the Mori's approach (Scheme 15). The synthetic intermediate lactol **92** showed very poor reactivity to various transformations because of its tight and stable diamond-type structure. For example, not only Corey–Fucks olefination and dithioacetalization, but also hydride reduction of **92** did not proceed at all.



Scheme 15. Attempt to cleavage of lactol **92** by Mori

To overcome this issue, Mori attached an acetylene unit for facile cleavage of C–O bond of lactol **92**. Alkenyl alcohol **97** was obtained by Birch reduction of propargyl ether **96** (Scheme 16). As a result, this synthetic route was inefficient, which required 29 steps from commercially available (±)-α-ionone (**86**). These results led the author to undertake a synthetic study of brasilicardins A–D (**3**–**6**) through the development of an efficient methodology for constructing the *anti-syn-anti*-fused perhydrophenanthrene skeleton.



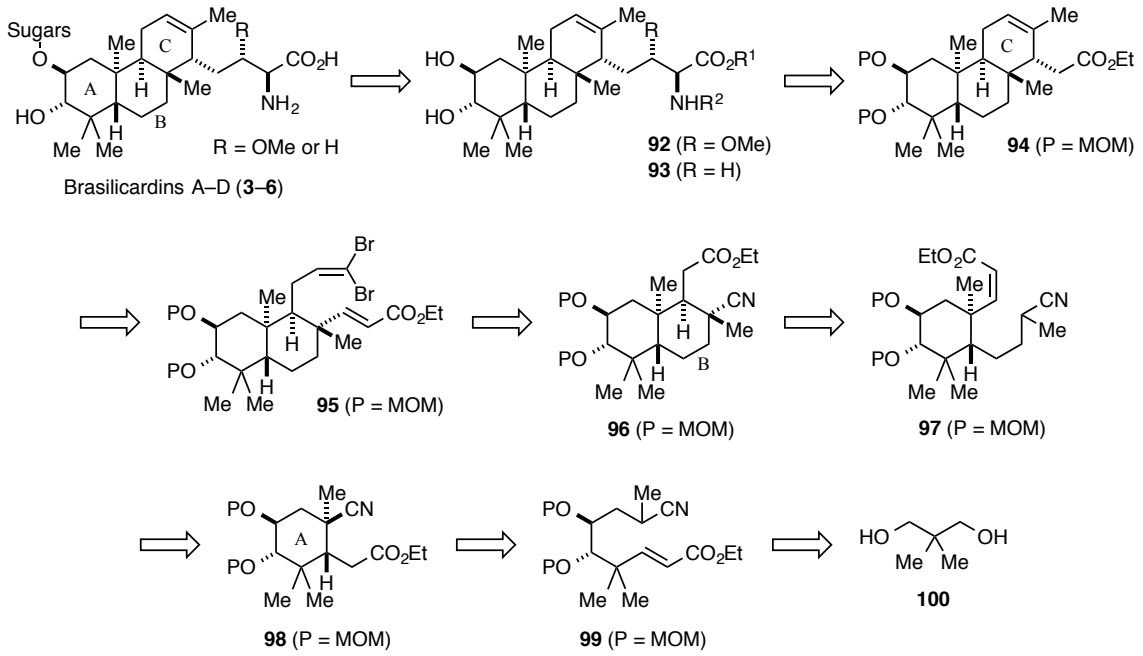
Scheme 16. Cleavage of lactol **92** using Birch reduction

In this dissertation, asymmetric total synthesis of brasilicardins A–D (**3**–**6**) is described. In chapter 1, the stereoselective construction of the *anti-syn-anti*-fused perhydrophenanthrene skeleton by triple intramolecular Michael additions as the key steps is described. In chapter 2, installation of the amino acid component corresponding to brasilicardins A–D (**3**–**6**) is described. In chapter 3, the stereoselective glycosylation and the unified total synthesis of brasilicardins A–D (**3**–**6**) are described.

Chapter 1

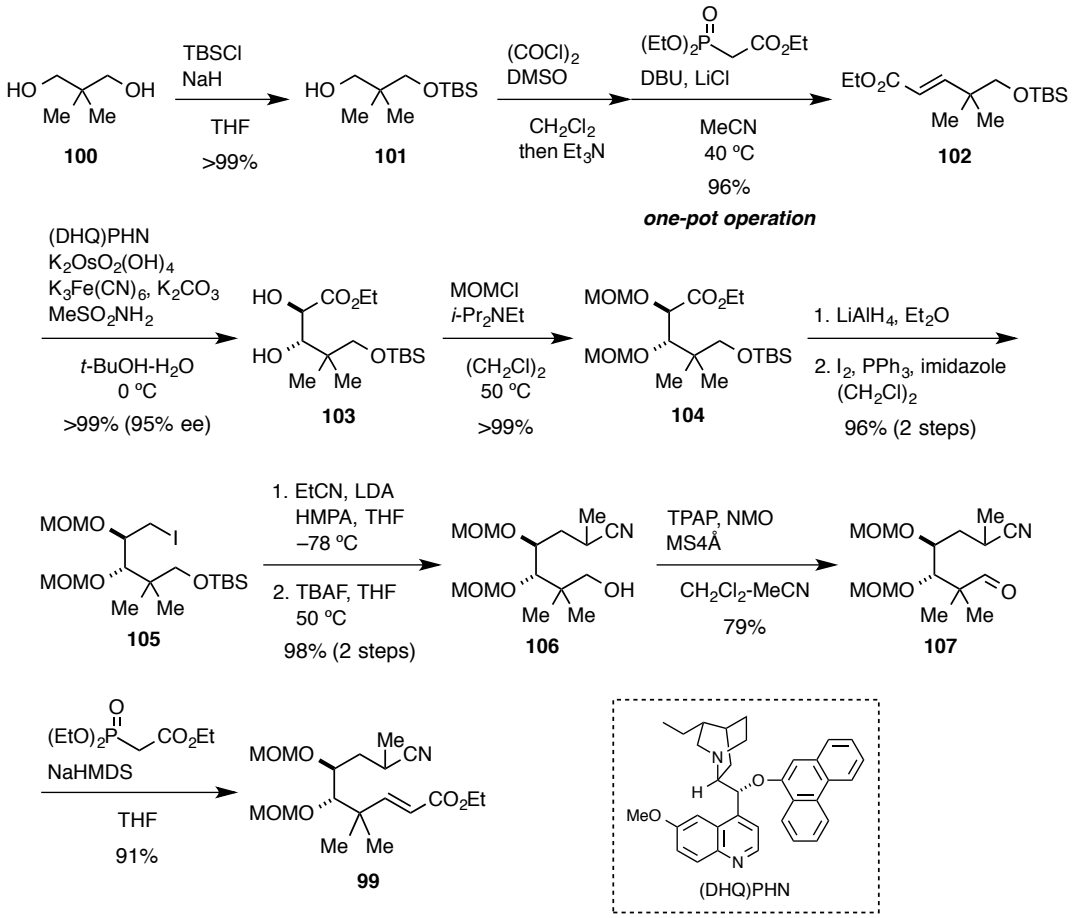
Construction of the *anti-syn-anti*-fused perhydrophenanthrene skeleton (the ABC-ring system)

Considering the previous studies by Mori, the author designed the alternative new strategy toward brasilicardins A–D (**3**–**6**) (Scheme 17). The key feature of the strategy is an intramolecular conjugate addition (Michael addition) of an acyclic α,β-unsaturated ester for construction of the *trans*-decalin skeleton (the AB-ring system), which could avoid the undesired lactol formation. Also, with a view to provide various synthetic analogues and well-defined substructures for exploring the structure–activity relationships in future, the author designed the synthetic route toward brasilicardins A–D (**3**–**6**) including stepwise construction of each rings. Thus, the saccharide moiety was to be installed through regioselective glycosylation to the protected aglycons **92** or **93** at the final stage of the synthesis. Aglycons **92** or **93** were to be derived from ester **94** via construction of the amino acid component. Thus, the author envisioned that the tricyclic core **94** could serve as an advanced intermediate for the unified synthesis. The requisite core **94** could be synthesized by a Michael addition-based strategy. More specifically, **94** could be obtained from α,β-unsaturated ester **95** through a novel intramolecular Michael addition promoted by Me_2CuLi.[27] The dibromide **95** could be synthesized from bicyclic compound **96** via homologation of the side chains. The B-ring could be constructed through an intramolecular nitrile Michael addition of acyclic (*Z*)-α,β-unsaturated ester **97**. Ester **97** would be derived from nitrile **98**. The A-ring could be constructed by a similar Michael addition of acyclic (*E*)-α,β-unsaturated ester **99**. This compound, in turn, could be accessed from commercially available 2,2-dimethylpropane-1,3-diol (**100**). The author selected a small methoxymethyl (MOM) group as the protecting group of the diol to reduce a gauche repulsion during the nitrile cyclization of **99**.



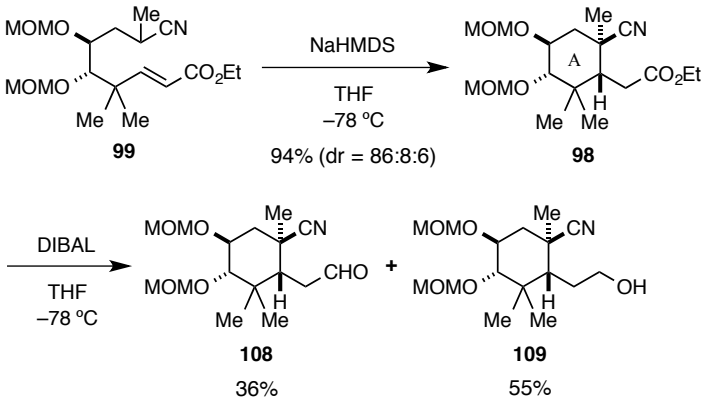
Scheme 17. Retrosynthetic analysis for brasilicardins A–D

The author's initial objective focused on the stereoselective synthesis of the crucial precursor **99** for the first intramolecular nitrile Michael addition (Scheme 18). Monosilylation of 2,2-dimethylpropane-1,3-diol (**100**) followed by Swern oxidation of the remaining alcohol afforded the corresponding aldehyde, which underwent one-pot Horner–Wadsworth–Emmons olefination under Masamune–Roush conditions[28] to furnish (*E*)-α,β-unsaturated ester **102** as the sole product. Asymmetric dihydroxylation of **102** by using the dihydroquinine-based 9'-phenanthryl ether ligand (DHQ)PHN[29] quantitatively gave the optically active diol **103** with 95% ee.[30] Protection of **103** with MOM groups, followed by reduction of the ethyl ester and iodination of the resulting alcohol, yielded alkyl iodide **105**. Alkylation of **105** with deprotonated propionitrile and the subsequent desilylation afforded alcohol **106**. This compound underwent oxidation with TPAP and Horner–Wadsworth–Emmons olefination to give (*E*)-α,β-unsaturated ester **99** as the substrate for an intramolecular Michael addition.



Scheme 18. Synthesis of the cyclization precursor **99**

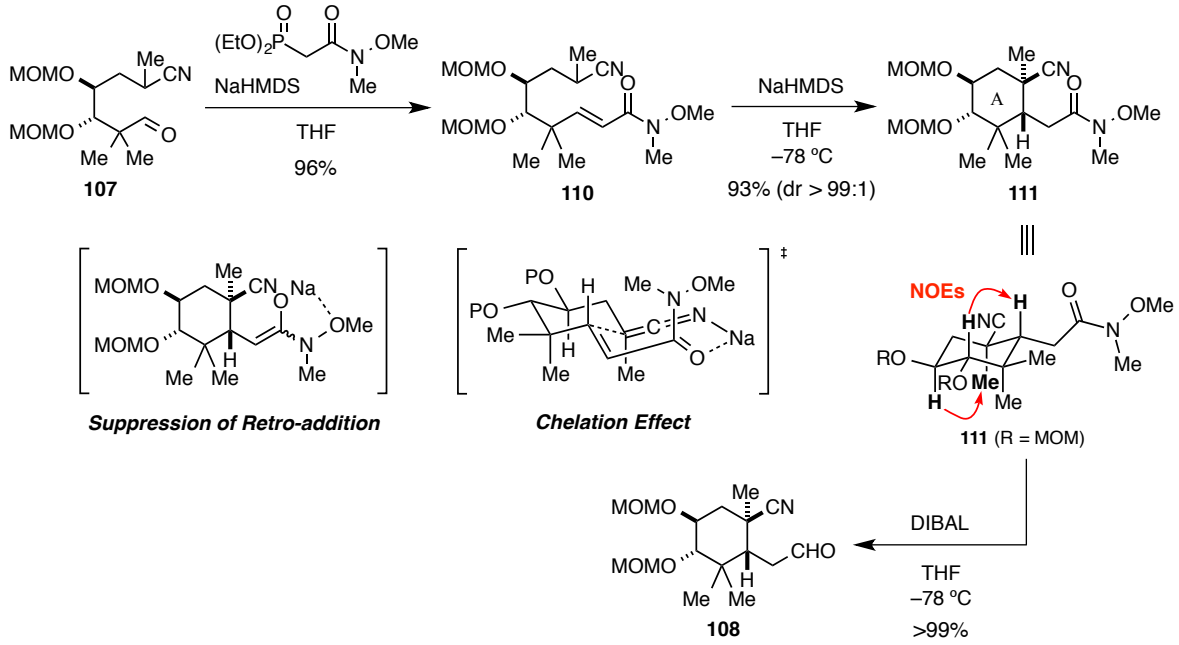
With **99** in hand, construction of the A-ring was examined (Scheme 19). Thus, upon treatment with NaHMDS, (*E*)-α,β-unsaturated ester **99** underwent the Michael addition of the in situ generated α-cyano carbanion to the α,β-unsaturated ester moiety, and cyclohexane derivative **98** was obtained in high yield with high diastereoselectivity. However, DIBAL reduction of ester **98** afforded the desired aldehyde **108** in low yield accompanied with over-reduced primary alcohol **109** as a major product. To access aldehyde **108** with high chemocontorol, the author focused on *N*-methoxy-*N*-methylamides (commonly named Weinreb amides).[31]



Scheme 19. Intramolecular Michael addition of α,β-unsaturated ester **99** for the forming of A-ring

The intramolecular Michael addition of α,β-unsaturated Weinreb amide **110** also proceeded, which resulted in the successful formation of the A-ring (Scheme 20). Thus, the requisite cyclization precursor, i.e., (*E*)-α,β-unsaturated Weinreb amide **110**, was synthesized from aldehyde **107** through Horner–Wadsworth–Emmons olefination. In an extensive screening of reaction conditions, it was found that when a THF solution of **110** was treated with NaHMDS at –78 °C, intramolecular Michael addition proceeded stereoselectively to furnish the desired product **111** in 93% yield as a single isomer. Note that the yield of **111** was decreased with recovery of **110** by the combined use of LiHMDS, HMPA, and TIPSCl.[26,32] Interestingly, one-pot Horner–Wadsworth–Emmons olefination–intramolecular Michael addition process of aldehyde **107** directly furnished the cyclization product **111** albeit in lower yield (81% yield). The stereochemistry of **111** was unambiguously determined by nuclear Overhauser effect (NOE) experiments. The observed complete stereocontrol for **111** was suggested to arise as a consequence of chelation control, wherein the keteniminate and α,β-unsaturated amide were both oriented equatorially in an antiparallel dipolar arrangement in the transition state model. Also, the chelate formation after the ring closure was suggested to trap the resulting ketene *N*,*O*-acetal enolate to prevent the undesired retro-Michael reaction. Thus, the Weinreb amide unit shows the dual effects in the Michael addition such as enhancement of the reactivity and stereoselectivity. Additionally, chemoselective reduction of the Weinreb amide over

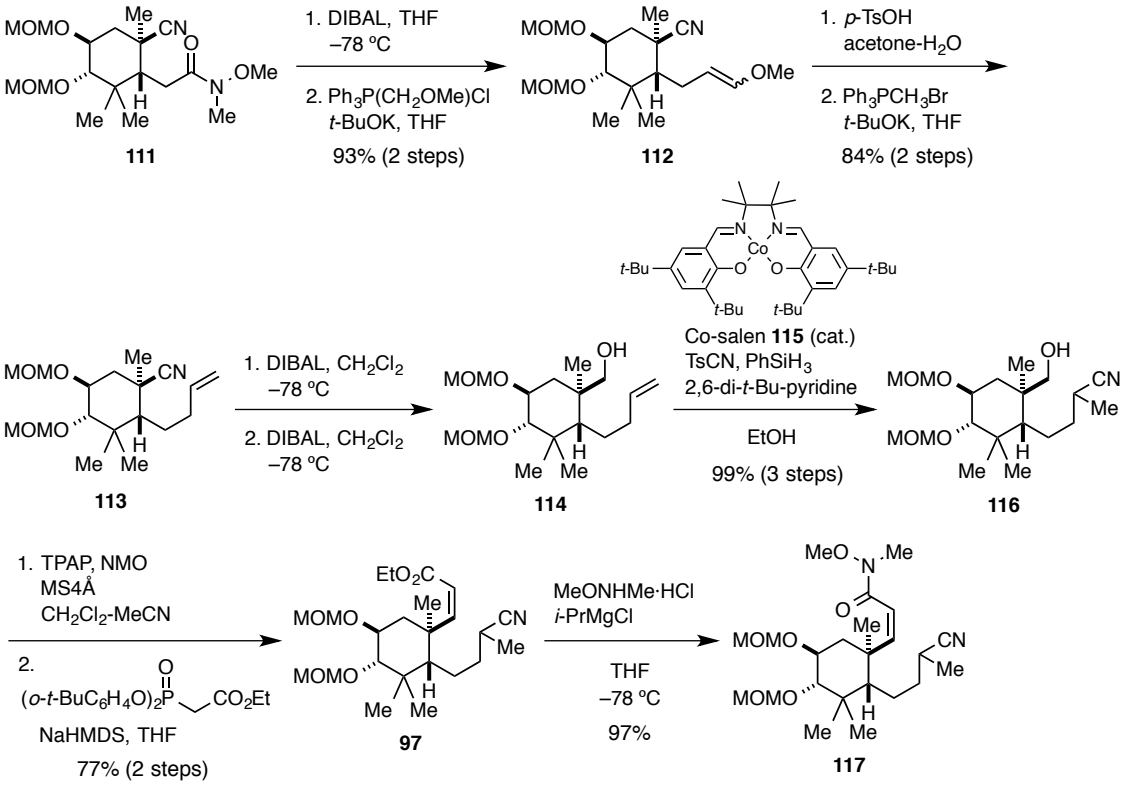
the cyano group in **111** with DIBAL afforded aldehyde **108**. In this way, by utilizing a α,β-unsaturated Weinreb amide as a Michael donor, conversion to aldehyde was greatly improved.



Scheme 20. Improved intramolecular Michael addition of α,β-unsaturated Weinreb amide **110**

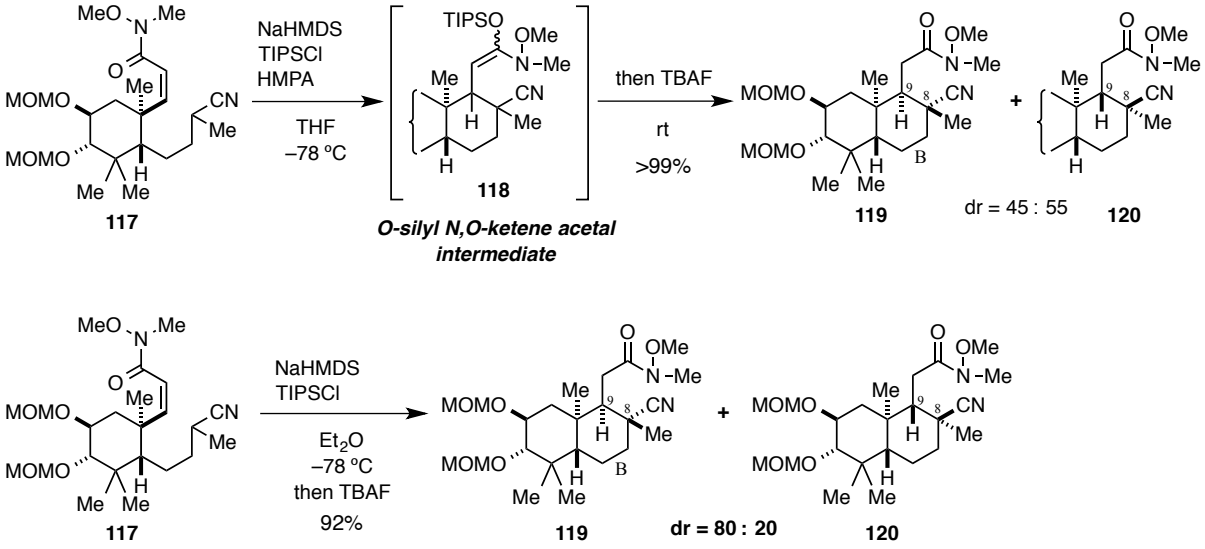
The successful realization of an intramolecular nitrile Michael addition using the Weinreb amide led the author to the next phase of the synthesis: construction of the B-ring. Elongation of the side chain for preparing the cyclization precursor is shown in Scheme 21. To this end, chemoselective reduction of the Weinreb amide over the cyano group in **111** with DIBAL in THF followed by one-carbon homologation of the resulting aldehyde by a Wittig reagent produced enol methyl ether **112**. The product **112** was further converted to terminal alkene **114** in four steps. Introduction of the cyano group into **114** was achieved by cobalt-catalyzed hydrocyanation according to Carreira's procedure[33] to give secondary nitrile **116** regioselectively. Oxidation of alcohol **116** with TPAP afforded the corresponding aldehyde, which was treated with Ando's reagent via a Horner–Wadsworth–Emmons reaction[34] to afford (*Z*)-α,β-unsaturated ester **97** with excellent *Z*-selectivity (*Z*/*E* > 99:1). The product **97** was directly converted to (*Z*)-α,β-unsaturated

Weinreb amide **117** using *N*,*O*-dimethylhydroxylamine hydrochloride (MeONHMe·HCl) and isopropylmagnesium chloride.[35]



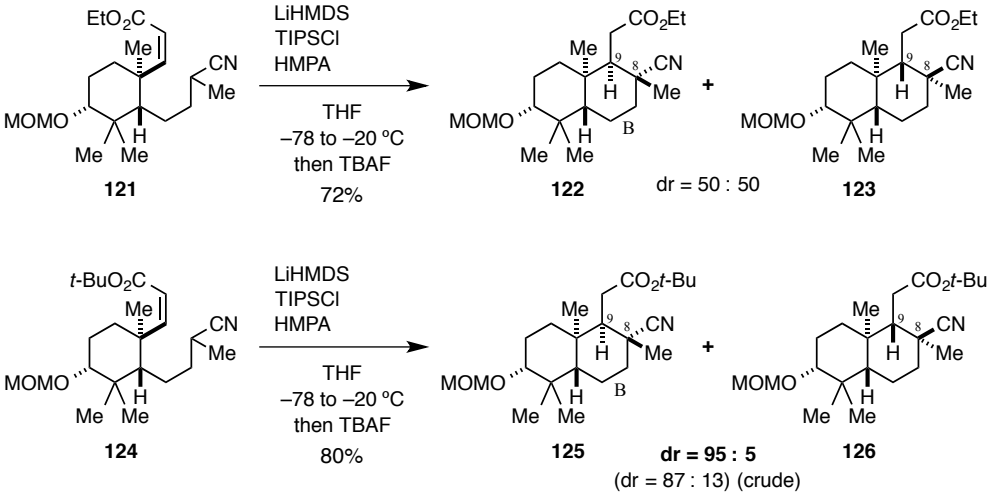
Scheme 21. Synthesis of the cyclization precursor **117**

The second intramolecular nitrile Michael addition of **117** was the crucial factor in the present synthesis; thus, the author explored the optimal reaction conditions for this step (Scheme 22). Firstly, (*Z*)-α,β-unsaturated Weinreb amide **117** was treated with NaHMDS in the presence of TIPSCl and HMPA in THF at –78 °C, which produced *O*-silyl *N*,*O*-ketene acetal **118** in situ. Upon addition of TBAF to **118** in situ, a mixture of the desired cyclization product **119** and its C8,9-diastereomer **120** was obtained as a 45:55 inseparable mixture of diastereomeric products. Upon exploration of the solvent, additives, and reaction temperature, it was found that the use of Et_2O as a solvent without addition of HMPA gave superior regioselectivity (dr = 80:20). The stereochemistry of the desired product **119** was determined by the NOESY experiment.



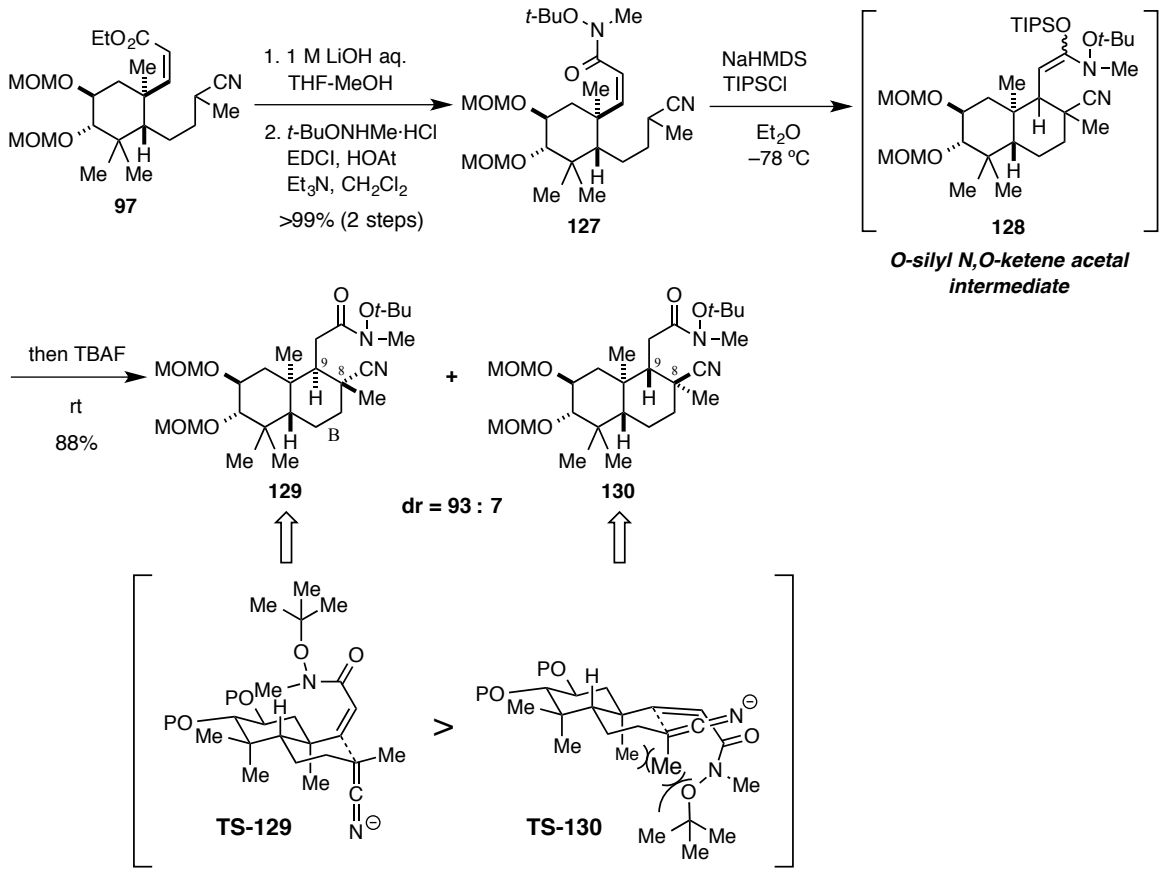
Scheme 22. Solvent effects in the second intramolecular Michael addition

In this context, Torizuka in the author's laboratory have revealed that the bulkiness of the ester substituent greatly affects the stereoselectivity in the intramolecular Michael addition of the B-ring formation (Scheme 23).[36] Thus, the cyclization reaction of ethyl ester **121** gave a 50:50 mixture of the desired cyclization product **122** and its C8,9-diastereomer **123**. On the other hand, cyclization of the corresponding bulky *tert*-butyl ester **124** afforded the cyclization product **125** with high stereoselectivity (dr = 87:13). Considering these results, owing to improve stereoselectivity, the author decided to change the methoxy group on the Weinreb amide to more bulky *tert*-butoxy group.



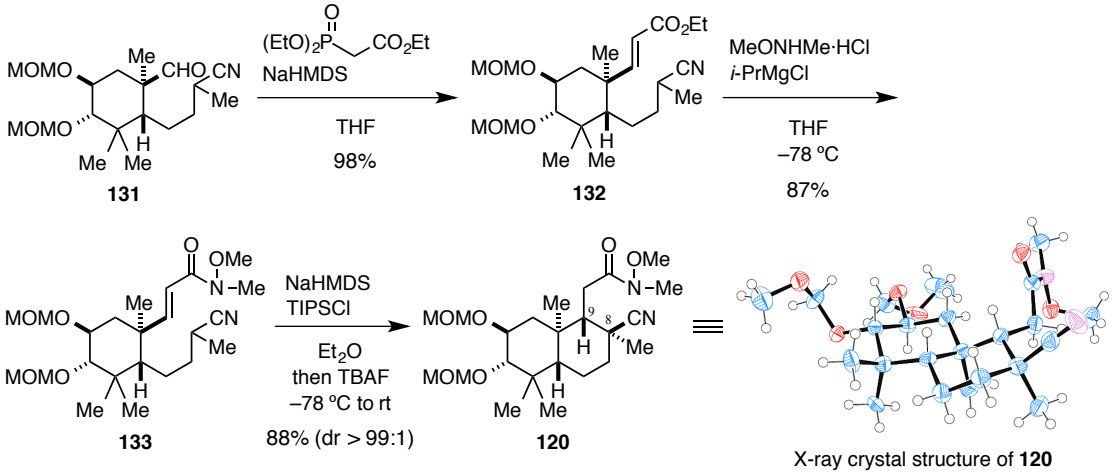
Scheme 23. Substituent effects in the second intramolecular Michael addition

As expected, the substituent on the Weinreb amide moiety had a significant impact on the ratio of the cyclization products (Scheme 24). Thus, saponification of **97** and the subsequent condensation of the resulting carboxylic acid with *N*-methyl-*O*-*tert*-butylhydroxylamine produced the modified Weinreb amide, namely, *N*-*tert*-butoxy-*N*-methylamide **127**.[37] Similar to the cyclization of **117**, the cyclization of **127** proceeded by the treatment of a mixture of **127** and TIPSCl with NaHMDS in Et_2O at –78 °C, which produced *O*-silyl *N*,*O*-ketene acetal **128** in situ. Upon addition of TBAF to **128**, the desired cyclization product **129** was obtained as a 93:7 inseparable mixture of diastereomeric products. The steric repulsions between the large substituents are likely to account for the stereochemical outcome (cf. **TS-129** vs **TS-130**). These key nitrile Michael additions (i.e., **110→111** and **127→129**) were reliably performed on a gram scale, which demonstrated the significant synthetic utility of this methodology.



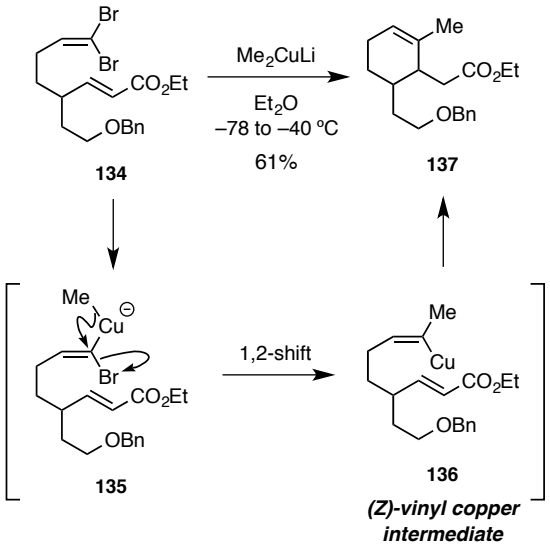
Scheme 24. Optimized conditions by using O*t*-Bu substituted modified Weinreb amide

As a comparison, the intramolecular Michael addition of the corresponding (*E*)-α,β-unsaturated Weinreb amide **133** was examined (Scheme 25). The cyclization precursor **133** was synthesized from aldehyde **131** through Horner–Wadsworth–Emmons olefination followed by amidation with MeONHMe·HCl. Under the same conditions as *Z*-isomers **117** or **127**, intramolecular Michael addition of **133** proceeded, giving rise to cyclization product **120** as a single isomer. Interestingly, different stereochemical outcomes were observed depending on olefin geometric isomers. The stereostructure of **120** was verified by X-ray crystallographic analysis (CCDC 1551802). From the above cyclization studies, the use of the bulky *O-tert*-butyl Weinreb amide, (*Z*)-configuration of the olefin, and addition of TIPSCl[38] were all indispensable to achieve a high level of stereocontrol at the newly formed stereocenters of the B-ring product **129**.



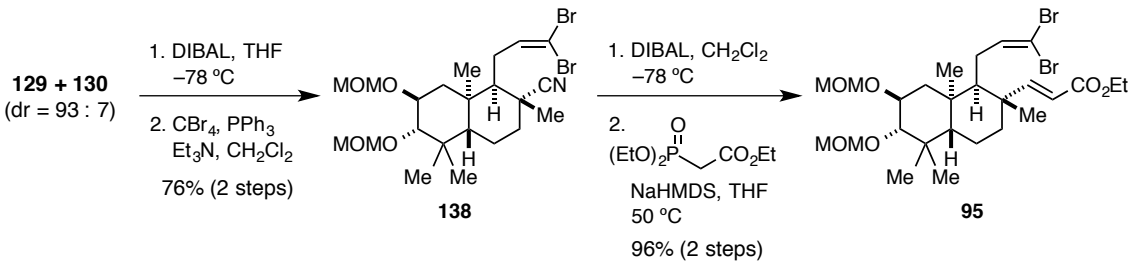
Scheme 25. Cyclization of *E*-isomer

Having developed a method for the construction of the AB-ring system including two quaternary asymmetric stereocenters based on the strategic nitrile Michael additions, the author next focused on the third intramolecular Michael addition, which leads to the ABC-ring system of brasilicardins A–D. The C-ring of tricyclic compound would be constructed by an intramolecular Michael addition of a (*Z*)-vinyl copper species generated from 1,1-dibromoalkene moiety to an α,β-unsaturated ester.[27] This reaction was developed in author's laboratory, and details in the reaction mechanism are explained in Scheme 26. When the 1,1-dibromoalkene derivative **134** was treated with an excess amount of Me_2CuLi at –78 °C followed by warming up to –40 °C, cyclohexane derivative **137** was obtained in 61% yield. Details of the reaction mechanism of this reaction is as follows: First, a halogen–metal exchange reaction at the less hinderd *exo* position generated the α-bromo organocopper intermediate **135**. Second, 1,2-shift of the methyl group in **135** with inversion of the configuration gave the (*Z*)-vinyl copper intermediate **136**. This intermediate then underwent an intramolecular Michael addition to afford **137**.



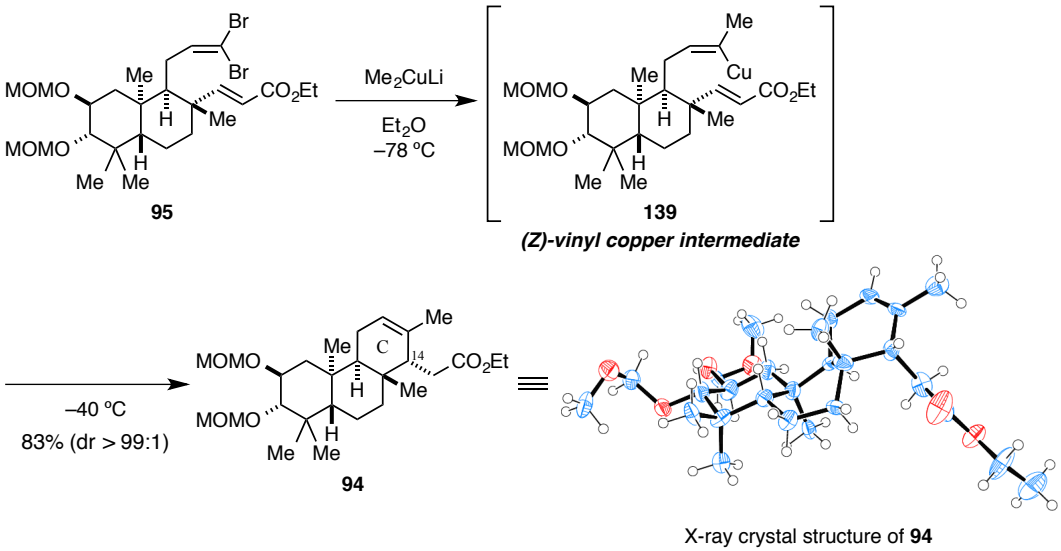
Scheme 26. Synthesis of a six-membered carbocycle through an intramolecular Michael addition of in situ generated (*Z*)-vinyl copper species

Preparation the cyclization precursor is shown in Scheme 27. Thus, Weinreb amide **129** was converted to 1,1-dibromoalkene **95**, the requisite cyclization precursor, in a four-step sequence: (1) chemoselective DIBAL reduction of the Weinreb amide moiety to an aldehyde, (2) Corey–Fuchs olefination using CBr_4 and PPh_3, wherein the minor diastereomer **130** in the cyclization was separated, (3) reduction of the cyano group to an aldehyde, and (4) Horner–Wadsworth–Emmons olefination of the resulting aldehyde, resulting in 73% overall yield.



Scheme 27. Installation of 1,1-dibromoalkene side chain

The third intramolecular Michael addition for constructing the C-ring proceeded smoothly under the reaction conditions used (Scheme 28).[27] Thus, treating **95** with Me_2CuLi (5 equiv.) in Et_2O at –78 °C for 30 min generated the (*Z*)-vinylcopper species **139** in situ. After the reaction mixture was warmed up to –40 °C and then stirred at this temperature for 1 h, the subsequent conjugate addition of **139** to the α,β-unsaturated ester moiety proceeded smoothly in the one-pot system to furnish the tricyclic compound **94** with controlled stereochemistry at the C14 position. The structure of **94** was verified by X-ray crystallographic analysis (CCDC 1550053).



Scheme 28. Stereoselective construction of the C-ring

The suggested stereochemical outcome of this cyclization reaction is shown in Figure 4. In order to form the C-ring, the B-ring needs to adopt a boat conformer. The stereoselectivity at the newly formed C14 position might be rationalized by assuming the transition state **TS-139** over **TS-139'** to avoid steric repulsion between the hydrogen at the α position of the unsaturated ester and the axial methyl group at the C8 position.

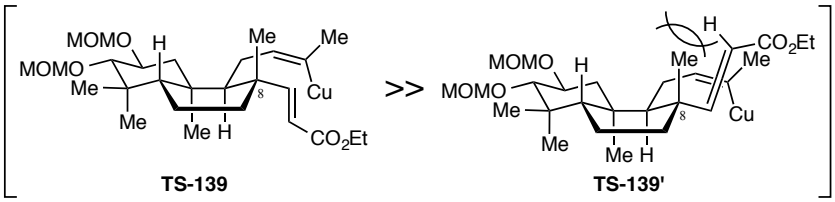


Figure 4. Suggested transition state models of cyclization of **95**

In summary of this chapter, the author has established a novel method for the stereoselective construction of the *anti-syn-anti*-fused perhydrophenanthrene skeleton (the ABC-ring system) by triple intramolecular Michael additions as the key steps. The A-ring was constructed by an intramolecular Michael addition of α-cyano carbanion to an acyclic (*E*)-α,β-unsaturated Weinreb amide, which allows simultaneous ring formation and construction of contiguous quaternary–tertiary asymmetric stereocenters. This intramolecular Michael addition was applied for the cyclization of the B-ring. The C-ring was constructed by an intramolecular Michael addition of a (*Z*)-vinyl copper species generated from 1,1-dibromoalkene moiety to an α,β-unsaturated ester. Thus, the author expects that the newly developed intramolecular nitrile Michael addition would be a powerful tool not only in brasilicardins synthesis but also in various types of terpenoids synthesis.

Experimental Section of Chapter 1

General Information

The reactions were performed using flame-dried glasswares under a positive pressure of argon. Dry tetrahydrofuran (THF) and diethyl ether (Et_2O) was distilled from sodium benzophenone ketyl. Anhydrous acetone, acetonitrile (MeCN), 1,2-dichloroethane ($(CH_2Cl)_2$), dichloromethane (CH_2Cl_2), *N*,*N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), ethanol (EtOH), methanol (MeOH), pyridine, and toluene were purchased from Kanto Chemical Co. Diisopropylamine, diisopropylethylamine (*i*-Pr_2NEt) and triethylamine (Et_3N) was distilled from CaH_2 under argon and stored in the presence of NaOH (pellets). Hexamethylphosphoric triamide (HMPA) was distilled from CaH_2 under argon and stored in the presence of MS4Å. All other reagents and solvents were used as received from commercial sources without further purification.

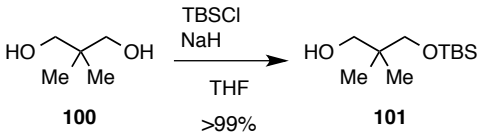
^{1}H-NMR spectra were measured using a JEOL ECA-500 (500 MHz) or JEOL ECA-600 (600 MHz) in $CDCl_3$ (δ_H 7.26), CD_3OD (δ_H 3.31). Chemical shifts are reported in parts per million (ppm) from internal tetramethylsilane, and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), and multiplet (m). Coupling constants are reported in Hz. ^{13}C-NMR spectra were measured using a JEOL ECA-500 (125 MHz) or JEOL ECA-600 (151 MHz) in $CDCl_3$ (δ_C 77.0), CD_3OD (δ_C 49.0). High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-T100GCV or a JEOL JMS-SX102A at GC-MS & NMR Laboratory, Faculty of Agriculture, Hokkaido University, or Instrumental Analysis Service, Global Facility Center, Hokkaido University. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrophotometer. X-ray crystallographic data were recorded with a Rigaku XtaLAB Synergy Diffractometer at the Faculty of Science, Hokkaido University. Melting points (m.p.) are uncorrected.

Analytical thin layer chromatography (TLC) was performed using 0.25 mm E. Merck Silica gel ($60F_{254}$) plates. Preparative TLC (PTLC) was performed using 0.50 mm E. Merck silica gel ($60F_{254}$) plates. Reaction components were visualized by illumination with ultraviolet light (254 nm) and by

staining with 6% ethanolic *p*-anisaldehyde (includes 6% conc. sulfuric acid and 1% acetic acid), 8% ethanolic phosphomolybdic acid, ceric ammonium molybdate in 10% sulfuric acid, or basic potassium permanganate solution. Kanto Chem. Co. Silica Gel 60N (particle size 0.040–0.050 mm) or Nakarai tesque Cosmosil 140C_{18}-PREP were used for flash column chromatography. High performance liquid chromatography (HPLC) was recorded on a Jasco PU-2089 *Plus* instrument with UV detection at 220 nm.

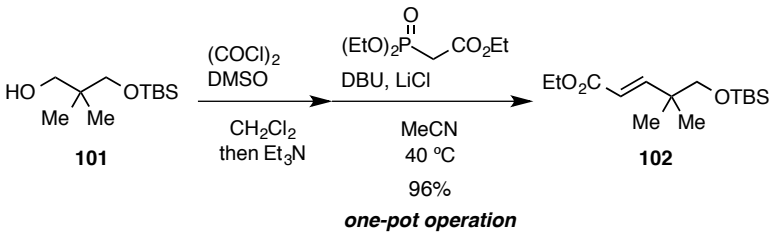
Experimental Procedure for Chapter 1

Compound 101



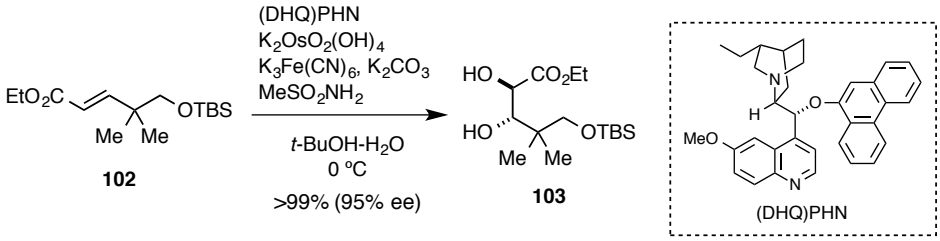
A solution of 2,2-dimethylpropane-1,3-diol (10.9 g, 105 mmol) in THF (60 mL) was added to a suspension of NaH (55% in mineral oil, 4.58 g, 105 mmol) in THF (80 mL) at 0 °C. After being stirred at 0 °C for 1 h, a solution of *tert*-butyldimethylsilyl chloride (TBSCl) (15.1 g, 100 mmol) in THF (60 mL) was added at 0 °C. After being stirred at room temperature for 1.5 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (300 mL) and water (100 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (100 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~400 g, *n*-hexane/ethyl acetate (EtOAc) = 4:1) afforded alcohol **101** (21.8 g, 100.0 mmol, >99%) as a colorless oil: IR (ATR): ν 3389, 2954, 2929, 2858, 1472, 1389, 1362, 1252, 1093, 1045, 834, 773 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 3.46 (4H, s), 0.90 (9H, s), 0.88 (6H, s), 0.06 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 72.88, 72.37, 36.32, 25.81, 21.43, 18.14, –5.69; HRMS (FD): Calcd for $C_{11}H_{27}O_2Si$ $[M+H]^+$: 219.1780; found: 219.1767.

Compound 102



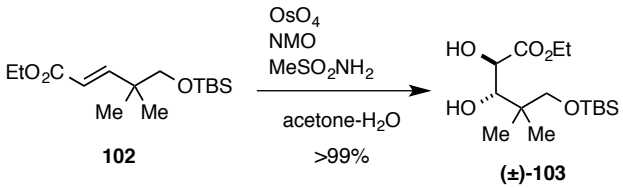
A solution of DMSO (9.0 mL, 125.3 mmol) in CH_2Cl_2 (19 mL) was added to a solution of oxalyl chloride (6.0 mL, 70.1 mmol) in CH_2Cl_2 (40 mL) at –78 °C. After being stirred at –78 °C for 15 min, a solution of alcohol **101** (11.0 g, 50.1 mmol) in CH_2Cl_2 (25 mL) was slowly added over 10 min. The mixture was stirred at –78 °C for 30 min, and then Et_3N (34.9 mL, 250.5 mmol) was added. The resulting reaction mixture was allowed to warm to room temperature and stirred at this temperature for 9 h. Meanwhile, a mixture of lithium chloride (5.30 g, 125.3 mmol), triethyl phosphonoacetate (19.8 mL, 100.2 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (15.0 mL, 100.2 mmol) in MeCN (37 mL) was prepared and stirred at 0 °C for 30 min. The resulting solution of Horner–Wadsworth–Emmons reagent, which was rinsed with MeCN (80 mL), was added to the above Swern oxidation solution. After being stirred at 40 °C for 24 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl (100 mL) solution and water (50 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (150 mL×3). The combined organic layers were washed with H_2O (100 mL×2), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~500 g, *n*-hexane/EtOAc = 10:1) afforded (*E*)-unsaturated ester **102** (13.9 g, 48.3 mmol, 96%) as a yellow oil: IR (ATR): ν 2957, 2930, 2857, 1719, 1651, 1472, 1364, 1308, 1258, 1180, 1097, 835, 774 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.97 (1H, d, *J* = 16.0 Hz), 5.77 (1H, d, *J* = 16.1 Hz), 4.19 (2H, q, *J* = 6.9 Hz), 3.36 (2H, s), 1.29 (3H, t, *J* = 6.9 Hz), 1.03 (6H, s), 0.88 (9H, s), 0.02 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.46, 167.05, 159.13, 155.89, 118.71, 70.94, 60.13, 39.13, 25.82, 23.20, 18.24, 14.25, –5.55 (two peaks missing); HRMS (FD): Calcd for $C_{15}H_{31}O_3Si$ $[M+H]^+$: 287.2043; found: 287.2091.

Compound 103



To a mixture of $K_3Fe(CN)_6$ (27.7 g, 84.0 mmol), K_2CO_3 (11.6 g, 84.0 mmol), $MeSO_2NH_2$ (2.66 g, 28.0 mmol), (DHQ)PHN (703.7 mg, 1.40 mmol) in *t*-BuOH–H_2O (1:1, 280 mL) was added $K_2OsO_2(OH)_4$ (103.2 mg, 0.280 mmol) at room temperature. After stirred at room temperature for 10 min, the mixture was cooled to 0 °C, and a solution of (*E*)-unsaturated ester **102** (8.02 g, 28.0 mmol) in *t*-BuOH (20 mL) was added. After being stirred at 0 °C for 3 h, to the reaction mixture were added $Na_2S_2O_3$ (6.00 g, 38.0 mmol), and the mixture was stirred at 0 °C for 1 h. After the layers were separated, the aqueous layer was extracted with EtOAc (60 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~250 g, *n*-hexane/EtOAc = 3:1) afforded the optically active diol **103** (8.97 g, 28.0 mmol, >99%, 95% ee) as a yellow oil. Enantiomeric excess (ee) was determined by HPLC analysis (CHIRALCEL AD-H column, 5.0 μm, 250×4.6 mm, *n*-hexane-isopropanol (98:2 v/v as an eluent), flow rate = 1.0 mL/min, λ = 220 nm, minor enantiomer t_R = 11.5 min, major enantiomer t_R = 14.5 min); $[\alpha]_D^{25}$ +10.5 (c 1.10, $CHCl_3$); IR (ATR): ν 3486, 2956, 2930, 2858, 1734, 1472, 1394, 1252, 1211, 1093, 816, 774 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.33 (1H, d, *J* = 6.3 Hz), 4.30-4.23 (2H, m), 3.75 (1H, d, *J* = 6.9 Hz), 3.72 (1H, d, *J* = 6.9 Hz), 3.64 (1H, d, *J* = 9.8Hz), 3.61 (1H, d, *J* = 6.3 Hz), 3.49 (1H, d, *J* = 9.8 Hz), 1.31 (3H, t, *J* = 6.9 Hz), 1.02 (3H, s), 0.99 (3H, s), 0.90 (9H, s), 0.08 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 173.88, 78.60, 71.29, 70.76, 61.72, 38.67, 25.75, 23.28, 20.90, 18.11, 14.14, –5.68, –5.75 (two peaks missing); HRMS (FD): Calcd for $C_{15}H_{33}O_5Si$ $[M+H]^+$: 321.2097; found: 321.2091.

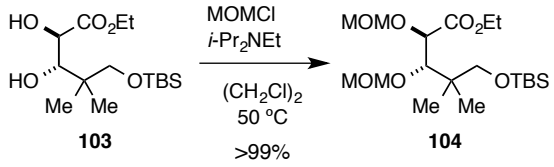
Compound (±)-103



Racemic diol (±)-**103** for chiral HPLC analysis was prepared as follows.

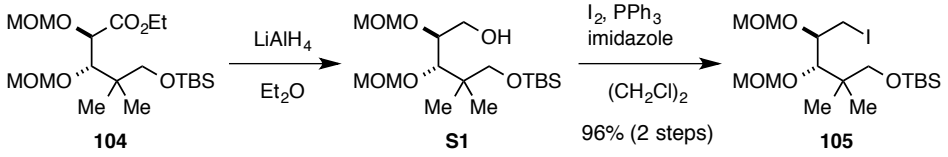
To a mixture of (*E*)-unsaturated ester **102** (85.9 mg, 0.300 mmol), *N*-methylmorpholine *N*-oxide (NMO) (94 μL, 4.8 M in H_2O, 0.450 mmol), $MeSO_2NH_2$ (38.3 mg, 0.450 mmol) in acetone–H_2O (1:1, 1.0 mL) was added OsO_4 (0.152 M in *t*-BuOH, 10 μL, 15.0 μmol) at room temperature. After being stirred at room temperature for 12.5 h, to the reaction mixture were added $Na_2S_2O_3$ (100 mg) at 0 °C. The mixture was stirred at room temperature for 3 h, and filtered through a pad of Celite®, which was rinsed with EtOAc (5 mL). To the filtrate was added H_2O (2 mL), after the aqueous phase was separated, and extracted with EtOAc (2 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~5 g, *n*-hexane/EtOAc = 4:1) afforded racemic diol (±)-**103** (95.1 mg, 0.297 mmol, 99%) as a yellow oil: IR (ATR): ν 3492, 2955, 2930, 2857, 1735, 1472, 1390, 1363, 1252, 1212, 1093, 835, 774 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.33 (1H, d, *J* = 6.3 Hz), 4.30-4.24 (2H, m), 3.75 (1H, d, *J* = 7.4 Hz), 3,72 (1H, d, *J* = 7.5 Hz), 3.64 (1H, d, *J* = 9.7 Hz), 3.61 (1H, d, *J* = 6.3 Hz), 3.49 (1H, d, *J* = 9.8 Hz), 1.31 (3H, t, *J* = 6.9 Hz), 1.02 (3H, s), 0.99 (3H, s), 0.90 (9H, s), 0.08 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 173.82, 78.34, 71.17, 70.70, 61.59, 38.63, 25.67, 23.08, 20.80, 18.02, 14.05, –5.77, –5.83 (two peaks missing); HRMS (FD): Calcd for $C_{15}H_{33}O_5Si$ $[M+H]^+$: 321.2097; found: 321.2082.

Compound 104



To a solution of the optically active diol **103** (23.8 g, 74.3 mmol) in $(CH_2Cl)_2$ (74 mL) and *i*-Pr_2NEt (75.8 mL, 445.8 mmol) was added methoxymethyl chloride (MOMCl) (16.8 mL, 222.9 mmol) at 0 °C. After being stirred at 50 °C for 24 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (300 mL) at 0 °C. After the layers were separated, the aqueous layer was extracted with Et_2O (100 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~300 g, *n*-hexane/EtOAc = 6:1) afforded ester **104** (30.1 g, 73.6 mmol, >99%) as a yellow oil: $[\alpha]_D^{23}$ +39.0 (c 1.04, $CHCl_3$); IR (ATR): ν 2956, 2930, 2896, 2858, 1752, 1472, 1390, 1362, 1253, 1202, 1150, 1096, 1024, 921, 836, 774 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.76 (1H, d, *J* = 7.5 Hz), 4.74 (1H, d, *J* = 7.5 Hz), 4.67 (1H, d, *J* = 6.3 Hz), 4.59 (1H, d, *J* = 6.3 Hz), 4.42 (1H, d, *J* = 1.7 Hz), 4.19 (2H, q, *J* = 7.5 Hz), 4.01 (1H, d, *J* = 1.7 Hz), 3.46 (3H, s), 3.45 (1H, d, *J* = 9.7 Hz), 3.35 (3H, s), 3.27 (1H, d, *J* = 9.7 Hz), 1.28 (3H, t, *J* = 7.5 Hz), 1.00 (3H, s), 0.99 (3H, s), 0.90 (9H, s), 0.04 (3H, s), 0.04 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.45, 99.02, 96.87, 82.73, 76.21, 69.54, 60.92, 57.19, 56.51, 40.34, 25.82, 21.64, 20.86, 18.15, 14.07, –5.59, –5.62 (two peaks missing); HRMS (FD): Calcd for $C_{19}H_{41}O_7Si$ $[M+H]^+$: 409.2622; found: 409.2635.

Compound 105

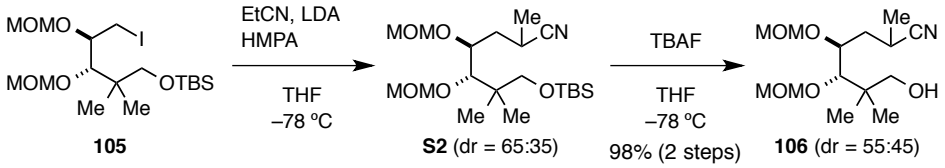


To a mixture of lithium aluminum hydride ($LiAlH_4$) (4.83 g, 127.2 mmol) in Et_2O (100 mL) was added dropwise a solution of ester **104** (26.0 g, 63.6 mmol) in Et_2O (100 mL) at 0 °C over 15 min. After being stirred at 0 °C for 1.5 h, the reaction mixture was diluted with Et_2O (200 mL). To the reaction mixture were added dropwise sequentially H_2O (5 mL), 15% aqueous NaOH solution (5 mL), and H_2O (15 mL) at 0 °C. Then, the resulting suspension was stirred at room temperature for 1 h, dried over $MgSO_4$ for 1 h with stirring, and filtered through a pad of Celite®, which was rinsed with EtOAc (300 mL). The filtrate was concentrated under reduced pressure. The crude alcohol **S1** (23.2 g, colorless oil) was used for the next step without further purification.

To a solution of the above crude alcohol **S1** (23.2 g) in $(CH_2Cl)_2$ (130 mL) were added I_2 (21.0 g, 82.7 mmol), PPh_3 (21.7 g, 82.7 mmol), imidazole (6.06 g, 89.0 mmol) at 0 °C in the dark. After being stirred at room temperature for 1.5 h, the reaction mixture was diluted with Et_2O (150 mL), and the reaction mixture was quenched with a saturated aqueous $Na_2S_2O_3$ solution (200 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (100 mL×3). The combined organic layers were washed with a saturated aqueous $Na_2S_2O_3$ solution (50 mL×3) and brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~300 g, *n*-hexane/EtOAc = 5:1) afforded iodide **105** (28.9 g, 60.7 mmol, 96% for 2 steps) as a colorless oil: $[\alpha]_D^{24}$ –12.3 (c 1.46, $CHCl_3$); IR (ATR): ν 2953, 2928, 2886, 2856, 1471, 1361, 1252, 1148, 1093, 1022, 919, 835, 774 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.77 (1H, d, *J* = 7.5 Hz), 4.77 (1H, d, *J* = 6.3 Hz), 4.75 (1H, d, *J* = 6.3 Hz), 4.74 (1H, d, *J* = 7.5 Hz), 3.96 (1H, d, *J* = 4.6 Hz), 3.94 (1H, d, *J* = 4.6 Hz), 4.01-3.98 (1H, m), 3.97 (1H, d, *J* = 3.4 Hz), 3.51-3.44 (3H, m), 3.44 (6H, s), 3.18 (1H, d, *J* = 9.8 Hz), 0.93 (3H, s), 0.92 (3H, s), 0.90 (9H, s), 0.04 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 99.24, 97.43, 81.03, 78.61, 69.73, 56.41, 56.14, 40.05, 25.89, 21.90,

20.46, 18.20, 7.50, –5.52, –5.55 (two peaks missing); HRMS (FD): Calcd for $C_{17}H_{38}IO_5Si$ $[M+H]^+$: 477.1533; found: 477.1540.

Compound 106

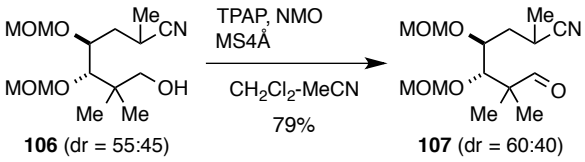


To a 0.60 M THF solution of $CH_3CHLiCN$ (175.8 mmol), which was prepared by treatment of EtCN (12.4 mL, 175.8 mmol) with lithium diisopropylamide (LDA) (0.60 M THF solution, 291 mL, 175.8 mmol) at –78 °C for 30 min, was added hexamethylphosphoramide (HMPA) (45.9 mL, 263.7 mmol) at –78 °C. After being stirred at –78 °C for 10 min, a solution of iodide **105** (41.9 g, 87.9 mmol) in THF (100 mL) was added at –78 °C. After being stirred at –78 °C for 12.5 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (300 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (150 mL×3). The combined organic layers were washed with H_2O (100 mL×2) and brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude nitrile **S2** (42.6 g, yellow oil) was used for the next step without further purification.

To a solution of the above crude nitrile **S2** (42.6 g) in THF (88 mL) was added tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 130 mL, 130 mmol) at room temperature. After being stirred at 50 °C for 24 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (300 mL) at room temperature. After the layers were separated, the aqueous layer was extracted with EtOAc (150 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~500 g, *n*-hexane/EtOAc = 1:2 to 1:3) afforded alcohol **106** (24.9 g, 86.0 mmol, inseparable 55:45 diastereomeric mixture, 98% for 2 steps) as a yellow oil: $[\alpha]_D^{25}$ –94.3 (c 1.06, $CHCl_3$); IR (ATR): ν 3487, 2980, 2887, 2359, 2341, 1473, 1463, 1382, 1148, 1097, 1016, 917

cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 4.75 (1.1H, d, *J* = 7.4 Hz), 4.73 (0.9H, d, *J* = 5.2 Hz), 4.68 (0.9H, d, *J* = 8.0 Hz), 4.67 (1.1H, d, *J* = 5.2 Hz), 3.95 (0.55H, ddd, *J* = 10.3, 4.6, 2.3 Hz), 3.86 (0.45H, ddd, *J* = 9.8, 4.0, 1.7 Hz), 3.48 (0.45H, d, *J* = 6.9 Hz), 3.45 (0.55H, d, *J* = 6.9 Hz), 3.48 (0.55H, d, *J* = 5.2 Hz), 3.45 (0.45H, d, *J* = 5.2 Hz), 3.44 (1.65H, s), 3.44 (1.65H, s), 3.43 (1.35H, s), 3.42 (1.35H, s), 3.26 (0.45H, d, *J* = 11.5 Hz), 3.23 (0.55H, d, *J* = 11.5 Hz), 2.94 (0.55H, qt, *J* = 7.5, 6.9 Hz), 2.82 (0.45H, qt, *J* = 7.5, 6.9 Hz), 2.05 (0.45H, ddd, *J* = 14.3, 8.0, 6.3 Hz), 1.85 (1H, m), 1.79 (0.55H, ddd, *J* = 14.3, 10.3, 4.0 Hz), 1.36 (3H, d, *J* = 7.5 Hz), 1.00 (3H, s), 0.92 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 122.82, 122.42, 98.76, 98.47, 97.29, 97.00, 82.95, 82.84, 75.70, 74.89, 70.04, 69.88, 56.35, 56.27, 56.24, 39.73, 39.26, 37.48, 22.90, 22.15, 22.12, 21.75, 21.17, 21.08, 18.38, 17.43 (two peaks missing); HRMS (FD): Calcd for $C_{14}H_{27}NO_5$ $[M]^+$: 289.1889; found: 289.1883.

Compound 107

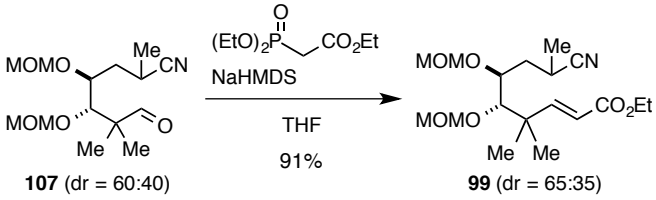


106 (dr = 55:45) **107** (dr = 60:40)

To a mixture of alcohol **106** (16.9 g, 58.5 mmol), freshly activated and powdered molecular sieves 4Å (MS4Å) (29.3 g), and NMO (10.3 g, 87.8 mmol) in CH_2Cl_2–MeCN (10:1, 110 mL) was added tetrapropylammonium perruthenate (TPAP) (1.03 g, 2.93 mmol) at 0 °C, and the mixture was stirred at room temperature for 3 h. Further TPAP (1.03 g, 2.93 mmol) was added at 0 °C, and the mixture was stirred at room temperature for additional 1.5 h. The reaction mixture was filtered through a pad of Celite®, which was rinsed with EtOAc (600 mL). The filtrate was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~200 g, *n*-hexane/EtOAc = 1:1) afforded aldehyde **107** (13.2 g, 46.0 mmol, inseparable 60:40 diastereomeric mixture, 79%) as a yellow oil: $[\alpha]_D^{27}$ –39.7 (c 0.96, $CHCl_3$); IR (ATR): ν 2940, 2896, 2826, 1719, 1456, 1397, 1210, 1148, 1098, 1079, 1020, 917 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.63 (0.4H, s), 9.61 (0.6H, s), 4.79 (0.4H, d, *J* = 6.3 Hz), 4.77 (0.6H, d, *J* = 6.9 Hz), 4.73 (0.4H, d, *J* = 6.9 Hz), 4.73

(0.6H, d, *J* = 6.9 Hz), 4.59 (1.2H, d, *J* = 6.9 Hz), 4.57 (0.8H, d, *J* = 8.1 Hz), 3.88 (0.6H, dt, *J* = 9.8, 2.9 Hz), 3.85 (0.4H, dt, *J* = 10.3, 2.9 Hz), 3.68 (0.6H, d, *J* = 4.0 Hz), 3.57 (0.4H, d, *J* = 2.9 Hz), 3.44 (1.8H, s), 3.42 (1.2H, s), 3.38 (1.8H, s), 3.36 (1.2H, s), 3.00-2.92 (0.6H, m), 2.88-2.81 (0.4H, m), 2.02 (0.4H, ddd, *J* = 13.7, 9.2, 6.3 Hz), 1.97-1.89 (1H, m), 1.77 (0.6H, ddd, *J* = 13.8, 9.2, 4.6 Hz), 1.35 (3H, d, *J* = 6.9 Hz), 1.17 (1.2H, s), 1.16 (1.8H, s), 1.12 (1.8H, s), 1.12 (1.2H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 203.70, 203.55, 122.63, 122.42, 99.49, 98.95, 97.76, 97.35, 85.46, 84.84, 77.43, 75.86, 56.63, 56.42, 56.33, 49.67, 49.51, 37.27, 35.33, 22.95, 21.86, 20.86, 20.24, 19.57, 19.29, 18.47, 18.00 (one peak missing); HRMS (FD): Calcd for $C_{14}H_{25}NO_5$ $[M]^+$: 287.1733; found: 287.1731.

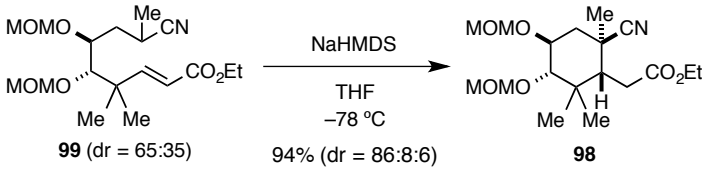
Compound 99



To a solution of triethyl phosphonoacetate (227 μL, 1.15 mmol) was slowly added sodium bis(trimethylsilyl)amide (NaHMDS) (1.10 M in THF, 1.05 mL, 1.15 mmol) at 0 °C over 5 min. After the mixture was stirred at 0 °C for 30 min, a solution of aldehyde **107** (255.1 mg, 0.888 mmol) in THF (8.9 mL) was added at 0 °C over 5 min. After being stirred at room temperature for 2.5 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (10 mL) and H_2O (10 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (5 mL×4). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~30 g, *n*-hexane/EtOAc = 3:1) afforded (*E*)-unsaturated ester **99** (287.5 mg, 0.804 mmol, inseparable 65:35 diastereomeric mixture, 91%) as a colorless oil: $[\alpha]_D^{27}$ –124.0 (c 0.99, $CHCl_3$); IR (ATR): ν 2978, 2940, 2894, 1714, 1648, 1465, 1388, 1366, 1309, 1294, 1269, 1149, 1098, 1042, 918, 866 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.88 (1H, d, *J* = 6.9 Hz), 4.74 (1H, d, *J* = 6.9 Hz), 4.70 (1H, d, *J* = 6.9 Hz), 4.67 (1H, d, *J* = 6.9 Hz),

4.18 (2H, q, *J* = 6.9 Hz), 3.65 (1H, ddd, *J* = 12.1, 9.8, 4.6 Hz), 3.41 (3H, s), 3.38 (3H, s), 3.14 (1H, d, *J* = 9.8 Hz), 2.55 (1H, dd, *J* = 17.8, 7.5 Hz), 2.46 (1H, dd, *J* = 17.8, 4.6 Hz), 2.44 (1H, dd, *J* = 11.5, 7.5 Hz), 2.32 (1H, dd, *J* = 13.2, 4.0 Hz), 1.96 (1H, t, *J* = 12.6 Hz), 1.41 (3H, s), 1.28 (3H, t, *J* = 6.9 Hz), 1.30 (1.8H, s), 1.02 (3H, s), 0.90 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.76, 166.67, 154.75, 154.63, 122.77, 122.46, 118.49, 118.38, 100.33, 98.65, 98.36, 97.31, 97.12, 85.15, 85.05, 76.12, 75.09, 60.27, 60.22, 56.53, 56.24, 56.19, 49.82, 41.28, 41.24, 38.84, 37.22, 24.96, 24.79, 23.67, 22.80, 21.95, 18.40, 17.47, 14.24 (one peak missing); HRMS (FD): Calcd for $C_{18}H_{31}NO_6$ $[M]^+$: 357.2151; found: 357.2165.

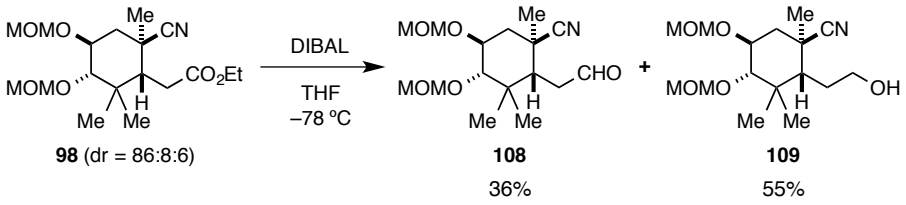
Compound 98



To a solution of (*E*)-unsaturated ester **99** (71.5 mg, 0.200 mmol) in THF (1.0 mL) was slowly added NaHMDS (1.14 M in THF, 351 μL, 0.400 mmol) at –78 °C over 10 min. After being stirred at –78 °C for 24 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (1 mL) and H_2O (1 mL) at –78 °C. Then, the mixture was allowed to warm up to room temperature. After the layers were separated, the aqueous layer was extracted with EtOAc (1 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~5 g, *n*-hexane/EtOAc = 2:1) afforded monocyclic compound **98** (67.2 mg, 0.188 mmol, 91%, dr = 86:8:6) as a colorless oil: $[\alpha]_D^{28}$ –45.6 (c 1.00, $CHCl_3$); IR (ATR): ν 2980, 2937, 2894, 2826, 1734, 1466, 1394, 1377, 1302, 1265, 1191, 1146, 1103, 1018, 915, 759 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.11 (1H, d, *J* = 16.1 Hz), 5.78 (0.65H, d, *J* = 16.1 Hz), 5.76 (0.35H, d, *J* = 16.0 Hz), 4.74 (0.65H, d, *J* = 6.9 Hz), 4.73 (0.35H, d, *J* = 6.9 Hz), 4.64 (1H, d, *J* = 6.3 Hz), 4.64 (0.65H, d, *J* = 6.3 Hz),4.63 (0.35H, d, *J* = 6.3 Hz), 4.60 (0.65H, d, *J* = 6.9 Hz), 4.57 (0.35H, d, *J* = 7.5 Hz), 4.18 (2H, q, *J* = 7.5 Hz), 3.82 (1H, ddd, *J* = 9.8,

6.3, 4.0 Hz), 3.76-3.72 (0.35H, m), 3.41 (1.95H, s), 3.40 (1.05H, s), 3.38 (1.95H, s), 3.36 (1.05H, s), 3.36 (0.65H, d, *J* = 3.5 Hz), 3.31 (0.35H, d, *J* = 3.5 Hz), 2.92-2.76 (1H, m), 1.94 (0.35H, dt, *J* = 13.8, 7.4 Hz), 1.82-1.77 (0.65H, m), 1.70 (0.65H, dd, *J* = 10.5, 4.0 Hz), 1.67 (0.35H, dd, *J* = 10.3, 4.6 Hz), 1.29 (3H, t, *J* = 7.5 Hz), 1.27 (3H, t, *J* = 6.9 Hz), 1.16 (3H, s), 1.13 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.24, 124.41, 99.05, 96.41, 86.75, 73.18, 61.01, 56.34, 55.50, 46.40, 41.27, 40.62, 37.29, 32.72, 27.85, 20.36, 17.64, 14.00; HRMS (FD): Calcd for $C_{18}H_{31}NO_6$ $[M]^+$: 357.2151; found: 357.2149.

Compound 108 and 109



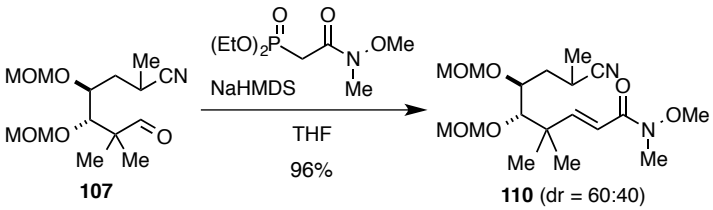
98 (dr = 86:8:6) **108** 36% **109** 55%

To a solution of monocyclic compound **98** (26.0 mg, 72.7 μmol) in THF (0.36 mL) was slowly added diisobutylaluminum hydride (DIBAL) (1.02 M in *n*-hexane, 150 μL, 0.153 mmol) at –78 °C over 3 min, and the mixture was allowed to warm up to –50 °C over a period of 2 h. Additional DIBAL (1.03 M in *n*-hexane, 36 μL, 36.4 μmol) at –78 °C, and the mixture was allowed to warm up to –50 °C over a period of 3.5 h. The reaction was quenched by dropwise addition of EtOAc (0.5 mL), and the mixture was stirred at –78 °C for 15 min. Then, to the mixture was added a saturated aqueous sodium potassium tartrate solution (ca. 1 mL) at –78 °C, and the mixture was vigorously stirred at room temperature until both phases became clear. After the layers were separated, the aqueous layer was extracted with EtOAc (1 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~3 g, *n*-hexane/EtOAc = 3:1) afforded aldehyde **108** (8.2 mg, 26.2 μmol, 36%) as a colorless oil and alcohol **109** (12.7 mg, 40.4 μmol, 55%) as a colorless oil.

Aldehyde 108: $[\alpha]_D^{26}$ –50.0 (c 1.09, $CHCl_3$); IR (ATR): ν 2940, 2893, 2824, 1726, 1471, 1391, 1365, 1147, 1104, 1055, 1032, 917, 771 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.82 (1H, s), 4.89 (1H, d, *J*

= 6.3 Hz), 4.74 (1H, d, *J* = 6.9 Hz), 4.70 (1H, d, *J* = 6.3 Hz), 4.67 (1H, d, *J* = 6.9 Hz), 3.75 (3H, s), 3.66 (1H, ddd, *J* = 12.6, 10.2, 4.6 Hz), 3.40 (3H, s), 3.38 (3H, s), 3.16 (1H, d, *J* = 9.7 Hz), 2.72 (1H, dd, *J* = 18.3, 6.9 Hz), 2.59 (1H, dd, *J* = 18.3, 3.5 Hz), 2.53 (1H, dd, *J* = 6.3, 3.5 Hz), 2.34 (1H, dd, *J* = 13.2, 4.6 Hz), 1.97 (1H, t, *J* = 12.6 Hz), 1.41 (3H, s), 0.95 (3H, s), 0.90 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 199.25, 124.43, 98.96, 96.36, 86.61, 73.08, 56.29, 55.46, 43.43, 42.14, 40.96, 40.36, 37.42, 28.21, 20.26, 17.73; HRMS (FD): Calcd for $C_{16}H_{27}NO_5$ $[M]^+$: 313.1889; found: 313.1904; **Alcohol 109:** $[\alpha]_D^{26}$ –45.5 (c 0.97, $CHCl_3$); IR (ATR): ν 23391, 2953, 2890, 2824, 1455, 1395, 1218, 1148, 1103, 1029, 918, 776 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.89 (1H, d, *J* = 6.3 Hz), 4.73 (1H, d, *J* = 6.9 Hz), 4.70 (1H, d, *J* = 6.3 Hz), 4.67 (1H, d, *J* = 6.9 Hz), 3.82 (2H, br), 3.64 (1H, ddd, *J* = 12.6, 9.7, 4.6 Hz), 3.41 (3H, s), 3.38 (3H, s), 3.07 (1H, d, *J* = 9.7 Hz), 2.31 (1H, dd, *J* = 13.2, 4.6 Hz), 1.91-1.85 (1H, m), 1.88 (1H, t, *J* = 12.6 Hz), 1.73-1.64 (4H, m), 1.43 (3H, s), 1.07 (3H, s), 0.90 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 125.45, 98.98, 96.34, 87.25, 73.21, 62.75, 56.29, 55.44, 46.40, 41.58, 40.77, 37.07, 30.52, 28.24, 19.95, 17.54; HRMS (FD): Calcd for $C_{16}H_{30}NO_5$ $[M+H]^+$: 316.2124; found: 316.2137.

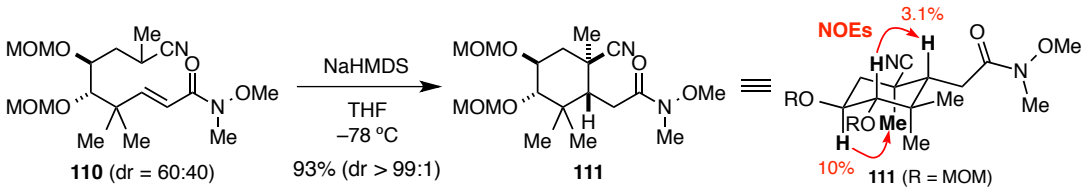
Compound 110



To a solution of diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate (18.0 mL, 87.5 mmol) in THF (55 mL) was slowly added sodium NaHMDS (1.10 M in THF, 76.7 mL, 84.4 mmol) at 0 °C over 5 min. After the mixture was stirred at 0 °C for 30 min, a solution of aldehyde **107** (18.0 g, 62.5 mmol) in THF (70 mL) was added at 0 °C over 5 min. After being stirred at room temperature for 15 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (300 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (200 mL×3). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and

concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~300 g, *n*-hexane/EtOAc = 1:1 to 1:4) afforded (*E*)-unsaturated Weinreb amide **110** (22.5 g, 60.3 mmol, inseparable 60:40 diastereomeric mixture, 96%) as a yellow oil: $[\alpha]_D^{23}$ –61.8 (c 1.00, $CHCl_3$); IR (ATR): ν 2980, 2889, 2359, 2341, 1659, 1626, 1463, 1380, 1149, 1098, 1021, 918, 735 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.11 (0.4H, d, *J* = 15.5 Hz), 7.08 (0.6H, d, *J* = 16.0 Hz), 6.38 (0.6H, d, *J* = 16.0 Hz), 6.36 (0.4H, d, *J* = 16.0 Hz), 4.76 (0.6H, d, *J* = 6.9 Hz), 4.74 (0.4H, d, *J* = 6.9 Hz), 4.68 (0.6H, d, *J* = 6.9 Hz), 4.65 (0.6H, d, *J* = 6.9 Hz), 4.62 (0.4H, d, *J* = 6.9 Hz), 4.60 (0.4H, d, *J* = 6.9 Hz), 3.82 (0.6H, ddd, *J* = 10.3, 5.2, 2.3 Hz), 3.76 (0.4H, dt, *J* = 9.8, 5.2 Hz), 3.71 (1.8H, s), 3.70 (1.2H, s), 3.43 (1.8H, s), 3.42 (1.2H, s), 3.39 (1.8H, s), 3.38 (1.2H, s), 3.36 (0.6H, d, *J* = 5.2 Hz), 3.34 (0.4H, d, *J* = 3.4 Hz), 3.25 (1.8H, s), 3.24 (1.2H, s), 2.90 (0.6H, qt, *J* = 7.5, 6.9 Hz), 2.80 (0.4H, qt, *J* = 7.4, 6.9 Hz), 1.96 (0.4H, dt, *J* = 13.8, 7.5 Hz), 1.80 (0.6H, ddd, *J* = 13.8, 11.5, 2.9 Hz), 1.68 (0.6H, ddd, *J* = 14.3, 10.3, 4.0 Hz), 1.32 (1.8H, s), 1.31 (1.2H, s), 1.30 (1.8H, s), 1.29 (1.2H, s), 1.20 (1.2H, s), 1.19 (1.8H, s), 1.17 (1.8H, s), 1.16 (1.2H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.78, 153.14, 152.92, 122.82, 122.32, 116.20, 115.94, 98.52, 98.29, 97.17, 96.95, 85.11, 84.91, 75.59, 75.09, 61.57, 61.54, 56.41, 56.36, 56.08, 56.06, 41.21, 39.20, 37.45, 32.33, 24.75, 24.25, 24.15, 23.91, 22.71, 21.95, 18.31, 17.31 (three peaks missing); HRMS (FD): Calcd for $C_{18}H_{32}N_2O_6$ $[M]^+$: 372.2260; found: 372.2273.

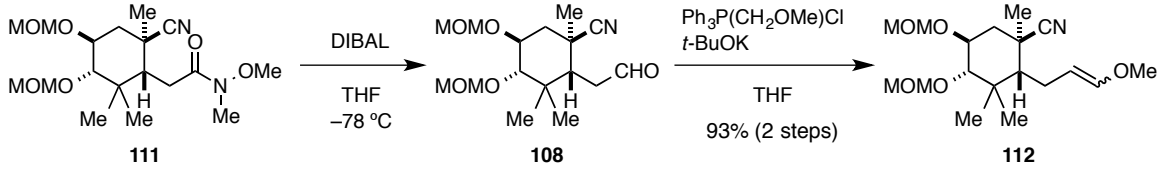
Compound 111



To a solution of (*E*)-unsaturated Weinreb amide **110** (22.5 g, 60.3 mmol) in THF (120 mL) was slowly added NaHMDS (1.10 M in THF, 110 mL, 120.6 mmol) at –78 °C over 10 min. After being stirred at –78 °C for 24 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (300 mL) at –78 °C. Then, the mixture was allowed to warm up to room temperature. After

the layers were separated, the aqueous layer was extracted with EtOAc (300 mL×3). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Recrystallization from EtOAc afforded monocyclic compound **111** (13.4 g) as a colorless solid. The mother liquid was concentrated under reduced pressure, and the residue was recrystallized from EtOAc afforded monocyclic compound **111** (3.48 g) as a colorless solid. The mother liquid was concentrated under reduced pressure. Purification of the residue by flash column chromatography (SiO_2~100 g, *n*-hexane/EtOAc = 1:1 to 1:2) afforded additional **111** (4.98 g) as a colorless solid. Thus, monocyclic compound **111** (20.8 g, 55.9 mmol, 93%, dr > 99:1) was obtained: M.p. 103-106 °C; $[\alpha]_D^{28}$ –51.9 (c 0.95, $CHCl_3$); IR (ATR): ν 2939, 2904, 2359, 2341, 2332, 1660, 1457, 1416, 1389, 1146, 1107, 1029, 915 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.87 (1H, d, *J* = 6.3 Hz), 4.74 (1H, d, *J* = 6.9 Hz), 4.71 (1H, d, *J* = 6.3 Hz), 4.67 (1H, d, *J* = 6.9 Hz), 3.75 (3H, s), 3.66 (1H, ddd, *J* = 9.8, 4.6, 4.0 Hz), 3.41 (3H, s), 3.38 (3H, s), 3.21 (3H, s), 3.16 (1H, d, *J* = 9.7 Hz), 2.70 (1H, dd, *J* = 16.6, 5.7 Hz), 2.63 (1H, dd, *J* = 10.3, 5.7 Hz), 2.54 (1H, dd, *J* = 16.1, 4.1 Hz), 2.31 (1H, dd, *J* = 13.2, 4.6 Hz), 1.97 (1H, t, *J* = 12.6 Hz), 1.46 (3H, s), 1.02 (3H, s), 0.92 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.57, 124.58, 99.19, 96.47, 86.99, 73.31, 61.30, 56.32, 55.48, 45.27, 41.52, 40.67, 37.33, 32.76, 29.84, 27.93, 20.70, 17.95; HRMS (FD): Calcd for $C_{18}H_{32}N_2O_6$ $[M]^+$: 372.2260; found: 372.2273.

Compound 112



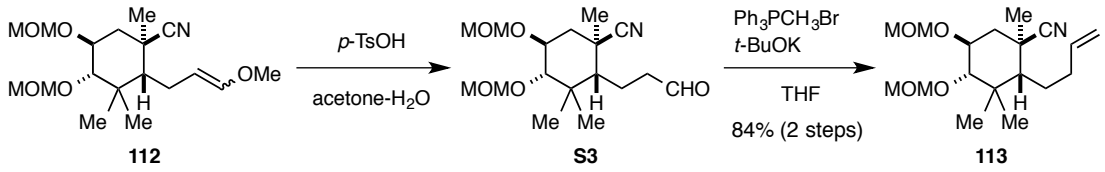
To a solution of monocyclic compound **111** (13.4 g, 35.9 mmol) in THF (180 mL) was slowly added DIBAL (1.03 M in *n*-hexane, 41.8 mL, 43.1 mmol) at –78 °C over 10 min, and the mixture was stirred at –78 °C for 1 h. Additional DIBAL (1.03 M in *n*-hexane, 10.5 mL, 10.8 mmol) at –78 °C, and the mixture was stirred at –78 °C for additional 20 min. Further DIBAL (1.03 M in

n-hexane, 10.5 mL, 10.8 mmol) at –78 °C, and the mixture was stirred at –78 °C for additional 30 min. The reaction was quenched by dropwise addition of EtOAc (50 mL), and the mixture was stirred at –78 °C for 15 min. Then, to the mixture was added a saturated aqueous sodium potassium tartrate solution (ca. 250 mL) at –78 °C, and the mixture was vigorously stirred at room temperature until both phases became clear. After the layers were separated, the aqueous layer was extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude aldehyde **108** (12.2 g, colorless oil) was used for the next step without further purification.

Commercially available methoxymethyl triphenylphosphonium chloride (18.8 g, 53.9 mmol) was dried under vacuum at 80 °C for 1 h with stirring. After cooling to 0 °C, to this reagent was added THF (42 mL), followed by *t*-BuOK (5.64 g, 50.3 mmol), and the mixture was stirred at 0 °C for 30 min. To the mixture was added a solution of the above crude aldehyde **108** (12.2 g) in THF (30 mL). After being stirred at room temperature for 2 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (100 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~300 g, *n*-hexane/EtOAc = 3:1) afforded methyl enol ether **112** (11.5 g, 33.8 mmol, 93% for 2 steps) as a yellow oil: $[\alpha]_D^{28}$ –66.4 (c 1.03, $CHCl_3$); IR (ATR): ν 2978, 2940, 2892, 2359, 1656, 1463, 1390, 1210, 1146, 1103, 1026, 916 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.38 (0.5H, d, *J* = 12.6 Hz), 5.90 (0.5H, d, *J* = 5.7 Hz),4.91-4.85 (0.5H, m), 4.89 (1H, d, *J* = 6.9 Hz), 4.73 (1H, d, *J* = 6.9 Hz), 4.70 (1H, d, *J* = 6.9 Hz), 4.66 (1H, d, *J* = 6.9 Hz), 4.52 (0.5H, dt, *J* = 13.2, 6.9 Hz), 3.64-3.59 (1H, m), 3.61 (1.5H, s), 3.54 (1.5H, s), 3.41 (3H, s), 3.37 (3H, s), 3.05 (1H, d, *J* = 9.2 Hz), 2.43 (0.5H, dt, *J* = 15.5, 5.8 Hz), 2.33-2.23 (2H, m), 2.11 (0.5H, dt, *J* = 15.5, 7.5 Hz), 1.88 (1H, t, *J* = 12.6 Hz), 1.66 (1H, dt, *J* = 12.6, 6.9 Hz), 1.41 (1.5H, s), 1.40 (1.5H, s), 1.11 (1.5H, s), 1.10 (1.5H, s), 0.91 (1.5H, s), 0.89 (1.5H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 147.73, 146.65, 125.73, 125.61, 106.35, 102.39, 99.07, 99.05, 96.36, 87.46, 87.31, 73.17, 73.12, 59.46, 56.32, 55.66, 55.49, 55.46, 51.49, 50.77, 42.53, 42.51, 41.13, 41.04, 36.83, 36.52, 28.60, 28.40, 25.94, 22.15, 19.83,

19.74, 17.44, 17.41 (two peaks missing); HRMS (FD): Calcd for $C_{18}H_{31}NO_5$ $[M]^+$: 341.2202; found: 341.2211.

Compound 113

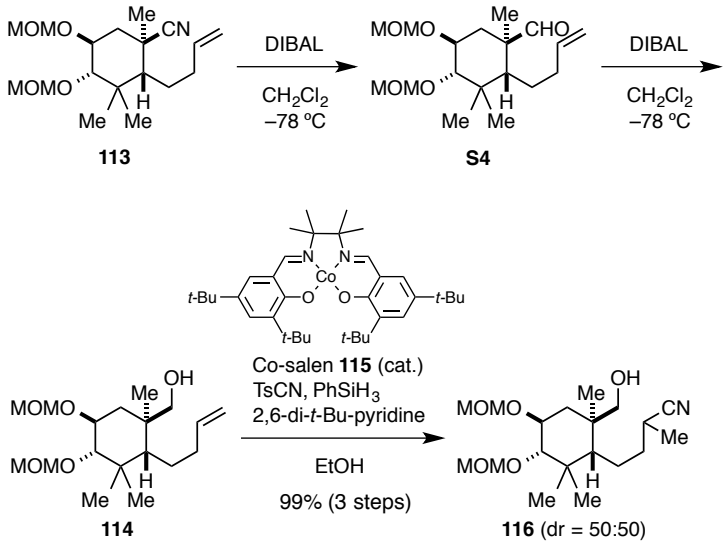


To a solution of methyl enol ether **112** (11.5 g, 33.8 mmol) in acetone–H_2O (80:1, 223 mL) was added *p*-TsOH·H_2O (642.9 mg, 3.38 mmol) at room temperature. After being stirred at room temperature for 6 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (100 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude aldehyde **S3** (11.3 g, brown oil) was used for the next step without further purification.

Commercially available methyl triphenylphosphonium bromide (18.1 g, 50.7 mmol) was dried under vacuum at 80 °C for 1 h with stirring. After cooling to 0 °C, to this reagent was added THF (45 mL), and *t*-BuOK (5.31 g, 47.3 mmol), and the mixture was stirred at 0 °C for 30 min. To the mixture was added a solution of the above crude aldehyde **S3** (11.3 g) in THF (40 mL). After being stirred at room temperature for 1 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (100 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~300 g, *n*-hexane/EtOAc = 6:1 to 5:1) afforded terminal olefin **113** (9.28 g, 28.5 mmol, 84% for 2 steps) as a colorless oil: $[\alpha]_D^{28}$ –61.7 (c 1.10, $CHCl_3$); IR (ATR): ν 2978, 2943, 2891, 2359, 1640, 1455, 1392, 1146, 1105, 1026, 915 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.83 (1H, tdd, *J* = 16.6, 10.3, 6.3 Hz), 5.07 (1H, dd, *J* = 17.2, 1.7 Hz), 5.00 (1H, d, *J* = 10.4 Hz), 4.89 (1H, d, *J* = 6.9

Hz), 4.73 (1H, d, J = 6.9 Hz), 4.69 (1H, d, J = 6.9 Hz), 4.66 (1H, d, J = 6.9 Hz), 3.63 (1H, td, J = 9.8, 4.6 Hz), 3.41 (3H, s), 3.37 (3H, s), 3.06 (1H, d, J = 9.8 Hz), 2.43-2.36 (1H, m), 2.30 (1H, dd, J = 13.2, 4.6 Hz), 2.26-2.19 (1H, m), 1.86 (1H, t, J = 12.6 Hz), 1.67-1.60 (1H, m), 1.56-1.49 (2H, m), 1.41 (3H, s), 1.07 (3H, s), 0.88 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 137.90, 125.40, 115.20, 99.01, 96.38, 87.34, 73.32, 56.31, 55.45, 49.91, 41.87, 41.02, 36.99, 35.54, 28.36, 27.03, 20.05, 17.58; HRMS (FD): Calcd for $C_{18}H_{31}NO_4$ $[M]^+$: 325.2253; found: 325.2239.

Compound 116



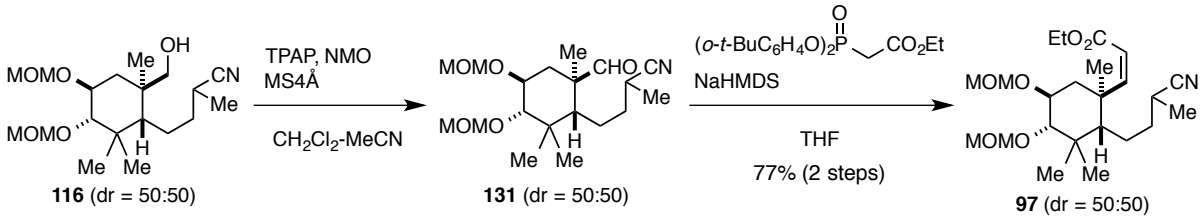
To a solution of terminal olefin **113** (9.28 g, 28.5 mmol) in CH_2Cl_2 (95 mL) was slowly added DIBAL (1.03 M in *n*-hexane, 41.6 mL, 42.8 mmol) at –78 °C over 10 min, and the mixture was stirred at –78 °C for 1.5 h. The reaction was quenched by dropwise addition of EtOAc (50 mL), and the mixture was stirred at –78 °C for 15 min. Then, to the mixture was added 10% aqueous tartaric acid solution (100 mL) at –78 °C, and the mixture was stirred vigorously at room temperature until both phases became clear. After the layers were separated, the aqueous layer was extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude aldehyde **S4** (9.55 g, colorless oil) was used for the next step without further purification.

To a solution of the above crude aldehyde **S4** (9.55 g) in CH_2Cl_2 (95 mL) was slowly added DIBAL (1.03 M in *n*-hexane, 41.6 mL, 42.8 mmol) at –78 °C over 10 min, and the mixture was stirred at –78 °C for 1 h. The reaction was quenched by dropwise addition of EtOAc (50 mL) and the mixture was stirred at –78 °C for 15 min. Then, to the mixture was added a saturated aqueous sodium potassium tartrate solution (ca. 150 mL) at –78 °C, and the mixture was vigorously stirred at room temperature until both phases became clear. After the layers were separated, the aqueous layer was extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude alcohol **114** (9.50 g, colorless oil) was used for the next step without further purification.

To a mixture of the above crude alcohol **114** (9.50 g), Co-salen catalyst **115** (1.73 g, 2.85 mmol), TsCN (6.20 g, 34.2 mmol), and 2,6-di-*tert*-butylpyridine (7.0 mL, 31.4 mmol) in EtOH (140 mL) was added $PhSiH_3$ (3.9 mL, 31.4 mmol) at room temperature. After being stirred at room temperature for 3 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (200 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (70 mL×3). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~250 g, *n*-hexane/EtOAc = 1:3) afforded nitrile **116** (10.1 g, 28.3 mmol, inseparable 50:50 diastereomeric mixture, 99% for 3 steps) as a yellow oil: $[\alpha]_D^{26}$ –59.3 (c 0.98, $CHCl_3$); IR (ATR): ν 3479, 2940, 2882, 2335, 2339, 1457, 1393, 1214, 1146, 1103, 1027, 916 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.90 (0.5H, d, *J* = 6.3 Hz), 4.89 (0.5H, d, *J* = 6.3 Hz), 4.72 (1H, d, *J* = 7.5 Hz), 4.70 (1H, d, *J* = 7.5 Hz), 4.67 (1H, d, *J* = 6.3 Hz), 3.73 (1H, dt, *J* = 9.7, 4.6 Hz), 3.41 (3H, s), 3.36 (3H, s), 3.35 (0.5H, d, *J* = 10.9 Hz), 3.31 (1H, d, *J* = 10.9 Hz), 3.12 (0.5H, d, *J* = 9.8 Hz), 3.10 (0.5H, d, *J* = 10.3 Hz), 2.99 (1H, d, *J* = 9.2 Hz), 2.64-2.52 (1H, m), 1.76-1.62 (2H, m), 1.66 (1H, ddd, *J* = 13.2, 4.6, 2.9 Hz), 1.61-1.47 (2H, m), 1.50 (1H, t, *J* = 12.0 Hz), 1.46-1.35 (1H, m), 1.31 (1.5H, d, *J* = 7.5 Hz), 1.30 (1.5H, d, *J* = 6.9 Hz), 1.25-1.22 (1H, m), 1.04 (1.5H, s), 1.02 (1.5H, s), 0.92 (1.5H, s), 0.90 (1.5H, s), 0.85 (1.5H, s), 0.84 (1.5H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 123.01, 122.97, 99.03, 99.00, 96.10, 96.08, 88.62, 88.55, 75.15, 70.55, 70.36, 56.28, 56.26, 55.35, 47.17, 47.14, 41.12, 40.93, 40.24,

39.69, 39.58, 36.35, 36.22, 28.45, 28.43, 26.12, 25.94, 23.53, 23.21, 18.30, 18.26, 18.00, 17.87, 17.69 (four peaks missing); HRMS (FD): Calcd for $C_{19}H_{36}NO_5$ $[M]^+$: 358.2594; found: 358.2604.

Compound 97

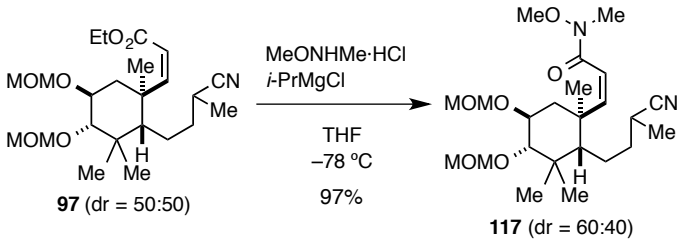


To a mixture of nitrile **116** (10.1 g, 28.3 mmol), freshly activated and powdered MS4Å (14.2 g), and NMO (4.98 g, 42.5 mmol) in CH_2Cl_2–MeCN (20:1, 84 mL) was added TPAP (499.0 mg, 1.42 mmol) at room temperature, and the mixture was stirred at room temperature for 30 min. Further TPAP (99.5 mg, 0.283 mmol) was added at room temperature, and the mixture was stirred at room temperature for additional 20 min. After the reaction mixture was concentrated under reduced pressure, the residue was filtered through a pad of silica gel, which was rinsed with EtOAc (1 L). Then, the filtrate was concentrated under reduced pressure. The crude aldehyde **131** (8.62 g, yellow oil) was used for the next step without further purification.

To a solution of ethyl [bis(*o*-*t*-butylphenyl)phosphono]acetate (18.4 g, 42.5 mmol) in THF (60 mL) was slowly added NaHMDS (1.10 M in THF, 36.0 mL, 39.6 mmol) at –78 °C over 5 min. After being stirred at –78 °C for 30 min, a solution of the above crude aldehyde **131** (8.62 g) in THF (40 mL) was added at –78 °C. After being stirred at room temperature for 9 h, benzaldehyde (2.9 mL, 28.3 mmol) was added to the reaction mixture for quenching the excess Horner–Wadsworth–Emmons reagent. After being stirred at room temperature for additional 1 h, to the mixture was added a saturated aqueous NH_4Cl solution (100 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~300 g, *n*-hexane/EtOAc = 5:1 to 2:1) afforded (*Z*)-unsaturated ester

97 (9.20 g, 21.6 mmol, inseparable 50:50 diastereomeric mixture, 77% for 2 steps) as a yellow oil: $[\alpha]_D^{25}$ –36.9 (c 1.04, $CHCl_3$); IR (ATR): ν 2979, 2940, 2892, 2367, 2356, 2332, 1718, 1635, 1471, 1387, 1180, 1146, 1102, 1026, 916 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.71 (1.5H, d, *J* = 12.1 Hz), 5.64 (0.5H, d, *J* = 13.2 Hz), 4.91 (1H, d, *J* = 6.9 Hz), 4.72 (1H, d, *J* = 6.9 Hz), 4.72 (1H, d, *J* = 6.3 Hz), 4.66 (1H, d, *J* = 6.3 Hz), 4.22-4.12 (2H, m), 3.70 (1H, ddd, *J* = 11.2, 9.2, 4.6 Hz), 3.42 (3H, s), 3.35 (3H, s), 3.13 (0.5H, d, *J* = 9.7 Hz), 3.10 (0.5H, d, *J* = 9.7 Hz), 2.60-2.49 (1H, m), 2.00 (0.5H, dd, *J* = 4.6, 4.0 Hz), 1.98 (0.5H, dd, *J* = 4.6, 4.1 Hz), 1.70 (0.5H, dd, *J* = 12.6, 12.0 Hz), 1.66-1.40 (5.5H, m), 1.29 (3H, d, *J* = 6.9 Hz), 1.29 (1.5H, t, *J* = 7.5 Hz), 1.29 (1.5H, t, *J* = 7.5 Hz), 1.23 (1.5H, s), 1.21 (1.5H, s), 1.06 (1.5H, s), 1.04 (1.5H, s), 0.93 (1.5H, s), 0.92 (1.5H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.92, 166.69, 153.75, 152.86, 122.95, 122.85, 119.79, 119.75, 99.09, 99.06, 96.11, 96.08, 88.27, 88.26, 74.63, 74.62, 60.58, 60.52, 56.30, 56.28, 55.39, 51.83, 51.49, 42.90, 42.68, 42.54, 42.19, 41.35, 41.29, 37.11, 36.61, 29.67, 28.89, 26.05, 25.78, 24.95, 24.48, 21.16, 20.60, 17.98, 17.65, 17.59, 14.13 (three peaks missing); HRMS (FD): Calcd for $C_{23}H_{39}NO_6$ $[M]^+$: 425.2777; found: 425.2773.

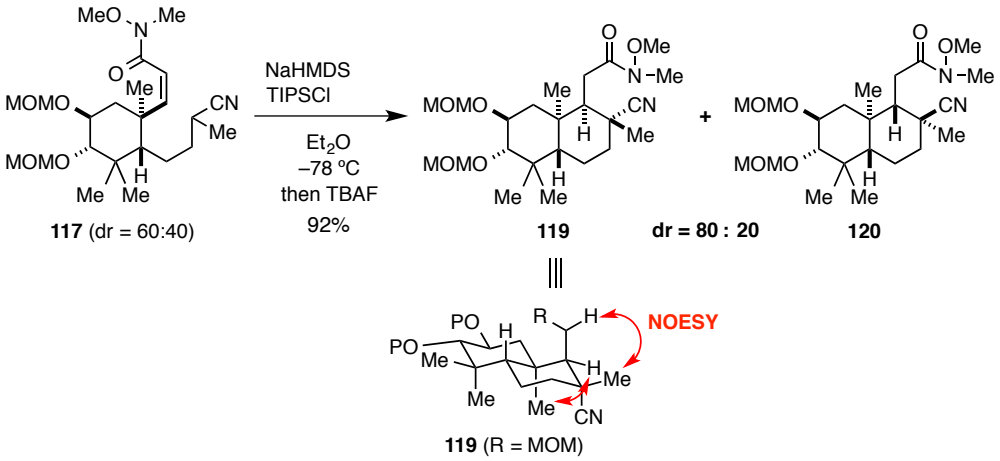
Compound 117



To a mixture of (*Z*)-unsaturated ester **97** (95.0 mg, 0.223 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (65.3 mg, 0.669 mmol) in THF (2.2 mL) was added *i*-PrMgCl (2.0 M in THF, 669 μL, 1.34 mmol) at –78 °C. After being stirred at –78 °C for 20 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (3 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (2 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash

column chromatography (SiO_2~5 g, *n*-hexane/EtOAc = 1:1 to 1:3) afforded (*Z*)-unsaturated Weinreb amide **117** (95.4 mg, 0.217 mmol, inseparable 60:40 diastereomeric mixture, 97%) as a colorless oil: $[\alpha]_D^{26}$ –20.9 (c 1.05, $CHCl_3$); IR (ATR): ν 2939, 2888, 2820, 1653, 1459, 1426, 1387, 1363, 1147, 1104, 1031, 1147, 1104, 1031, 916, 774 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.96 (0.4H, d, *J* = 17.2 Hz), 5.93 (0.6H, d, *J* = 14.4 Hz), 5.56 (0.4H, d, *J* = 13.2 Hz), 5.48 (0.6H, d, *J* = 12.6 Hz), 4.91 (1H, d, *J* = 6.9 Hz), 4.72 (1H, d, *J* = 6.3 Hz), 4.71 (1H, d, *J* = 6.3 Hz), 4.67 (1H, d, *J* = 6.9 Hz), 3.71 (1H, br), 3.66 (1.2H, s), 3.65 (1.8H, s), 3.42 (3H, s), 3.35 (3H, s), 3.19 (3H, s), 3.08 (0.4H, d, *J* = 9.2 Hz), 3.06 (0.6H, d, *J* = 9.2 Hz), 2.59 (1H, br), 1.94 (1H, dt, *J* = 9.2, 3.4 Hz), 1.76-1.69 (0.4H, m), 1.64-1.41 (5H, m), 1.30 (1.2H, d, *J* = 6.3 Hz), 1.29 (1.8H, d, *J* = 6.3 Hz), 1.27-1.23 (0.6H, m), 1.19 (1.2H, s), 1.17 (1.8H, s), 1.06 (1.8H, s), 1.04 (1.2H, s), 0.92 (1.8H, s), 0.91 (1.2H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.90, 168.73, 149.00, 148.46, 123.05, 122.96, 120.06, 119.98, 98.91, 98.89, 95.87, 95.82, 88.28, 88.26, 74.50, 61.20, 61.11, 56.11, 55.21, 52.31, 43.11, 42.82, 42.66, 42.61, 41.16, 41.09, 37.03, 36.43, 32.13, 28.82, 28.77, 25.84, 25.49, 24.53, 24.01, 19.87, 19.43, 17.93, 17.48, 17.42 (six peaks missing); HRMS (FD): Calcd for $C_{23}H_{40}N_2O_6$ $[M]^+$: 440.2886; found: 440.2877.

Compound 119 and 120



To a mixture of (*Z*)-unsaturated Weinreb amide **117** (70.0 mg, 0.159 mmol) and triisopropylsilyl chloride (TIPSCl) (68 μL, 0.318 mmol) in Et_2O (0.8 mL) was slowly added

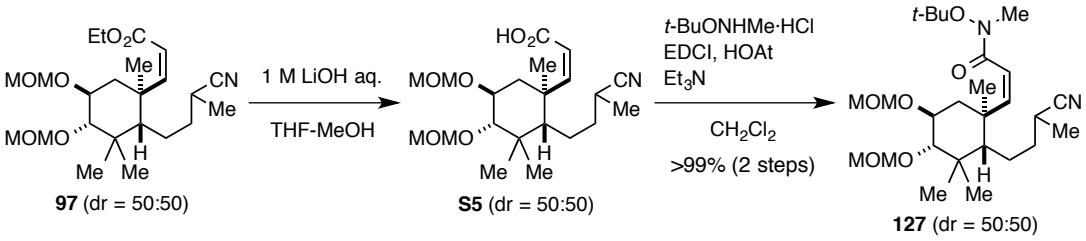
NaHMDS (1.14 M in THF, 418 μL, 0.477 mmol) at –78 °C over 10 min, and the reaction mixture was stirred at –78 °C for 24 h. Then, to the mixture was added TBAF (1.0 M in THF, 795 μL, 0.795 mmol) at –78 °C. After being stirred at room temperature for 3 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (2 mL) at –78 °C. The mixture was allowed to warm up to room temperature. After the layers were separated, the aqueous layer was extracted with Et_2O (2 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~5 g, *n*-hexane/EtOAc = 3:2 to 1:2) afforded bicyclic compound **119** (52.1 mg, 0.118 mmol, 74%) as a white amorphous foam and bicyclic compound **120** (12.9 mg, 29.3 μmol, 18%) as a white powder.

Bicyclic compound 119: $[\alpha]_D^{26}$ –32.6 (c 0.36, $CHCl_3$); IR (ATR): ν 2947, 2883, 2823, 1661, 1464, 1416, 1388, 1362, 1337, 1149, 1101, 1030, 910, 726, 647, 617 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.94 (1H, d, *J* = 6.9 Hz), 4.70 (1H, d, *J* = 5.7 Hz), 4.69 (1H, d, *J* = 5.8 Hz), 4.65 (1H, d, *J* = 6.3 Hz), 3.80 (1H, dt, *J* = 10.3, 4.6 Hz), 3.72 (3H, s), 3.42 (3H, s), 3.35 (3H, s), 3.17 (3H, s), 2.93 (1H, d, *J* = 9.8 Hz), 2.57 (1H, br), 2.53 (1H, br-d, *J* = 18.9 Hz), 2.27 (1H, br-d, *J* = 17.8 Hz), 2.00 (1H, d, *J* = 13.8 Hz), 1.79-1.69 (3H, m), 1.52 (3H, s), 1.38 (1H, dd, *J* = 13.8, 4.0 Hz), 1.33 (3H, s), 1.19 (1H, t, *J* = 12.0 Hz), 1.05 (3H, s), 0.97 (1H, d, *J* = 10.3 Hz), 0.86 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 173.02, 126.70, 99.08, 95.98, 89.09, 75.10, 61.40, 56.27, 55.49, 48.00, 46.14, 41.71, 39.44, 39.28, 34.92, 34.45, 32.74, 28.59, 27.47, 27.28, 24.80, 20.14, 17.19; HRMS (FD): Calcd for $C_{23}H_{40}N_2O_6$ $[M]^+$: 440.2886; found: 440.2893.

Bicyclic compound 120: $[\alpha]_D^{28}$ –60.3 (c 0.94, $CHCl_3$); IR (ATR): ν 2948, 1666, 1445, 1417, 1388, 1341, 1211, 1147, 1106, 1028, 915, 735 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.86 (1H, d, *J* = 6.3 Hz), 4.72 (1H, d, *J* = 6.3 Hz), 4.69 (1H, d, *J* = 6.9 Hz), 4.63 (1H, d, *J* = 6.9 Hz), 3.74 (3H, s), 3.64 (1H, dt, *J* = 11.5, 4.6 Hz), 3.42 (3H, s), 3.32 (3H, s), 3.19 (3H, s), 2.98 (1H, d, *J* = 9.8 Hz), 2.72 (1H, dd, *J* = 17.2, 6.3 Hz), 2.50 (1H, dd, *J* = 9.8, 6.3 Hz), 2.43 (1H, dd, *J* = 17.2, 3.5 Hz), 2.06 (1H, dt, *J* = 13.2, 3.5 Hz), 2.02 (1H, qd, *J* = 13.8, 4.0 Hz), 1.81 (1H, dd, *J* = 12.6, 4.6 Hz), 1.70 (1H, br-d, *J* = 13.8 Hz), 1.43 (1H, qd, *J* = 13.2, 4.1 Hz), 1.37 (3H, s), 1.18 (1H, t, *J* = 12.0 Hz), 1.14 (1H, d, *J* = 12.1 Hz), 1.04 (3H, s), 0.95 (3H, s), 0.82 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.73, 125.66,

99.23, 96.24, 88.63, 75.40, 61.31, 56.20, 55.27, 54.13, 49.56, 43.53, 39.54, 38.84, 38.41, 37.54, 32.67, 29.64, 28.52, 20.70, 17.42, 17.36, 17.32; HRMS (FD): Calcd for $C_{23}H_{40}N_2O_6$ $[M]^+$: 440.2886; found: 440.2877.

Compound 127

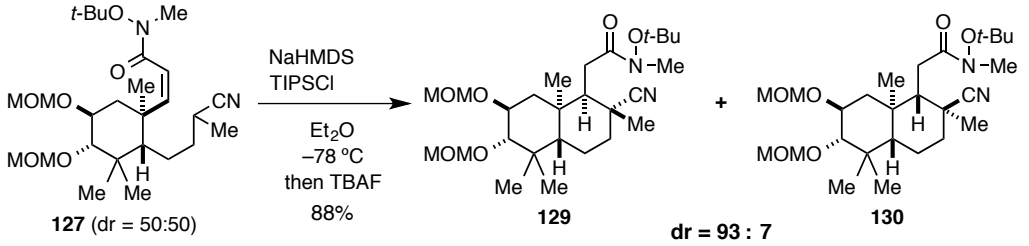


To a solution of (*Z*)-unsaturated ester **97** (9.20 g, 21.6 mmol) in THF–MeOH (5:1, 72 mL) was added a 1.0 M aqueous LiOH solution (108 mL, 108 mmol), and the mixtrure was stirred vigorously at room temperature for 7 h. Further a 1.0 M aqueous LiOH solution (108 mL, 108 mmol) was added at room temperature, and the mixture was stirred vigorously at room temperature for additional 50 h. The reaction mixture was acidified with 5% aqueous $KHSO_4$ solution (200 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (100 mL×5). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude (*Z*)-unsaturated carboxylic acid **S5** (8.79 g, yellow oil) was used for the next step without further purification.

To a mixture of the above crude (*Z*)-unsaturated carboxylic acid **S5** (8.79 g), *N*-*tert*-butoxy-*N*-methyl hydroxylamine hydrochloride (9.05 g, 64.8 mmol), and 1-hydroxy-7-azabenzotriazole (HOAt) (5.88 g, 43.2 mmol) in CH_2Cl_2 (108 mL) was added Et_3N (9.0 mL, 64.8 mmol) at room temperature. After the mixture was stirred at room temperature for 10 min, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (12.4 g, 64.8 mmol) was added. After being stirred at room temperature for 1.5 h, the reaction mixture was quenched with H_2O (100 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (100 mL×5). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and

concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~150 g, *n*-hexane/EtOAc = 3:1 to 1:1) afforded (*Z*)-unsaturated Weinreb amide **127** (10.3 g, 21.3 mmol, inseparable 50:50 diastereomeric mixture, >99% for 2 steps) as a yellow oil: $[\alpha]_D^{24}$ –16.1 (c 1.11, $CHCl_3$); IR (ATR): ν 2979, 2938, 2887, 2368, 1652, 1456, 1389, 1365, 1330, 1146, 1102, 1028, 916, 860, 785 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.98 (0.5H, d, *J* = 18.2 Hz), 5.93 (0.5H, d, *J* = 16.3 Hz), 5.51 (0.5H, d, *J* = 13.2 Hz), 5.42 (0.5H, d, *J* = 13.2 Hz), 4.90 (1H, d, *J* = 6.3 Hz), 4.72 (1H, d, *J* = 6.9 Hz), 4.71 (1H, d, *J* = 6.9 Hz), 4.67 (1H, d, *J* = 6.9 Hz), 3.70 (1H, t, *J* = 8.6 Hz), 3.42 (3H, s), 3.35 (3H, s), 3.24 (1.5H, s), 3.23 (1.5H, s), 3.09 (0.5H, d, *J* = 9.8 Hz), 3.07 (0.5H, d, *J* = 9.7 Hz), 2.58 (1H, qt, *J* = 12.6, 6.3 Hz), 1.96 (0.5H, t, *J* = 12.6 Hz), 1.95 (0.5H, t, *J* = 12.6 Hz), 1.74-1.36 (6H, m), 1.30 (1.5H, d, *J* = 7.5 Hz), 1.29 (1.5H, d, *J* = 7.5 Hz), 1.28 (9H, s), 1.18 (1.5H, s), 1.16 (1.5H, s), 1.07 (1.5H, s), 1.05 (1.5H, s), 0.93 (1.5H, s), 0.92 (1.5H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.48, 172.46, 148.45, 147.48, 123.16, 123.05, 121.57, 121.40, 99.01, 9.99, 95.96, 95.91, 88.44, 88.39, 82.88, 82.84, 74.67, 74.63, 56.21, 55.26, 52.54, 52.37, 52.36, 42.73, 42.48, 41.98, 41.97, 41.25, 41.19, 39.32, 37.12, 36.46, 28.90, 28.88, 27.62, 25.96, 25.57, 24.71, 24.06, 19.90, 19.26, 18.02, 17.58, 17.53, 17.48 (seven peaks missing); HRMS (FD): Calcd for $C_{26}H_{46}N_2O_6$ $[M]^+$: 482.3356; found: 482.3353.

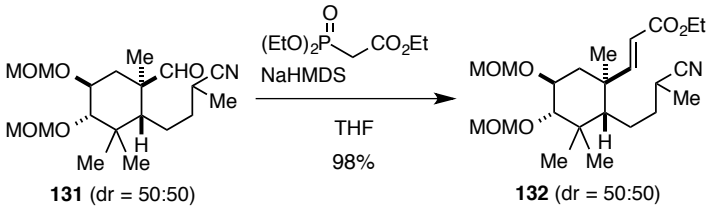
Compound 129



To a mixture of (*Z*)-unsaturated Weinreb amide **127** (8.42 g, 17.4 mmol) and TIPSCl (7.4 mL, 34.8 mmol) in Et_2O (90 mL) was slowly added NaHMDS (1.10 M in THF, 47.5 mL, 52.2 mmol) at –78 °C over 10 min, and the reaction mixture was stirred at –78 °C for 24 h. Then, the mixture was added TBAF (1.0 M in THF, 87.0 mL, 87.0 mmol) at –78 °C. After being stirred at room

temperature for 5 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (100 mL) at –78 °C. Then, the mixture was allowed to warm up to room temperature. After the layers were separated, the aqueous layer was extracted with Et_2O (60 mL×5). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~300 g, *n*-hexane/EtOAc = 1:1 to 1:2) afforded bicyclic compound **129** (7.41 g, 15.4 mmol, 88%, dr = 93:7) as a yellow amorphous foam: $[\alpha]_D^{21}$ –11.2 (c 1.73, $CHCl_3$); IR (ATR): ν 2979, 2944, 2888, 2369, 2360, 2338, 2324, 1667, 1471, 1388, 1366, 1320, 1150, 1102, 1032, 917, 858 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.92 (1H, d, *J* = 6.9 Hz), 4.72 (1H, d, *J* = 6.9 Hz), 4.69 (1H, d, *J* = 6.3 Hz), 4.65 (1H, d, *J* = 6.9 Hz), 3.79 (1H, dt, *J* = 10.3, 4.6 Hz), 3.42 (3H, s), 3.35 (3H, s), 3.23 (3H, s), 2.90 (1H, d, *J* = 9.8 Hz), 2.53 (2H, br-s), 2.28 (1H, dd, *J* = 13.2, 4.6 Hz), 2.00 (1H, d, *J* = 14.3 Hz), 1.80-1.64 (2H, m), 1.70 (1H, dd, *J* = 12.6, 4.6 Hz), 1.51 (3H, s), 1.33 (9H, s), 1.32-1.26 (1H, m), 1.18 (1H, t, *J* = 12.1 Hz), 1.05 (3H, s), 0.93 (1H, d, *J* = 10.3 Hz), 0.87 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 126.64, 99.21, 95.98, 89.31, 82.67, 75.16, 56.19, 55.43, 49.28, 46.44, 41.82, 39.94, 39.45, 39.34, 35.14, 34.49, 28.82, 28.47, 27.83, 27.58, 24.70, 20.23, 17.13 (three peaks missing); HRMS (FD): Calcd for $C_{26}H_{46}N_2O_6Na$ $[M+Na]^+$: 505.3254; found: 505.3255.

Compound 132

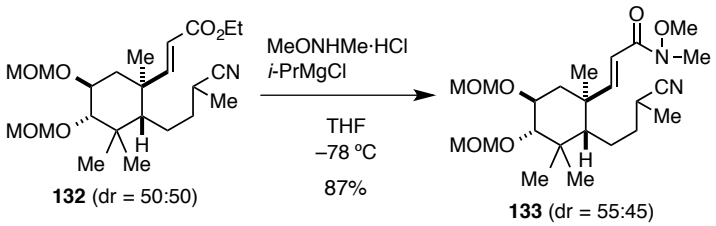


131 (dr = 50:50) **132** (dr = 50:50)

To a solution of ethyl phosphonoacetate (70 μL, 0.353 mmol) was slowly added NaHMDS (1.14 M in THF, 309 μL, 0.353 mmol) at 0 °C over 5 min. After the mixture was stirred at 0 °C for 30 min, a solution of aldehyde **131** (83.7 mg, 0.253 mmol) in THF (1.6 mL) was added at 0 °C over 5 min. After being stirred at room temperature for 2 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (2 mL). After the layers were separated, the aqueous layer was

extracted with Et_2O (2 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~10 g, *n*-hexane/EtOAc = 4:1) afforded (*E*)-unsaturated ester **132** (97.6 mg, inseparable 50:50 diastereomeric mixture, 0.229 mmol, 98%) as a colorless oil: $[\alpha]_D^{28}$ –59.6 (c 0.97, $CHCl_3$); IR (ATR): ν 2938, 2894, 1714, 1648, 1459, 1392, 1366, 1308, 1281, 1180, 1146, 1102, 1026, 916, 753, 665 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.73 (0.5H, d, *J* = 16.1 Hz), 6.72 (0.5H, d, *J* = 16.1 Hz), 5.76 (0.5H, d, *J* = 16.1 Hz), 5.73 (0.5H, d, *J* = 16.0 Hz), 4.92 (1H, d, *J* = 6.3 Hz), 4.73 (1H, d, *J* = 6.9 Hz), 4.72 (1H, d, *J* = 6.3 Hz), 4.66 (1H, d, *J* = 6.9 Hz), 4.23-4.16 (2H, m), 3.74 (1H, dt, *J* = 12.1, 4.6 Hz), 3.43 (3H, s), 3.35 (3H, s), 3.05 (1H, d, *J* = 9.8 Hz), 2.58-2.42 (1H, m), 1.77 (1H, dd, *J* = 13.2, 2.9 Hz), 1.60-1.41 (6H, m), 1.29 (3H, t, *J* = 7.5 Hz), 1.26 (1.5H, t, *J* = 6.9 Hz), 1.25 (1.5H, t, *J* = 6.9 Hz), 1.16 (1.5H, s), 1.14 (1.5H, s), 1.08 (1.5H, s), 1.06 (1.5H, s), 0.96 (1.5H, s), 0.95 (1.5H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.59, 166.57, 158.21, 158.06, 122.54, 122.31, 118.63, 118.52, 98.99, 98.97, 96.12, 88.34, 88.29, 74.63, 74.61, 60.29, 60.27, 56.20, 55.29, 52.54, 52.30, 42.95, 42.88, 41.76, 41.20, 41.09, 36.58, 35.86, 28.76, 28.75, 25.85, 25.49, 24.19, 23.59, 18.20, 18.17, 17.86, 17.57, 17.54, 14.15 (six peaks missing); HRMS (FD): Calcd for $C_{23}H_{39}NO_6$ $[M]^+$: 425.2777; found: 425.2780.

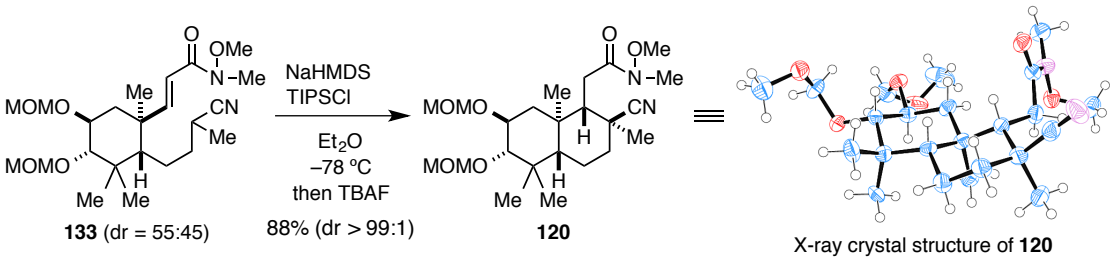
Compound 133



To a mixture of (*E*)-unsaturated ester **132** (15.0 mg, 35.2 μmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (10.3 mg, 0.106 mmol) in THF (0.35 mL) was added *i*-PrMgCl (2.0 M in THF, 106 μL, 0.211 mmol) at –78 °C. After being stirred at –78 °C for 15 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (1 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (1 mL×3). The combined organic

layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~5 g, *n*-hexane/EtOAc = 1:2) afforded (*E*)-unsaturated Weinreb amide **133** (13.5 mg, inseparable 55:45 diastereomeric mixture, 30.6 µmol, 87%) as a white amorphous foam: $[\alpha]_D^{25}$ –72.2 (c 0.80, $CHCl_3$); IR (ATR): ν 2941, 2891, 2821, 1660, 1627, 1462, 1412, 1379, 1146, 1103, 946, 916, 854 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.74 (1H, d, *J* = 15.5 Hz), 6.32 (0.45H, d, *J* = 15.5 Hz), 6.30 (0.55H, d, *J* = 15.5 Hz), 4.92 (1H, d, *J* = 6.3 Hz), 4.73 (1H, d, *J* = 6.3 Hz), 4.72 (1H, d, *J* = 6.3 Hz), 4.67 (1H, d, *J* = 6.3 Hz), 3.75 (1H, td, *J* = 12.0, 4.0 Hz), 3.71 (3H, s), 3.43 (3H, s), 3.35 (3H, s), 3.24 (3H, s), 3.06 (1H, d, *J* = 9.8 Hz), 2.56-2.43 (1H, m), 1.79 (0.45H, t, *J* = 4.6 Hz), 1.76 (0.55H, t, *J* = 4.6 Hz), 1.61-1.30 (5H, m), 1.25 (1.8H, d, *J* = 6.9 Hz), 1.24 (1.2H, d, *J* = 6.9 Hz), 1.20 (1.2H, s), 1.17 (1.8H, s), 1.16-1.08 (1H, m), 1.07 (1.8H, s), 1.06 (1.2H, s), 0.96 (1.8H, s), 0.95 (1.2H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.70, 166.64, 156.95, 156.90, 122.72, 122.52, 115.81, 115.75, 99.09, 99.07, 96.25, 88.50, 88.45, 74.89, 74.85, 61.77, 61.71, 56.30, 55.40, 52.65, 52.26, 43.31, 43.20, 41.91, 41.88, 41.32, 41.17, 36.43, 35.86, 32.37, 28.85, 25.96, 25.78, 24.12, 23.93, 18.54, 18.43, 17.96, 17.79, 17.69, 17.63 (five peaks missing); HRMS (FD): Calcd for $C_{23}H_{40}N_2O_6$ $[M]^+$: 440.2886; found: 440.2904.

Compound 120

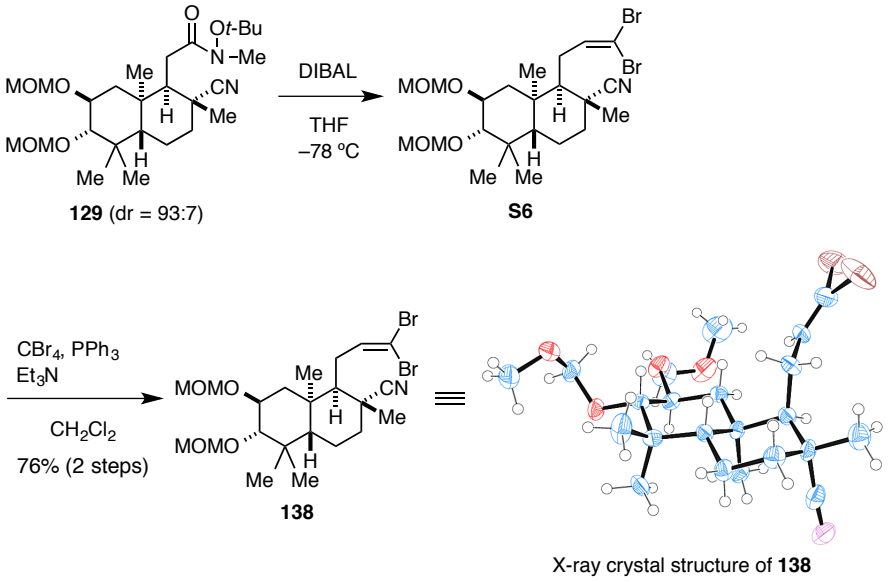


133 (dr = 55:45) **120**

To a mixture of (*E*)-unsaturated Weinreb amide **133** (13.5 mg, 30.6 µmol) and TIPSCl (13 µL, 61.2 µmol) in Et_2O (0.2 mL) was slowly added NaHMDS (1.14 M in THF, 81 µL, 91.8 µmol) at –78 °C over 10 min, and the reaction mixture was stirred at –78 °C for 24 h. Then, to the mixture was added TBAF (1.0 M in THF, 153 µL, 0.153 mmol) at –78 °C. After being stirred at room temperature for 3 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (1

mL) at –78 °C. Then, the mixture was allowed to warm up to room temperature. After the layers were separated, the aqueous layer was extracted with EtOAc (1 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~5 g, *n*-hexane/EtOAc = 1:2) afforded bicyclic compound **120** (11.8 mg, 26.8 μmol, 88%, dr > 99:1) as a white powder. Recrystallization of this powder from *n*-hexane afforded colorless needles, which were analyzed by X-ray: M.p. 114–115 °C (*n*-hexane).

Compound 138

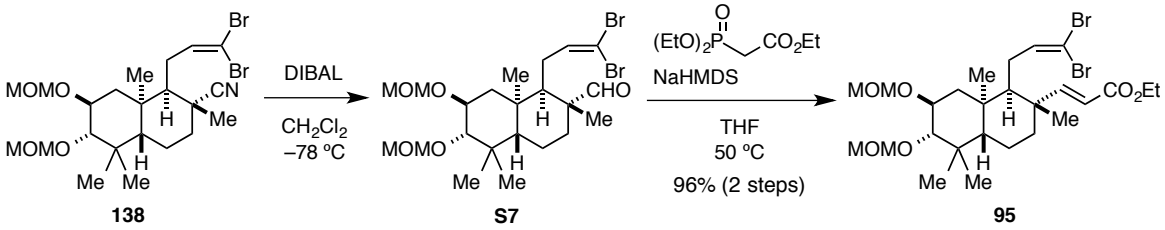


To a solution of bicyclic compound **129** (7.41 g, 15.4 mmol) in THF (80 mL) was slowly added DIBAL (1.03 M in *n*-hexane, 29.9 mL, 30.8 mmol) at –78 °C over 10 min and the mixture was stirred at –78 °C for 6.5 h. Further DIBAL (1.03 M in *n*-hexane, 15.0 mL, 15.4 mmol) at –78 °C, and the mixture was stirred at –78 °C for additional 17.5 h. The reaction was quenched by dropwise addition of EtOAc (30 mL), and the mixture was stirred at –78 °C for 15 min. Then, to the mixture was added a saturated aqueous sodium potassium tartrate solution (ca. 150 mL) at –78 °C, and the mixture was vigorously stirred at room temperature until both phases became clear. After the layers were separated, the aqueous layer was extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced

pressure. The crude aldehyde **S6** (6.52 g, yellow oil) was used for the next step without further purification.

To a solution of CBr_4 (10.2 g, 30.8 mmol) in CH_2Cl_2 (40 mL) were added PPh_3 (16.2 g, 61.6 mmol) and Et_3N (17.1 mL, 123.2 mmol) at 0 °C, and the mixture was stirred for 10 min. Then, the mixture was added a solution of the above crude aldehyde **S6** (6.52 g) in CH_2Cl_2 (40 mL) at 0 °C. After being stirred for 2 h at room temperature, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (100 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (50 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~300 g, *n*-hexane/EtOAc = 5:1 to 2:1) afforded dibromoalkene **138** (6.29 g, 11.7 mmol, 76% for 2 steps) as a white solid. Recrystallization of this powder from *n*-hexane afforded colorless needles, which were analyzed by X-ray: M.p. 112-113 °C (*n*-hexane); $[\alpha]_D^{25}$ +54.2 (c 1.02, $CHCl_3$); IR (ATR): ν 2948, 2882, 2822, 2364, 2229, 1465, 1388, 1364, 1304, 1213, 1148, 1102, 1029, 915, 803, 752 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.29 (1H, t, *J* = 6.3 Hz), 4.92 (1H, d, *J* = 6.3 Hz), 4.75 (1H, d, *J* = 6.9 Hz), 4.72 (1H, d, *J* = 6.9 Hz), 4.68 (1H, d, *J* = 6.9 Hz), 3.79 (1H, dt, *J* = 9.7, 4.0 Hz), 3.43 (3H, s), 3.38 (3H, s), 2.96 (1H, d, *J* = 9.8 Hz), 2.19 (1H, dt, *J* = 17.8, 5.2 Hz), 2.01 (1H, ddd, *J* = 13.8, 6.9, 4.0 Hz), 1.98 (1H, dd, *J* = 9.8, 4.0 Hz), 1.76-1.68 (2H, m), 1.70 (1H, dd, *J* = 11.5, 3.4 Hz), 1.60 (1H, dd, *J* = 4.0, 3.5 Hz), 1.56-1.36 (2H, m), 1.47 (3H, s), 1.44 (3H, s), 1.05 (3H, s), 1.04-1.00 (1H, m), 0.86 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 139.00, 126.47, 99.12, 96.45, 88.84, 88.75, 75.92, 56.26, 55.45, 54.26, 45.41, 42.25, 39.94, 39.33, 34.90, 34.39, 29.39, 28.56, 28.12, 25.05, 20.03, 17.16; HRMS (FD): Calcd for $C_{22}H_{35}NO_4Br_2Na$ $[M+Na]^+$: 558.0831; found: 558.0829.

Compound 95

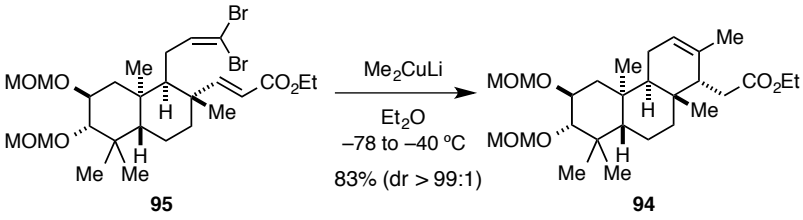


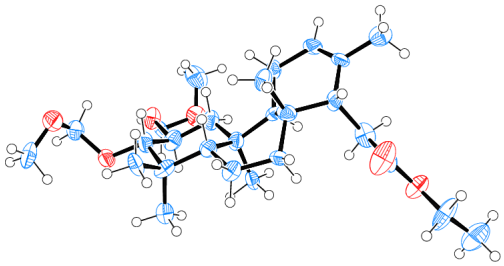
To a solution of dibromoalkene **138** (6.29 g, 11.7 mmol) in CH_2Cl_2 (40 mL) was slowly added DIBAL (1.03 M in *n*-hexane, 17.1 mL, 17.6 mmol) at –78 °C over 10 min and the mixture was stirred at –78 °C for 8 h. The reaction was quenched by dropwise addition of EtOAc (30 mL) and the mixture was stirred at –78 °C for 15 min. Then, to the mixture was added 10% aqueous tartaric acid solution (100 mL) at –78 °C and the mixture was stirred vigorously at room temperature until both phases became clear. After the layers were separated, the aqueous layer was extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude aldehyde **S7** (6.42 g, white solid) was used for the next step without further purification.

To a solution of ethyl phosphonoacetate (4.6 mL, 23.4 mmol) in THF (10 mL) was slowly added NaHMDS (1.10 M in THF, 21.3 mL, 23.4 mmol) at 0 °C over 5 min. After the mixture was stirred at 0 °C for 30 min, a solution of the above crude aldehyde **S7** (6.42 g) in THF (30 mL) was added at 0 °C over 5 min. After being stirred at 50 °C for 24 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (100 mL) at room temperature. After the layers were separated, the aqueous layer was extracted with EtOAc (30 mL×3). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~150 g, *n*-hexane/EtOAc = 6:1 to 2:1) afforded (*E*)-unsaturated ester **95** (6.88 g, 11.3 mmol, 96% for 2 steps) as a yellow oil: $[\alpha]_D^{24}$ –8.70 (c 1.04, $CHCl_3$); IR (ATR): ν 2981, 2883, 1711, 1641, 1464, 1387, 1296, 1264, 1149, 1101, 1029, 916, 754 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.11 (1H, d, *J* = 16.0 Hz), 6.32 (1H, t, *J* = 6.3 Hz), 5.70 (1H, d, *J* = 16.6 Hz), 4.91 (1H, d, *J* = 6.3 Hz), 4.73 (1H, d, *J* = 6.9 Hz), 4.71 (1H, d, *J* = 6.9 Hz), 4.67 (1H, d,

J = 6.3 Hz), 4.24-4.14 (2H, m), 3.48 (1H, dt, J = 10.9, 4.6 Hz), 3.41 (3H, s), 3.37 (3H, s), 2.95 (1H, d, J = 9.2 Hz), 2.23 (1H, dt, J = 11.5, 5.8 Hz), 2.16 (1H, ddd, J = 16.6, 5.7, 3.5 Hz), 1.89 (1H, d, J = 13.2 Hz), 1.61 (1H, dd, J = 12.6, 4.6 Hz), 1.58-1.31 (4H, m), 1.30 (1H, t, J = 7.5 Hz), 1.03 (3H, s), 1.02 (3H, s), 0.98 (3H, s), 0.77 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 167.23, 160.30, 140.58, 114.69, 99.16, 96.38, 89.10, 87.64, 76.16, 60.23, 57.98, 56.24, 55.41, 45.68, 42.50, 40.85, 40.23, 39.34, 31.57, 30.71, 30.08, 28.75, 25.42, 18.81, 17.24, 14.26; HRMS (FD): Calcd for $C_{26}H_{42}O_6Br_2Na$ $[M+Na]^+$: 631.1246; found: 631.1238.

Compound 94





X-ray crystal structure of **94**

To a mixture of CuI (545.6 mg, 2.87 mmol, 99.0% purity, purchased from KANTO CHEMICAL CO., INC.) in Et_2O (0.73 mL) was slowly added MeLi (1.13 M in Et_2O, 5.1 mL, 5.73 mmol) at 0 °C over 10 min, and the mixture was stirring at 0 °C for 30 min. To the resulting Me_2CuLi solution was slowly added a solution of (*E*)-unsaturated ester **95** (350.0 mg, 0.573 mmol) in Et_2O (5.0 mL) at –78 °C over 5 min, and the mixture was stirred at –78 °C for 30 min. Then, the reaction mixture was warmed to –40 °C, and the mixture was stirred at –40 °C for additional 1 h. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution (9 mL) and an aqueous NH_3 solution (1 mL) at –40 °C, and the mixture was stirred vigorously at room temperature until the aqueous layer became clear dark blue solution. The layers were separated, and the aqueous layer

was extracted with Et_2O (5 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~20 g, *n*-hexane/EtOAc = 12:1) afforded tricyclic compound **94** (221.4 mg, 0.474 mmol, 83%) as a white powder. Recrystallization of this powder from *n*-hexane afforded colorless needles, which were analyzed by X-ray: M.p. 99-102 °C (*n*-hexane); $[\alpha]_D^{25}$ +64.6 (c 1.01, $CHCl_3$); IR (ATR): ν 2941, 2887, 1733, 1457, 1373, 1265, 1148, 1102, 1031, 916 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.38 (1H, d, *J* = 2.9 Hz), 4.91 (1H, d, *J* = 6.9 Hz), 4.74 (1H, d, *J* = 6.3 Hz), 4.71 (1H, d, *J* = 6.9 Hz), 4.69 (1H, d, *J* = 6.9 Hz), 4.14 (2H, qd, *J* = 6.9, 2.9 Hz), 3.73 (1H, ddd, *J* = 11.5, 9.8, 4.0 Hz), 3.42 (3H, s), 3.38 (3H, s), 2.96 (1H, d, *J* = 9.8 Hz), 2.37 (1H, dd, *J* = 16.6, 8.0 Hz), 2.21 (1H, dd, *J* = 16.6, 3.5 Hz), 2.09 (1H, d, *J* = 8.1 Hz), 1.91 (1H, br), 1.83 (1H, br), 1.76 (1H, dd, *J* = 13.2, 4.6 Hz), 1.64 (3H, s), 1.68-1.47 (4H, m), 1.35 (1H, t, *J* = 12.6 Hz), 1.31-1.25 (1H, m), 1.27 (1H, t, *J* = 6.9 Hz), 1.76 (1H, dd, *J* = 13.2, 4.6 Hz), 1.08 (3H, s), 1.00 (3H, s), 0.98 (3H, s), 0.91 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 173.96, 135.61, 123.70, 98.98, 96.07, 89.23, 76.20, 60.35, 56.16, 55.28, 50.98, 45.88, 43.07, 42.15, 39.99, 36.43, 36.19, 35.14, 29.22, 28.69, 28.40, 25.74, 22.40, 22.09, 17.54, 17.42, 14.15; HRMS (FD): Calcd for $C_{27}H_{46}O_6$ $[M]^+$: 466.3294; found: 466.3312.

Chapter 2

Installation of the amino acid component

In chapter 1, the synthesis of the *anti-syn-anti*-fused perhydrophenanthrene skeleton of brasilicardins A–D (**3**–**6**) was described. In order to synthesize brasilicardins A–D (**3**–**6**), the next task is the construction of amino acid side chain onto the *anti-syn-anti*-fused perhydrophenanthrene skeleton. In this context, the selection of the protecting groups in an amino group and a carboxylic acid is also important for the total synthesis of brasilicardins A–D (**3**–**6**) because of the following two reasons. The first is that a glycosidic linkage, a special type of acetal linkage, is labile to acidic conditions. The second is that an amino acid is easy to epimerize under non-neutral conditions. Therefore, it is necessary to use the protecting groups that could be removal under mild conditions at the late-stage of the synthesis. With this in mind, the author undertook the construction of amino acid moiety.

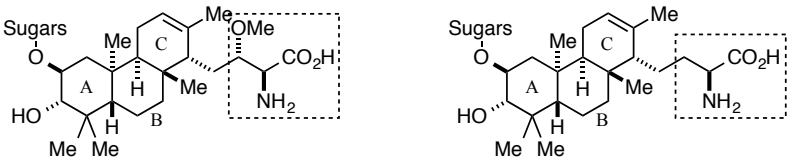
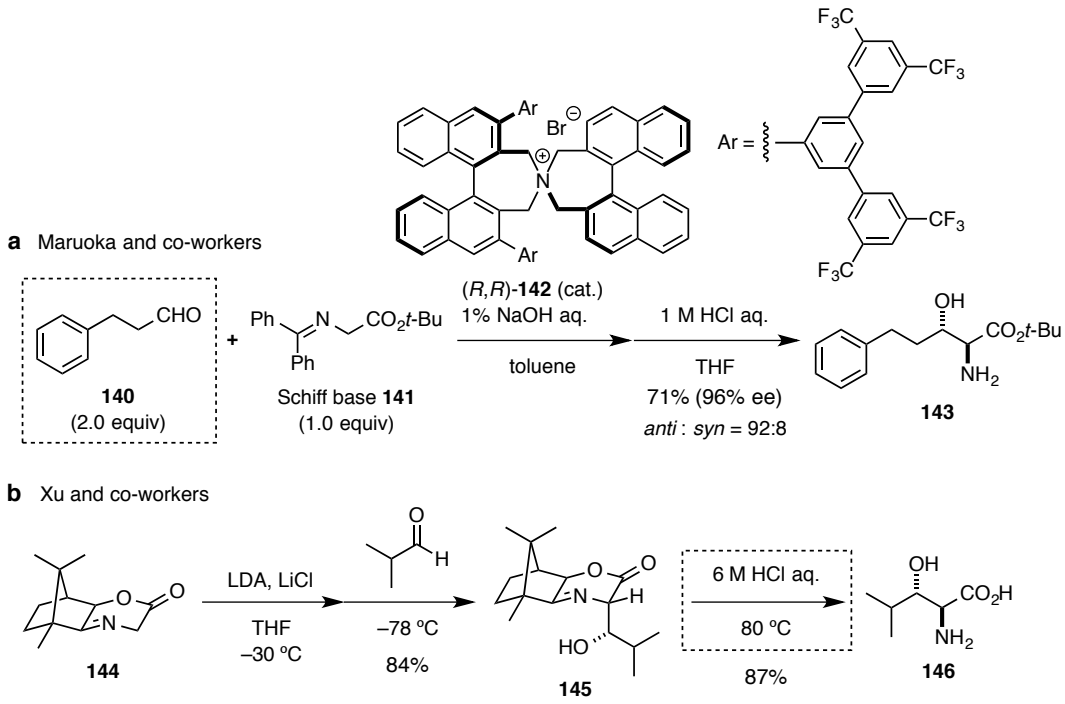


Figure 5. Amino acid side chain of brasilicardins A–D

Initially, the author investigated installation of a β-methoxy-α-amino acid for brasilicardins A (**3**) and C (**5**). β-Hydroxy-α-amino acids are found in a number of naturally occurring organic compounds and biologically active compounds and are also used as a chiral synthon. Because such amino acids can have four possible stereoisomers, asymmetric synthesis of theme is important for synthetic chemistry. Many methods for asymmetric synthesis of β-hydroxy-α-amino acids have been developed so far.[39] Representative examples are shown in Scheme 29.

Maruoka and co-workers reported a diastereo- and enantioselective aldol reaction of glycine Schiff base **141** with aldehyde **140** using *N*-spiro-C_2 symmetric chiral phase-transfer catalyst **142** (Scheme 29a).[40] Although this method directly produce *anti*-β-hydroxy-α-amino acid **143** with high enatiopurity, excess amount of aldehyde **140** is required. Therefore, it is not appropriate to the brasilicardins synthesis because the corresponding aldehyde substrate (the ABC-ring aldehyde) is much precious than Schiff base **141**.

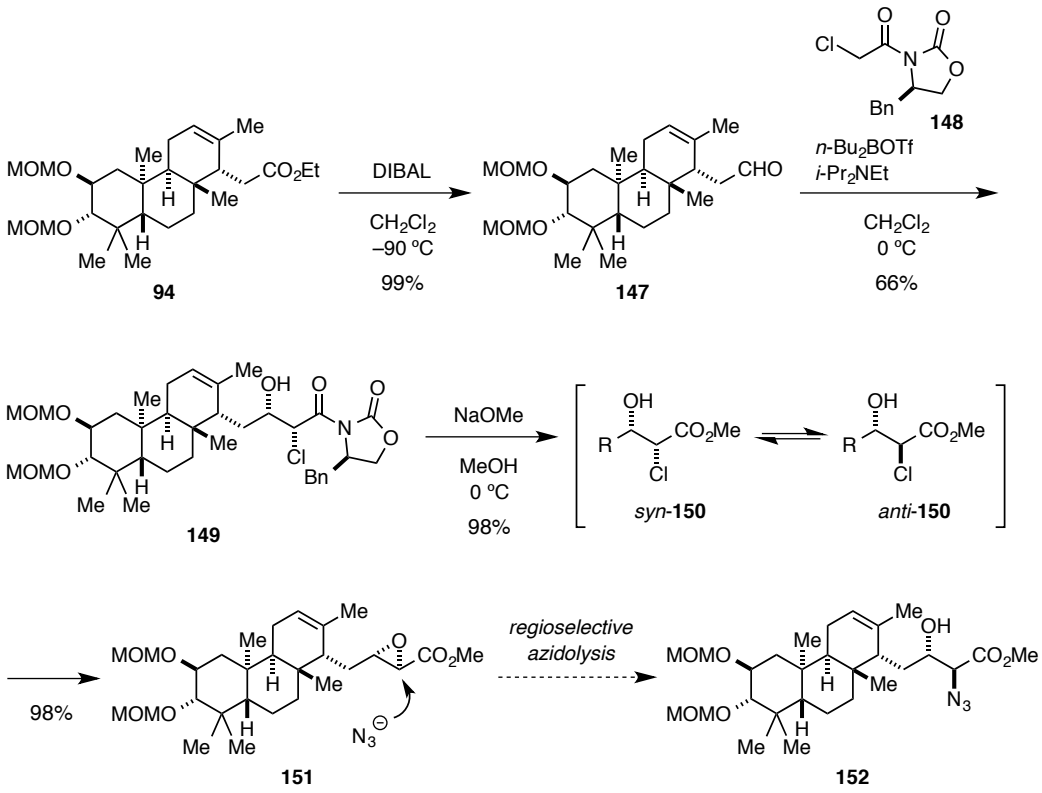
The Xu's aldol reaction using the chiral imino lactone **144** derived from (+)-camphor is a useful method,[41] and was utilized in the total synthesis of a complex natural product, chiriquitoxin (Scheme 29b).[42] However, strongly acidic conditions, such as treatment with 6 M HCl at 60 °C, is required to remove the chiral camphor auxiliary; thus, application to brasilicardins A (**3**) and C (**5**) is difficult in consideration of the protecting group of the hydroxyl groups on the A-ring.



Scheme 29. Examples of installation of β-hydroxy-α-amino acid moiety

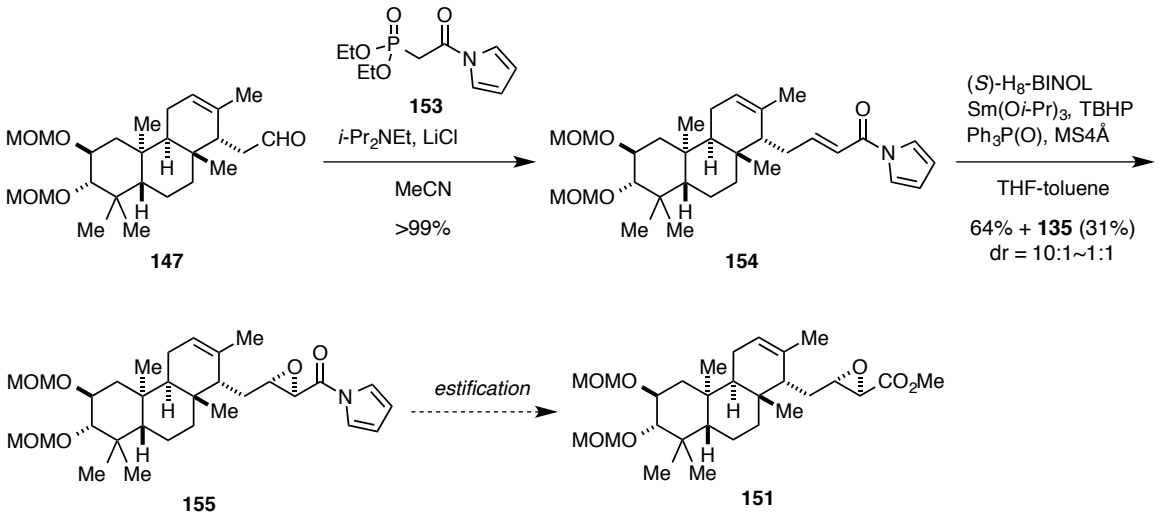
Based on these considerations, the author investigated the construction of the amino acid moiety by a stepwise approach that consists of an asymmetric epoxidation and a regio- and stereoselective epoxide-opening reaction with azide.

First, the author decided to use the Evans asymmetric aldol reaction, wherein an asymmetric auxiliary group can be directly converted to carboxylic acid derivatives under mild conditions (Scheme 30). Thus, tricyclic compound **94** was converted to aldehyde **147** by DIBAL-mediated half-reduction. Aldehyde **147** was subjected to the Evans aldol reaction condition using dibutylboryl trifluoromethanesulfonate (*n*-Bu_2BOTf) and diisopropylethylamine (*i*-Pr_2NEt) with oxazolidinone **148**, which afforded *syn*-α-chloro-β-hydroxy oxazolidinone **149** as a single isomer.[43] However, this reaction was poor in reproducibility. Other Evans-type asymmetric aldol reactions by using oxazolidinethione[44] and thiazolidinethione[45] auxiliaries were unsuccessful. Treatment of the resulting product **149** with sodium methoxide allowed smooth epoxide formation and esterification to afford *trans*-epoxy methyl ester **151**, which involved in situ epimerization at the α-position of the ester giving rise to *anti*-chlorohydrin **150** followed by ring closure.[46] Epoxy ester **151** would be a potential synthetic intermediate for the total synthesis (cf. azidolyisis of **151**).



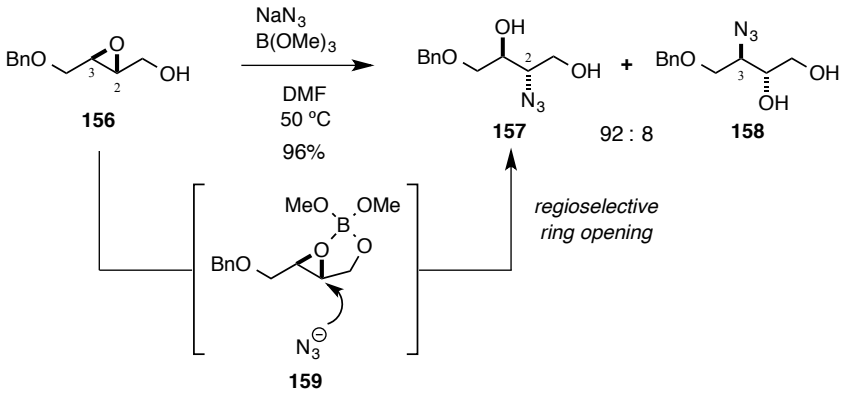
Scheme 30. Synthesis of epoxy ester **151**

Next, the author designed a route via epoxy pyrrole amide **155**, which is the same oxidation state to the above epoxy ester **151** (Scheme 31). This amide **155** would be synthesized by asymmetric epoxidation reaction of α,β-unsaturated *N*-acylpyrrole **154** developed by Shibasaki and co-workers.[47] Thus, aldehyde **147** was converted to **154** through Horner–Wadsworth–Emmons olefination under Masamune–Roush conditions.[28,48] Asymmetric epoxidation of **154** resulted in the formation of epoxy pyrrole amide **155** in moderate yiled, however, the diastereomeric ratio of **154** varied between 10:1 and 1:1, and reproducibility could not be obtained.



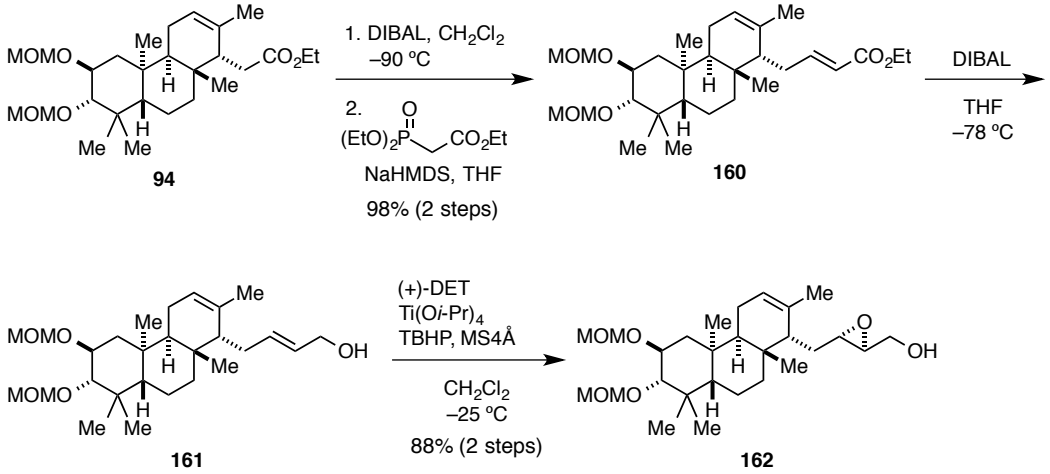
Scheme 31. Asymmetric epoxidation of α,β-unsaturated *N*-acylpyrrole **154**

Katsuki–Sharpless asymmetric epoxidation of an allyl alcohol is an asymmetric epoxidation reaction[49] which is highly reliable and widely used even at the final stage of the total synthesis of natural products. In this connection, the author's laboratory developed the C2-selective azide substitution reaction of a 2,3-epoxy alcohol obtained by Katsuki–Sharpless asymmetric epoxidation (Scheme 32).[50] Thus, treatment of *trans*-epoxy alcohol **156** with sodium azide (NaN_3) in the presence of trimethoxy borate ($B(OMe)_3$) produced the C2 substitution product **157** with high regioselectivity (dr = 92:8). An intramolecular boron chelate **159** played a key role in the high C2 selectivity. Therefore, the author planned to use this reaction as the key step for the installation of the amino acid moiety.



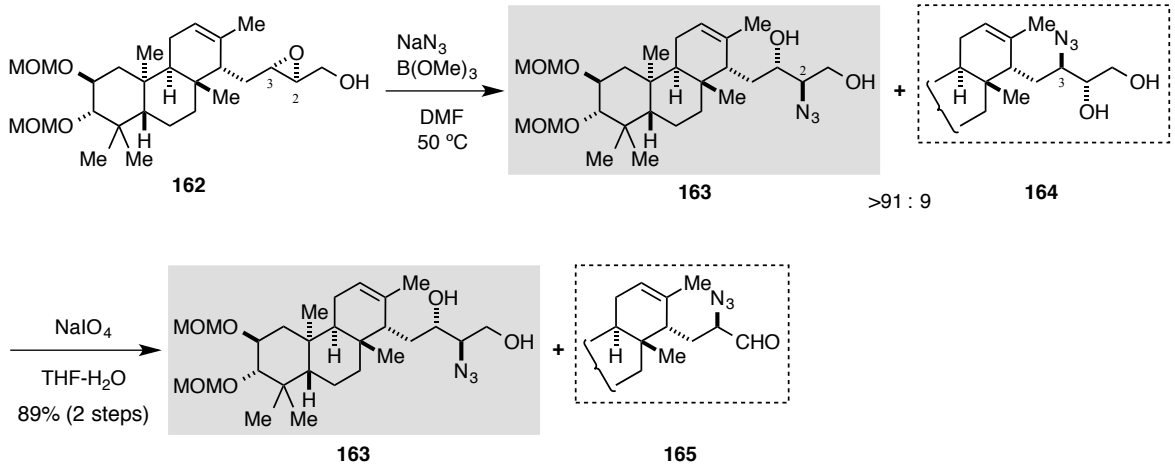
Scheme 32. Substitution reaction of *trans*-epoxy alcohol

Preparation of 2,3-epoxy alcohol **162** is shown in Scheme 33. Thus, half-reduction of **94** using DIBAL followed by Horner–Wadsworth–Emmons olefination of the resulting aldehyde yielded α,β-unsaturated ester **160**. This compound was converted to 2,3-epoxy alcohol **162** as a single diastereomer through DIBAL reduction and Katsuki–Sharpless asymmetric epoxidation of the resulting allyl alcohol **161**.



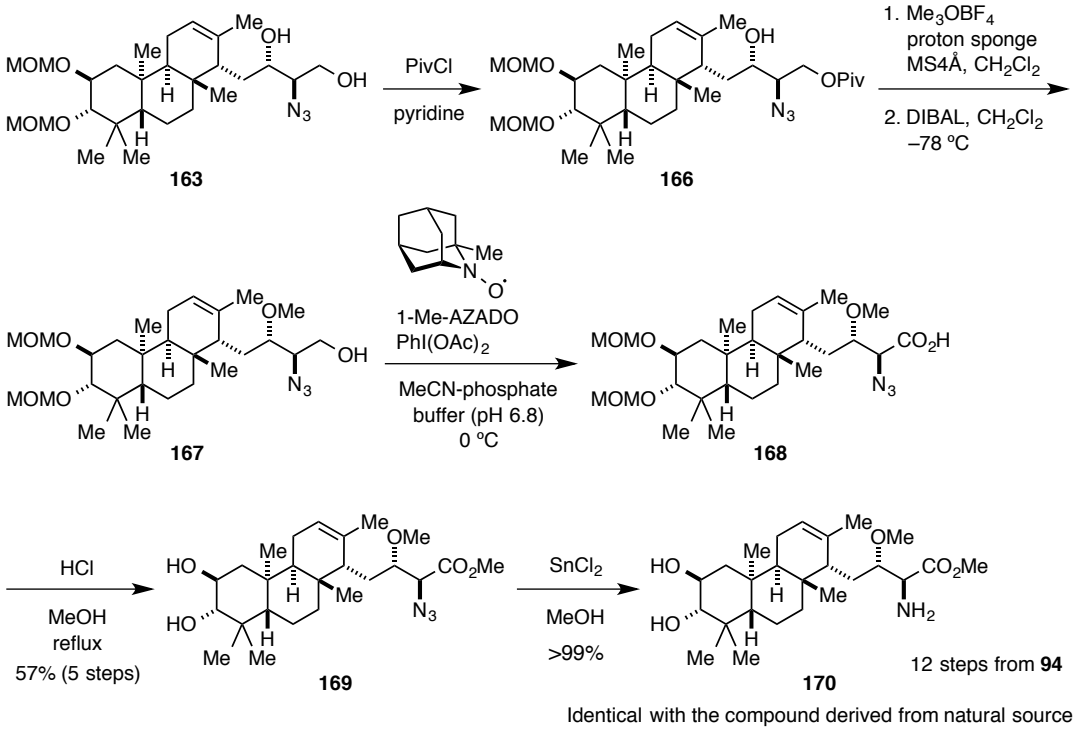
Scheme 33. Preparation of 2,3-epoxy alcohol **162**

Regioselective azide substitution reaction was carried out (Scheme 34).[50] Thus, C2-selective epoxide opening reaction of 2,3-epoxy alcohol **162** with azide was performed by treatment with NaN_3 and $B(OMe)_3$. The desired C2 azide **163** was obtained as a >91:9 inseparable mixture of diastereomeric products. Treatment of the mixture of **163** and **164** with $NaIO_4$, where oxidative cleavage of **164** to aldehyde **165** occurred, followed by purification by silica gel column chromatography afforded C2 azide **163** in pure form.



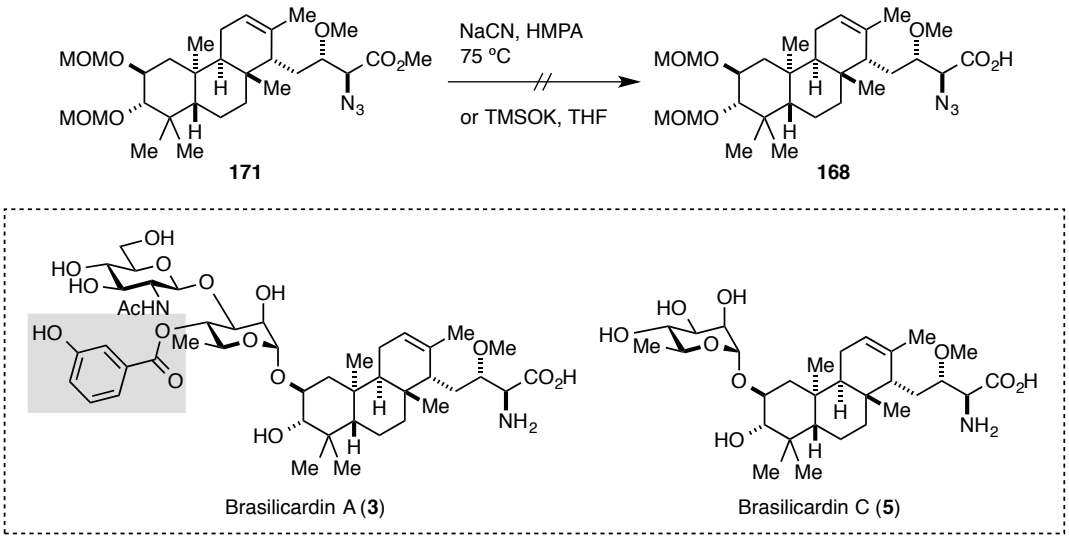
Scheme 34. C2 selective nucleophilic substitution reaction of 2,3-epoxy alcohol **162**

Next, the author examined the conversion of **163** to the amino acid methyl ester **170** because the spectral data of **170** derived from natural braslicardin A (**3**) were reported by Kobayashi and co-workers (Scheme 35).[3] Thus, selective protection of the primary alcohol in 1,3-diol **163** as a pivalate alcohol **166**. The class-selective oxidation of a primary alcohol to a carboxylic acid was achieved in a model compound according to the Iwabuchi's procedure using DMN-AZADO catalyst.[51,52] However, this oxidation could not be applicable to **163**; thus, protection of the primary alcohol in **163** was mandatory. *O*-Methylation of **166** with trimethyloxonium tetrafluoroborate (Me_3OBF_4) followed by deprotection of pivaloyl group using DIBAL yielded primary alcohol **167**. Site-selective oxidation of **167** by 1-Me-AZADO directly afforded carboxylic acid **168**.[53] Other oxidants (e.g., AZADO, TEMPO, Dess–Martin periodinane) resulted in the lower site-selectivity or lower yield of **168**. Esterification of carboxylic acid **168** with HCl-methanol afforded methyl ester **169** accompanied with deprotection of both MOM groups. Finally, reduction of azide in **169** with $SnCl_2$ gave methyl ester **170** of brasilicardin A (**3**) and C (**5**) aglycon. Synthetic methyl ester **170** was identical to its derived from natural brasilicardin A (**3**), including ^{1}H- and ^{13}C-NMR, IR, and HRMS spectra and optical rotation.[3]



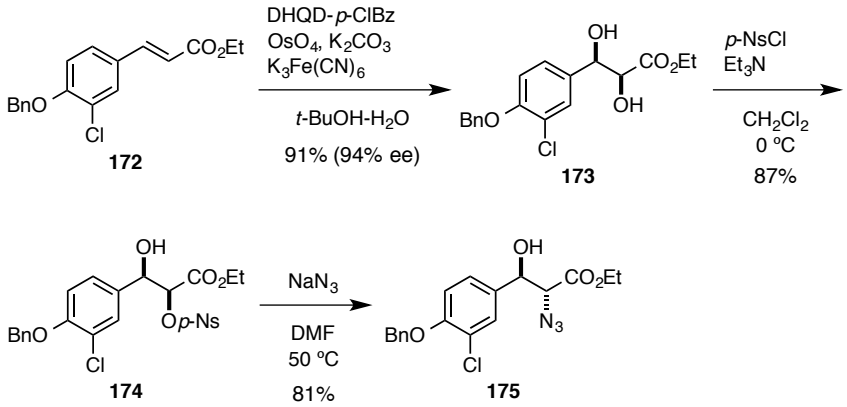
Scheme 35. Synthesis of β-methoxy amino acid moiety

In order to achieve the total synthesis of brasilicardins A (**3**), hydrolysis of the methyl ester would be needed in the presence of the base-sensitive benzoate on the disaccharide moiety; therefore, the author tested hydrolysis of methyl ester **171** (Scheme 36). However, the desired carboxylic acid **168** was not obtained despite of the several conditions examined.[54,55] In addition, inefficient 12 steps were required for the conversion of **94** to **170**, mainly due to adjustment of the oxidation state of the amino acid moiety. Therefore, the author decided to investigate the alternative synthetic route.



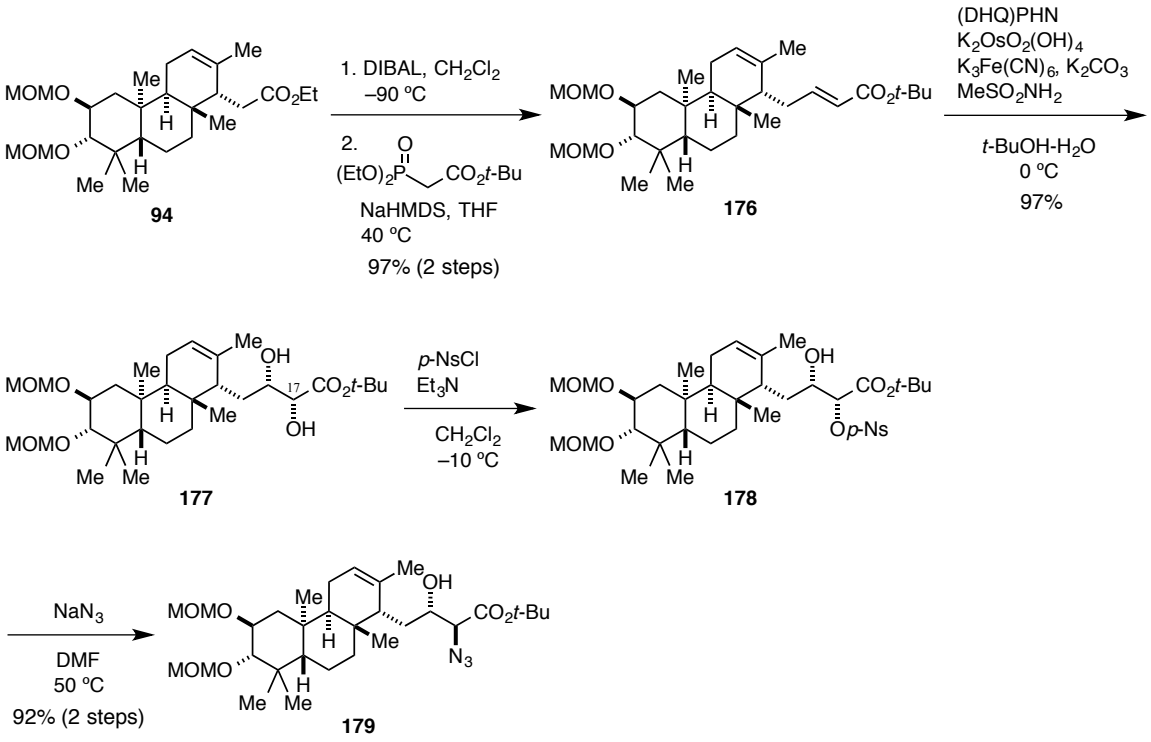
Scheme 36. Attempted conversion to carboxylic acid **168**

In their synthetic study of vancomycin, Rama Rao and co-workers reported an efficient approach for the synthesis of β-hydroxy-α-amino acid (Scheme 37).[56] Thus, Sharpless asymmetric dihydroxylation of (*E*)-α,β-unsaturated ester **172** resulted in the *syn*-dihydroxy ester **173** in 94% ee. Regioselective α-nosylation of diol **173** with 4-nitrobenzenesulfonyl chloride (*p*-NsCl) produced mono nosylate **174** exclusively. Treatment of **174** with NaN_3 in DMF at 50 °C afforded α-azide ester **175** as a sole isomer. The author decided to apply this synthetic method to the amino acid moiety of brasilicardins A (**3**) and C (**5**).



Scheme 37. Approach by the Rama Rao's group

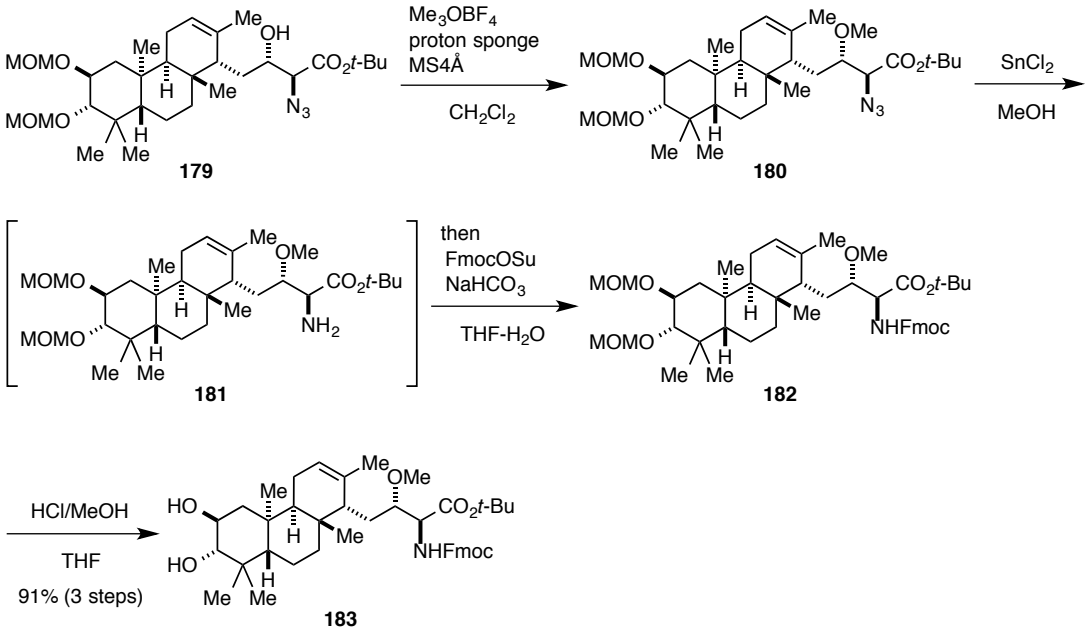
Improved synthesis of the β-methoxy amino acid for brasilicardins A (**3**) and C (**5**) is shown in Scheme 38. Thus, half-reduction of **94** using DIBAL at –90 °C followed by Horner–Wadsworth–Emmons olefination of the resulting aldehyde yielded α,β-unsaturated *tert*-butyl ester **176**. At this time, the protecting group of carboxylic acid was selected as its *tert*-butyl ester because it could be removed under mild acidic conditions. Asymmetric dihydroxylation of **176** using (DHQ)PHN-ligand[29] afforded diol **177** as a single diastereomer. Regioselective nosylation at the C17 alcohol of **177** with *p*-NsCl produced mononosylate **178**, and subsequent treatment of **178** with NaN_3 afforded α-azide **179** with complete inversion of the configuration.



Scheme 38. Synthesis of β-hydroxy-α-azide ester **179**

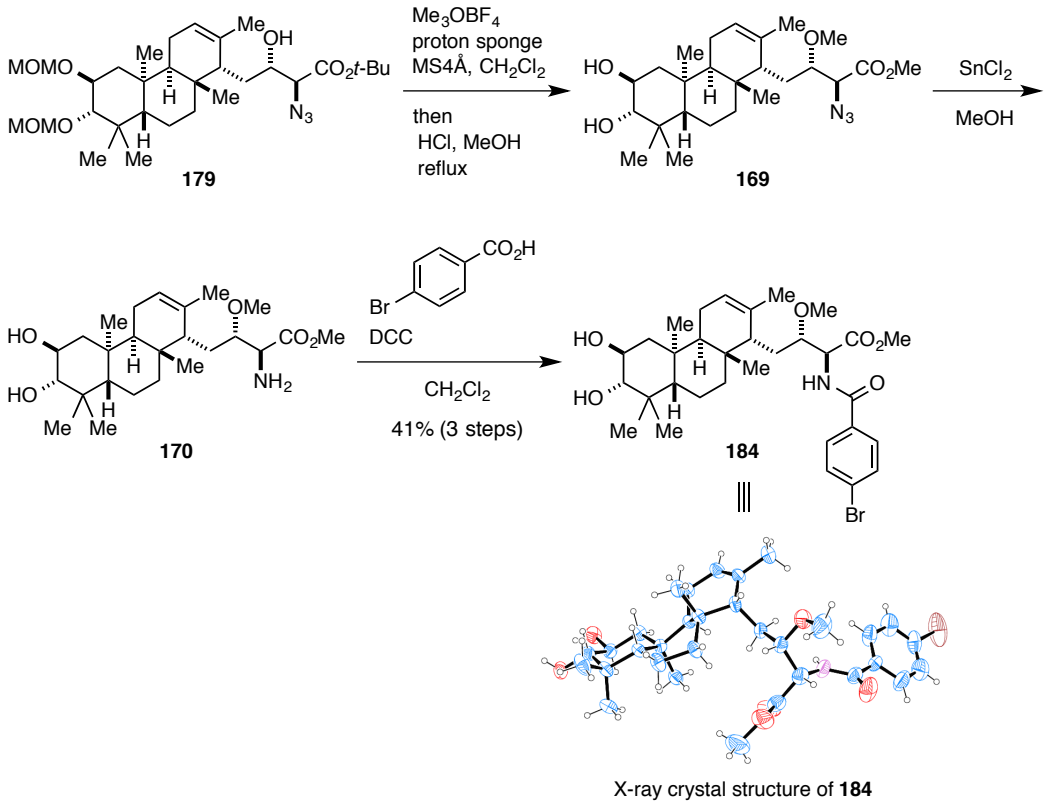
Azide **179** was successfully converted to the protected brasilicardin A (**3**) and C (**5**) aglycon (Scheme 39). Thus, *O*-methylation of **179** with Me_3OBF_4 followed by reduction of azide **180** and protection of the resulting amine **181** with a 9-fluorenylmethyloxycarbonyl (Fmoc) group in one-pot resulted in the formation of the protected amino acid of brasilicardins A (**3**) and C (**5**). The author

selected the Fmoc group as the protecting group of the amine to easy deprotection even possessing a glycosidic linkage at the final stage of the total synthesis. Finally, removal of both MOM groups with HCl in methanol produced diol **183**.



Scheme 39. Synthesis of brasilicardin A and C aglycon **183**

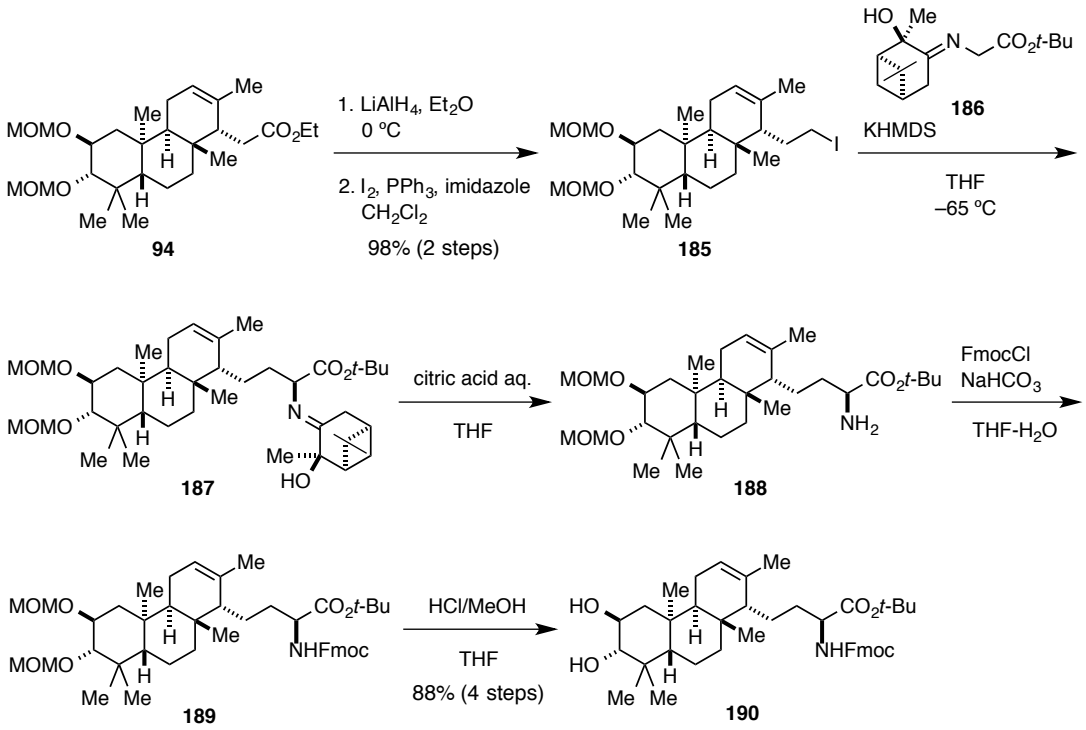
Stereochemistry of the amino acid component was verified by X-ray crystallographic analysis (CCDC 1566258) after the conversion to the corresponding *p*-bromobenzamide derivative of **183** in a three-step sequence (Scheme 40).



Scheme 40. X-ray crystallographic analysis of **184**

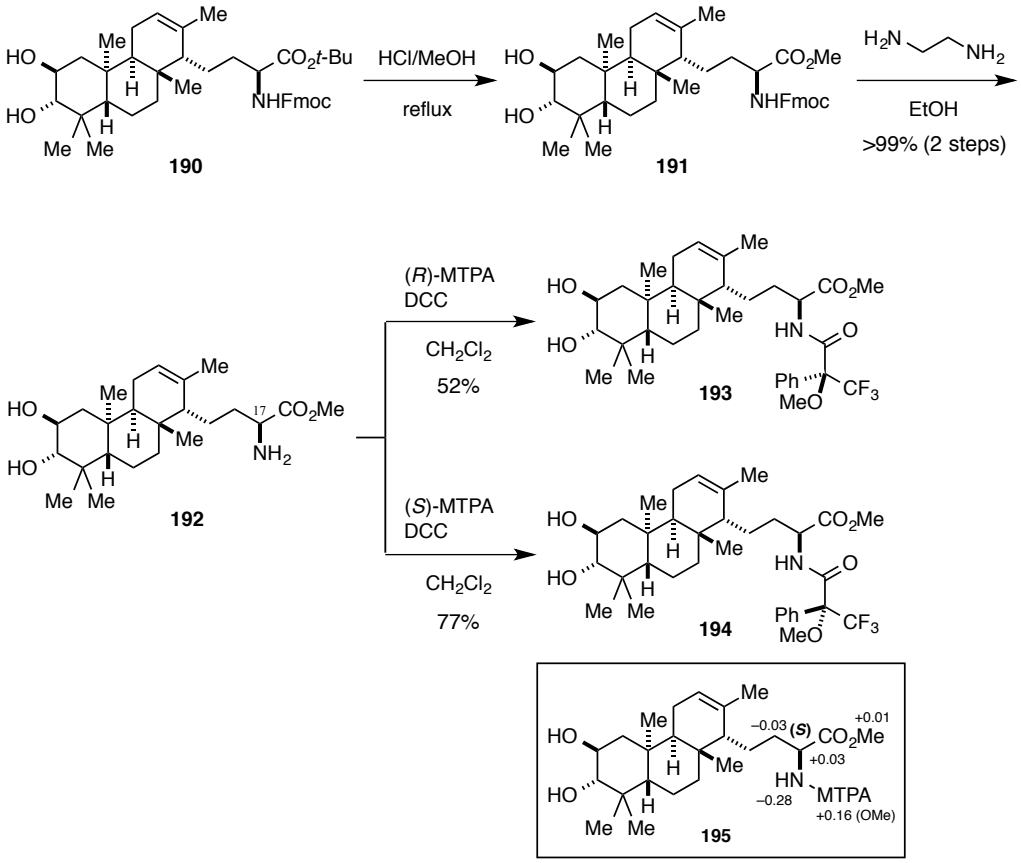
Conversely, installation of the amino acid component of brasilicardins B (**4**) and D (**6**) was performed by Yamada's asymmetric alkylation of the chiral Schiff base as the key step (Scheme 41).[57] Thus, tricyclic compound **94** was converted to iodide **185** through lithium aluminum hydride ($LiAlH_4$) reduction and iodination of the resulting alcohol. Alkylation of the chiral Schiff base **186** derived from glycine with proceeded smoothly when potassium bis(trimethylsilyl)amide (KHMDS) was used as the base, providing the alkylation product **187** as the sole isomer. The use of KHMDS gave superior results than lithium diisopropylamide (LDA) in this reaction, which is contrast to Yamada's original conditions.[57] This compound was converted to diol **190** in three steps involving (1) removal of the chiral auxiliary, (2) Fmoc-protection of the resulting free-amine, and (3) deprotection of the both MOM groups on the diol.

These protected aglycons **183** and **190** were used in the following glycosylation studies.



Scheme 41. Synthesis of brasilicardin B and D aglycon **190**

Stereochemistry of the amino acid portion was unambiguously determined by the modified Mosher's method (Scheme 42).[58] Thus, secondary amine **190** was converted to (*S*)- and (*R*)-2-methoxy-2-trifluoromethylphenylacetamides (MTPA amides) **193** and **194**, respectively, in a three-step sequence. The Δδ values obtained for the MTPA amides [δ(*S*-MTPA amide) – δ(*R*-MTPA amide)] indicated that the absolute configuration at the C17 position of **192** was *S*.



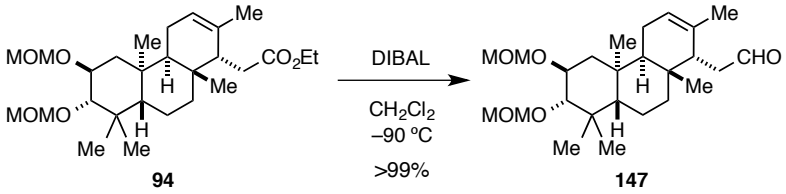
Scheme 42. Determination of stereochemistry by modified Mosher's method

In summary of this chapter, the author has established the installation of amino acid components of brasilicardins A–D (**3**–**6**), and completed the synthesis of their protected aglycons. The β-methoxy-α-amino acid moiety of brasilicardins A (**3**) and C (**5**) was constructed by Sharpless asymmetric dihydroxylation of α,β-unsaturated ester followed by the regioselective azide substitution as the key steps. Conversely, installation of the amino acid component of brasilicardins B (**4**) and D (**6**) was performed by asymmetric alkylation of the chiral Schiff base as the key step. Thus, the protected brasilicardin aglycons **183** or **190** could be synthesized from the common intermediate **94** by choosing appropriate methods.

Experimental Section of Chapter 2

Experimental Procedure for Chapter 2

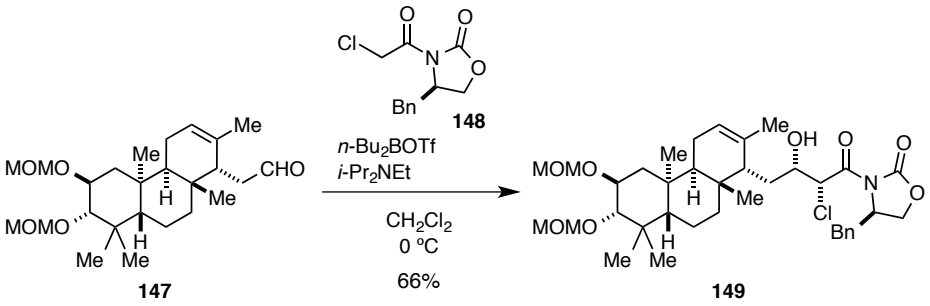
Compound 147



To a solution of tricyclic compound **94** (60.0 mg, 0.129 mmol) in CH_2Cl_2 (1.3 mL) was slowly added DIBAL (1.03 M in *n*-hexane, 150 μL, 0.155 mmol) at –90 °C and the mixture was stirred at –90 °C for 30 min. The reaction was quenched by dropwise addition of EtOAc (1 mL), and the mixture was stirred at –90 °C for 15 min. Then, to the mixture was added a saturated aqueous sodium potassium tartrate solution (ca. 2 mL) at –90 °C, and the mixture was vigorously stirred at room temperature until both phases became clear. After the layers were separated, the aqueous layer was extracted with EtOAc (1 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~5 g, *n*-hexane/EtOAc = 8:1) afforded aldehyde **147** (54.1 mg, 0.128 mmol, 99%) as a colorless oil: $[\alpha]_D^{24}$ +55.8 (c 1.06, $CHCl_3$); IR (ATR): ν 2948, 2889, 2842, 2820, 2712, 1723, 1442, 1382, 1215, 1196, 1148, 1102, 1028, 913, 730, 647 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.81 (1H, s), 5.42 (1H, br), 4.91 (1H, d, *J* = 6.9 Hz), 4.73 (1H, d, *J* = 6.9 Hz), 4.71 (1H, d, *J* = 6.3 Hz), 4.68 (1H, d, *J* = 6.3 Hz), 3.72 (1H, dt, *J* = 6.3 Hz), 3.42 (3H, s), 3.38 (3H, s), 2.96 (1H, d, *J* = 9.8 Hz), 2.59 (1H, dd, *J* = 17.8, 8.0 Hz), 2.30, (1H, d, *J* = 17.8 Hz), 2.15 (1H, d, *J* = 6.9 Hz), 1.94 (1H, br-dt), 1.83 (1H, dd, *J* = 16.6, 12.6 Hz), 1.77 (1H, dd, *J* = 12.6, 4.1 Hz), 1.70-1.49 (3H, m), 1.63 (3H, s), 1.43-1.35 (1H, m), 1.35 (1H, t, *J* = 12.1 Hz), 1.25-1.17 (1H, m), 1.19 (1H, dd, *J* = 10.9, 2.3 Hz), 1.07 (3H, s), 1.03 (3H, s), 0.98 (3H, s), 0.91 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 202.53, 135.08, 124.10, 99.00, 96.12,

89.21, 76.20, 56.20, 55.32, 48.95, 46.30, 44.99, 43.19, 42.14, 40.00, 36.31, 36.22, 30.58, 28.69, 28.38, 25.74, 22.44, 22.14, 17.52, 17.41; HRMS (FD): Calcd for $C_{25}H_{42}O_5$ $[M]^+$: 422.3032; found: 422.3031.

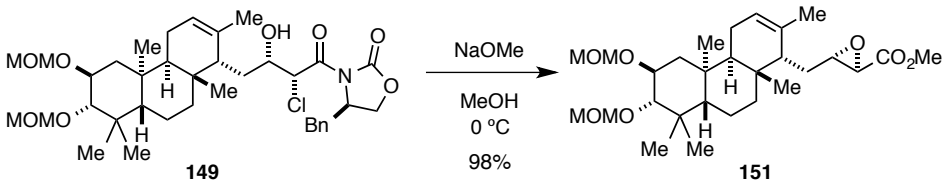
Compound 149



To a solution of (*R*)-chloroacetyloxazolidinone **148** (31.5 mg, 0.124 mmol) in CH_2Cl_2 (0.23 mL) were added *i*-Pr_2NEt (36 μL, 0.270 mmol), and dibutylboryl trifluoromethanesulfonate (*n*-Bu_2BOTf) (1.0 M in CH_2Cl_2, 166 μL, 0.166 mmol) at –78 °C. After being stirred at room temperature for 1 h, the reaction mixture was cooled to –78 °C. Then, to the mixture was added aldehyde **147** (35.0 mg, 82.8 μmol) in CH_2Cl_2 (0.6 mL) at –78 °C and the mixture was stirred at 0 °C for 20 h. To the reaction mixture were added phosphate buffer (pH 7.41, 0.8 mL) and 30% aqueous H_2O_2 solution–MeOH (1:2 v/v, 2.5 mL) at 0 °C, and the mixture was stirred at room temperature for additional 1 h. After the layers were separated, the aqueous layer was extracted with CH_2Cl_2 (1 mL×3). The combined organic layers were washed with a saturated NH_4Cl solution (1 mL) and brine (1 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~20 g, *n*-hexane/EtOAc = 5:1 to 2:1) afforded oxazolidinone **149** (37.0 mg, 54.7 μmol, 66%) as a white amorphous foam: $[\alpha]_D^{26}$ +11.4 (c 1.02, $CHCl_3$); IR (ATR): ν 3434, 2930, 2888, 1780, 1704, 1445, 1383, 1360, 1209, 1147, 1102, 1029, 915, 751, 700, 552 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.35(2H, dd, *J* = 7.5, 6.3 Hz), 7.29 (1H, dd, *J* = 7.4, 6.9 Hz), 7.22 (2H, d, *J* = 6.9 Hz), 5.65 (1H, d, *J* = 3.5 Hz), 5.33 (1H, br), 4.91 (1H, d, *J* = 6.3 Hz), 4.74-4.68 (1H, m), 4.74 (1H, d, *J* = 6.9 Hz), 4.71 (1H, d, *J* = 6.9 Hz), 4.68 (1H, d, *J* = 6.9 Hz), 4.30-4.24 (2H, m),

4.11-4.09 (1H, m), 3.72 (1H, dt, *J* = 12.1, 4.0 Hz), 3.42 (3H, s), 3.38 (3H, s), 3.29 (1H, dd, *J* = 13.7, 2.3 Hz), 2.97 (1H, d, *J* = 9.7 Hz), 2.86 (1H, dd, *J* = 13.8, 9.2 Hz), 2.59 (1H, d, *J* = 6.3 Hz), 1.90 (1H, br-dt), 1.81 (1H, t, *J* = 13.2 Hz), 1.77-1.49 (7H, m), 1.75 (1H, dd, *J* = 13.2, 4.0 Hz), 1.67 (3H, s), 1.36 (1H, t, *J* = 12.1 Hz), 1.31-1.22 (3H, m), 1.09 (3H, s), 0.99 (3H, s), 0.99 (3H, s), 0.93 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.08, 152.60, 137.26, 134.50, 129.44, 129.07, 127.57, 122.58, 99.04, 96.12, 89.32, 76.22, 71.75, 66.46, 60.38, 56.24, 55.41, 55.36, 50.45, 46.11, 43.08, 42.20, 40.10, 37.17, 37.13, 36.17, 35.15, 29.75, 28.71, 28.30, 25.97, 22.45, 22.39, 17.61, 17.50 (two peaks missing); HRMS (FD): Calcd for $C_{37}H_{54}ClNO_8$ $[M]^+$: 675.3538; found: 675.3534.

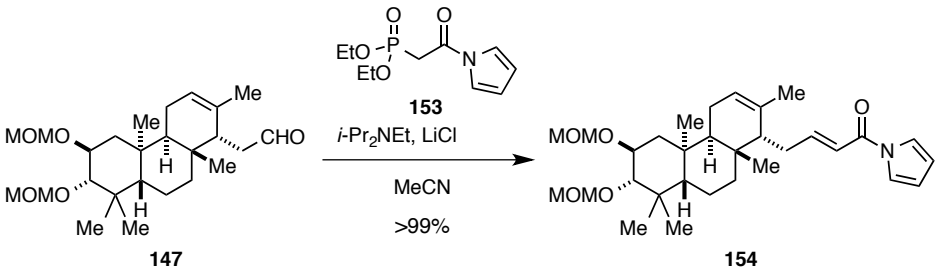
Compound 151



To a solution of oxazolidinone **149** (20.0 mg, 29.6 μmol) in MeOH (0.3 mL) was added NaOMe (5.0 M in MeOH, 18 μL, 90.0 μmol) at 0 °C. After being stirred at 0 °C for 2 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (0.5 mL) at 0 °C. After the layers were separated, the aqueous layer was extracted with Et_2O (1 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~5 g, *n*-hexane/EtOAc = 6:1) afforded epoxy ester **151** (14.4 mg, 29.1 μmol, 98%) as a white amorphous foam: $[\alpha]_D^{27}$ +48.6 (c 0.72, $CHCl_3$); IR (ATR): ν 2946, 2927, 2888, 2822, 1755, 1739, 1443, 1380, 1289, 1203, 1148, 1102, 1031, 917, 808, 742 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.38 (1H, br), 4.91 (1H, d, *J* = 6.3 Hz), 4.73 (1H, d, *J* = 6.3 Hz), 4.71 (1H, d, *J* = 6.9 Hz), 4.68 (1H, d, *J* = 6.3 Hz), 3.78 (3H, s), 3.73 (1H, dt, *J* = 10.3, 4.0 Hz), 3.42 (3H, s), 3.38 (3H, s), 3.25 (1H, s), 3.19-3.17 (1H, m), 2.97 (1H, d, *J* = 9.7 Hz), 1.95-1.90 (2H, m), 1.82 (1H, t, *J* = 14.3 Hz), 1.76 (1H, dd, *J* = 12.6, 4.0 Hz), 1.72-1.57 (4H, m), 1.65 (3H, s), 1.41-1.25 (3H, s), 1.35 (1H, t, *J* = 11.5 Hz), 1.27 (1H, dd, *J* = 12.6, 4.6 Hz), 1.09 (3H, s), 0.99 (3H, s), 0.99 (3H, s), 0.92 (3H, s);

^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.59, 135.80, 123.46, 99.04, 96.16, 89.29, 76.27, 58.80, 56.23, 55.35, 54.14, 52.54, 52.43, 46.08, 43.30, 42.16, 40.06, 36.58, 36.26, 32.61, 30.34, 28.74, 28.35, 25.88, 22.60, 22.37, 17.65, 17.47; HRMS (FD): Calcd for $C_{28}H_{46}O_7$ $[M]^+$: 494.3244; found: 494.3249.

Compound 154



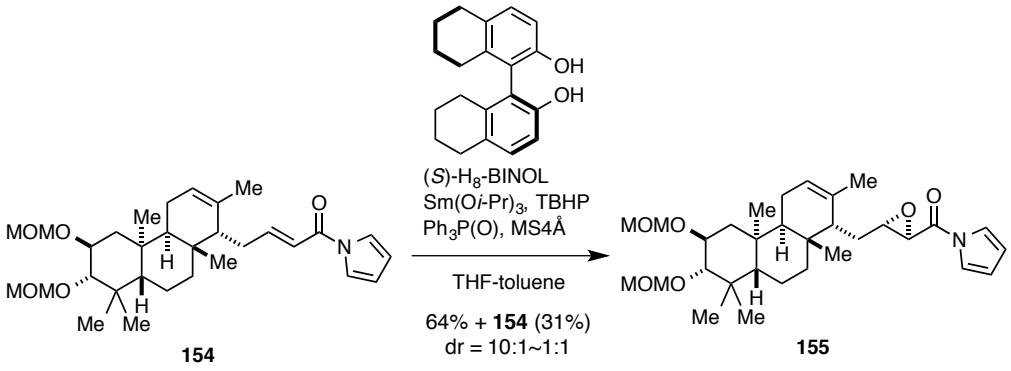
Anhydrous LiCl (10.2 mg, 0.241 mmol) was prepared by flame drying prior to use. Then, a solution of *N*-acylpyrrole phosphonate **153** (29.6 mg, 0.121 mmol) in MeCN (0.2 mL) and *i*-Pr_2NEt (42 μL, 0.241 mmol) was added to the above anhydrous LiCl at 0 °C. After being stirred at 0 °C for 30 min, a solution of aldehyde **147** (17.0 mg, 40.2 μmol) in MeCN (0.6 mL) was added. After being stirred at room temperature for 24 h, the reaction mixture was quenched with H_2O (1 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (1 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~5 g, *n*-hexane/EtOAc = 15:1 to 4:1) afforded (*E*)-unsaturated *N*-acylpyrrole **154** (20.7 mg, 40.2 μmol, >99%) as a white amorphous foam: $[\alpha]_D^{24}$ +89.7 (c 1.04, $CHCl_3$); IR (ATR): ν 2946, 2886, 1698, 1635, 1467, 1345, 1294, 1275, 1148, 1101, 1031, 917, 743 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.37 (2H, br), 7.35-7.29 (1H, m), 6.54 (1H, d, *J* = 14.9 Hz), 6.32 (2H, br), 5.45 (1H, br), 4.90 (1H, d, *J* = 6.3 Hz), 4.72 (1H, d, *J* = 6.3 Hz), 4.70 (1H, d, *J* = 6.9 Hz), 4.67 (1H, d, *J* = 6.9 Hz), 3.70 (1H, dt, *J* = 10.9, 4.0 Hz), 3.42 (3H, s), 3.37 (3H, s), 2.96 (1H, d, *J* = 9.8 Hz), 2.55 (1H, dt, *J* = 15.5, 6.3 Hz), 2.42 (1H, ddd, *J* = 14.9, 8.6, 3.5 Hz), 1.95 (1H, br-dt), 1.82 (1H, t, *J* = 13.7 Hz), 1.76 (1H, dd, *J* = 12.6, 4.0 Hz), 1.72-1.55 (5H, m), 1.68 (3H, s), 1.35-1.31

(3H, m), 1.03 (3H, s), 0.98 (3H, s), 0.98 (3H, s), 0.90 (3H, s); HRMS (FD): Calcd for $C_{31}H_{47}NO_5$ $[M]^+$: 513.3454; found: 513.3444.

Preparation of Sm-(*S*)-H_8-BINOL Catalyst in THF[47]

To a mixture of freshly activated and powdered MS4Å (38.9 mg) and (*S*)-H_8-BINOL (0.20 M in THF, 9.7 μL, 1.95 μmol) in THF (0.39 mL) was added samarium isopropoxide (Sm(O*i*-Pr)$_3$) (0.20 M in THF, 9.7 μL, 1.95 μmol) at room temperature. After being stirred at room temperature for 20 min, *tert*-butyl hydroperoxide (TBHP) (5.5 M in nonane, 11 μL, 60.5 μmol) was added. The stirring was continued at room temperature for another 20 min to afford Sm-(*S*)-H_8-BINOL Catalyst in THF. The resulting suspension was immediately used for the catalytic asymmetric epoxidation.

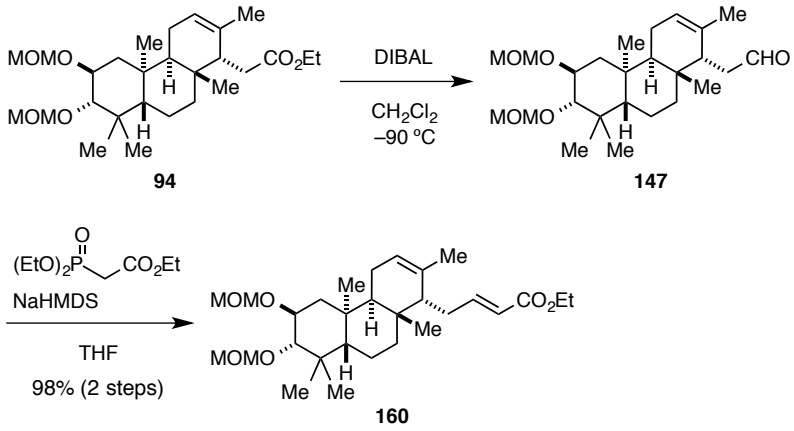
Compound 155



To a mixture of (*E*)-unsaturated *N*-acylpyrrole **154** (20.0 mg, 38.9 μmol) and triphenylphosphine oxide (10.8 mg, 38.9 μmol) in toluene (0.39 mL) was added the above Sm-(*S*)-H_8-BINOL Catalyst suspension at room temperature. After being stirred at room temperature for 2 h, the reaction mixture was quenched with 2.5% aqueous citric acid (1 mL). The mixture was filtered through a pad of Celite®, which was rinsed with EtOAc (1 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (1 mL×3). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (1 mL×2), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by preparative TLC (SiO_2, *n*-hexane/EtOAc =

5:2) afforded epoxy *N*-acylpyrrole **155** (13.1 mg, 24.7 μmol, 64%, dr = 80:20) as a white amorphous foam with recovery of (*E*)-unsaturated *N*-acylpyrrole **154** (6.1 mg, 11.9 μmol, 31%) as a white amorphous foam: $[\alpha]_D^{25}$ +60.6 (c 0.66, $CHCl_3$); IR (ATR): ν 2945, 2886, 1726, 1470, 1440, 1362, 1316, 1287, 1149, 1102, 1034, 918, 746 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.43 (2H, s), 6.37 (2H, s), 5.41 (1H, br), 4.91 (1H, d, *J* = 6.3 Hz), 4.73 (1H, d, *J* = 6.9 Hz), 4.71 (1H, d, *J* = 6.9 Hz), 4.68 (1H, d, *J* = 6.3 Hz), 3.79 (1H, s), 3.72 (1H, dt, *J* = 10.9, 4.0 Hz), 3.42 (3H, s), 3.38 (3H, s), 3.32 (1H, br), 2.97 (1H, d, *J* = 9.7 Hz), 2.04 (1H, dt, *J* = 15.5, 5.2 Hz), 1.92 (1H, br-dt), 1.83 (1H, t, *J* = 13.2 Hz), 1.75 (1H, dd, *J* = 12.1, 3.5 Hz), 1.71-1.65 (3H, m), 1.67 (3H, s), 1.61-1.50 (3H, m), 1.37-1.25 (3H, m), 1.28 (1H, dd, *J* = 12.6, 4.6 Hz), 1.08 (3H, s), 1.00 (3H, s), 0.98 (3H, s), 0.92 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 165.53, 135.48, 123.91, 119.06, 113.96, 99.04, 96.16, 89.27, 76.24, 59.74, 56.24, 55.36, 54.79, 52.64, 46.20, 43.27, 42.14, 40.05, 36.57, 36.29, 32.62, 30.45, 28.74, 28.40, 25.87, 22.66, 22.43, 17.60, 17.47 (two peaks missing); HRMS (FD): Calcd for $C_{31}H_{47}NO_6$ $[M]^+$: 529.3403; found: 529.3401.

Compound 160

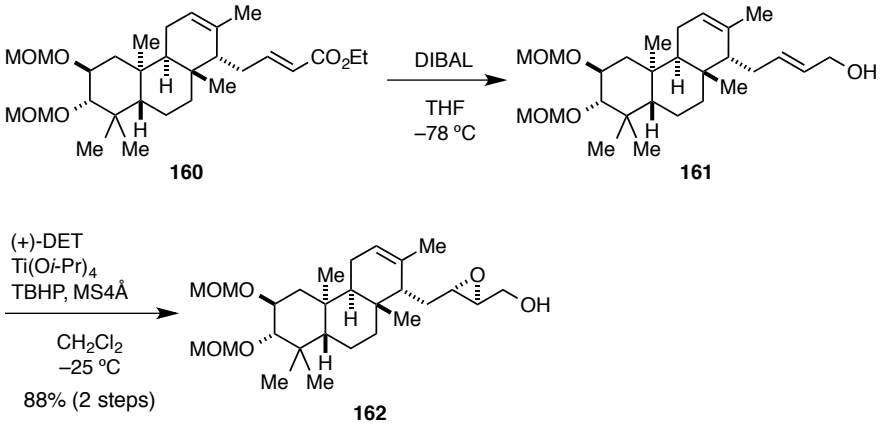


To a solution of tricyclic compound **94** (100.0 mg, 0.214 mmol) in CH_2Cl_2 (2.1 mL) was slowly added DIBAL (1.03 M in *n*-hexane, 249 μL, 0.257 mmol) at –90 °C and the mixture was stirred at –90 °C for 30 min. The reaction was quenched by dropwise addition of EtOAc (2 mL), and the mixture was stirred at –90 °C for 15 min. Then, to the mixture was added a saturated aqueous

sodium potassium tartrate solution (ca. 2 mL) at –90 °C, and the mixture was vigorously stirred at room temperature until both phases became clear. After the layers were separated, the aqueous layer was extracted with EtOAc (2 mL×3). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude aldehyde **147** (99.2 mg, white amorphous foam) was used for the next step without further purification.

To a solution of triethyl phosphonoacetate (85 μL, 0.428 mmol) was slowly added NaHMDS (1.14 M in THF, 375 μL, 0.428 mmol) at 0 °C over 5 min. After the mixture was stirred at 0 °C for 30 min, a solution of the above crude aldehyde **147** (99.2 mg) in THF (1.1 mL) was added at 0 °C over 5 min. After being stirred at room temperature for 2 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (2 mL) and H_2O (1 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (2 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~10 g, *n*-hexane/EtOAc = 10:1 to 8:1) afforded (*E*)-unsaturated ester **160** (103.3 mg, 0.210 mmol, 98% for 2 steps) as a colorless oil: $[\alpha]_D^{25}$ +75.5 (c 0.87, $CHCl_3$); IR (ATR): ν 2939, 2883, 2844, 2820, 1718, 1651, 1443, 1367, 1305, 1264, 1207, 1147, 1101, 917, 755 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.99 (1H, dt, *J* = 15.5, 7.5 Hz), 5.81 (1H, d, *J* = 16.0 Hz), 5.41 (1H, br), 4.90 (1H, d, *J* = 6.3 Hz), 4.73 (1H, d, *J* = 6.9 Hz), 4.71 (1H, d, *J* = 6.3 Hz), 4.68 (1H, d, *J* = 6.9 Hz), 4.18 (2H, d, *J* = 6.9 Hz), 3.72 (1H, td, *J* = 10.9, 4.0 Hz), 3.42 (3H, s), 3.38 (3H, s), 2.96 (1H, d, *J* = 9.8 Hz), 2.41 (1H, dt, *J* = 16.1, 5.7 Hz), 2.30-2.24 (1H, br-ddd), 1.92 (1H, br-dt), 1.80 (1H, t, *J* = 13.8 Hz), 1.76 (1H, dd, *J* = 12.6, 4.0 Hz), 1.70-1.65 (1H, m), 1.65 (3H, s), 1.60-1.55 (3H, m), 1.35-1.26 (4H, m), 1.28 (3H, t, *J* = 6.9 Hz), 1.04 (3H, s), 0.98 (3H, s), 0.96 (3H, s), 0.91 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.48, 149.84, 135.14, 123.86, 121.12, 98.95, 96.04, 89.23, 76.16, 60.02, 56.10, 55.24, 54.51, 46.01, 43.29, 42.10, 39.97, 36.72, 36.48, 32.72, 30.27, 28.67, 28.12, 25.67, 22.77, 22.54, 17.59, 17.39, 14.21; HRMS (FD): Calcd for $C_{29}H_{48}O_6$ $[M]^+$: 492.3451; found: 492.3444.

Compound 162

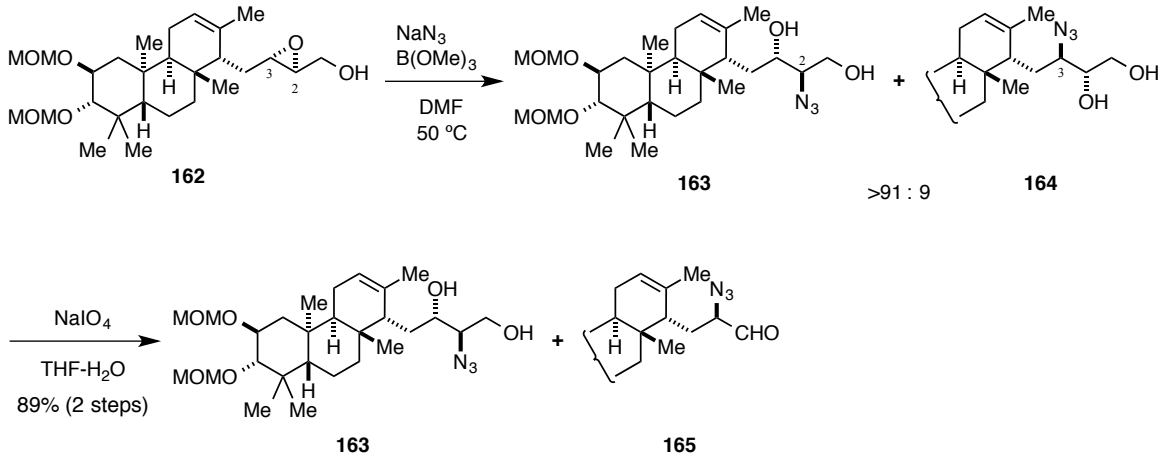


To a solution of (*E*)-unsaturated ester **160** (97.3 mg, 0.197 mmol) in THF (2.0 mL) was slowly added DIBAL (1.03 M in *n*-hexane, 574 μL, 0.591 mmol) at –78 °C and the mixture was stirred at –78 °C for 1 h. The reaction was quenched by dropwise addition of EtOAc (1 mL), and the mixture was stirred at –78 °C for 15 min. Then, to the mixture was added a saturated aqueous sodium potassium tartrate solution (ca. 5 mL) at –78 °C, and the mixture was vigorously stirred at room temperature until both phases became clear. After the layers were separated, the aqueous layer was extracted with EtOAc (2 mL×3). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude allyl alcohol **161** (83.3 mg, colorless oil) was used for the next step without further purification.

To a mixture of (+)-diethyl tartrate (50 μL, 0.296 mmol), freshly activated and powdered MS4Å (39 mg) in CH_2Cl_2 (0.6 mL) was slowly added titanium isopropoxide (81 μL, 0.296 mmol) at –25 °C over 3 min. After being stirred at –25 °C for 30 min, TBHP (5.5 M in nonane, 179 μL, 0.985 mmol) was slowly added at –25 °C over 3 min. After being stirred at –25 °C for 1 h, a solution of the above allyl alcohol **161** (83.3 mg) in CH_2Cl_2 (1.4 mL) was added at –25 °C over 5 min. After being stirred at –25 °C for 2 h, the reaction mixture was quenched with a 10% aqueous NaOH solution (1.5 mL). After being stirred at room temperature for additional 1 h, the mixture was filtered through a pad of Celite®, which was rinsed with EtOAc (5 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (2 mL×3). The combined organic layers

were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~10 g, *n*-hexane/EtOAc = 5:1 to 4:1) afforded epoxy alcohol **162** (80.5 mg, 0.173 mmol, 88% for 2 steps) as a colorless oil: $[\alpha]_D^{26}$ +52.3 (c 1.03, $CHCl_3$); IR (ATR): ν 3445, 2947, 1442, 1380, 1148, 1102, 1032, 918, 805, 772, 686, 669 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.37 (1H, br), 4.91 (1H, d, *J* = 6.3 Hz), 4.74 (1H, d, *J* = 6.3 Hz), 4.71 (1H, d, *J* = 6.3 Hz), 4.68 (1H, d, *J* = 6.9 Hz), 3.91 (1H, dd, *J* = 12.6, 2.9 Hz), 3.72 (1H, dt, *J* = 11.5, 4.1 Hz), 3.64 (1H, ddd, *J* = 15.5, 7.5, 4.0 Hz), 3.42 (3H, s), 3.38 (3H, s), 3.00-2.94 (2H, m), 2.97 (1H, d, *J* = 9.8 Hz), 1.92 (1H, br-dt), 1.85-1.80 (1H, m), 1.77 (1H, dd, *J* = 13.2, 4.6 Hz), 1.72-1.67 (1H, m), 1.66 (3H, s), 1.63-1.54 (5H, m), 1.44 (1H, ddd, *J* = 14.9, 6.9, 3.5 Hz), 1.38-1.25 (2H, m), 1.31 (1H, dd, *J* = 12.6, 4.6 Hz), 1.09 (3H, s), 0.99 (3H, s), 0.99 (3H, s), 0.92 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 136.21, 123.07, 99.00, 96.10, 89.29, 76.26, 61.53, 59.79, 56.24, 56.19, 55.31, 52.77, 46.04, 43.28, 42.12, 40.03, 36.55, 36.24, 32.68, 30.36, 28.71, 28.31, 25.88, 22.67, 22.40, 17.66, 17.44; HRMS (FD): Calcd for $C_{27}H_{46}O_6$ $[M]^+$: 466.3294; found: 466.3288.

Compound 163

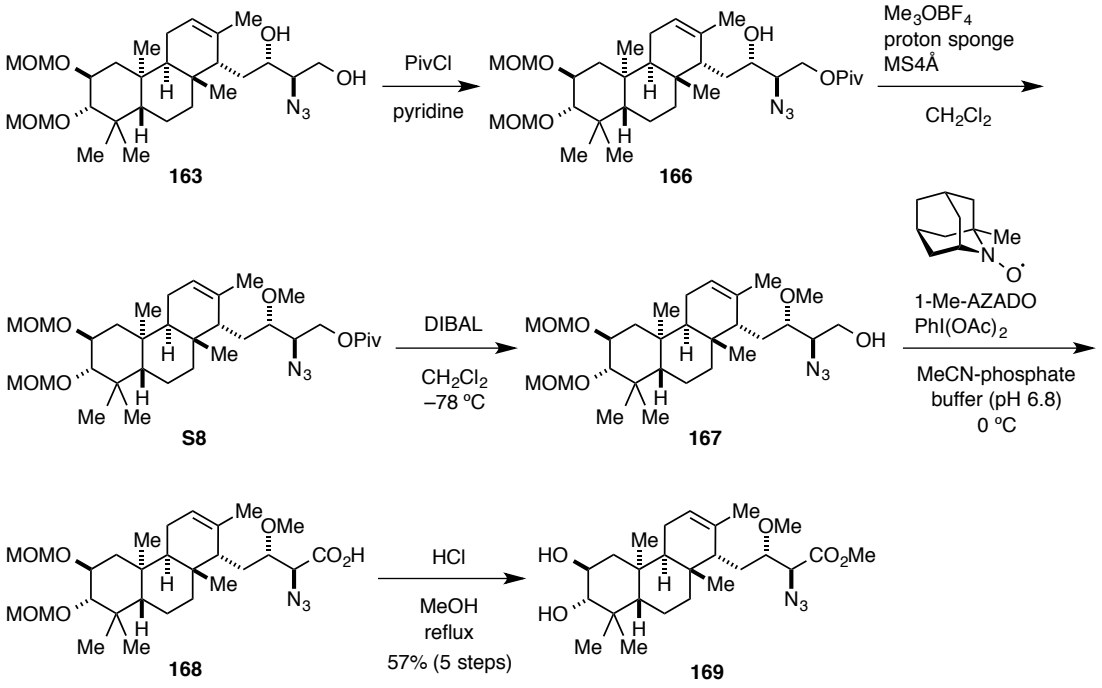


To a mixture of epoxy alcohol **162** (53.1 mg, 0.114 mmol) and trimethoxyborane (40 μL, 0.342 mmol) in DMF (0.76 mL) was added sodium azide (22.2 mg, 0.342 mmol) at room temperature. After being stirred at 50 °C for 12 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (2 mL) at 0 °C, and the mixture was stirred at 0 °C for additional 30 min. After the

layers were separated, the aqueous layer was extracted with EtOAc (2 mL×3). The combined organic layers were washed with H_2O (2 mL×2), dried over $MgSO_4$, and concentrated under reduced pressure. The crude inseparable >91:9 mixture of desired 2-azide-1,3-diol **163** and 3-azide-1,2-diol **164** (63.3 mg, as a yellow amorphous foam) was used for the next step without further purification.

To a solution of the above mixture of crude diols **163** and **164** (63.3 mg) in THF–H_2O (4:1 v/v, 1.0 mL) was added sodium periodate (24.4 mg, 0.114 mmol) at room temperature. After being stirred at room temperature for 3 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (2 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (2 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~5 g, *n*-hexane/EtOAc = 4:1 to 1:1) afforded diol **163** (51.6 mg, 0.101 mmol, 89% for 2 steps) as a white amorphous foam: $[\alpha]_D^{27}$ +64.9 (c 1.44, $CHCl_3$); IR (ATR): ν 3447, 2941, 2895, 2102, 1457, 1376, 1270, 1147, 1101, 1032, 770 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.36 (1H, br), 4.91 (1H, d, *J* = 6.3 Hz), 4.74 (1H, d, *J* = 6.9 Hz), 4.71 (1H, d, *J* = 6.3 Hz), 4.69 (1H, d, *J* = 6.9 Hz), 3.92 (2H, br), 3.75-3.71 (2H, m), 3.42 (3H, s), 3.40-3.36 (1H, m), 3.38 (3H, s), 2.97 (1H, d, *J* = 9.8 Hz), 2.13 (2H, br), 1.92 (1H, br-dt), 1.85-1.74 (2H, m), 1.77 (1H, dd, *J* = 13.2, 4.6 Hz), 1.72-1.56 (6H, m), 1.67 (3H, s), 1.39-1.25 (3H, m), 1.30 (1H, dd, *J* = 17.2, 5.2 Hz), 1.10 (3H, s), 1.00 (3H, s), 0.99 (3H, s), 0.93 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 136.96, 122.76, 99.00, 96.11, 89.31, 76.24, 72.82, 67.46, 62.53, 56.22, 55.35, 51.07, 46.09, 43.03, 42.19, 40.08, 37.22, 36.15, 35.35, 29.86, 28.68, 28.29, 25.96, 22.45, 22.39, 17.59, 17.44; HRMS (FD): Calcd for $C_{27}H_{48}N_3O_6$ $[M+H]^+$: 510.3543; found: 510.3541.

Compound 169



To a solution of diol **163** (51.6 mg, 0.101 mmol) in pyridine (0.67 mL) was added pivaloyl chloride (24.9 μL, 0.202 mmol) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was quenched with H_2O (2 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (2 mL×3). The combined organic layers were washed with 5% aqueous $KHSO_4$ solution (2 mL×2), dried over $MgSO_4$, and concentrated under reduced pressure. The crude pivalate **166** (65.7 mg, yellow amorphous foam) was used for the next step without further purification.

To a mixture of the above crude pivalate **166** (65.7 mg), 1,8-bis(dimethylamino)naphthalene (proton sponge) (216.5 mg, 1.01 mmol), and freshly activated and powdered MS4Å (222 mg) in CH_2Cl_2 (1.0 mL) was added trimethyloxonium tetrafluoroborate (Me_3OBF_4) (104.6 mg, 0.707 mmol) at 0 °C. After being stirred at room temperature for 5 h, the reaction mixture was filtered through a pad of Celite®, which was rinsed with EtOAc (50 mL). The organic layers were washed with a saturated aqueous $NaHCO_3$ solution (10 mL×2), 5% aqueous $KHSO_4$ solution (15 mL×3), and dried over $MgSO_4$, and concentrated under reduced pressure. The residue was filtered through a

pad of silica gel (SiO_2~10 g, *n*-hexane/EtOAc = 10:1, 100 mL), and concentrated under reduced pressure. The crude methyl ether **S8** (52.9 mg, white amorphous foam) was used for the next step without further purification.

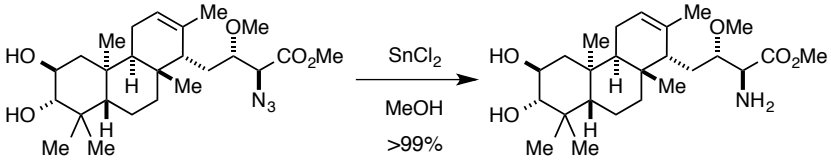
To a solution of the above crude methyl ether **S8** (52.9 mg) in CH_2Cl_2 (1.0 mL) was slowly added DIBAL (1.03 M in *n*-hexane, 196 µL, 0.202 mmol) at –78 °C and the mixture was stirred at –78 °C for 30 min. The reaction was quenched by dropwise addition of EtOAc (1 mL), and the mixture was stirred at –78 °C for 15 min. Then, to the mixture was added a saturated aqueous sodium potassium tartrate solution (ca. 3 mL) at –78 °C, and the mixture was vigorously stirred at room temperature until both phases became clear. After the layers were separated, the aqueous layer was extracted with EtOAc (2 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude alcohol **167** (49.2 mg, white amorphous foam) was used for the next step without further purification.

To a solution of the above crude alcohol **167** (49.2 mg) in MeCN–phosphate buffer (pH 6.8) (1:1 v/v, 1.0 mL) were added iodobenzene diacetate (97.6 mg, 0.303 mmol) and 1-Me-AZADO (3.4 mg, 20.2 µmol) at 0 °C in order. After being stirred at 0 °C for 3 h, the reaction mixture was quenched with a saturated aqueous $Na_2S_2O_3$ solution (2 mL), and the mixture was stirred at room temperature for additional 1 h. After the layers were separated, the aqueous layer was extracted with EtOAc (2 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude carboxylic acid **168** (81.0 mg, white amorphous foam) was used for the next step without further purification.

To the above crude carboxylic acid **168** (81.0 mg) in a test tube with screw cap was added HCl in MeOH (5–10%, 2.0 mL, purchased from TCI) at room temperature. After being stirred at 85 °C for 10 h, the reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~5 g, *n*-hexane/EtOAc = 4:1 to 2:1) afforded diol **169** (26.6 mg, 57.4 µmol, 57% for 5 steps) as a white amorphous foam: $[\alpha]_D^{26}$ +115.4 (c 1.33, $CHCl_3$); IR (ATR): ν 3376, 2938, 2873, 2844, 2109, 1748, 1439, 1376, 1264, 1205, 1115, 1052, 756 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.32 (1H, br), 4.29 (1H, d, *J* = 4.0 Hz), 3.81 (3H, s), 3.70 (1H, dt, *J* = 9.8, 3.5 Hz), 3.57

(1H, dd, *J* = 9.2, 4.0 Hz), 3.47 (3H, s), 2.97 (1H, d, *J* = 9.2 Hz), 2.13 (1H, br), 2.05 (1H, br), 1.90 (1H, br-dt), 1.82 (1H, d, *J* = 13.8 Hz), 1.78-1.68 (1H, m), 1.73 (1H, dd, *J* = 12.6, 4.6 Hz), 1.65 (3H, s), 1.62-1.50 (5H, m), 1.35 (1H, t, *J* = 12.1 Hz), 1.30-1.24 (3H, m), 1.06 (3H, s), 1.00 (3H, s), 0.99 (3H, s), 0.91 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.05, 137.29, 122.30, 83.77, 82.56, 69.41, 63.41, 58.65, 52.67, 50.87, 45.90, 43.18, 43.01, 39.58, 37.19, 36.50, 32.30, 30.00, 28.62, 28.26, 26.01, 22.56, 22.24, 17.60, 16.66; HRMS (FD): Calcd for $C_{25}H_{41}N_3O_5Na$ $[M+Na]^+$: 486.2942; found: 486.2938.

Compound 170

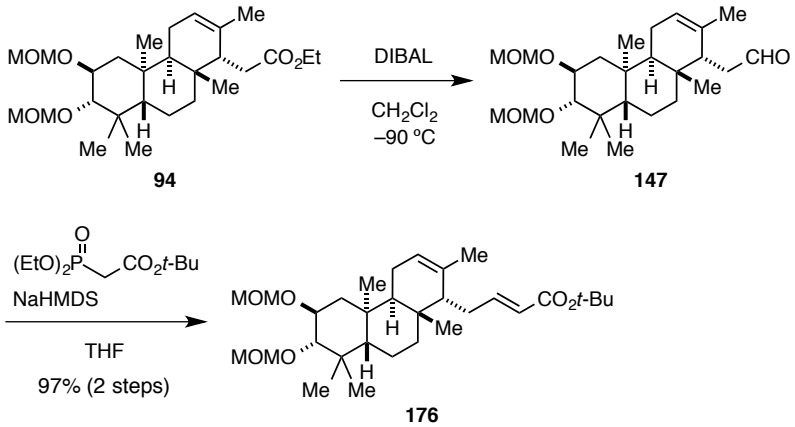


169 **170**

To a solution of diol **169** (22.1 mg, μmol) in MeOH (0.48 mL) was added $SnCl_2$ (27.1 mg, 0.143 mmol) at 0 °C. After being stirred at room temperature for 10 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (3 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (2 mL×5). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~10 g, *n*-hexane/EtOAc = 1:1 to 1:5 followed by EtOAc/MeOH = 50:1) afforded amine **170** (20.9 mg, 47.7 μmol, >99%) as a white amorphous foam: $[\alpha]_D^{25}$ +61.1 (c 1.21, $CHCl_3$); IR (ATR): ν 3355, 2937, 2873, 1741, 1438, 1378, 1103, 1053, 810, 665 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.29 (1H, br), 3.90 (1H, d, *J* = 3.5 Hz), 3.74 (3H, s), 3.70 (1H, dt, *J* = 11.5, 4.6 Hz), 3.46-3.39 (1H, m), 3.42 (3H, s), 2.96 (1H, d, *J* = 9.8 Hz), 1.90-1.75 (4H, m), 1.72 (1H, dd, *J* = 12.6, 4.0 Hz), 1.66-1.50 (5H, m), 1.63 (3H, s), 1.50 (9H, s), 1.44-1.22 (5H, m), 1.05 (3H, s), 0.99 (3H, s), 0.99 (3H, s), 0.90 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 173.82, 137.72, 122.02, 83.73, 82.84, 69.34, 57.87, 55.20, 52.04, 50.90, 45.93, 43.21, 43.01, 39.56, 37.24, 36.49, 30.66, 29.89, 28.64, 28.28, 26.01, 22.56, 22.27, 17.64, 16.68; HRMS (FD): Calcd for $C_{25}H_{43}NO_5$ $[M]^+$: 437.3141; found: 437.3159.

All spectra were identical with those derived from natural brasilicardin A (**3**).[3]

Compound 176

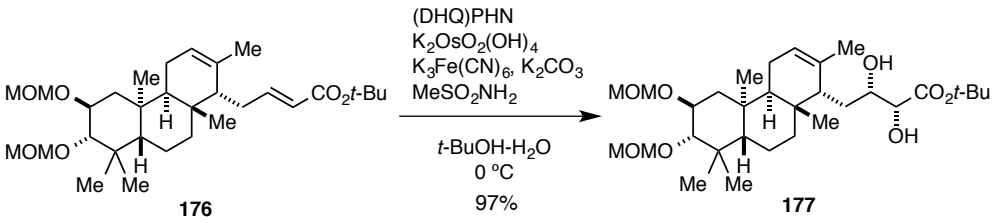


To a solution of tricyclic compound **94** (120.0 mg, 0.257 mmol) in CH_2Cl_2 (2.6 mL) was slowly added DIBAL (1.03 M in *n*-hexane, 299 μL, 0.308 mmol) at –90 °C and the mixture was stirred at –90 °C for 35 min. The reaction was quenched by dropwise addition of EtOAc (2 mL), and the mixture was stirred at –90 °C for 15 min. Then, to the mixture was added a saturated aqueous sodium potassium tartrate solution (ca. 5 mL) at –90 °C, and the mixture was vigorously stirred at room temperature until both phases became clear. After the layers were separated, the aqueous layer was extracted with EtOAc (2 mL×3). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude aldehyde **147** (121.7 mg, white amorphous foam) was used for the next step without further purification.

To a solution of *tert*-butyl diethylphosphonoacetate (121 μL, 0.514 mmol) was slowly added NaHMDS (1.14 M in THF, 451 μL, 0.514 mmol) at 0 °C over 5 min. After the mixture was stirred at 0 °C for 30 min, a solution of the above crude aldehyde **147** (121.7 mg) in THF (2.6 mL) was added at 0 °C over 5 min. After being stirred at 40 °C for 10 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (5 mL) and H_2O (2 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (3 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column

chromatography (SiO_2~10 g, *n*-hexane/EtOAc = 10:1 to 8:1) afforded (*E*)-unsaturated ester **176** (129.2 mg, 0.248 mmol, 97% for 2 steps) as a white amorphous foam: $[\alpha]_D^{26}$ +87.1 (c 0.79, $CHCl_3$); IR (ATR): ν 2971, 1715, 1366, 1149, 1035, 949 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.89 (1H, ddd, *J* = 15.5, 8.6, 6.3 Hz), 5.73 (1H, d, *J* = 15.5 Hz), 5.41 (1H, d, *J* = 4.0 Hz), 4.90 (1H, d, *J* = 6.3 Hz), 4.73 (1H, d, *J* = 6.3 Hz), 4.71 (1H, d, *J* = 6.3 Hz), 4.68 (1H, d, *J* = 6.3 Hz), 3.72 (1H, td, *J* = 10.9, 4.6 Hz), 3.42 (3H, s), 3.38 (3H, s), 2.96 (1H, d, *J* = 9.8 Hz), 2.38 (1H, tdd, *J* = 14.3, 6.3, 1.2 Hz), 2.24 (1H, ddd, *J* = 16.6, 8.6, 3.5 Hz), 1.92 (1H, td, *J* = 17.2, 4.0 Hz), 1.81 (1H, br), 1.76 (1H, dd, *J* = 12.6, 4.6 Hz), 1.70-1.64 (1H, m), 1.65 (3H, s), 1.60-1.53 (3H, m), 1.48 (9H, s), 1.35-1.25 (3H, m), 1.03 (3H, s), 0.98 (3H, s), 0.96 (3H, s), 0.91 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 166.06, 148.69, 135.33, 123.81, 122.77, 99.03, 96.11, 89.35, 80.00, 76.24, 56.22, 55.35, 54.51, 46.04, 43.39, 42.20, 40.04, 36.78, 36.57, 32.61, 30.27, 28.75, 28.15, 28.12, 25.74, 22.82, 22.63, 17.66, 17.46 (two peaks missing); HRMS (FD): Calcd for $C_{31}H_{52}O_6$ $[M]^+$: 520.3764; found: 520.3777.

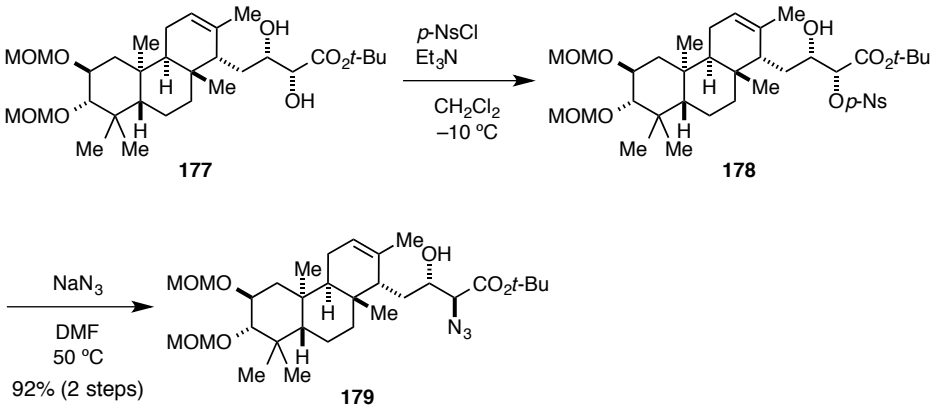
Compound 177



To a mixture of $K_3Fe(CN)_6$ (237.1 mg, 0.720 mmol), K_2CO_3 (99.5 mg, 0.720 mmol), DHQ-PHN (12.1 mg, 24.0 μmol) in *t*-BuOH–H_2O (1:1, 2.4 mL) was added $K_2OsO_2(OH)_4$ (1.8 mg, 4.80 μmol), and the mixture was stirred at room temperature for 1 h. To the mixture was added $MeSO_2NH_2$ (34.2 mg, 0.360 mmol). After the mixture was stirred at 0 °C for 30 min, the resulting solution was added to (*E*)-unsaturated ester **176** (125.0 mg, 0.240 mmol) at 0 °C. After being stirred at 0 °C for 2.5 h, to the reaction mixture were added $Na_2S_2O_3$ (100.0 mg, 0.632 mmol), and the mixture was stirred at 0 °C for 1 h. After the layers were separated, the aqueous layer was extracted with EtOAc (3 mL×5). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~10 g, *n*-hexane/EtOAc

= 4:1 to 1:1) afforded diol **177** (129.5 mg, 0.233 mmol, 97%) as a white amorphous foam: $[\alpha]_D^{27}$ +48.1 (c 0.90, $CHCl_3$); IR (ATR): ν 3472, 2946, 1732, 1446, 1369, 1289, 1251, 1149, 1103, 1032, 951, 917, 846 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.32 (1H, d, *J* = 2.3 Hz), 4.90 (1H, d, *J* = 6.3 Hz), 4.74 (1H, d, *J* = 6.9 Hz), 4.72 (1H, d, *J* = 6.9 Hz), 4.69 (1H, d, *J* = 6.3 Hz), 3.98 (1H, br), 3.83 (1H, br), 3.73 (1H, dt, *J* = 10.9, 4.0 Hz), 3.43 (3H, s), 3.38 (3H, s), 3.05 (1H, br), 2.97 (1H, d, *J* = 9.2 Hz), 1.91 (1H, br), 1.85 (1H, br), 1.79-1.56 (5H, m), 1.76 (1H, dd, *J* = 13.2, 4.0 Hz), 1.66 (3H, s), 1.52 (9H, s), 1.44-1.25 (3H, m), 1.28 (1H, dd, *J* = 12.6, 4.6 Hz), 1.09 (3H, s), 1.01 (3H, s), 0.99 (9H, s), 0.93 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.56, 137.23, 122.39, 99.04, 96.11, 89.31, 83.37, 83.34, 76.24, 73.64, 72.98, 56.24, 55.35, 50.78, 46.13, 43.14, 42.19, 40.08, 37.14, 36.18, 35.17, 29.69, 28.71, 28.40, 28.01, 25.96, 22.60, 22.40, 17.66, 17.46 (one peak missing); HRMS (FD): Calcd for $C_{31}H_{54}O_8$ $[M]^+$: 554.3819; found: 554.3838.

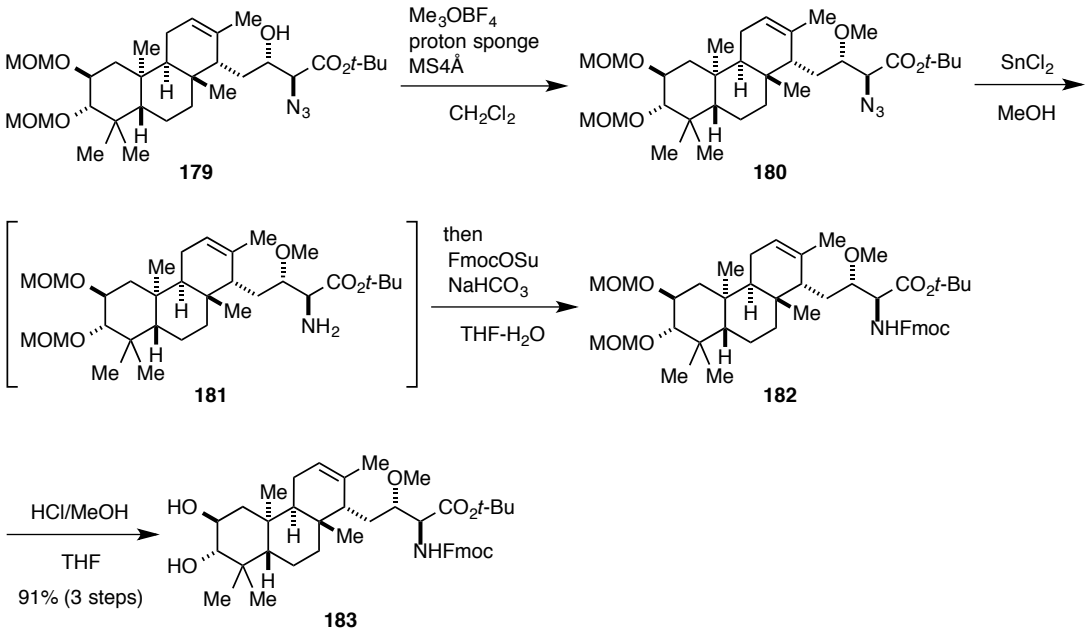
Compound 179



To a solution of diol **177** (125.0 mg, 0.225 mmol) in CH_2Cl_2 (2.3 mL) were added Et_3N (63 μL, 0.450 mmol) and *p*-nitrobenzenesulfonyl chloride (*p*-NsCl) (59.8 mg, 0.270 mmol) at –10 °C. After being stirred at –10 °C for 4 h, the reaction mixture was quenched with acetic acid (1.0 M in THF, 1.0 mL, 1.00 mmol) and H_2O (2 mL) at –78 °C. After the layers were separated, the aqueous layer was extracted with EtOAc (1 mL×4). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude nosylate **178** (174.8 mg, yellow oil) was used for the next step without further purification.

To a solution of the above crude nosylate **178** (174.8 mg) in dimtheylformamide (DMF) (1.1 mL) was added NaN_3 (73.1 mg, 1.13 mmol) at 0 °C, and the mixture was stirred at 50 °C for 5 h. After the mixture was cooled to 0 °C, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (1 mL) and H_2O (1 mL), and the mixture was stirred at 0 °C for 30 min. After the layers were separated, the aqueous layer was extracted with EtOAc (3 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~10 g, *n*-hexane/EtOAc = 8:1 to 7:1) afforded azide **179** (119.8 mg, 0.207 mmol, 92% for 2 steps) as a white amorphous foam: $[\alpha]_D^{26}$ +30.0 (c 0.94, $CHCl_3$); IR (ATR): ν 3452, 2936, 2889, 2109, 1734, 1446, 1369, 1256, 1216, 1149, 1103, 1030, 917, 841, 756 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.33 (1H, d, *J* = 4.0 Hz), 4.91 (1H, d, *J* = 6.3 Hz), 4.74 (1H, d, *J* = 6.9 Hz), 4.71 (1H, d, *J* = 6.3 Hz), 4.68 (1H, d, *J* = 6.9 Hz), 3.85 (1H, br), 3.81 (1H, d, *J* = 5.7 Hz), 3.72 (1H, ddd, *J* = 13.8, 9.8, 4.0 Hz), 3.42 (3H, s), 3.38 (3H, s), 3.97 (1H, d, *J* = 9.2 Hz), 2.32 (1H, d, *J* = 6.4 Hz), 1.90 (1H, dt, *J* = 16.6, 4.0 Hz), 1.82 (1H, d, *J* = 13.2 Hz), 1.75 (1H, dd, *J* = 12.6, 4.0 Hz), 1.73-1.50 (7H, m), 1.65 (3H, s), 1.53 (9H, s), 1.40-1.28 (3H, m), 1.26 (1H, dd, *J* = 13.2, 5.2 Hz), 1.08 (3H, s), 0.99 (3H, s), 0.98 (3H, s), 0.92 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 168.04, 137.02, 122.60, 98.98, 96.06, 89.26, 83.72, 76.17, 71.81, 67.08, 56.19, 55.30, 50.37, 46.08, 42.96, 42.17, 40.03, 37.12, 36.09, 34.08, 29.62, 28.65, 28.32, 28.00, 25.91, 22.36, 22.31, 17.51, 17.41 (two peaks missing); HRMS (FD): Calcd for $C_{31}H_{54}N_3O_7$ $[M+H]^+$: 580.3962; found: 580.3956.

Compound 183



To a mixture of azide **179** (115.0 mg, 0.198 mmol), 1,8-bis(dimethylamino)naphthalene (proton sponge) (424.3 mg, 1.98 mmol), and freshly activated and powdered MS4Å (435 mg) in CH_2Cl_2 (2.0 mL) was added trimethyloxonium tetrafluoroborate (Me_3OBF_4) (205.0 mg, 1.39 mmol) at 0 °C. After being stirred at room temperature for 3.5 h, the reaction mixture was filtered through a pad of Celite®, which was rinsed with EtOAc (100 mL). The organic layers were washed with a saturated aqueous $NaHCO_3$ solution (20 mL×2), 5% aqueous $KHSO_4$ solution (30 mL×3), brine (20 mL), and dried over $MgSO_4$, and concentrated under reduced pressure. The crude methyl ether **180** (116.4 mg, pale violet red oil) was used for the next step without further purification.

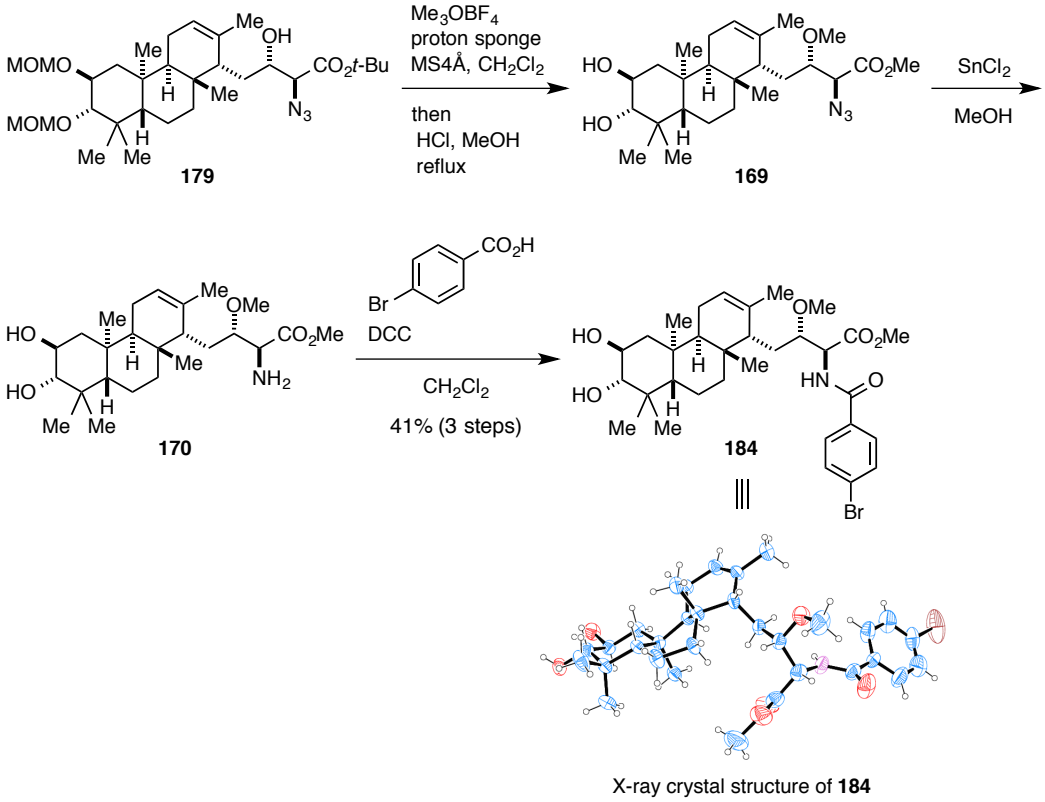
To a solution of the above crude methyl ether **180** (116.4 mg) in MeOH (2.0 mL) was added $SnCl_2$ (112.6 mg, 0.594 mmol) at 0 °C, and the mixture was stirred at room temperature for 3 h. After the mixture was cooled to 0 °C, to the mixture were added THF–H_2O (3:1, 2.0 mL), $NaHCO_3$ (83.2 mg, 0.990 mmol), and *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (Fmoc-OSu) (80.1 mg, 0.238 mmol). After being stirred at room temperature for 3 h, the reaction mixture was quenched with 5% aqueous $KHSO_4$ solution (5 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (10 mL×3). The combined organic layers were washed with brine (20 mL),

dried over $MgSO_4$, and concentrated under reduced pressure. The residue was filtered through a pad of silica gel (SiO_2~15 g, *n*-hexane/EtOAc = 5:1, 200 mL), and concentrated under reduced pressure. The crude carbamate **182** (165.4 mg, white amorphous foam) was used for the next step without further purification.

To a solution of the above crude carbamate **182** (165.4 mg) in THF (6.6 mL) was added HCl in MeOH (5–10%, 3.3 mL) at 0 °C. After being stirred at room temperature for 3 h, the mixture was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~10 g, *n*-hexane/EtOAc = 2:1 to 1:2) afforded diol **183** (126.5 mg, 0.180 mmol, 91% for 3 steps) as a white amorphous foam: $[\alpha]_D^{24}$ +89.8 (c 0.74, $CHCl_3$); IR (ATR): ν 3378, 2979, 2888, 1740, 1462, 1381, 1252, 1157, 952, 817 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.76 (2H, d, *J* = 8.1 Hz), 7.60 (2H, d, *J* = 7.5 Hz), 7.40 (2H, t, *J* = 7.5 Hz), 7.30 (2H, t, *J* = 7.5 Hz), 5.39 (1H, d, *J* = 9.2 Hz), 5.32 (1H, br), 4.63 (1H, dd, *J* = 8.6, 2.9 Hz), 4.41-4.34 (1H, m), 4.37 (1H, dd, *J* = 7.5, 6.3 Hz), 4.24 (1H, dd, *J* = 7.5, 6.9 Hz), 3.70 (1H, br), 3.48 (1H, br), 3.45 (3H, s), 2.97 (1H, dd, *J* = 9.7, 4.0 Hz), 2.11 (1H, d, *J* = 4.0 Hz), 2.05 (1H, d, *J* = 2.9 Hz), 1.92 (1H, br), 1.83 (1H, br), 1.73 (1H, dd, *J* = 12.1, 4.1 Hz), 1.70-1.48 (6H, m), 1.67 (3H, s), 1.50 (9H, s), 1.42-1.28 (3H, m), 1.26 (1H, dd, *J* = 12.0, 5.2 Hz), 1.06 (3H, s), 1.00 (3H, s), 0.99 (3H, s), 0.88 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.69, 156.07, 143.86, 143.77, 141.24, 137.84, 127.66, 127.02, 125.14, 122.05, 119.93, 83.80, 82.63, 82.13, 69.41, 67.07, 58.34, 55.88, 50.80, 47.08, 46.13, 43.16, 42.98, 39.54, 37.08, 36.45, 31.86, 29.76, 28.60, 28.44, 28.07, 26.00, 22.56, 22.43, 17.39, 16.61 (seven peaks missing); HRMS (FD): Calcd for $C_{43}H_{59}NO_7$ $[M]^+$: 701.4292; found: 701.4300.

Determination of the stereochemistry of 179

Compound 184



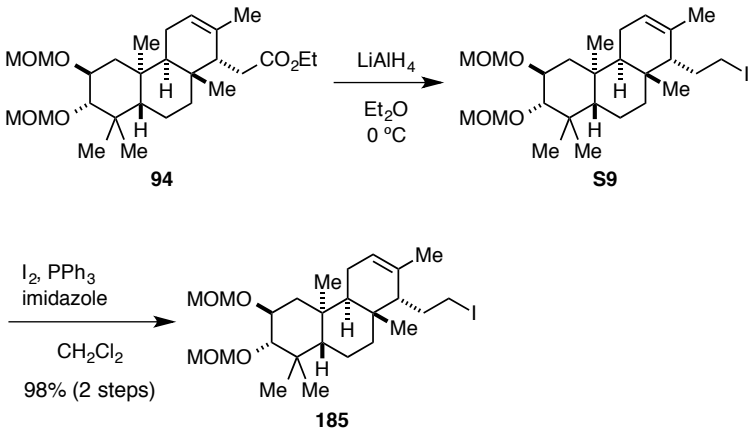
To a mixture of azide **179** (7.0 mg, 12.1 μmol), proton sponge (25.9 mg, 0.120 mmol), and freshly activated and powdered MS4Å (6.1 mg) in CH_2Cl_2 (0.12 mL) in a test tube with screw cap was added Me_3OBF_4 (8.9 mg, 60.5 μmol) at 0 °C. After being stirred at room temperature for 4 h, to the reaction mixture was added HCl in MeOH (5–10%, 2.0 mL, purchased from TCI) at 0 °C. After being stirred at 85 °C for 2 h, the reaction mixture was concentrated under reduced pressure. The residue was filtered through a pad of Celite®, which was rinsed with EtOAc (5 mL). To the filtrate was added H_2O (2 mL), after the aqueous phase was separated, and extracted with EtOAc (1 mL×3). The organic layers were washed with 5% aqueous $KHSO_4$ solution (1 mL×3), and dried over $MgSO_4$, and concentrated under reduced pressure. The residue was filtered through a pad of silica gel (SiO_2~5 g, *n*-hexane/EtOAc = 2:1, 30 mL), and concentrated under reduced pressure. The crude

methyl ether **169** (5.0 mg, white amorphous foam) was used for the next step without further purification.

To a solution of the above crude methyl ether **169** (5.0 mg) in MeOH (0.12 mL) was added $SnCl_2$ (6.9 mg, 36.3 μmol) at 0 °C. After being stirred at room temperature for 9 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (1.5 mL). After the layers were separated, the aqueous layer was extracted with $CHCl_3$–MeOH (9:1 v/v, 1 mL×5). The combined organic layers were washed with brine (1 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was filtered through a pad of silica gel (SiO_2~5 g, EtOAc/MeOH = 10:1, 30 mL), and concentrated under reduced pressure. The crude amine **170** (4.3 mg, white amorphous foam) was used for the next step without further purification.

To a solution of the above crude amine **170** (4.3 mg) and *p*-bromobenzoic acid (12.2 mg, 60.5 μmol) in CH_2Cl_2 (0.4 mL) was added *N,N'*-dicyclohexylcarbodiimide (DCC) (0.5 M in CH_2Cl_2, 0.12 mL, 60.5 μmol) at room temperature. After being stirred at room temperature for 24 h, the mixture was concentrated under reduced pressure. Purification by preparative TLC (SiO_2, *n*-hexane/EtOAc = 1:2) afforded *p*-bromobenzamide **184** (3.1 mg, 4.99 μmol, 41% for 3 steps) as a white powder. Recrystallization of this power from EtOH afforded colorless needles, which were analyzed by X-ray: M.p. 284-285 °C (EtOH) [lit.[3] M.p. 286-287 °C]; $[\alpha]_D^{29}$ +118 (c 0.14, $CHCl_3$) [lit.[3] $[\alpha]_D^{27}$ +118 (c 0.32, $CHCl_3$)]; IR (ATR): ν 3357, 2970, 2932, 2884, 1653, 1466, 1379, 1307, 1160, 1128, 950, 816, 772 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.68 (2H, d, *J* = 8.6 Hz), 7.59 (2H, d, *J* = 8.6 Hz), 6.63 (1H, d, *J* = 8.1 Hz), 5.33 (1H, br), 5.16 (1H, dd, *J* = 8.1, 3.5 Hz), 3.80 (3H, s), 3.71 (1H, dt, *J* = 9.8, 4.0 Hz), 3.62 (1H, dd, *J* = 8.6, 2.9 Hz), 3.48 (3H, s), 2.97 (1H, d, *J* = 9.8 Hz), 2.13 (1H, br), 2.09 (1H, br), 1.92 (1H, d, *J* = 16.6 Hz), 1.83 (1H, dd, *J* = 14.9, 13.8 Hz), 1.73 (2H, dd, *J* = 11.5, 3.5 Hz), 1.64 (3H, s), 1.64-1.53 (3H, m), 1.44-1.23 (6H, m), 1.05 (3H, s), 1.00 (3H, s), 0.99 (3H, s), 0.90 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.01, 166.40, 137.55, 132.72, 131.86, 128.75, 126.62, 122.36, 83.83, 82.12, 69.39, 58.60, 54.00, 52.56, 51.22, 46.07, 43.13, 43.02, 39.57, 37.22, 36.51, 32.34, 29.90, 29.69, 28.61, 28.36, 26.03, 22.53, 22.36, 17.65, 16.65 (one peak missing); HRMS (FD): Calcd for $C_{32}H_{46}BrNO_6$ $[M]^+$: 619.2509; found: 619.2515.

Compound 185

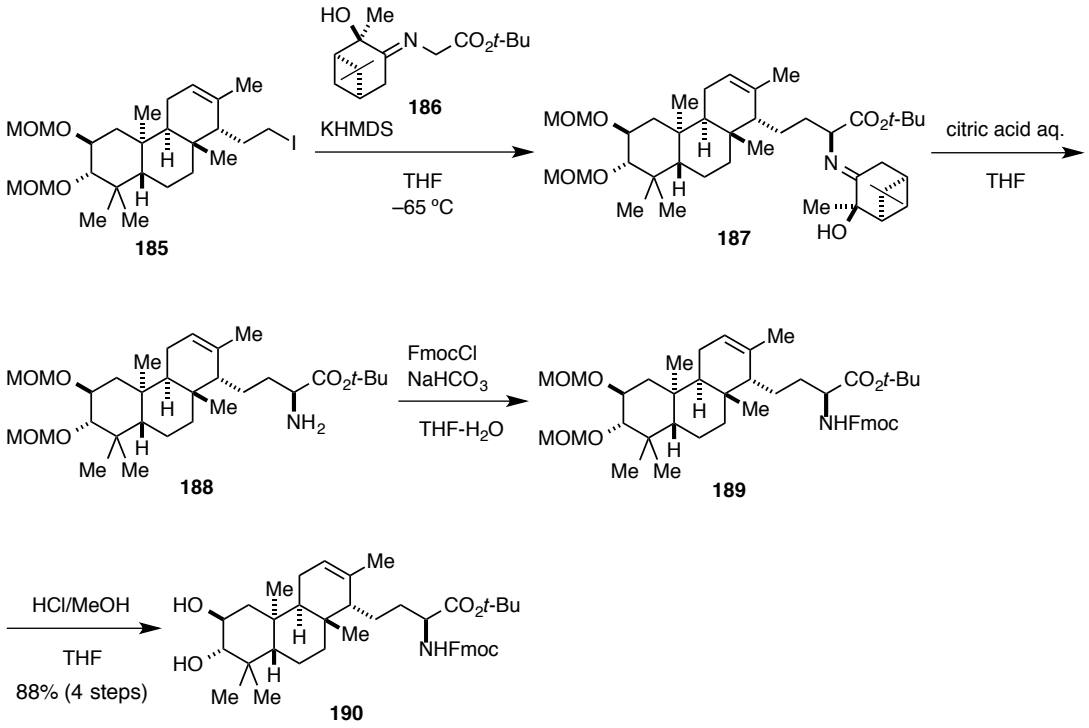


To a solution of tricyclic compound **94** (65.0 mg, 0.139 mmol) in Et_2O (1.4 mL) was added $LiAlH_4$ (10.6 mg, 0.278 mmol) at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was diluted with Et_2O (3 mL). To the reaction mixture were added dropwise sequentially H_2O (15 μL), 15% aqueous NaOH solution (15 μL), and H_2O (45 μL) at 0 °C. Then, the suspension was stirred at room temperature for 10 min, and dried over $MgSO_4$ for 1 h, and filtered through a pad of Celite®, which was rinsed with Et_2O (20 mL). The filtrate was concentrated under reduced pressure. The crude alcohol **S9** (61.5 mg, white amorphous foam) was used for the next step without further purification.

To a solution of the above crude alcohol **S9** (61.5 mg) in CH_2Cl_2 (1.4 mL) were added I_2 (45.9 mg, 0.181 mmol), PPh_3 (47.5 mg, 0.181 mmol), imidazole (13.2 mg, 0.195 mmol) at 0 °C in the dark. After being stirred at room temperature for 1.5 h, the reaction mixture was diluted with Et_2O (2 mL), and quenched with a saturated aqueous $Na_2S_2O_3$ solution (3 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (2 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~10 g, *n*-hexane/EtOAc = 10:1 to 8:1) afforded iodide **185** (73.1 mg, 0.137 mmol, 98% for 2 steps) as a white amorphous foam: $[\alpha]_D^{27}$ +171.3 (c 1.06, $CHCl_3$); IR (ATR): ν 2942, 2884, 1445, 1379, 1214, 1146, 1102, 1027, 989, 916, 812 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.34 (1H, d, *J* = 3.5 Hz), 4.91 (1H, d, *J* = 6.9 Hz), 4.73 (1H, d, *J* = 6.3 Hz), 4.71 (1H, d, *J* = 6.9

Hz), 4.68 (1H, d, *J* = 6.9 Hz), 3.73 (1H, td, *J* = 9.2, 4.6 Hz), 3.42 (3H, s), 3.37 (3H, s), 3.26 (1H, td, *J* = 9.2, 4.6 Hz), 3.17 (1H, td, *J* = 9.2, 7.5 Hz), 2.96 (1H, d, *J* = 9.2 Hz), 2.03 (1H, ddd, *J* = 14.9, 10.3, 5.2 Hz), 1.93-1.84 (2H, m), 1.81 (1H, d, *J* = 14.9 Hz), 1.76 (1H, dd, *J* = 12.6, 4.1 Hz), 1.72-1.56 (3H, m), 1.67 (3H, s), 1.34 (2H, dd, *J* = 17.2, 16.6 Hz), 1.34-1.24 (3H, m), 1.09 (3H, s), 0.99 (3H, s), 0.97 (3H, s), 0.92 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 135.86, 123.00, 99.00, 96.10, 89.23, 76.19, 57.02, 56.19, 55.31, 46.71, 43.21, 42.12, 40.01, 36.81, 36.31, 35.59, 30.14, 28.71, 28.36, 25.85, 22.79, 22.50, 17.60, 17.43, 7.42; HRMS (FD): Calcd for $C_{25}H_{43}IO_4$ $[M]^+$: 534.2206; found: 534.2215.

Compound 190



To a solution of chiral iminoglycinate **186** (347.1 mg, 1.37 mmol) in THF (0.5 mL) was added potassium bis(trimethylsilyl)amide (KHMDS) (1.0 M in THF, 1.37 mL, 1.37 mmol) at –78 °C. After being stirred at –78 °C for 10 min, a solution of iodide **185** (73.1 mg, 0.137 mmol) in THF (2.3 mL) was added at –78 °C. After being stirred at –65 °C for 72 h, the reaction mixture was quenched with acetic acid (1.0 M in THF, 2.06 mL, 2.06 mmol). The mixture was concentrated under reduced

pressure, and to the residue was added H_2O (10 mL). After the aqueous layer was extracted with Et_2O (5 mL×3), and the combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~20 g, *n*-hexane/EtOAc = 10:1 to 4:1) afforded the crude ester **187** (176.0 mg, yellow oil). The crude ester **187** was used for the next step without further purification.

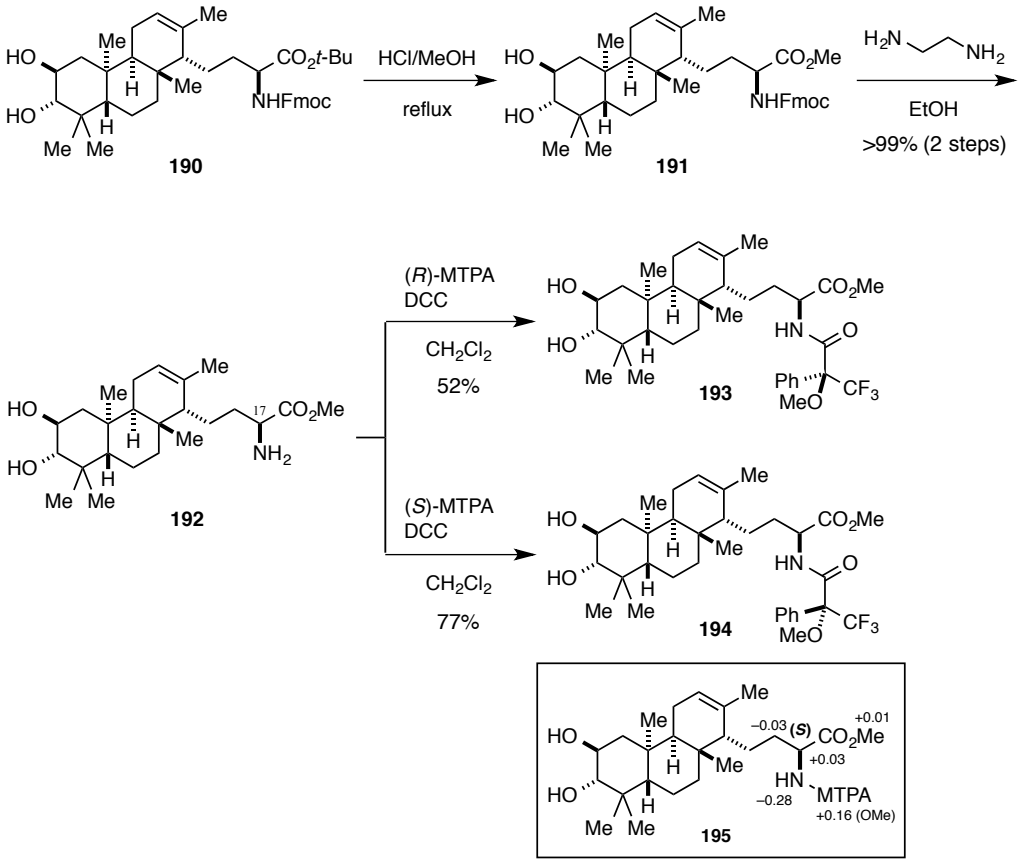
To a solution of the above crude ester **187** (176.0 mg) in THF (2.7 mL) was added 15% aqueous citric acid (4.1 mL) at room temperature. After being stirred at room temperature for 72 h, the reaction mixture was basified with powdered K_2CO_3 (2.0 g). After the layers were separated, the aqueous layer was extracted with EtOAc (5 mL×3). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The residue was filtered through a pad of silica gel (SiO_2~5 g, *n*-hexane/EtOAc = 2:1 followed by EtOAc/MeOH = 50:1), and concentrated under reduced pressure. The crude amine **188** (66.4 mg, yellow oil) was used for the next step without further purification.

To a mixture of the above crude amine **188** (66.4 mg), $NaHCO_3$ (57.5 mg, 0.685 mmol) in THF–H_2O (3:1, 1.4 mL) was added 9-fluorenylmethyl chloroformate (FmocCl) (39.0 mg, 0.151 mmol) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was quenched with 5% aqueous $KHSO_4$ solution (2 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (1 mL×4). The carbamate **189** (123.8 mg, yellow oil) was used for the next step without further purification.

To a solution of the above crude carbamate **189** (123.8 mg) in THF (3.4 mL) was added HCl in MeOH (5–10%, 3.4 mL, purchased from TCI) at 0 °C. After being stirred at room temperature for 4 h, the mixture was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~5 g, *n*-hexane/EtOAc = 1:1 to 1:5) afforded diol **190** (81.3 mg, 0.121 mmol, 88% for 4 steps) as a white amorphous foam: $[\alpha]_D^{23}$ +97.9 (c 1.00, $CHCl_3$); IR (ATR): ν 3361, 2936, 2873, 2314, 1714, 1507, 1450, 1369, 1249, 1156, 1050, 755, 740 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.76 (2H, d, *J* = 7.5 Hz), 7.60 (2H, t, *J* = 6.9 Hz), 7.40 (2H, t, *J* = 7.5 Hz), 7.31 (2H, t, *J* = 7.5 Hz), 5.36 (1H, d, *J* = 8.0 Hz), 5.32 (1H, br), 4.40-4.32 (1H, m), 4.36 (1H, dd, *J* = 11.5, 7.5 Hz), 4.26 (1H,

dd, *J* = 12.6, 6.9 Hz), 4.22 (1H, dd, *J* = 14.4, 7.5 Hz), 3.69 (1H, br), 2.96 (1H, dd, *J* = 9.2, 4.0 Hz), 2.09 (1H, d, *J* = 4.6 Hz), 2.05 (1H, br), 1.90 (1H, d, *J* = 17.8 Hz), 1.80 (1H, dd, *J* = 17.2, 13.8 Hz), 1.76-1.43 (4H, m), 1.72 (1H, dd, *J* = 12.0, 4.0 Hz), 1.62 (3H, s), 1.49 (9H, s), 1.38-1.25 (6H, m), 1.04 (3H, s), 0.98 (3H, s), 0.96 (3H, s), 0.87 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.52, 155.80, 143.84, 143.82, 141.24, 136.81, 127.68, 127.02, 125.07, 122.37, 119.96, 83.86, 82.15, 69.46, 67.01, 55.10, 54.57, 47.15, 47.12, 46.29, 43.22, 43.10, 39.51, 36.94, 36.71, 36.69, 34.13, 30.03, 28.63, 28.36, 28.02, 25.89, 25.69, 22.83, 17.53, 16.62 (six peaks missing); HRMS (FD): Calcd for $C_{42}H_{57}NO_6$ $[M]^+$: 671.4186; found: 671.4184.

Compound 193 and 194



To diol **190** (9.0 mg, 13.4 μmol) in a test tube with screw cap was added HCl in MeOH (5–10%, 1.0 mL, purchased from TCI) at room temperature. After being stirred at 85 °C for 18 h, the reaction mixture was concentrated under reduced pressure. The residue was filtered through a pad of

amino silica gel (SiO_2~5 g, *n*-hexane/EtOAc = 1:3, 30 mL), and concentrated under reduced pressure. The crude ester **191** (9.7 mg, white amorphous foam) was used for the next step without further purification.

To a solution of the above crude ester **191** (9.7 mg) in EtOH (0.36 mL) was added ethylenediamine (40 μL) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure. The residue was filtered through a pad of amino silica gel (FUJI SILYSIA CHEMICAL LTD. NH Silica Gel (DM 1020) ~5 g, *n*-hexane/EtOAc = 2:1 to 1:2), and concentrated under reduced pressure. The semi-pure compound **192** (5.8 mg, white amorphous foam) was used for the next step without further purification.

To a solution of the above semi-pure amine **192** (2.5 mg, 6.13 μmol) and (*R*)-(–)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ((*R*)-(–)-MTPA) (4.3 mg, 18.4 μmol) in CH_2Cl_2 (0.3 mL) was added DCC (0.50 M in CH_2Cl_2, 37 μL, 18.4 μmol) at room temperature. After being stirred at room temperature for 1 h, the mixture was concentrated under reduced pressure. Purification by preparative TLC (SiO_2, *n*-hexane/EtOAc = 1:2) afforded (*R*)-MTPA amide **193** (2.1 mg, 3.20 μmol, 52%) as a white powder: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.53 (2H, m), 7.48 (1H, d, *J* = 8.6 Hz), 7.43-7.39 (1H, m), 7.41 (2H, dd, *J* = 5.2, 1.7 Hz), 5.33 (1H, d, *J* = 2.9 Hz), 4.63 (1H, dt, *J* = 7.5, 4.6 Hz), 3.76 (3H, s), 3.72 (1H, br), 3.36 (3H, s), 2.97 (1H, dd, *J* = 9.2, 2.9 Hz), 2.12 (1H, d, *J* = 3.5 Hz), 2.06 (1H, d, *J* = 1.7 Hz), 2.06-1.99 (1H, m), 1.91 (1H, d, *J* = 16.6 Hz), 1.88-1.78 (2H, m), 1.74 (1H, dd, *J* = 12.6, 4.0 Hz), 1.72-1.52 (4H, m), 1.62 (3H, s), 1.48-1.23 (6H, m), 1.08 (3H, s), 0.99 (3H, s), 0.96 (3H, s), 0.91 (3H, s); HRMS (FD): Calcd for $C_{34}H_{48}F_3NO_6$ $[M]^+$: 623.3434; found: 623.3426.

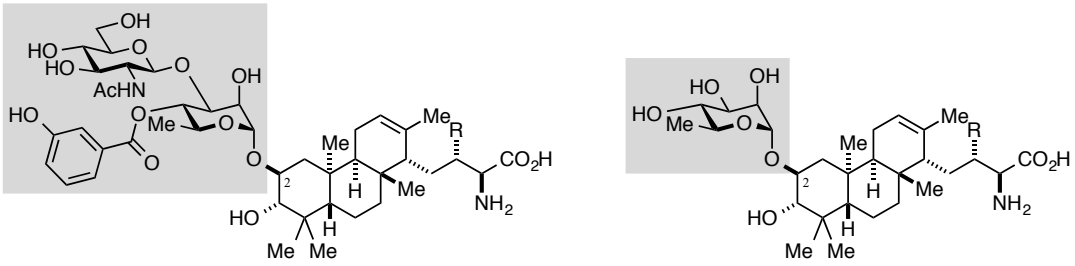
To a solution of the above semi-pure amine **192** (2.5 mg, 6.13 μmol) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ((*S*)-(+)-MTPA) (4.3 mg, 18.4 μmol) in CH_2Cl_2 (0.3 mL) was added DCC (0.50 M in CH_2Cl_2, 37 μL, 18.4 μmol) at room temperature. After being stirred at room temperature for 1 h, the mixture was concentrated under reduced pressure. Purification by preparative TLC (SiO_2, *n*-hexane/EtOAc = 1:2) afforded (*S*)-MTPA amide **194** (3.1 mg, 4.73 μmol, 77%) as a white powder: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.55 (2H, m), 7.38 (3H, m),

7.20 (1H, d, *J* = 8.1 Hz), 5.29 (1H, d, *J* = 2.3 Hz), 4.66 (1H, dt, *J* = 6.9, 5.2 Hz), 3.77 (3H, s), 3.70 (1H, br), 3.52 (3H, s), 2.95 (1H, dd, *J* = 9.8, 4.6 Hz), 2.09 (1H, d, *J* = 4.0 Hz), 2.06 (1H, d, *J* = 3.5 Hz), 1.98-1.88 (1H, m), 1.86-1.75 (3H, m), 1.71 (1H, dd, *J* = 12.6, 4.6 Hz), 1.70-1.51 (3H, m), 1.46 (3H, s), 1.32 (2H, t, *J* = 12.6 Hz), 1.30-1.22 (2H, m), 1.21 (1H, dd, *J* = 12.6, 4.6 Hz), 1.20-1.16 (2H, m), 1.00 (3H, s), 0.98 (3H, s), 0.92 (3H, s), 0.90 (3H, s); HRMS (FD): Calcd for $C_{34}H_{48}F_3NO_6$ $[M]^+$: 623.3434; found: 623.3433.

Chapter 3

Stereoselective glycosylation and completion of the unified total synthesis of Brasilicardins A–D

The remaining task in the synthesis was the challenging glycosylation of aglycons **183** and **190** toward the total synthesis of brasilicardins A–D (**3**–**6**). For this purpose, it was necessary to achieve regioselctive glycosylation at the C2 position of aglycons **183** and **190**. First, the author explored the glycosylation of **183** toward brasilicardin A (**3**) because it was the author's priority target for this work.



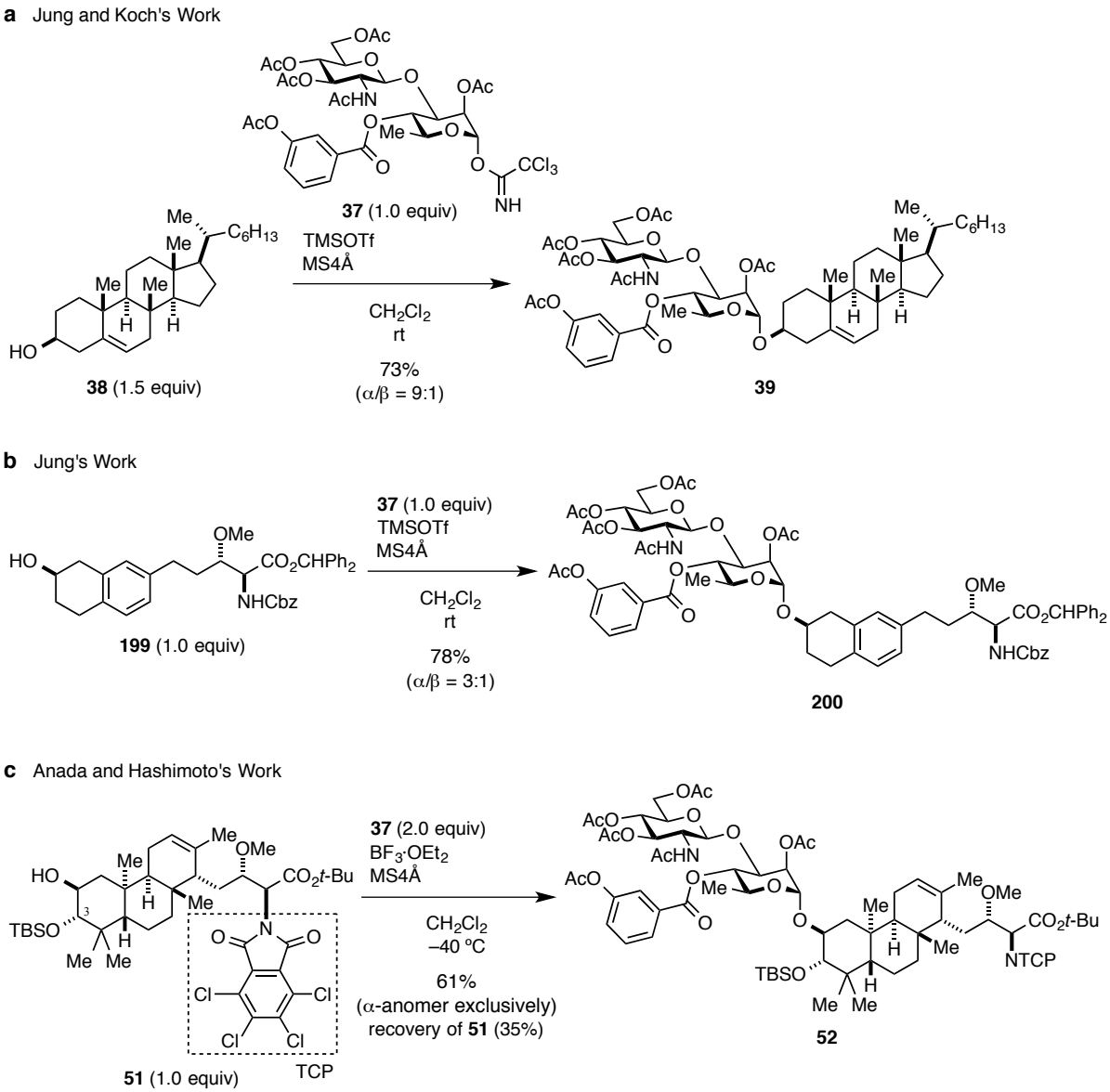
Brasilicardins A (**3**) and B (**4**) Brasilicardins C (**5**) and D (**6**)

Figure 6. Saccharide units of brasilicardins A–D

In this context, glycosylation study of the disaccharide unit corresponding to brasilicardin A (**3**) has been reported by Jung's group,[10,13] and Anada and Hashimoto's group (Scheme 43).[8] Jung and Koch reported an efficient synthesis of the peracetylated disaccharide **37** of brasilicardin A (**3**). They demonstrated that a cyclic secondary alcohol, e.g., cholesterol **38** as a brasilicardin model, could be successfully coupled with **37** using TMSOTf as an activator under Schimdt glycosylation,[59] which led to the desired α-anomeric linkage in a 9:1 α/β ratio and in 73% yield (Scheme 43a).[13] Jung and co-workers applied this coupling reaction to synthesize brasilicardin A (**3**) analogue with a simplified core **199**, and they obtained the desired glycoside **200** in 78% yield (Scheme 43b).[10] In this glycosylation, the selectivity was decreased to a 3:1 α/β ratio.

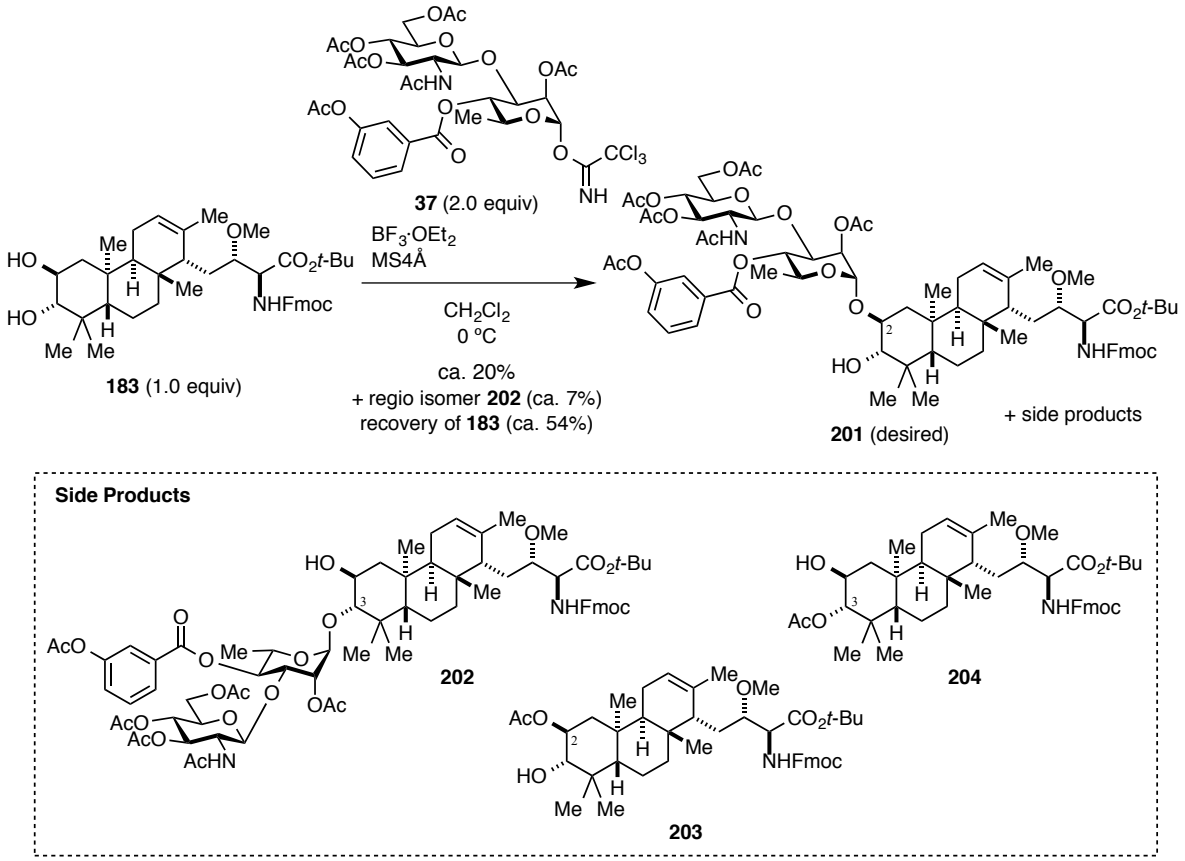
Anada, Hashimoto, and co-workers accomplished the installation of the brasilicardin A (**3**) saccharide moiety using the Jung's procedure (Scheme 43c).[8] Thus, the glycosylation of the C3 protected aglycon **51** with trichloroacetimidate **37** using $BF_3 \cdot OEt_2$ as a promoter afforded the desired glycoside **52** as a sole product in 61% yield.

In this way, it was shown in the previous studies that Schmidt's glycosylation was found to be superior method for introduction of the saccharide unit of brasilicardin A (**3**).



Scheme 43. Glycosylation studies by other groups

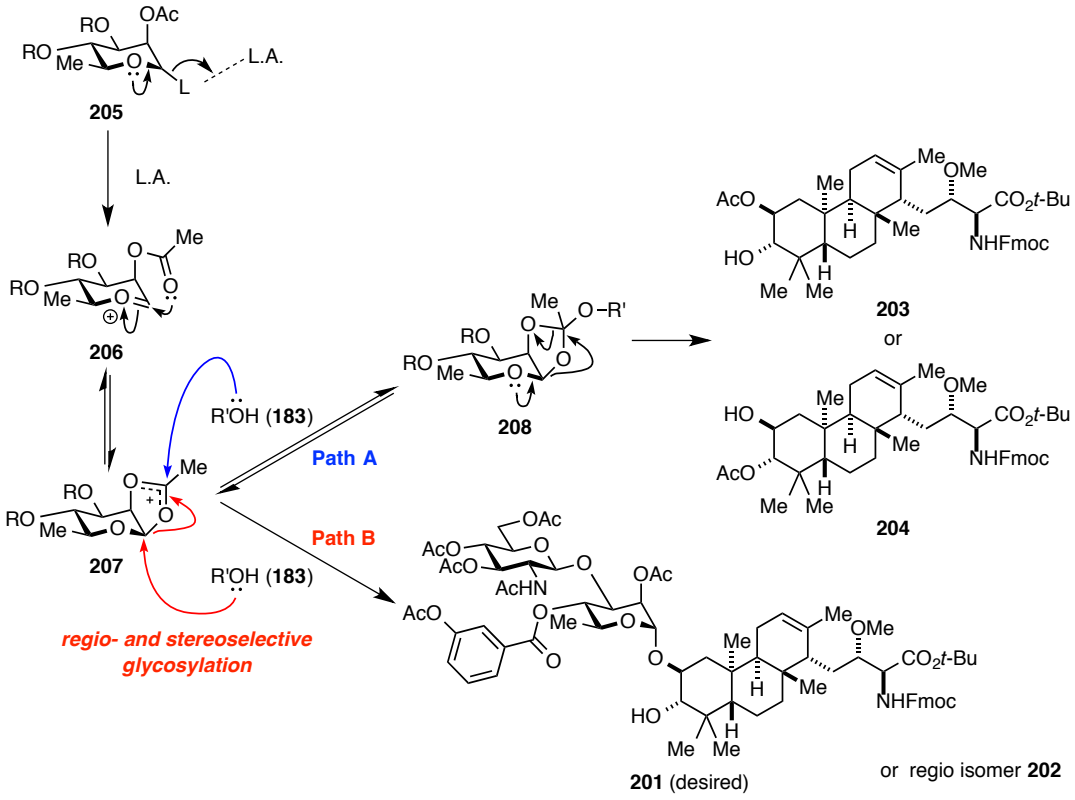
Based on the previous reports, the author examined the glycosylation of aglycon **183** with trichloroacetimidate **37** under Schmidt's condition using $BF_3 \cdot OEt_2$ as a promoter first (Scheme 44). However, the desired glycoside **201** was obtained only in ca. 20% as a minor product accompanied by a mixture of the undesired C3 glycoside **202**, the C2 acetate **203**, and the C3 acetate **204**. Clearly, it was difficult to control regiochemical outcome using Schmidt's glycosylation.



Scheme 44. Attempts at glycosylation under Schmidt's condition

Plausible mechanism for the formation of acetates **203** and **204** in shown in Scheme 45.[60] Initially, oxocarbonium **206** was generated from imidate **205** by action of Lewis acid. Subsequently, participation from the acetate at C2 lead to acetoxonium **207**. When alcohol **183** attacked the dioxolenium carbon atom of the acetoxonium ion **208**, the C2 and C3 acetates (**203** and **204**, respectively) were formed via isomerization of the 1,2-orthoacetate intermediate **209** (Path A). On the other hand, when alcohol **183** attack occurred at the anomeric center of acetoxonium **208**, the

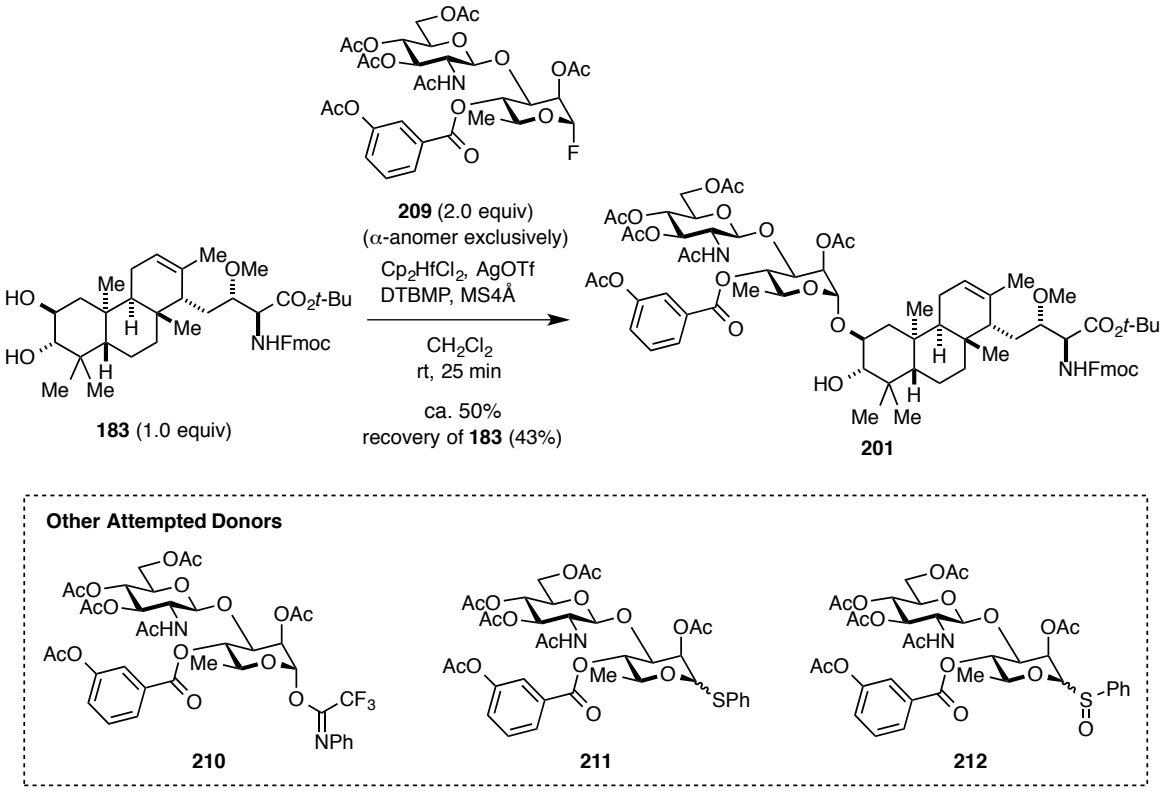
stereoselective glycosylation proceeded, leading to the desired α-glycoside **201** or its regio isomer **202** (Path B).



Scheme 45. The stereochemical outcome of the glycosylation of diol **183** and the mechanism for the formation of the acetates

To achieve the regio- and stereoselective glycosylation to diol **183**, the author explored the glycosyl donors and their activation conditions, and it was found that the metallocene-based activator $Cp_2HfCl_2/AgOTf$[61] gave the best results (Scheme 46). Thus, coupling of peracetyl glycosyl fluoride **209** (2 equiv) with acceptor **183** provided the desired α-glycoside **201** (with 43% of **183** recovered). Because the prolonged reaction time caused an undesired reaction at the C3 alcohol, this coupling was carefully stopped before full consumption of **183**, with recovery of unreacted **183**. Other glycosylation protocols using (*N*-phenyl)trifluoroacetimidate **210**,[62] thiosugar **211**,[63] and glycolsyl sulfoxide **212**[64] were also investigated. However, the use of **210** led to the similar result

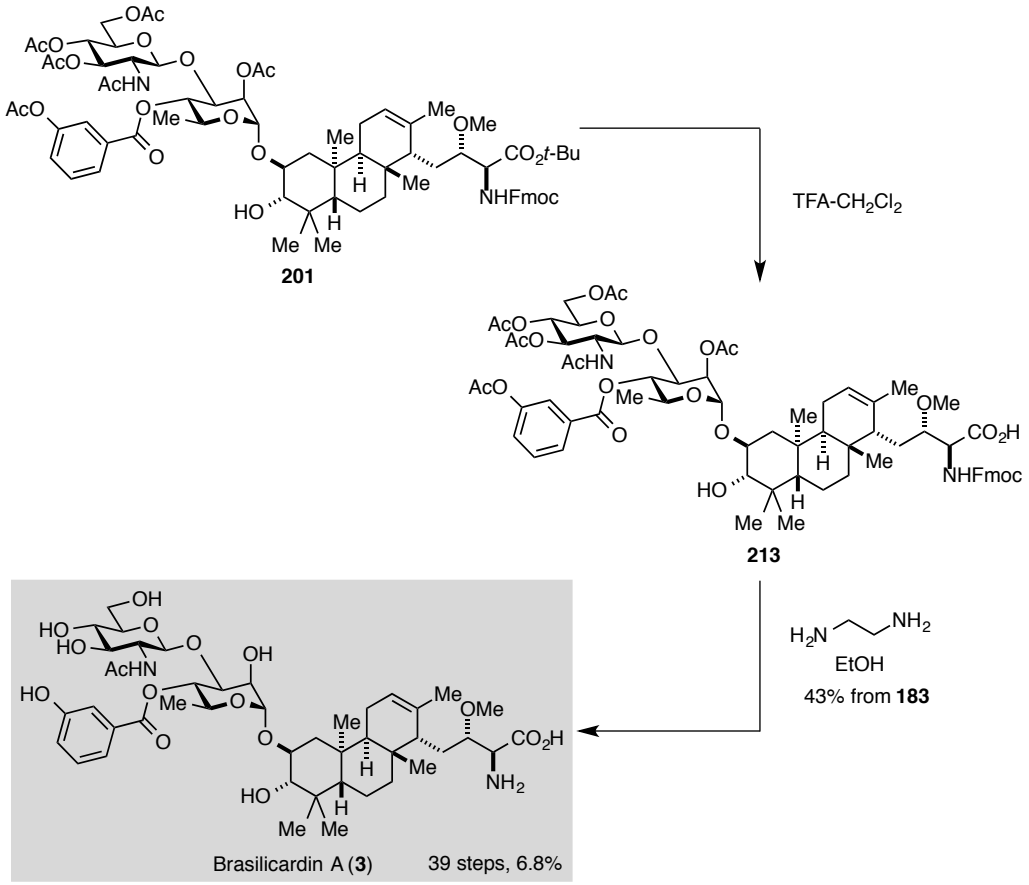
with trichloroacetimidate **37** and the reaction with **211** did not react at all. In addition, when **212** was used, the substrate **183** could not tolerate the activation conditions of **212**, causing degradation of **183**.



Scheme 46. Attempts at glycosylation of other donors with acceptor **183**

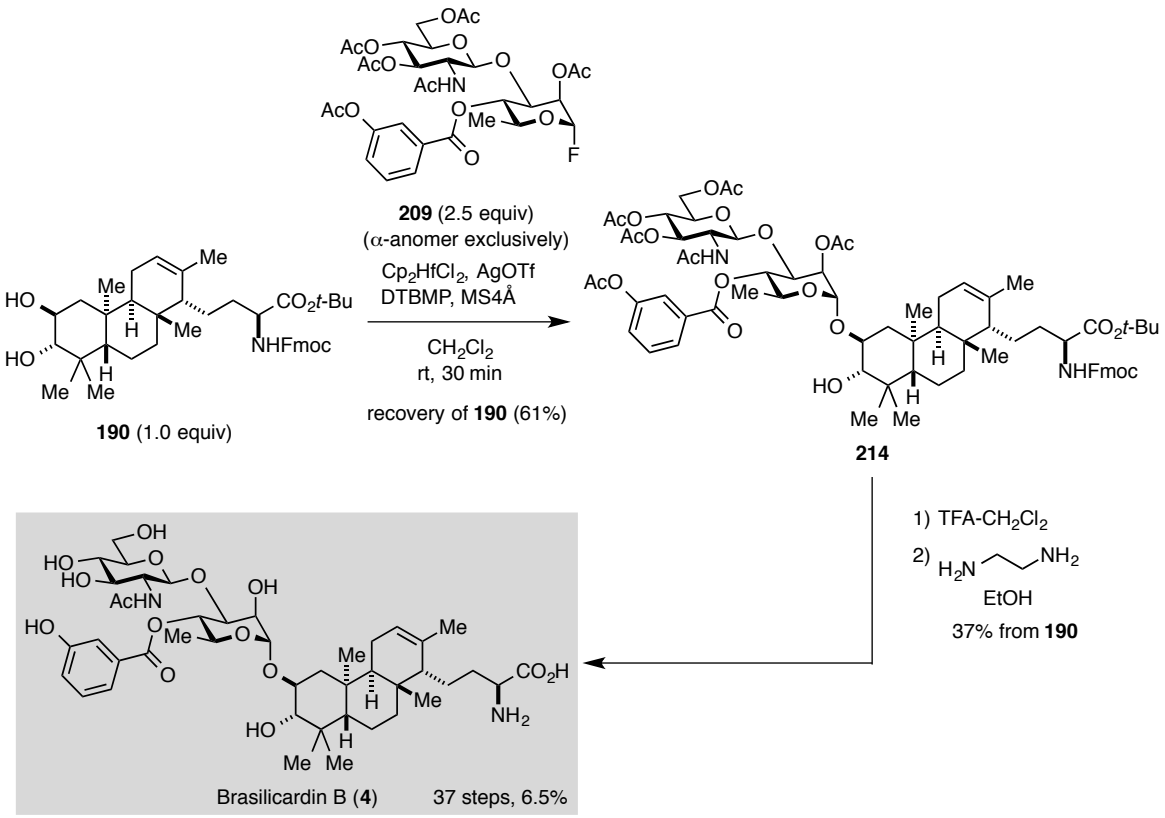
After removal of the protecting groups in **201**, the author accomplished the total synthesis of brasilicardin A (**3**) (Scheme 47). Thus, removal of the *tert*-butyl ester in **201** using trifluoroacetic acid (TFA) and the subsequent treatment with 1,2-ethylenediamine to remove concurrently the five acetyl and Fmoc groups completed the synthesis of brasilicardin A (**3**) (43% yield, 3 steps). Confirming the identity of the author's synthesized sample was very difficult because the ^{1}H-NMR spectrum of the compound proved highly dependent on the concentration and pH. However, its identification was finally achieved using ^{1}H-NMR spectrum of a mixture of synthetic and natural brasilicardin A (**3**) in a 1:1 ratio after both materials were purified by reverse phase semi-preparative HPLC (Capcell Pak C18

SG120). Additionally, the fact that the ^{13}C-NMR, IR, and HRMS spectra and optical rotation results for the synthesized product matched those of the natural sample supported successful synthesis of the author's desired product, as did the narrow range for the melting temperature of the mixture. [3]



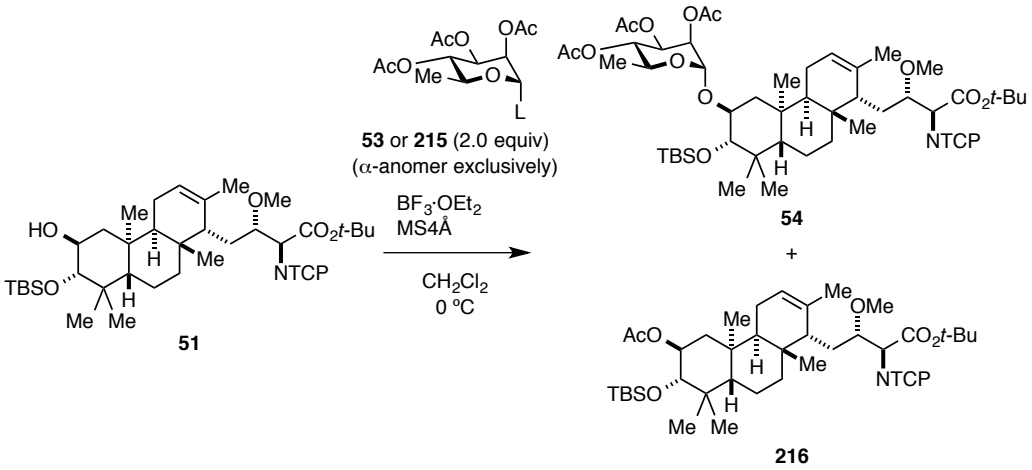
Scheme 47. Total synthesis of brasilicardin A (**3**)

Brasilicardin B (**4**) was also synthesized from **190** using the similar sequence as those used for brasilicardin A (**3**) (Scheme 48).



Scheme 48. Total synthesis of brasilicardin B (**4**)

Achievement of the total synthesis of brasilicardins A (**3**) and B (**4**) with disaccharide unit prompted the author to pursue the total synthesis of brasilicardins C (**5**) and D (**6**) with monosaccharide unit. In this context, Anada, Hashimoto, and co-workers reported the successful glycosylation of L-rhamnose, leading to brasilicardin C (**5**) (Table 2).[8] Thus, the glycosylation of the C3 protected aglycon **51** with trichloroacetimidate **215** using $BF_3 \cdot OEt_2$ as a promoter afforded the desired glycoside **54** as a sole product in 23% yield (29% brsm), and the C2 acetate **216** was also produced in 45% yield (entry 1). The use of *P*,*P*-diphenyl-*N*-(*p*-toluenesulfonyl)-phosphimidate **53**[16] developed by them as a glycosyl donor gave superior results, and the glycosylation product **54** was obtained in 45% yield (82% brsm) along with 8% of **216** (entry 2).



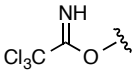
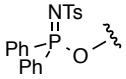
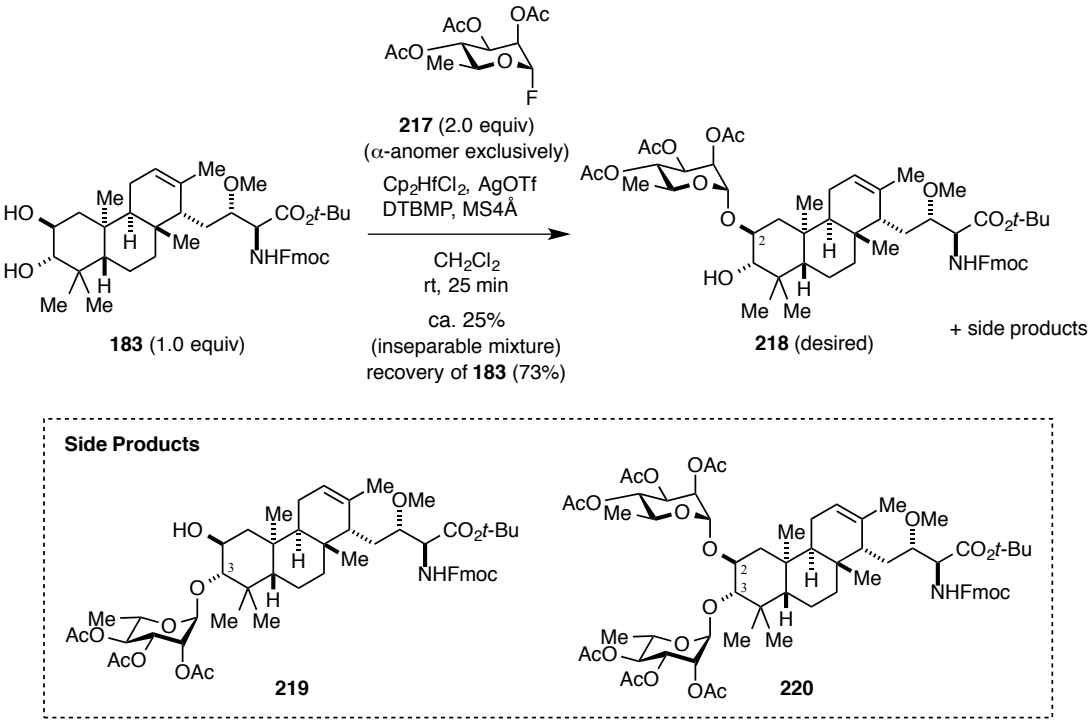
entry	L	result	entry	L	result
1	 **215**	**54** : 23% (29% brsm), **216** : 45%	2	 **53**	**54** : 45% (82% brsm), **216** : 8%

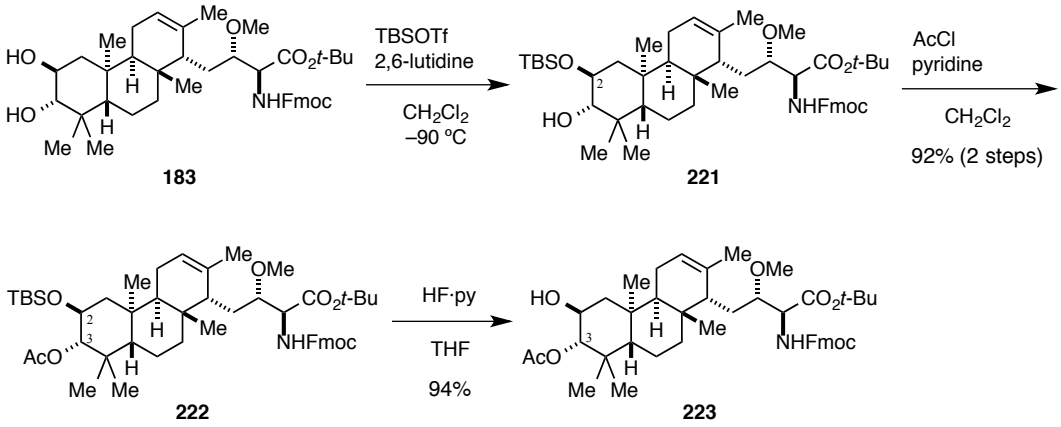
Table 2. Glycosylation study of L-rhamnose by Anada and Hashimoto's group

Although glycosyl fluoride **209** was effective for regioselective glycosylation with diol **183** towards brasilicardins A (**3**) and B (**4**), the glycosylation of peracetyl glycosyl fluoride **217** derived from L-rhamnose resulted in low yield of the desired C3-glycosylation product **218** with side products **219** and **220**, and the regioselectivity was below the synthetically useful level (Scheme 49). The author also investigated glycosylation with other rahmnose donors, but it was difficult to control regiochemichal outcome.[65]



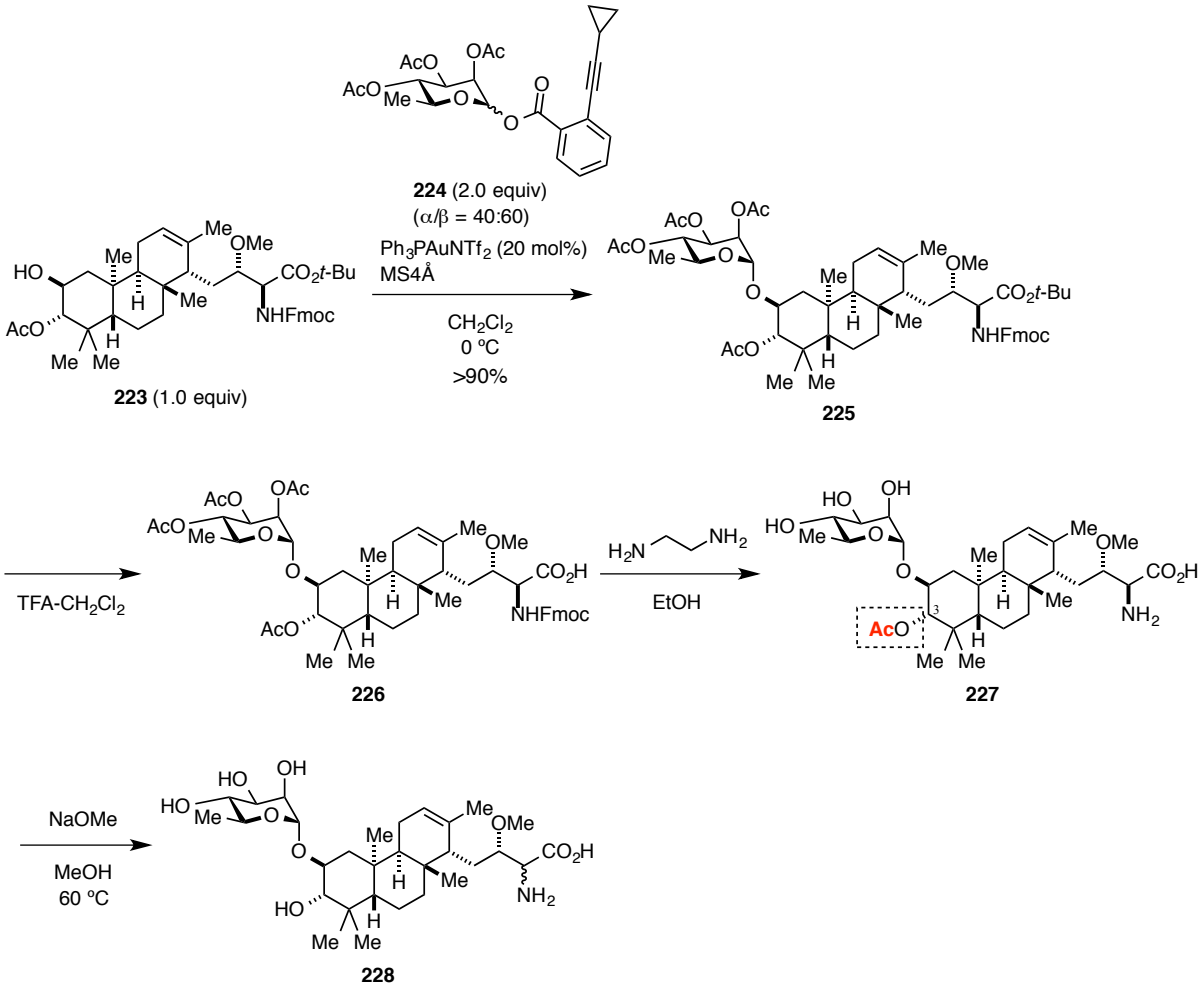
Scheme 49. Attempts at glycosylation of glycosyl fluoride **217** with acceptor **183**

Consequently, the C3 alcohol was temporary protected as an acetyl group (Scheme 50). Thus, monosilylation at the C2 position of diol **183** followed by acetylation of the remaining C3 alcohol afforded acetate **222**. Removal of the TBS group was effected by treatment with hydrogen fluoride-pyridine complex (HF·py) to furnish the C3 protected alcohol **223**.



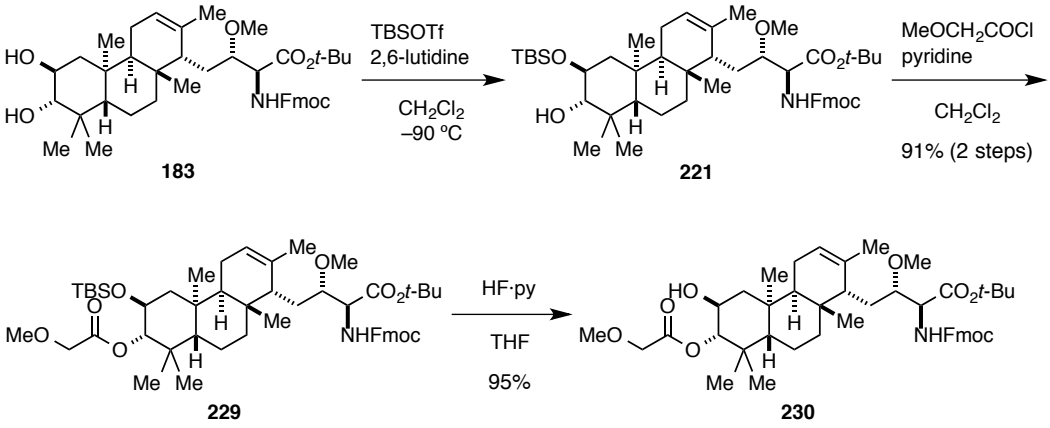
Scheme 50. Synthesis of the C3 protected alcohol **223**

Glycosylation and conversion to brasilicardin C (**5**) were examined (Scheme 51). The author found that gold-catalyzed coupling[66] of glycosyl *o*-cyclopropylethynylbenzoate **224** with **223** proved to be the most effective method for stereoselective installation of a L-rhamnose, affording the glycosylation product **225** in good yield. Attempted other donors did not react at all. The author tried to convert to brasilicardin C (**5**) with the same conditions as in the total synthesis of brasilicardins A (**3**) and B (**4**), but the C3 acetate remained intact contrary to expectation. Thus, acetate **227** was treated with sodium methoxide at 60 ºC to remove the acetate, however, it resulted in the epimerization of the amino acid moiety.



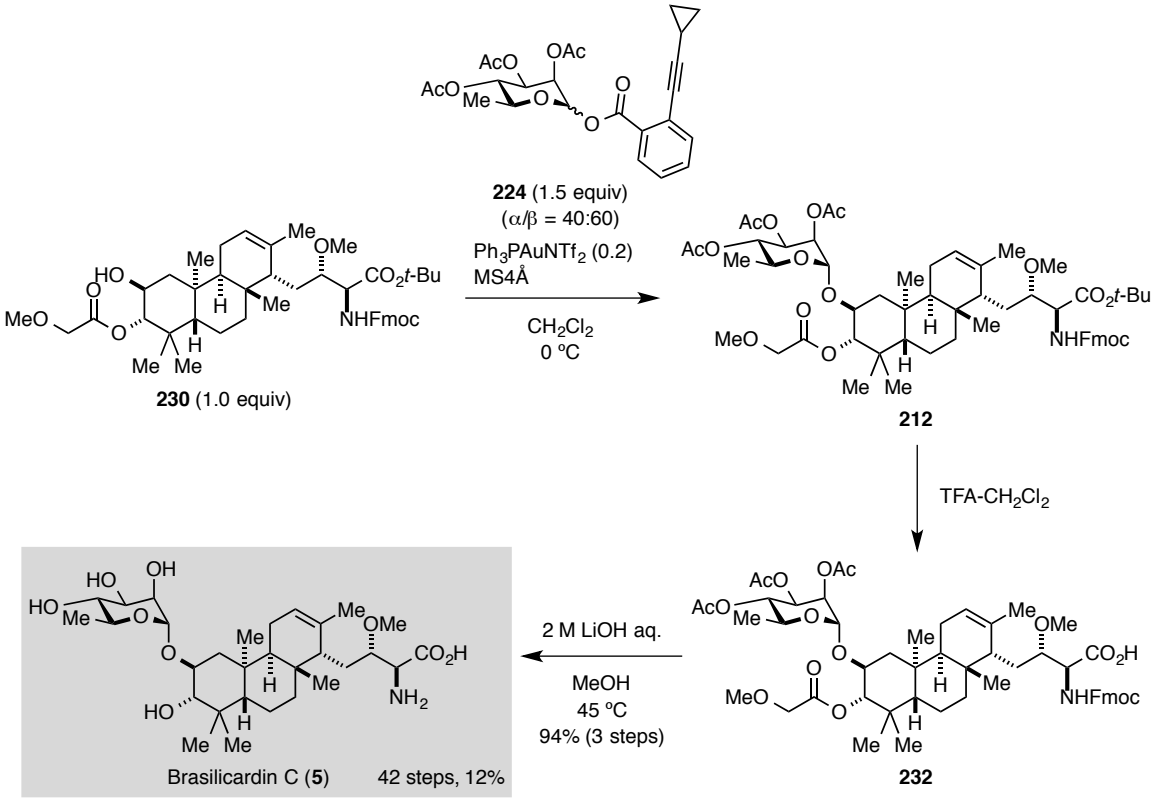
Scheme 51. Attempts at conversion to brasilicardin C (**5**)

Therefore, the author decided to use an easily deprotectable methoxyacetyl group[67] instead of acetyl group (Scheme 52). Thus, the requisite monoalcohol **230** was synthesized from **183** through a three-step conversion as with the synthesis of the acetate **223**.[68]



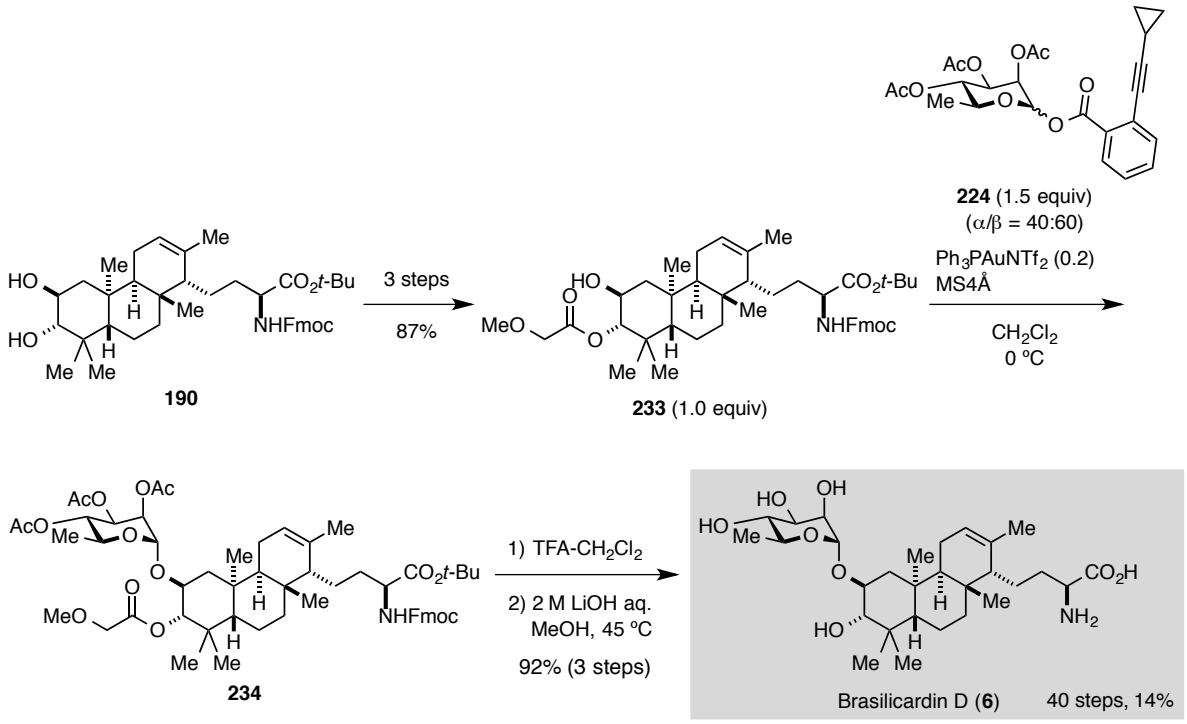
Scheme 52. Synthesis of the C3 protected alcohol **230**

With the C3 protected acceptor **230** in hand, the final stage was set for completion of the total synthesis of brasilicardin C (**5**) (Scheme 53). Thus, Au^{I}-catalyzed glycosylation of alcohol **230** with *o*-cyclopropylethynylbenzoate **224** procceded smoothly to afford glycoside **231** in good yield. Finally, glycoside **231** was successfully converted to brasilicardin C (**5**) via TFA-mediated removal of *tert*-butyl ester and the subsequent global deprotection of the remaining three acetyl, methoxyacetyl, and Fmoc groups with aqueous lithium hydroxide solution.



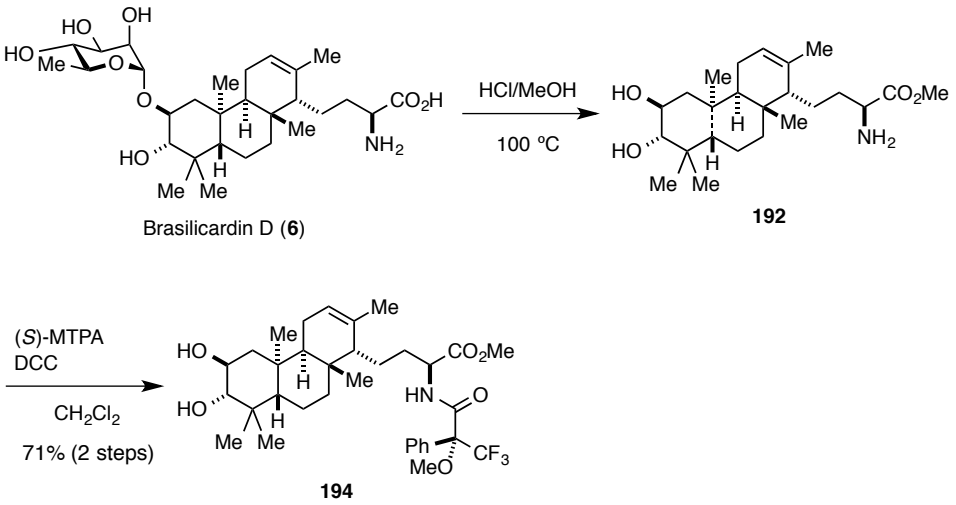
Scheme 53. Completion of total synthesis of brasilicardin C (**5**)

Brasilicardin D (**6**) was also synthesized from **190** using the similar sequence as those used for brasilicardin C (**5**) (Scheme 54).



Scheme 54. Total synthesis of brasilicardin D (**6**)

The author confirmed that epimerization of the amino acid moiety of brasilicardin D (**6**) did not occur during the deprotection conditions using aqueous LiOH (Scheme 55). Thus, hydrolysis of synthetic brasilicardin D (**6**) with HCl/MeOH yielded methyl ester **192**. Amidation of **192** gave Moscher amide **194**. ^{1}H-NMR spectrum of synthetic methyl ester **192** was identical to its derived from natural brasilicardin D (**6**) and ^{1}H-NMR spectrum of **194** revealed no epimerization (see, Chapter 2, Scheme 42).



Scheme 55. Confirmation of no epimerization of amino acid

In summary, the author has developed a stereoselective synthetic route to synthesize brasilicardins A–D (**3**–**6**) with potent immunosuppressive activity and accomplished the asymmetric total synthesis of brasilicardin A (39 linear steps, 6.8% yield), brasilicardin B (37 linear steps, 6.5% yield), brasilicardin C (42 linear steps, 12% yield), and brasilicardin D (40 linear steps, 14% yield) from commercially available 2,2-dimethylpropane-1,3-diol. This is the first total synthesis of brasilicardins B (**5**) and D (**6**). The synthesis features of the unified and stereoselective total synthesis of all four brasilicardins A–D (**3**–**6**) based on the strategic use of an intramolecular conjugate addition. The highly strained *anti*-*syn*-*anti*-fused perhydrophenanthrene skeleton (the ABC-ring system) was constructed with a novel intramolecular nitrile Michael addition, i.e., stereoselective intramolecular conjugate addition of an α-cyano carbanion to an α,β-unsaturated Weinreb amide, which allows simultaneous ring formation and construction of contiguous quaternary–tertiary asymmetric stereocenters, and in situ-generated (*Z*)-vinyl copper species. The late-stage common intermediate was subjected to stereoselective installation of the amino acid component to the terpenoid core, followed by the introduction of the saccharide unit via regio- and stereoselective glycosylation using glycosyl fluoride or *o*-alkynylbenzoate as the glycosyl donor to accomplish the unified synthesis of all brasilicardins A–D (**3**–**6**). Importantly, the strategy potentially allows for the introduction of a variety of saccharides and amino acid side chains into the

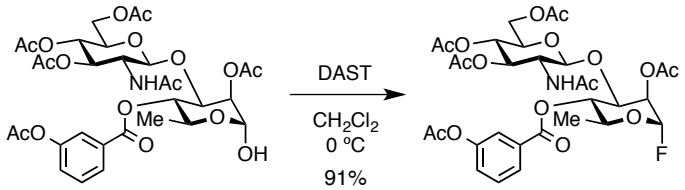
core structure. The novel synthetic route developed here would accelerate the synthesis and biological studies of brasilicardins A–D (**3**–**6**) and a wide variety of their analogues that were previously inaccessible by syntheses or from natural products as well as aid in obtaining in-depth SAR toward the development of new immunosuppressive drugs.

Experimental Section of Chapter 3

Experimental Procedure for Chapter 3

Compound 209

Hemiacetal **S10** was prepared according to the procedure of Jung and Koch.[13]



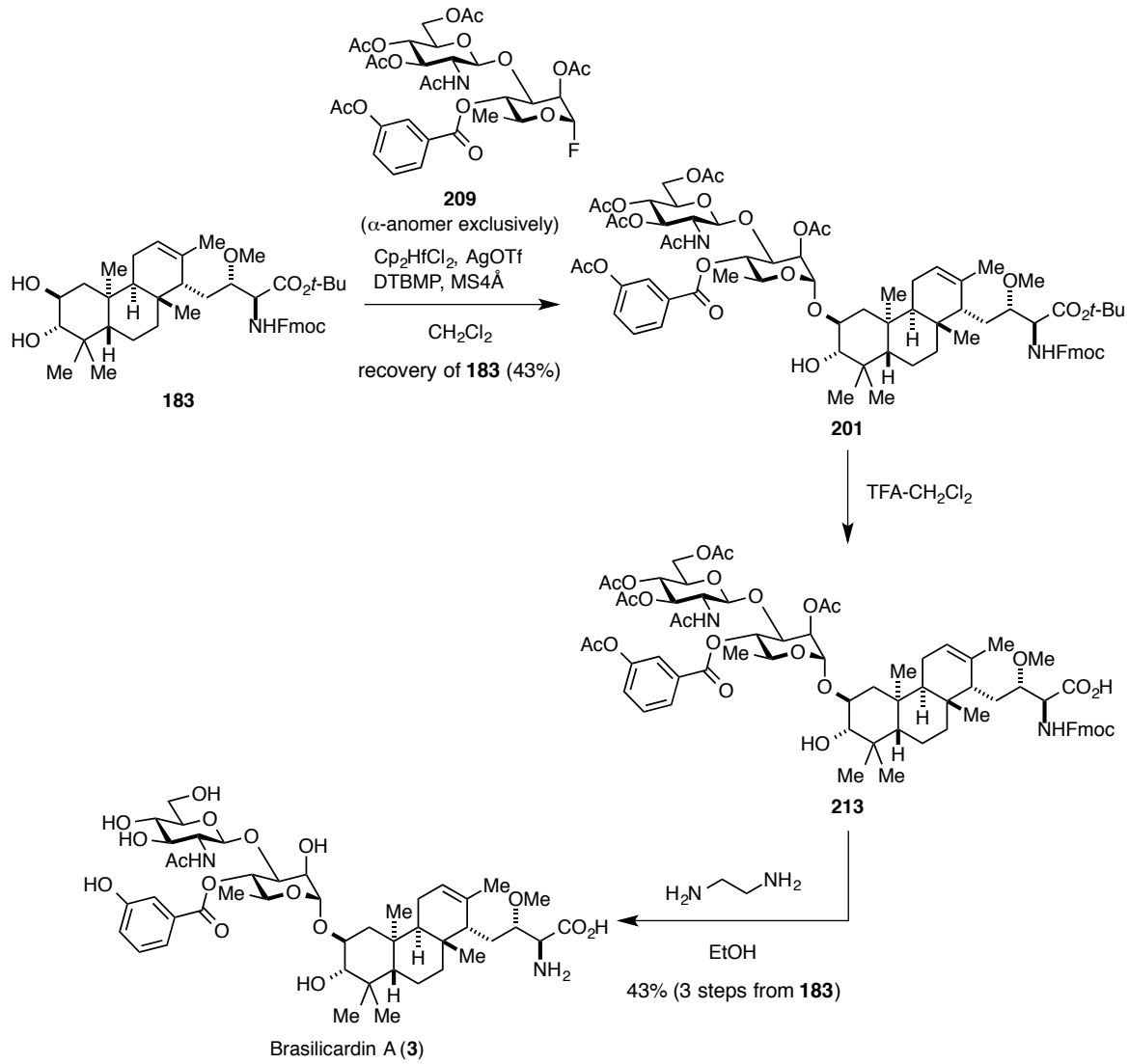
S10 (α-anomer exclusively) **209** (α-anomer exclusively)

To a solution of hemiacetal **S10** (697.6 mg, 1.00 mmol, α-anomer exclusively) in CH_2Cl_2 (20 mL) was added diethylaminosulfur trifluoride (DAST) (262 μL, 2.00 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with a saturated aqueous $NaHCO_3$ solution (50 mL), brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL), to the mixture was added *n*-hexane (20 mL) at 0 °C. The resulting white precipitated was filtered through a kiriyama funnel, and the resulting powder was dried under high vacuum for 1 h. Glycosyl fluoride **209** (635.2 mg, 0.908 mmol, 91%, α-anomer exclusively) was obtained as a white powder: M.p. 194-195 °C; $[\alpha]_D^{24}$ +11.6 (c 1.36, $CHCl_3$); IR (ATR): ν 2367, 2356, 2339, 2321, 1737, 1664, 1541, 1374, 1241, 1196, 1104, 1046, 947, 749 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.95 (1H, d, *J* = 8.1 Hz), 7.81 (1H, d, *J* = 1.8 Hz), 7.52 (1H, d, *J* = 8.1 Hz), 7.31 (1H, dd, *J* = 8.1, 1.8 Hz), 5.55 (1H, dd, *J* = 48.7, 1.2 Hz), 5.44-5.43 (2H, m), 5.29 (1H, dd, *J* = 10.3, 9.8 Hz), 5.21 (1H, dd, *J* = 10.3, 9.2 Hz), 4.95 (1H, dd, *J* = 9.8, 9.7 Hz), 4.76 (1H, d, *J* = 8.0 Hz), 4.18-4.11 (3H, m), 4.06 (1H, qd, *J* = 9.5, 5.8 Hz), 3.83 (1H, dd, *J* = 9.2, 2.3 Hz), 3.72 (1H, ddd, *J* = 9.8, 5.2, 2.9 Hz), 2.38 (3H, s), 2.16 (3H, s), 2.09 (3H, s), 2.00 (3H, s), 1.92 (3H, s), 1.30 (3H, d, *J* = 5.8 Hz), 1.12 (3H, s); ^{13}C-NMR (125 MHz,

$CDCl_3$): δ 170.74, 170.50, 170.04, 169.82, 169.74, 169.36, 164.05, 150.35, 130.54, 130.12, 127.40, 126.31, 123.17, 104.89 [d, ^2J(C,F) = 220.7 Hz], 102.02, 75.48, 72.14, 71.43, 70.09 [d, ^1J(C,F) = 39.6 Hz], 69.00, 68.67, 62.04, 54.25, 21.95, 21.24, 20.81, 20.59, 20.53, 17.52 (two peaks missing); HRMS (FD): Calcd for $C_{31}H_{39}FNO_{16}$ $[M+H]^+$: 700.2253; found: 700.2241.

Data for compound S10: White powder; M.p. 238-241 °C; $[\alpha]_D^{23}$ +6.48 (c 1.51, $CHCl_3$); IR (ATR): ν 3374, 3018, 2984, 2939, 2362, 2342, 1732, 1665, 1543, 1441, 1371, 1230, 1043, 751 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.96 (1H, d, *J* = 8.0 Hz), 7.82 (1H, d, *J* = 1.8 Hz), 7.52 (1H, t, *J* = 8.1 Hz), 7.31 (1H, ddd, *J* = 8.1, 2.3, 1.2 Hz), 5.39 (1H, d, *J* = 9.2 Hz), 5.31 (1H, dd, *J* = 3.5, 1.7 Hz), 5.26 (1H, dd, *J* = 10.3, 9.8 Hz), 5.21 (1H, dd, *J* = 10.9, 9.2 Hz), 5.21-5.19 (1H, m), 4.98 (1H, t, *J* = 9.8 Hz), 4.78 (1H, d, *J* = 8.6 Hz), 4.25 (1H, dd, *J* = 9.8, 3.5 Hz), 4.19 (1H, dd, *J* = 12.6, 1.4 Hz), 4.16-4.12 (2H, m), 3.81 (1H, dd, *J* = 9.2, 1.7 Hz), 3.70 (1H, ddd, *J* = 9.8, 4.6, 2.3 Hz), 2.97 (1H, d, *J* = 2.9 Hz), 2.15 (3H, s), 2.11 (3H, s), 2.00 (3H, s), 1.92 (3H, s), 1.25 (3H, d, *J* = 6.3 Hz), 1.16 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.00, 170.57, 170.41, 170.28, 169.71, 169.41, 164.27, 150.38, 130.92, 130.04, 127.33, 126.22, 123.16, 101.73, 91.87, 75.83, 73.40, 72.43, 72.28, 71.32, 68.61, 66.36, 61.85, 54.39, 22.02, 21.22, 21.04, 20.70, 20.62, 20.55, 17.70; HRMS (FD): Calcd for $C_{31}H_{40}NO_{17}$ $[M+H]^+$: 698.2296; found: 698.2293.

Brasilicardin A (3)



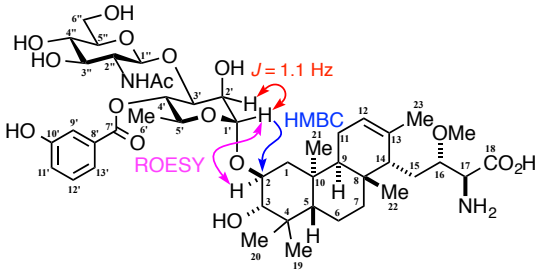
The promoter was prepared by stirring a mixture of hafnocene dichloride (Cp_2HfCl_2) (26.0 mg, 68.4 μmol), silver trifluoromethanesulfonate (AgOTf) (35.1 mg, 0.137 mmol), and freshly activated and powdered MS4Å (AW-300, 20.5 mg) in CH_2Cl_2 (0.71 mL) at room temperature for 10 min prior to the glycosylation. A mixture of the protected aglycon **183** (12.0 mg, 17.1 μmol), glycosyl donor **209** (23.9 mg, 34.2 μmol), and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (1.8 mg, 8.55 μmol) in CH_2Cl_2 (1.0 mL) was added to the above promoter suspension at –78 °C. After being stirred at room temperature for 25 min, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (3 mL). The mixture was filtered through a pad of Celite®, which was rinsed with EtOAc (5

mL). After the layers were separated, the aqueous layer was extracted with EtOAc (2 mL×5). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by preparative TLC (SiO_2, *n*-hexane/EtOAc = 1:4) afforded semi-pure glycoside **201** (11.8 mg, white amorphous foam) with recovery of the protected aglycon **183** (5.1 mg, 7.27 μmol, 43%, white amorphous foam). The semi-pure glycoside **201** was used for the next step without further purification.

To a solution of the above semi-pure glycoside **201** (11.8 mg) in CH_2Cl_2 (0.85 mL) was added trifluoroacetic acid (TFA) (0.85 mL) at 0 °C. After being stirred at room temperature for 5 h, the reaction mixture was concentrated under reduced pressure. The crude carboxylic acid **213** (12.8 mg, white amorphous foam) was used for the next step without further purification.

To a solution of the above crude carboxylic acid **213** (12.8 mg) in EtOH (1.5 mL) was added ethylenediamine (0.17 mL) at 0 °C. After being stirred at room temperature for 18 h, the reaction mixture was concentrated under reduced pressure. Purification by reverse-phase semi-preparative HPLC (column: Capcell Pak C18 SG120, Shiseido Co., Ltd., 5.0 μm, 250×10 mm; elution: linear gradient, 18 to 50% of MeCN with TFA 0.15% for 30 min; flow rate: 3.0 mL/min; detection: UV 220 nm) afforded brasilicardin A (**3**) (6.6 mg, 7.40 μmol, 43% for 3 steps) as a colorless amorphous solid: M.p. 269-273 °C, mixed M.p. 270-274 °C [lit.[3] M.p. 270-273 °C]; $[\alpha]_D^{25}$ +14.9 (c 0.40, MeOH) [lit.[3] $[\alpha]_D^{30}$ +15.0 (c 0.50, MeOH)]; IR (ATR): ν 3325, 2941, 2832, 1668, 1649, 1451, 1291, 1202, 1114, 1019, 903, 839, 806, 730, 717, 707, 680, 652, 593 cm^{-1}; ^{1}H-NMR (600 MHz, CD_3OD): δ 7.55 (1H, d, *J* = 7.6 Hz), 7.47 (1H, br), 7.34 (1H, t, *J* = 7.6 Hz), 7.06 (1H, dd, *J* = 8.2, 2.0 Hz), 5.35 (1H, br), 5.27 (1H, t, *J* = 9.7 Hz), 5.02 (1H, br), 4.53 (1H, d, *J* = 8.3 Hz), 4.44 (1H, d, *J* = 2.7 Hz), 4.34 (1H, br), 4.08 (1H, dd, *J* = 9.6, 2.8 Hz), 4.01 (1H, dq, *J* = 9.6, 6.2 Hz), 3.89 (1H, dd, *J* = 12.4, 1.4 Hz), 3.78 (1H, dd, *J* = 11.7, 2.1 Hz), 3.69 (1H, d, *J* = 11.7 Hz), 3.69 (1H, m), 3.55 (1H, dd, *J* = 9.6, 8.9 Hz), 3.49 (3H, s), 3.37 (1H, dd, *J* = 9.6, 8.3 Hz), 3.31 (1H, m), 3.28 (1H, m), 3.02 (1H, d, *J* = 9.6 Hz), 1.89 (1H, br), 1.88 (1H, br), 1.79 (1H, dd, *J* = 12.4, 4.1 Hz), 1.74 (2H, m), 1.65 (3H, s), 1.63 (2H, m), 1.57 (1H, m), 1.51 (1H, m), 1.49 (3H, s), 1.45 (1H, m), 1.40 (1H, m), 1.34 (1H, m), 1.27 (1H, m), 1.12 (3H, d, *J* = 6.2 Hz), 1.10 (3H, s), 1.05 (3H, s), 1.05 (3H, s), 1.00 (3H, s), 0.92

(3H, s); ^{13}C-NMR (151 MHz, CD_3OD): δ 174.06, 169.89, 167.01, 158.99, 138.46, 132.44, 130.88, 123.62, 122.00, 121.54, 117.44, 104.05, 103.11, 83.30, 80.47, 79.86, 79.78, 77.78, 75.31, 74.13, 72.10, 71.82, 68.07, 62.56, 58.49, 57.50, 54.66, 52.29, 47.39, 44.30, 44.00, 41.19, 38.54, 37.59, 32.01, 31.28, 29.23, 28.91, 27.06, 22.89, 22.63, 22.54, 18.71, 17.80, 17.31; HRMS (ESI): Calcd for $C_{45}H_{67}N_2O_{16}$ $[M–H]^+$: 891.4496; found: 891.4510.



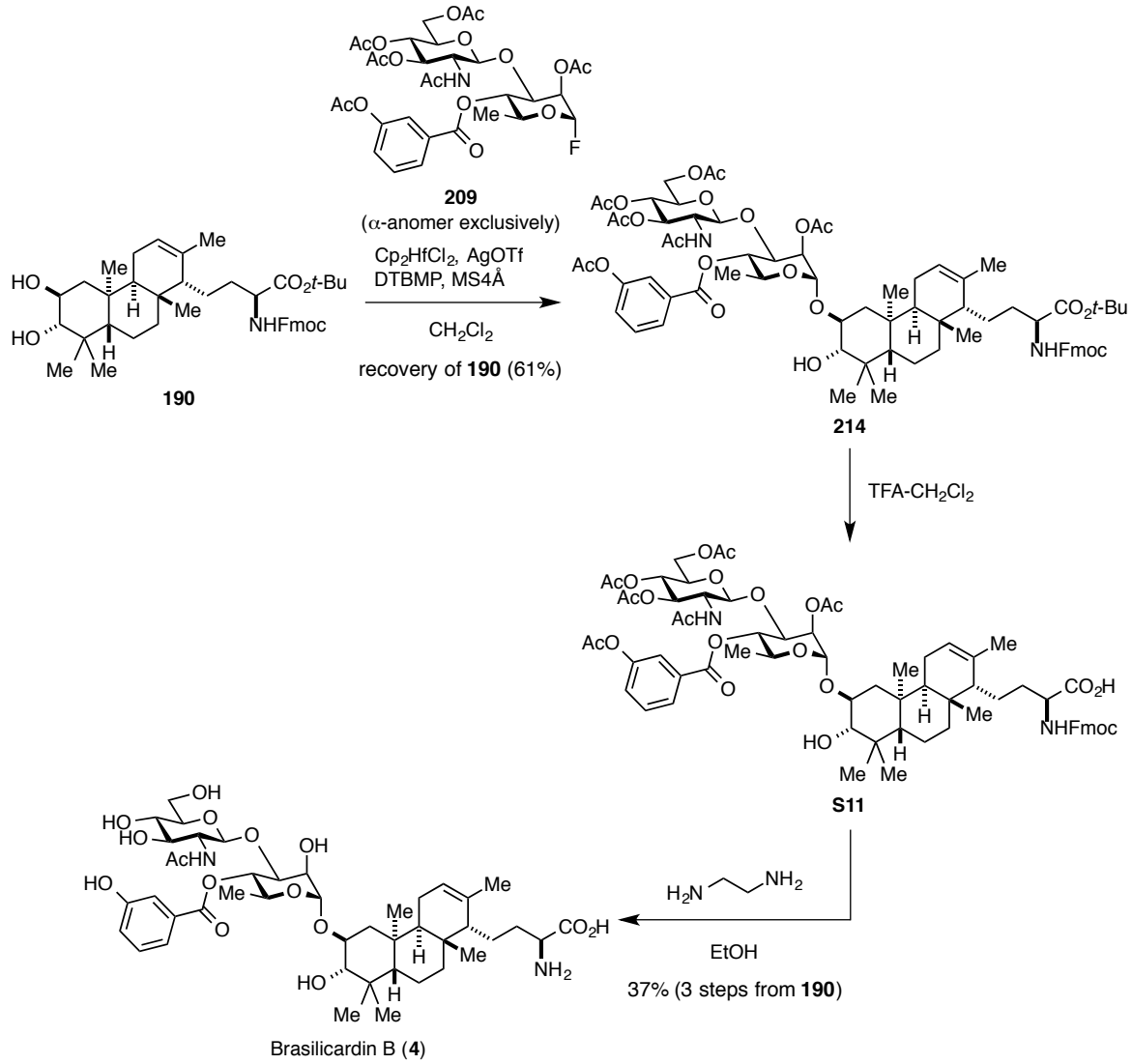
Synthetic brasilicardin A (**3**)

The stereostructure of synthetic brasilicardin A (**3**) was confirmed by ^{1}H–^{1}H coupling constant ($J_{1',2'}$ = 1.1 Hz), ROESY correlation observed between H-1′ and H-2, HMBC correlation of H-1′ to C-2, and ^{1}H–^{13}C coupling constant (C-1′, $^1J_{C,H}$ = 171.1 Hz; lit. $^1J_{C,H}$ = 171.0 Hz[3]) by an INEPT experiment.

Procedure for ^{1}H NMR Measurement of the Mixed Synthetic and Natural Brasilicardin A

6.6 Milligram of synthetic brasilicardin A (**3**) was prepared and purified by the above procedure. Natural brasilicardin A (**3**) (ca. 2.0 mg) was kindly obtained from professors Jun'ichi Kobayashi and Takaaki Kubota. This material was purified by the same procedure as for synthetic brasilicardin A, which afforded 1.6 milligram of pure natural brasilicardin A (**3**). The synthetic brasilicardin A (ca. 0.2 mg) and natural brasilicardin A (ca. 0.2 mg) were mixed and dissolved in methanol-d_4 (ca. 0.3 mL, 99.8 atom % D), and then ^{1}H-NMR spectra (500 MHz) was measured with the JEOL ECA-500 using Shigemi NMR tube (5 mmϕ, MMS-005J).

Brasilicardin B (4)



The promoter was prepared by stirring a mixture of Cp_2HfCl_2 (50.8 mg, 0.134 mmol), AgOTf (57.3 mg, 0.223 mmol), and freshly activated and powdered MS4Å (AW-300, 33.5 mg) in CH_2Cl_2 (0.5 mL) at room temperature for 10 min prior to the glycosylation. A mixture of the protected aglycon **190** (15.0 mg, 22.3 μmol), glycosyl donor **209** (39.0 mg, 55.8 μmol), and DTBMP (6.9 mg, 35.5 μmol) in CH_2Cl_2 (1.7 mL) was added to the above promoter suspension at –78 °C. After being stirred at room temperature for 30 min, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (2 mL). The mixture was filtered through a pad of Celite®, which was rinsed with EtOAc (5 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (1

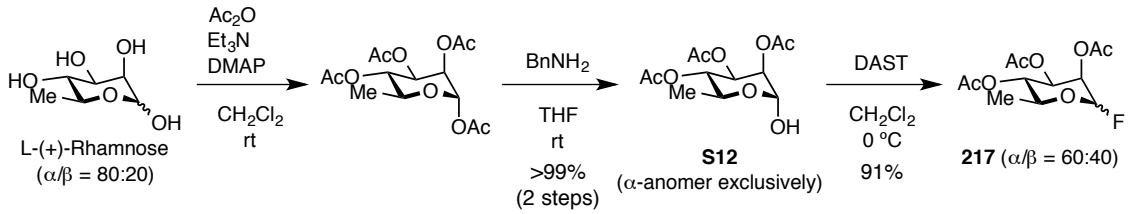
mL×5). The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by preparative TLC (SiO_2, *n*-hexane/EtOAc = 2:3) afforded semi-pure glycoside **214** (16.9 mg, white amorphous foam) with recovery of the protected aglycon **190** (9.2 mg, 13.7 μmol, 61%, white amorphous foam). The semi-pure glycoside **214** was used for the next step without further purification.

To a solution of the above semi-pure glycoside **214** (16.9 mg) in CH_2Cl_2 (1.3 mL) was added TFA (1.3 mL) at 0 °C. After being stirred at room temperature for 6 h, the reaction mixture was concentrated under reduced pressure. The crude carboxylic acid **S11** (16.5 mg, white amorphous foam) was used for the next step without further purification.

To a solution of the above crude carboxylic acid **S11** (16.5 mg) in EtOH (2.3 mL) was added ethylenediamine (0.25 mL) at 0 °C. After being stirred at room temperature for 16 h, the reaction mixture was concentrated under reduced pressure. Purification by reverse-phase semi-preparative HPLC (column; Capcell Pak C18 SG120, Shiseido Co., Ltd., 5.0 μm, 250×10 mm; elution: linear gradient, 18 to 50% of MeCN with TFA 0.15% for 30 min; flow rate: 3.0 mL/min; detection: UV 220 nm) afforded brasilicardin B (**4**) (7.1 mg, 8.24 μmol, 37% for 3 steps) as a colorless amorphous solid: $[\alpha]_D^{27}$ +16.9 (c 0.22, MeOH) [lit.[6] $[\alpha]_D^{23}$ +17.0 (c 1.00, MeOH)]; IR (ATR): ν 3401, 2938, 1671, 1289, 1201, 1137, 1116, 1076, 1031, 669 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD): δ 7.55 (1H, d, *J* = 8.1 Hz), 7.47 (1H, br), 7.34 (1H, t, *J* = 8.1 Hz), 7.06 (1H, dd, *J* = 8.0, 1.7 Hz), 5.38 (1H, br), 5.28 (1H, t, *J* = 9.8 Hz), 5.02 (1H, br), 4.53 (1H, d, *J* = 8.0 Hz), 4.34 (1H, br), 4.07 (1H, dd, *J* = 9.2, 2.3 Hz), 4.00 (1H, dq, *J* = 9.8, 6.3 Hz), 3.99 (1H, t, *J* = 5.7 Hz), 3.89 (1H, d, *J* = 10.9 Hz), 3.71 (1H, m), 3.69 (1H, dd, *J* = 11.5, 4.6 Hz), 3.54 (1H, dd, *J* = 9.8, 9.2 Hz), 3.36 (1H, m), 3.31 (1H, m), 3.02 (1H, d, *J* = 9.8 Hz), 2.00 (2H, m), 1.91 (1H, m), 1.90 (1H, m), 1.82 (1H, dd, *J* = 12.0, 4.0 Hz), 1.78 (1H, m), 1.75 (1H, m), 1.67 (3H, s), 1.65 (1H, m), 1.63 (1H, m), 1.54 (1H, m), 1.50 (3H, s), 1.45 (1H, m), 1.37 (1H, m), 1.35 (1H, m), 1.32 (1H, m), 1.30 (1H, m), 1.13 (3H, s), 1.13 (3H, d, *J* = 6.3 Hz), 1.03 (3H, s), 1.01 (3H, s), 0.93 (3H, s); ^{13}C-NMR (151 MHz, CD_3OD): δ 174.08, 174.04, 167.01, 158.99, 137.84, 132.44, 130.88, 123.77, 122.00, 121.54, 117.44, 104.05, 103.13, 83.36, 79.87 (2C), 77.79, 75.31, 74.14, 72.10, 71.83, 68.08, 62.56, 57.50, 56.77, 56.55, 47.62, 44.65, 44.01,

41.17, 38.25, 37.85, 32.82, 31.51, 29.32, 28.79, 26.96, 26.86, 23.29, 23.12, 22.64, 18.85, 17.81, 17.36; HRMS (ESI): Calcd for $C_{44}H_{66}N_2O_{15}Na$ $[M+Na]^+$: 885.4355; found: 885.4370.

Compound 217



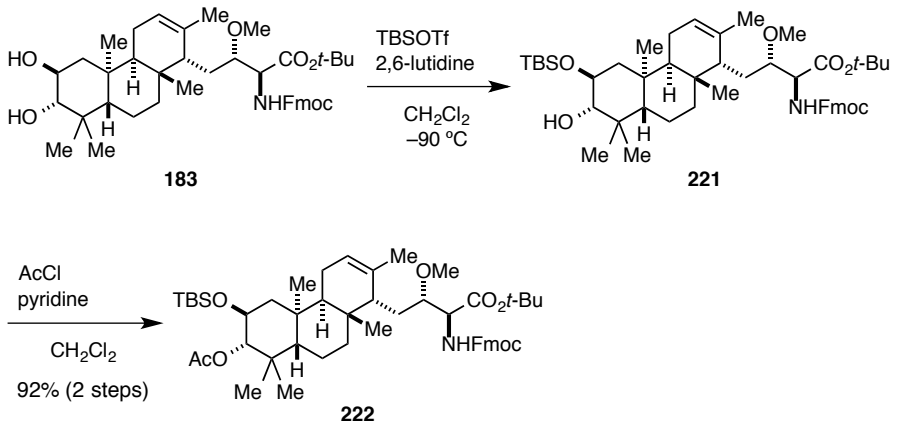
To a solution of hemiacetal **S12**[69] (300.0 mg, 1.03 mmol, α-anomer exclusively) in CH_2Cl_2 (21 mL) was added DAST (270 μL, 2.06 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with a saturated aqueous $NaHCO_3$ solution (20 mL×3), brine (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~30 g, *n*-hexane/EtOAc = 5:1 to 2:1) afforded α-glycosyl fluoride **217** (168.5 mg, 0.577 mmol, 56%, α-anomer exclusively) as a yellow oil and its regioisomeric β-glycosyl fluoride **217** (107.2 mg, 0.367 mmol, 35%, β-anomer exclusively) as a colorless oil.

α-Glycosyl fluoride 217: $[\alpha]_D^{26}$ –191.6 (c 1.00, $CHCl_3$); IR (ATR): ν 2988, 1746, 1433, 1369, 1241, 1212, 1173, 1055, 1022, 974, 945, 930, 886, 837, 794, 735, 683, 600, 577 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.49 (1H, dd, *J* = 48.7, 1.7 Hz), 5.38 (1H, br), 5.29 (1H, ddd, *J* = 10.3, 3.4, 1.7 Hz), 5.12 (1H, dd, *J* = 10.4, 9.7 Hz), 4.04 (1H, dq, *J* = 10.3, 6.3 Hz), 2.16 (3H, s), 2.06 (3H, s), 2.00 (3H, s), 1.27 (3H, d, *J* = 6.3 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.69, 169.66, 169.58, 104.00 [d, ^3J(C,F) = 215.8 Hz], 69.74, 68.74 [d, ^2J(C,F) = 3.6 Hz], 68.00 [d, ^1J(C,F) = 14.3 Hz], 67.62, 20.55, 20.45, 17.13 (one peak missing); HRMS (FD): Calcd for $C_{12}H_{17}FNO_7$ $[M]^+$: 292.0958; found: 292.0969;

β-Glycosyl fluoride 217: $[\alpha]_D^{26}$ +53.1 (c 1.00, $CHCl_3$); IR (ATR): ν 2989, 1746, 1434, 1371, 1322, 1212, 1184, 1125, 1094, 1055, 975, 952, 909, 734, 601, 522, 480 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 5.53-5.51 (1H, m), 5.46 (1H, dd, *J* = 51.0, 1.2 Hz), 5.10-5.04 (2H, m), 3.68 (1H, dq, *J* = 13.8, 6.9 Hz), 2.18 (3H, s), 2.07 (3H, s), 2.02 (3H, s), 1.36 (3H, d, *J* = 6.3 Hz); ^{13}C-NMR (125 MHz,

$CDCl_3$): δ 169.97, 169.82, 169.60, 104.00 [d, ^4J(C,F) = 215.8 Hz], 70.49 [d, ^3J(C,F) = 19.1 Hz], 69.89, 69.43 [d, ^2J(C,F) = 7.2 Hz], 67.38 [d, ^1J(C,F) = 19.1 Hz], 20.65, 20.59, 20.48, 17.48; HRMS (FD): Calcd for $C_{12}H_{17}FNO_7$ $[M]^+$: 292.0958; found: 292.0967.

Compound 222

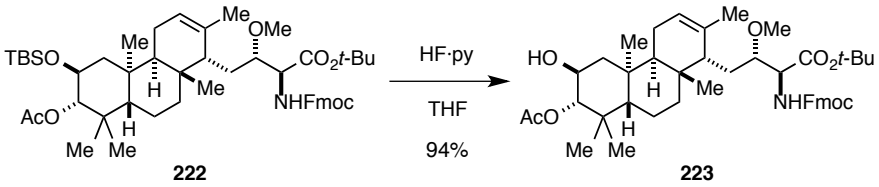


To a solution of diol **183** (15.0 mg, 21.4 μmol) in CH_2Cl_2 (0.43 mL) were added 2,6-lutidine (3.7 μL, 64.1 μmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (5.4 μL, 23.5 μmol) at –90 °C. After being stirred at –90 °C for 30 min, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (1 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (1 mL×3). The combined organic layers were washed with 5% aqueous $KHSO_4$ solution (1 mL×2), dried over $MgSO_4$, and concentrated under reduced pressure. The crude alcohol **221** (19.5 mg, white amorphous foam) was used for the next step without further purification.

To a solution of the above crude alcohol **221** (19.5 mg) in CH_2Cl_2 (0.43 mL) were added pyridine (17 μL, 0.214 mmol) and acetyl chloride (7.6 μL, 0.107 mmol) at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (1 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (1 mL×3). The combined organic layers were washed with 5% aqueous $KHSO_4$ solution (1 mL×2), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by preparative TLC (SiO_2, *n*-hexane/EtOAc = 3:1) afforded acetyl ester **222** (16.9 mg, 19.7 μmol, 92% for 2 steps) as a white

amorphous foam: $[\alpha]_D^{27}$ +78.3 (c 0.85, $CHCl_3$); IR (ATR): ν 2951, 2931, 2858, 1737, 1507, 1450, 1369, 1245, 1156, 1083, 1038, 868, 836, 774, 759, 739, 669 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.76 (2H, d, *J* = 7.5 Hz), 7.61 (2H, d, *J* = 7.5 Hz), 7.40 (2H, t, *J* = 6.9 Hz), 7.31 (2H, t, *J* = 7.5 Hz), 5.39 (1H, d, *J* = 8.6 Hz), 5.33 (1H, br), 4.61 (1H, d, *J* = 8.6 Hz), 4.56 (1H, d, *J* = 9.8 Hz), 4.41-4.34 (2H, m), 4.24 (1H, t, *J* = 7.5 Hz), 3.82 (1H, td, *J* = 10.3, 2.9 Hz), 3.47 (1H, d, *J* = 12.0 Hz), 3.45 (3H, s), 2.09 (3H, s), 1.90-1.81 (2H, m), 1.73-1.61 (3H, m), 1.67 (3H, s), 1.56-1.50 (4H, m), 1.50 (9H, s), 1.40 (1H, dd, *J* = 13.2, 11.5 Hz), 1.31-1.22 (3H, m), 1.07 (3H, s), 0.99 (3H, s), 0.91 (3H, s), 0.86 (9H, s), 0.82 (3H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 170.77, 169.66, 156.03, 143.89, 143.79, 141.26, 137.81, 127.67, 127.03, 125.15, 122.14, 119.95, 83.43, 82.58, 82.19, 68.07, 67.08, 58.45, 56.02, 50.85, 47.11, 46.26, 44.88, 42.56, 39.52, 37.10, 36.20, 31.98, 29.72, 28.51, 28.44, 28.10, 25.95, 25.66, 22.46, 22.43, 21.37, 17.89, 17.56, 17.34, −4.40, −4.81 (nine peaks missing); HRMS (FD): Calcd for $C_{51}H_{75}NO_8Si$ $[M]^+$: 857.5262; found: 857.5243.

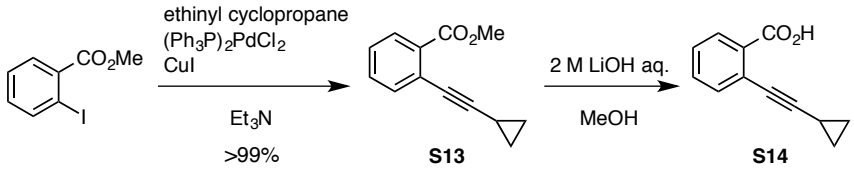
Compound 223



To a solution of acetyl ester **222** (16.0 mg, 18.6 μmol) in THF (1.0 mL) in a polypropylene test tube was added hydrogen fluoride-pyridine complex (HF·pyridine) (0.2 mL) at 0 °C. After being stirred at room temperature for 3 h, to the reaction mixture was added methoxytrimethylsilane (TMSOMe) (2.0 mL) slowly at 0 °C. The mixture was further stirred at room temperature for 2 h, and concentrated under reduced pressure. Purification by preparative TLC (SiO_2, *n*-hexane/EtOAc = 3:2) afforded alcohol **223** (13.0 mg, 17.5 μmol, 94%) as a white amorphous foam: $[\alpha]_D^{26}$ +90.5 (c 0.44, $CHCl_3$); IR (ATR): ν 3350, 2942, 2878, 1720, 1510, 1449, 1369, 1337, 1245, 1154, 1112, 1054, 986, 907, 847, 757, 740 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.76 (2H, d, *J* = 7.5 Hz), 7.60 (2H, d, *J* = 7.5 Hz), 7.40 (2H, t, *J* = 7.5 Hz), 7.30 (2H, t, *J* = 7.5 Hz), 5.39 (1H, d, *J* = 8.6 Hz), 5.33

(1H, br), 4.62 (1H, d, J = 8.0 Hz), 4.47 (1H, d, J = 10.3 Hz), 4.41-4.34 (2H, m), 4.24 (1H, t, J = 7.5 Hz), 3.81 (1H, br), 3.48 (1H, d, J = 10.9 Hz), 3.45 (3H, s), 2.15 (3H, s), 1.92 (1H, br-dt), 1.86-1.81 (2H, m), 1.74-1.61 (4H, m), 1.67 (3H, s), 1.56-1.38 (4H, m), 1.50 (3H, s), 1.34-1.25 (3H, m), 1.07 (3H, s), 1.00 (3H, s), 0.93 (3H, s), 0.85 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 172.35, 169.66, 156.05, 143.87, 143.78, 141.26, 137.85, 127.68, 127.03, 125.15, 122.03, 119.95, 84.80, 82.61, 82.20, 68.14, 67.08, 58.40, 55.99, 50.85, 47.11, 46.17, 44.43, 42.95, 39.52, 37.09, 36.38, 31.96, 29.68, 28.47, 28.36, 28.09, 25.99, 22.50, 22.41, 21.15, 17.44, 17.34 (seven peaks missing); HRMS (FD): Calcd for $C_{45}H_{61}NO_8$ $[M]^+$: 743.4397; found: 743.4407.

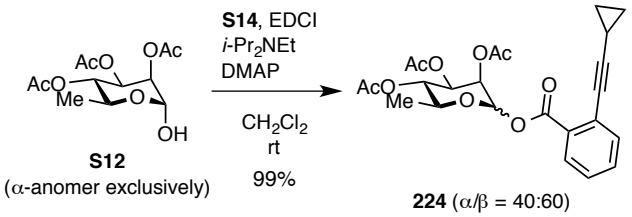
Compound S14



To a solution of ester **S13**[70] (834.2 mg, 4.10 mmol) in MeOH (21 mL) was added a 2.0 M aqueous LiOH solution (10.2 mL, 20.5 mmol) at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure. To the residue was added H_2O (20 mL), and the aqueous phase was extracted with Et_2O (10 mL×2) to remove neutral organic impurities. The aqueous phase was cooled to 0 °C, and acidified with 5% aqueous $KHSO_4$ solution (80 mL) until pH 3. After the layers were separated, the aqueous layer was extracted with Et_2O (20 mL×3). The combined organic layers were washed with H_2O (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Because carboxylic acid **S14**[71] (779.5 mg, yellow oil) was unstable on silica gel, the product was immediately used for the next step without further purification.

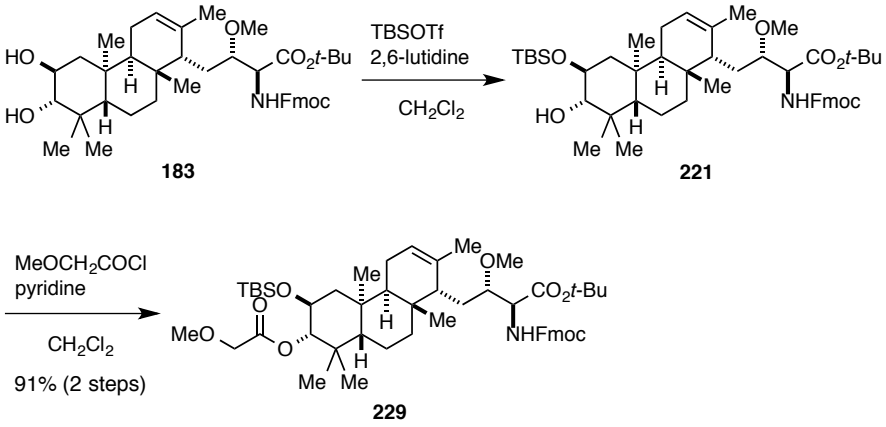
Data for S14 in a crude form: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.07 (1H, d, J = 7.5 Hz), 7.52 (1H, d, J = 8.0 Hz), 7.47 (1H, t, J = 7.5 Hz), 7.35 (1H, t, J = 7.5 Hz), 1.56-1.51 (1H, m), 0.96-0.88 (4H, m).

Compound 224



To a mixture of hemiacetal **S12** (650.0 mg, 2.24 mmol, α-anomer exclusively), carboxylic acid **S14** (763.5 mg, 4.10 mmol), *i*-Pr_2NEt (780 μL, 4.48 mmol), and *N,N'*-dimethyl-4-aminopyridine (DMAP) (273.7 mg, 2.24 mmol) in CH_2Cl_2 (22 mL) was added EDCI (786.0 mg, 4.10 mmol) at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL). The organic layers were washed with brine (50 mL), and dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~25 g, *n*-hexane/EtOAc = 4:1 to 3:1) afforded glycosyl alkynylbenzoate **224** (1.02 g, 2.22 mmol, 99%, α/β = 40:60) as a white amorphous foam: $[\alpha]_D^{23}$ −36.4 (c 1.13, $CHCl_3$); IR (ATR): ν 2970, 2931, 2897, 2857, 2359, 2341, 1735, 1718, 1507, 1457, 1369, 1246, 1155, 1083, 836, 775, 757, 741 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.92 (0.6H, d, *J* = 8.0 Hz), 7.82 (0.4H, d, *J* = 7.5 Hz), 7.51 (0.6H, d, *J* = 7.5 Hz), 7.47 (0.4H, d, *J* = 7.5 Hz), 7.46 (0.6H, t, *J* = 7.5 Hz), 7.42 (0.4H, t, *J* = 7.5 Hz), 7.34 (0.6H, t, *J* = 8.0 Hz), 7.27 (0.4H, t, *J* = 8.0 Hz), 6.28 (0.6H, d, *J* = 1.5 Hz), 6.07 (1H, s), 5.60 (0.4H, d, *J* = 1.2 Hz), 5.48 (0.6H, dd, *J* = 10.3, 3.5 Hz), 5.42 (0.6H, dd, *J* = 2.9, 2.3 Hz), 5.19 (1H, t, *J* = 10.3 Hz), 5.14 (0.4H, d, *J* = 3.5, 2.9 Hz), 4.17-4.11 (0.6H, m), 3.77-3.72 (0.4H, m), 2.24 (1.2H, s), 2.20 (1.8H, s), 1.32 (1.2H, s, *J* = 5.7 Hz), 1.27 (1.8H, s, *J* = 6.3 Hz), 0.96-0.86 (4H, m); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 170.16, 169.83, 169.81, 169.72, 169.68, 163.62, 163.24, 134.60, 134.13, 132.23, 132.21, 130.59, 130.41, 130.12, 129.81, 127.12, 126.85, 125.40, 125.04, 100.14, 100.04, 91.36, 90.75, 74.39, 74.01, 71.43, 70.70, 70.60, 70.31, 68.94, 68.85, 68.74, 68.63, 20.75, 20.73, 20.70, 20.67, 20.59, 20.51, 17.39, 17.33, 8.91, 8.89, 8.77, 0.57 (three peaks missing); HRMS (FD): Calcd for $C_{24}H_{26}O_9$ $[M]^+$: 458.1577; found: 458.1592.

Compound 229

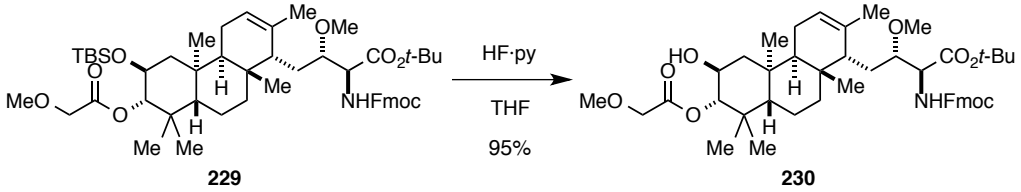


To a solution of diol **183** (30.0 mg, 42.7 μmol) in CH_2Cl_2 (0.85 mL) were added 2,6-lutidine (7.4 μL, 64.1 μmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (11 μL, 47.0 μmol) at –90 °C. After being stirred at –90 °C for 30 min, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (1 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (2 mL×3). The combined organic layers were washed with 5% aqueous $KHSO_4$ solution (2 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude alcohol **221** (36.6 mg, white amorphous foam) was used for the next step without further purification.

To a solution of the above crude alcohol **221** (36.6 mg) in CH_2Cl_2 (0.85 mL) were added pyridine (34 μL, 0.427 mmol) and methoxyacetyl chloride (20 μL, 0.214 mmol) at 0 °C. After being stirred at room temperature for 1.5 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (2 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (2 mL×3). The combined organic layers were washed with 5% aqueous $KHSO_4$ solution (2 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by preparative TLC (SiO_2, *n*-hexane/EtOAc = 3:1) afforded methoxyacetyl ester **229** (34.4 mg, 38.7 μmol, 91% for 2 steps) as a white amorphous foam: $[\alpha]_D^{26}$ +79.4 (c 0.83, $CHCl_3$); IR (ATR): ν 2949, 2930, 2858, 2365, 2343, 1755, 1725, 1507, 1450, 1369, 1285, 1251, 1191, 1156, 1130, 1113, 1084, 873, 837, 771, 758, 741 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.76 (2H, d, *J* = 8.0 Hz), 7.60 (2H, d, *J* = 7.5 Hz), 7.40 (2H, t, *J* = 7.5 Hz), 7.30 (2H, t, *J* = 7.5 Hz), 5.39 (1H, d, *J* = 8.6 Hz), 5.33 (1H, br), 4.67

(1H, d, *J* = 9.7 Hz), 4.61 (1H, dd, *J* = 9.2, 2.9 Hz), 4.41-4.34 (1H, m), 4.38 (1H, t, *J* = 6.9 Hz), 4.24 (1H, t, *J* = 6.9 Hz), 4.10 (1H, d, *J* = 16.1 Hz), 4.02 (1H, d, *J* = 16.1 Hz), 3.84 (1H, td, *J* = 9.7, 4.0 Hz), 3.48-3.44 (1H, m), 3.46 (3H, s), 3.45 (3H, s), 1.87 (2H, br), 1.74-1.49 (7H, m), 1.67 (3H, s), 1.50 (9H, s), 1.40 (1H, dd, *J* = 14.9, 10.9 Hz), 1.32-1.22 (3H, m), 1.07 (3H, s), 0.99 (3H, s), 0.91 (3H, s), 0.85 (9H, s), 0.83 (3H, s), 0.04 (3H, s), 0.02 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 169.99, 169.65, 156.03, 143.88, 143.79, 141.26, 137.84, 127.67, 127.03, 127.01, 125.15, 122.09, 119.95, 83.96, 82.58, 82.21, 69.88, 67.95, 67.08, 59.39, 58.47, 56.06, 50.86, 47.11, 46.25, 44.90, 42.55, 39.63, 37.10, 36.20, 32.02, 29.69, 28.57, 28.42, 28.09, 25.95, 25.67, 22.47, 22.42, 17.86, 17.60, 17.34, −4.33, −4.72 (eight peaks missing); HRMS (FD): Calcd for $C_{52}H_{77}NO_9Si$ $[M]^+$: 887.5368; found: 887.5378.

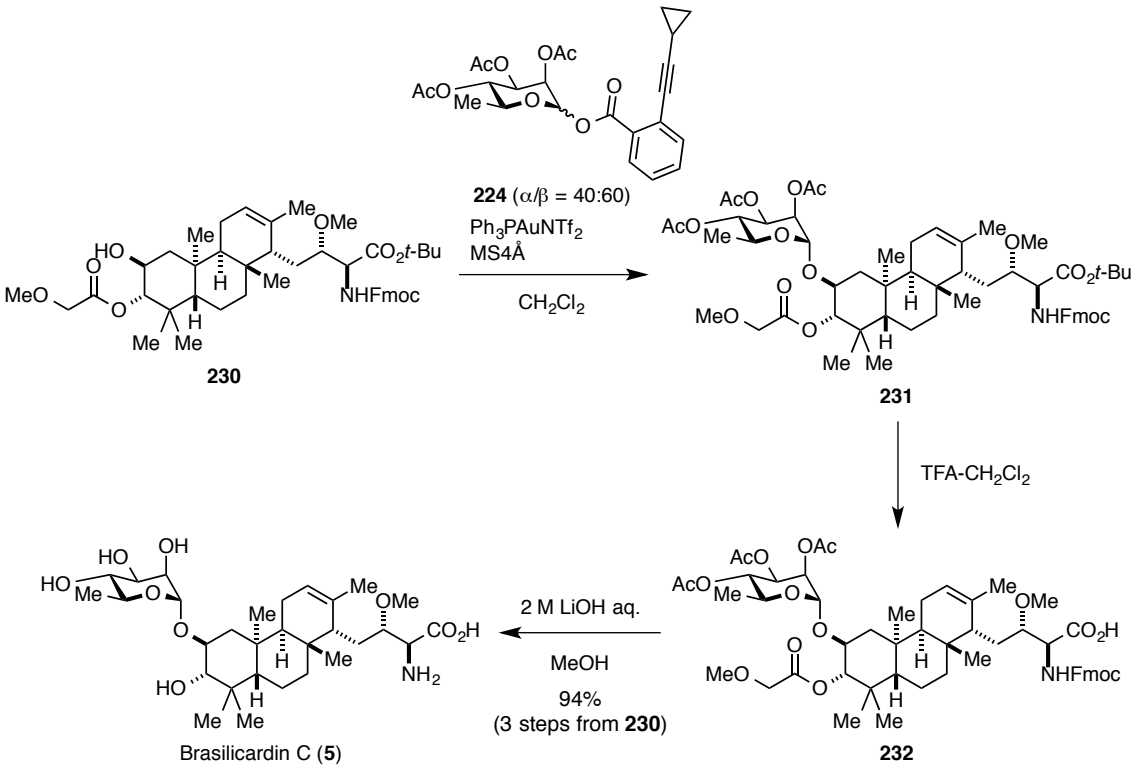
Compound 230



To a solution of methoxyacetyl ester **229** (32.0 mg, 36.0 μmol) in THF (1.0 mL) in a polypropylene test tube was added hydrogen fluoride-pyridine complex (HF·pyridine) (0.2 mL) at 0 °C. After being stirred at room temperature for 3 h, to the reaction mixture was added methoxytrimethylsilane (TMSOMe) (3.0 mL) slowly at 0 °C. The mixture was further stirred at room temperature for 2 h, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~5 g, *n*-hexane/EtOAc = 3:1 to 1:1) afforded alcohol **230** (26.5 mg, 34.2 μmol, 95%) as a white amorphous foam: $[\alpha]_D^{25}$ +79.3 (c 0.66, $CHCl_3$); IR (ATR): ν 3413, 2933, 2834, 2331, 1721, 1510, 1449, 1369, 1220, 1155, 1114, 1056, 988, 755 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.76 (2H, d, *J* = 7.5 Hz), 7.60 (2H, d, *J* = 7.5 Hz), 7.40 (2H, t, *J* = 7.5 Hz), 7.30 (2H, t, *J* = 7.5 Hz), 5.39 (1H, d, *J* = 9.2 Hz), 5.33 (1H, br), 4.61 (1H, dd, *J* = 8.6, 2.9 Hz), 4.57 (1H, d, *J* = 9.7 Hz), 4.41-4.34 (1H, m), 4.38 (1H, t, *J* = 6.9 Hz), 4.24 (1H, t, *J* = 6.9 Hz), 4.13 (2H, s), 3.81 (1H, br),

3.49-3.44 (1H, m), 3.48 (3H, s), 3.45 (3H, s), 1.94-1.86 (2H, m), 1.82 (1H, dd, J = 12.0, 3.4 Hz), 1.73-1.37 (8H, m), 1.67 (3H, s), 1.50 (9H, s), 1.33-1.25 (3H, m), 1.07 (3H, s), 0.93 (3H, s), 0.86 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.41, 169.65, 156.04, 143.87, 143.78, 141.26, 137.86, 127.68, 127.03, 125.13, 121.98, 119.95, 85.30, 82.61, 82.21, 69.81, 68.00, 67.08, 59.39, 58.43, 56.03, 50.85, 47.11, 46.16, 44.43, 42.96, 39.57, 37.09, 36.42, 31.99, 29.65, 28.50, 28.35, 28.09, 26.00, 22.51, 22.41, 17.46, 17.32 (seven peaks missing); HRMS (FD): Calcd for $C_{46}H_{63}NO_9$ $[M]^+$: 773.4503; found: 773.4515.

Brasilicardin C (5)



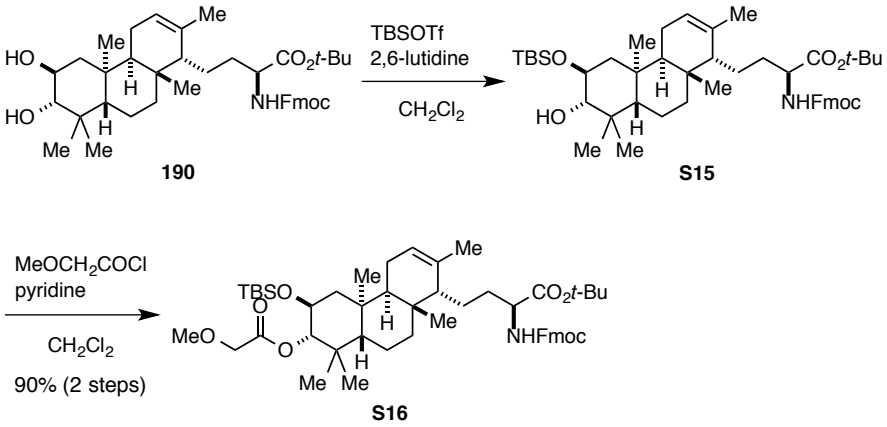
To a mixture of the protected aglycon **230** (15.0 mg, 19.4 μmol), glycosyl alkynylbenzoate **224** (13.3 mg, 29.1 μmol, α/β = 40:60), and freshly activated and powdered MS4Å (AW-300, 23.3 mg) in CH_2Cl_2 (1.9 mL) was added $Ph_3PAuNTf_2$ (2.9 mg, 3.88 μmol) at 0 °C. After being stirred at 0 °C for 5 min, the reaction mixture was filtered through a pad of Celite®, which was rinsed with CH_2Cl_2 (10 mL). After the mixture was concentrated under reduced pressure. Purification by flash column

chromatography (SiO_2~10 g, *n*-hexane/EtOAc = 4:1 to 3:2) afforded semi-pure glycoside **231** (21.7 mg, white amorphous foam). The semi-pure glycoside **231** was used for the next step without further purification.

To a solution of the above semi-pure glycoside **231** (21.7 mg) in CH_2Cl_2 (0.5 mL) was added TFA (0.5 mL) at 0 °C. After being stirred at room temperature for 6 h, the reaction mixture was concentrated under reduced pressure. The crude carboxylic acid **232** (22.4 mg, white amorphous foam) was used for the next step without further purification.

To a solution of the above crude carboxylic acid **232** (22.4 mg) in MeOH (0.97 mL) was added a 2.0 M aqueous LiOH solution (190 μL, 0.388 mmol) at 0 °C. After being stirred at 45 °C for 6 h, the reaction mixture was cooled to room temperature, and concentrated under reduced pressure. To the residue was added a 1.0 M aqueous HCl solution (0.25 mL) at 0 °C, and the solvent was removed by argon flow. Purification of the residue by reversed-phase flash column chromatography (Cosmosil 140C_{18}-PREP~5 g, H_2O/MeOH = 1:0 to 1:1) afforded brasilicardin C (**5**) (10.4 mg, 18.3 μmol, 94% for 3 steps) as a colorless amorphous solid: $[\alpha]_D^{28}$ +61.5 (c 0.71, MeOH) [lit.[6] $[\alpha]_D^{23}$ +65.0 (c 1.00, MeOH)]; IR (ATR): ν 3373, 2944, 2834, 1671, 1448, 1395, 1200, 1143, 1097, 1021, 645 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD): δ 5.32 (1H, br), 4.93 (1H, br), 4.43 (1H, d, *J* = 2.9 Hz), 3.92 (1H, dd, *J* = 2.9, 1.2 Hz), 3.77 (1H, dd, *J* = 10.9, 2.9 Hz), 3.69 (1H, dq, *J* = 9.2, 6.3 Hz), 3.64 (1H, m), 3.64 (1H, dd, *J* = 9.2, 3.4 Hz), 3.48 (3H, s), 3.37 (1H, t, *J* = 9.7 Hz), 2.97 (1H, d, *J* = 9.8 Hz), 1.87 (1H, br), 1.85 (1H, br), 1.76 (1H, dd, *J* = 12.6, 4.0 Hz), 1.71 (2H, m), 1.64 (3H, s), 1.61 (1H, m), 1.60 (1H, m), 1.55 (1H, m), 1.50 (1H, m), 1.39 (1H, m), 1.35 (1H, m), 1.33 (1H, m), 1.26 (1H, m), 1.23 (3H, d, *J* = 6.3 Hz), 1.08 (3H, s), 1.03 (3H, s), 0.97 (3H, s), 0.90 (3H, s); ^{13}C-NMR (125 MHz, CD_3OD): δ 170.14, 138.55, 123.51, 103.56, 83.32, 80.51, 79.00, 74.09, 72.47, 72.21, 69.85, 58.39, 54.78, 52.23, 47.33, 44.22, 44.11, 41.15, 38.50, 37.49, 31.93, 31.24, 29.22, 28.95, 27.02, 22.88, 22.58, 18.69, 17.88, 17.35; HRMS (ESI): Calcd for $C_{30}H_{52}NO_9$ $[M+H]^+$: 570.3637; found: 570.3647.

Compound S16

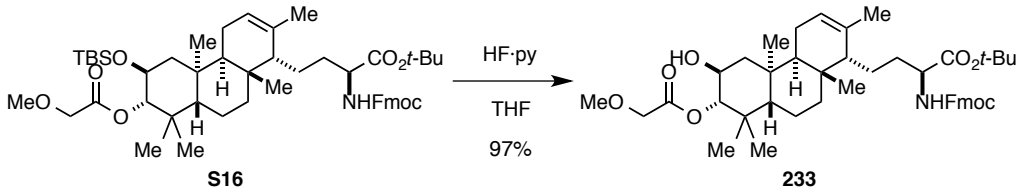


To a solution of diol **190** (30.0 mg, 44.6 μmol) in CH_2Cl_2 (0.89 mL) were added 2,6-lutidine (7.7 μL, 66.9 μmol) and TBSOTf (11 μL, 49.1 μmol) at –90 °C. After being stirred at –90 °C for 30 min, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (1 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (2 mL×3). The combined organic layers were washed with 5% aqueous $KHSO_4$ solution (2 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude alcohol **S15** (36.0 mg, white amorphous foam) was used for the next step without further purification.

To a solution of the above crude alcohol **S15** (36.0 mg) in CH_2Cl_2 (0.89 mL) were added pyridine (36 μL, 0.446 mmol) and methoxyacetyl chloride (20 μL, 0.223 mmol) at 0 °C. After being stirred at room temperature for 1.5 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (2 mL). After the layers were separated, the aqueous layer was extracted with Et_2O (2 mL×3). The combined organic layers were washed with 5% aqueous $KHSO_4$ solution (2 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Purification by preparative TLC (SiO_2, *n*-hexane/EtOAc = 4:1) afforded methoxyacetyl ester **S16** (34.6 mg, 40.3 μmol, 90% for 2 steps) as a white amorphous foam: $[\alpha]_D^{26}$ +90.9 (c 1.05, $CHCl_3$); IR (ATR): ν 2950, 2935, 2857, 2357, 2341, 2328, 1731, 1521, 1449, 1368, 1252, 1191, 1155, 1131, 1083, 837, 773, 760, 741 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.77 (2H, d, *J* = 7.5 Hz), 7.60 (1H, d, *J* = 6.9 Hz), 7.59 (1H, d, *J* = 6.9 Hz), 7.40 (2H, t, *J* = 7.5 Hz), 7.31 (2H, t, *J* = 7.5 Hz), 5.36 (1H, d, *J* = 8.6 Hz), 5.33 (1H, br),

4.66 (1H, d, *J* = 9.7 Hz), 4.39-4.33 (1H, m), 4.36 (1H, dd, *J* = 7.5, 4.6 Hz), 4.26 (1H, t, *J* = 6.9 Hz), 4.22 (1H, t, *J* = 6.9 Hz), 4.10 (1H, d, *J* = 16.1 Hz), 4.02 (1H, d, *J* = 16.7 Hz), 3.82 (1H, td, *J* = 9.8, 4.6 Hz), 3.46 (3H, s), 1.95-1.82 (2H, m), 1.79-1.61 (5H, m), 1.62 (3H, s), 1.57-1.44 (4H, m), 1.49 (9H, s), 1.37 (1H, br), 1.31-1.25 (3H, m), 1.05 (3H, s), 0.95 (3H, s), 0.89 (3H, s), 0.85 (9H, s), 0.82 (3H, s), 0.03 (3H, s), 0.01 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.49, 169.97, 155.76, 143.86, 143.82, 141.25, 136.79, 127.67, 127.02, 125.07, 122.43, 119.96, 83.98, 82.11, 69.87, 67.96, 67.01, 59.37, 55.08, 54.58, 47.12, 46.42, 44.85, 42.71, 39.60, 36.94, 36.40, 34.08, 29.92, 28.59, 28.35, 28.03, 25.86, 25.67, 22.85, 22.68, 17.84, 17.61, 17.46, −4.32, −4.73 (ten peaks missing); HRMS (FD): Calcd for $C_{51}H_{75}NO_8Si$ $[M]^+$: 857.5262; found: 857.5253.

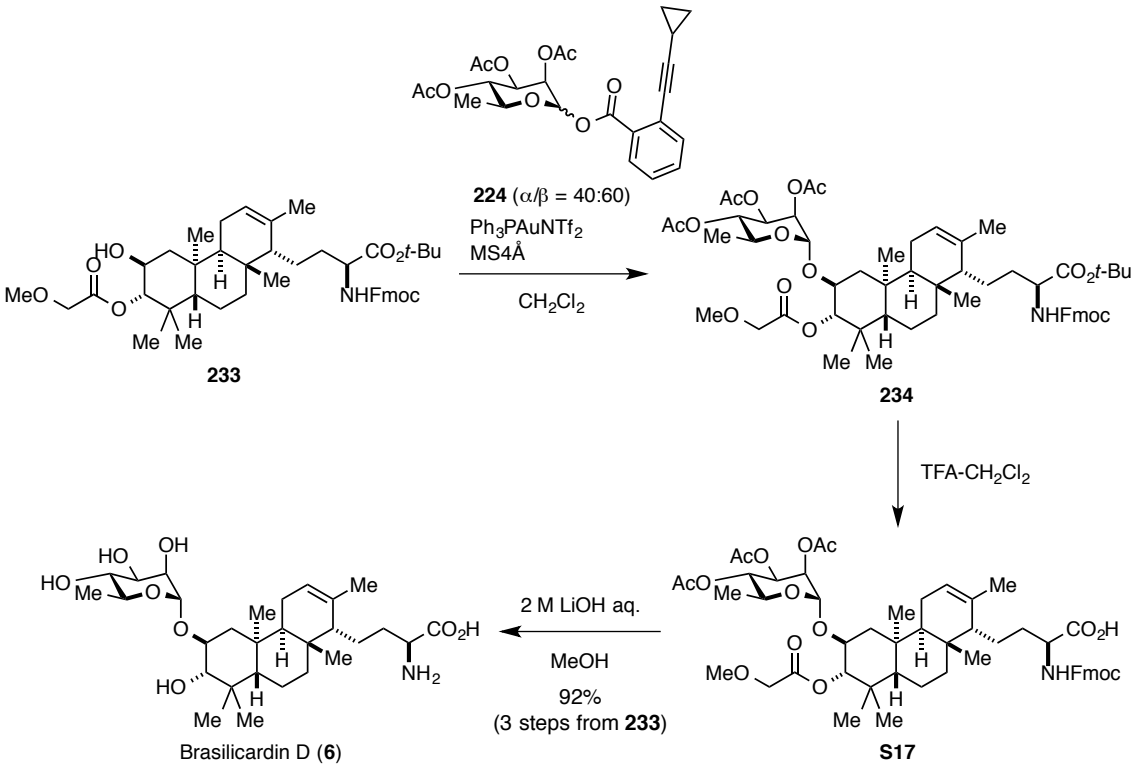
Compound 233



To a solution of methoxyacetyl ester **S16** (31.5 mg, 36.7 μmol) in THF (1.0 mL) in a polypropylene test tube was added HF·pyridine (0.2 mL) at 0 °C. After being stirred at room temperature for 3 h, to the reaction mixture was added TMSOMe (3.0 mL) at 0 °C. The mixture was further stirred at room temperature for 2 h, and concentrated under reduced pressure. Purification by preparative TLC (SiO_2, *n*-hexane/EtOAc = 3:2) afforded alcohol **233** (26.5 mg, 35.6 μmol, 97%) as a white amorphous foam: $[\alpha]_D^{26}$ +61.5 (c 0.71, $CHCl_3$); IR (ATR): ν 3437, 2962, 2945, 2875, 2365, 2343, 2334, 2324, 1718, 1522, 1450, 1368, 1222, 1197, 1155, 1129, 1051, 758, 742 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.76 (2H, d, *J* = 7.5 Hz), 7.60 (1H, d, *J* = 7.4 Hz), 7.59 (1H, d, *J* = 7.4 Hz), 7.40 (2H, t, *J* = 7.5 Hz), 7.30 (2H, t, *J* = 7.5 Hz), 5.36 (1H, d, *J* = 8.6 Hz), 5.33 (1H, br), 4.56 (1H, d, *J* = 9.7 Hz), 4.40-4.32 (1H, m), 4.36 (1H, dd, *J* = 10.9, 6.9 Hz), 4.26 (1H, t, *J* = 6.3 Hz), 4.22 (1H, t, *J* = 6.9 Hz), 4.12 (2H, s), 3.80 (1H, br), 3.47 (3H, s), 1.92-1.88 (2H, m), 1.84-1.48 (6H, m), 1.81 (1H, dd, *J* = 12.6, 4.0 Hz), 1.63 (3H, s), 1.49 (9H, s), 1.41 (1H, t, *J* = 12.0 Hz), 1.37-1.25 (2H, m),

1.33 (1H, dd, J = 12.6, 4.6 Hz), 1.05 (3H, s), 0.96 (3H, s), 0.91 (3H, s), 0.86 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 171.48, 171.39, 155.78, 143.82, 141.24, 136.80, 127.68, 127.01, 125.03, 122.32, 119.96, 85.31, 82.14, 69.79, 68.00, 67.00, 59.37, 55.07, 54.58, 47.12, 46.32, 44.37, 43.13, 39.53, 36.93, 36.62, 34.13, 29.89, 28.52, 28.27, 28.02, 25.89, 25.70, 22.83, 22.74, 17.46, 17.43 (eight peaks missing); HRMS (FD): Calcd for $C_{45}H_{61}NO_8$ $[M]^+$: 743.4397; found: 743.4403.

Brasilicardin D (6)



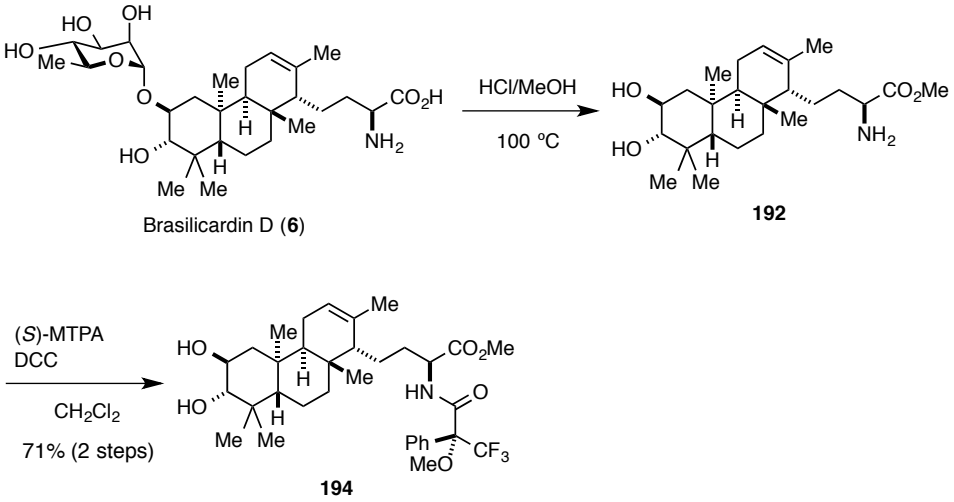
To a mixture of the protected aglycon **233** (16.0 mg, 21.5 μmol), glycosyl alkynylbenzoate **224** (14.8 mg, 32.3 μmol), and freshly activated and powdered MS4Å (AW-300, 25.8 mg) in CH_2Cl_2 (2.2 mL) was added $Ph_3PAuNTf_2$ (3.2 mg, 4.30 μmol) at 0 °C. After being stirred at 0 °C for 5 min, the reaction mixture was filtered through a pad of Celite®, which was rinsed with CH_2Cl_2 (10 mL). After the mixture was concentrated under reduced pressure. Purification by flash column chromatography (SiO_2~10 g, *n*-hexane/EtOAc = 4:1 to 1:1) afforded semi-pure glycoside **234** (22.7

mg, white amorphous foam). The semi-pure glycoside **234** was used for the next step without further purification.

To a solution of the above semi-pure glycoside **234** (22.7 mg) in CH_2Cl_2 (0.55 mL) was added TFA (0.55 mL) at 0 °C. After being stirred at room temperature for 6 h, the reaction mixture was concentrated under reduced pressure. The crude carboxylic acid **S17** (22.8 mg, white amorphous foam) was used for the next step without further purification.

To a solution of the above crude carboxylic acid **S17** (22.8 mg) in MeOH (1.1 mL) was added a 2.0 M aqueous LiOH solution (215 μL, 0.430 mmol) at 0 °C. After being stirred at 45 °C for 6 h, the reaction mixture was cooled to room temperature, and concentrated under reduced pressure. To the residue was added a 1.0 M aqueous HCl solution (0.25 mL) at 0 °C and the solvent was removed by argon flow. Purification of the residue by reversed-phase flash column chromatography (Cosmosil 140C_{18}-PREP~5 g, H_2O/MeOH = 1:0 to 1:3) afforded brasilicardin D (**6**) (10.7 mg, 19.8 μmol, 92% for 3 steps) as a colorless amorphous solid: $[\alpha]_D^{27}$ +75.6 (c 0.56, MeOH) [lit.[6] $[\alpha]_D^{20}$ +79.0 (c 0.50, MeOH)]; IR (ATR): ν 3401, 2935, 1674, 1533, 1437, 1200, 1142, 1053, 805, 668 cm^{-1}; ^{1}H-NMR (500 MHz, CD_3OD): δ 5.36 (1H, br), 4.94 (1H, br), 3.98 (1H, t, *J* = 5.2 Hz), 3.93 (1H, br), 3.70 (1H, dq, *J* = 9.2, 6.3 Hz), 3.67 (1H, m), 3.64 (1H, dd, *J* = 9.2, 2.9 Hz), 3.37 (1H, dd, *J* = 9.8, 9.2 Hz), 2.98 (1H, d, *J* = 9.8 Hz), 2.01 (2H, m), 1.88 (1H, m), 1.87 (1H, m), 1.79 (1H, dd, *J* = 12.6, 4.0 Hz), 1.77 (1H, m), 1.73 (1H, m), 1.67 (3H, s), 1.64 (1H, m), 1.61 (1H, m), 1.52 (1H, m), 1.39 (1H, m), 1.34 (2H, m), 1.30 (1H, m), 1.29 (1H, m), 1.24 (3H, t, *J* = 6.3 Hz), 1.12 (3H, s), 1.00 (3H, s), 0.97 (3H, s), 0.90 (3H, s); ^{13}C-NMR (125 MHz, CD_3OD): δ 171.75, 137.84, 123.73, 103.60, 83.37, 79.11, 74.10, 72.48, 72.23, 69.87, 56.45, 54.27, 47.60, 44.56, 44.10, 41.12, 38.22, 37.75, 32.67, 31.46, 29.28, 28.83, 26.93, 26.73, 23.25, 23.11, 18.83, 17.90, 17.40; HRMS (ESI): Calcd for $C_{29}H_{50}NO_8$ $[M+H]^+$: 540.3531; found: 540.3543.

Compound 194

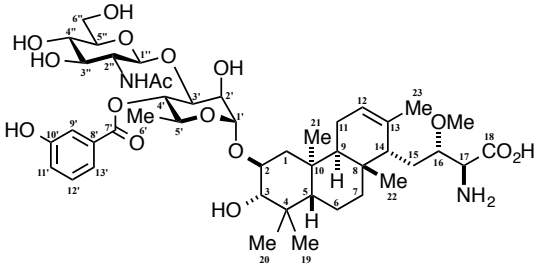


Synthetic brasilicardin D (**6**) (1.5 mg, 2.78 μmol) was dissolved in HCl in MeOH (5–10%, 0.50 mL, purchased from TCI) at room temperature in a test tube with screw cap. After being stirred at 100 °C for 24 h, the reaction mixture was concentrated under reduced pressure. To the residue was added a saturated aqueous $NaHCO_3$ solution (1 mL). After the aqueous layer was extracted with EtOAc (1 mL×3), the combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. The crude methyl ester **192** (1.3 mg, yellow amorphous foam) was used for the next step without further purification.

To a solution of the above crude methyl ester **192** (1.3 mg) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ((*S*)-(+)-MTPA) (0.10 M in CH_2Cl_2, 83 μL, 83.4 μmol) in CH_2Cl_2 (0.15 mL) was added DCC (0.10 M in CH_2Cl_2, 83 μL, 83.4 μmol) at room temperature. After being stirred at room temperature for 2 h, the mixture was concentrated under reduced pressure. Purification by preparative TLC (SiO_2, *n*-hexane/EtOAc = 1:2) afforded (*S*)-MTPA amide **194** (1.3 mg, 1.98 μmol, 71% for 2 steps) as a white powder.

^{1}H-NMR spectrum of synthetic methyl ester **192** was identical to its derived from natural brasilicardin D (**6**) and ^{1}H-NMR spectrum of **194** revealed no epimerization.

Table S1. Comparison of ^{1}H- and ^{13}C-NMR Spectra between Natural and Synthetic Brasilicardin A (**3**) in CD_3OD. [3]



Brasilicardin A (**3**)

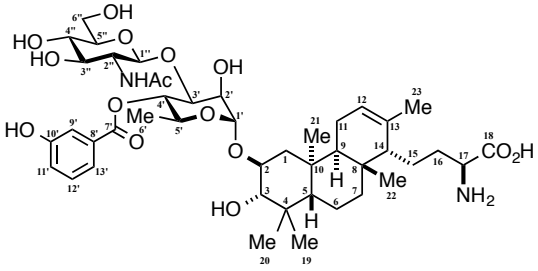
	^{1}H-NMR		^{13}C-NMR	
	Chemical shifts in ppm [multiplicity, *J* (Hz)]		Chemical shifts in ppm	
Carbon	Natural[a]	Synthetic[b]	Natural[a]	Synthetic[c]
1 (a)	1.49 (m)	1.45 (m)	44.53	44.00
1 (b)	1.82 (m)	1.79 (dd, 12.4, 4.1)		
2	3.73 (t, 9.0)	3.69 (m)	80.31	79.78
3	3.06 (d, 9.7)	3.02 (d, 9.6)	83.83	83.30
4			41.70	41.19
5	1.69 (m)	1.63 (m)	19.22	18.71
6 (a)	1.69 (m)	1.63 (m)	46.75	44.30
6 (b)	1.78 (m)	1.74 (m)		
7	1.41 (m)	1.74, 1.34 (m)	31.78	31.28
8			39.05	38.54
9	1.32 (m)	1.27 (m)	47.87	47.39
10			38.09	37.59
11	1.93 (brs)	1.89, 1.88 (br)	27.57	27.06
12	5.39 (brs)	5.35 (brs)	124.08	123.62
13			139.04	138.46
14	1.61 (m)	1.57 (m)	52.81	52.29
15 (a)	1.41 (m)	1.40 (m)	32.46	32.01
15 (b)	1.49 (m)	1.51 (m)		
16	3.81 (dd, 11.4, 3.3)	3.78 (dd, 11.7, 2.1)	81.07	80.47
OMe	3.53 (s)	3.49 (s)	58.90	58.49
17	4.46 (d, 3.5)	4.44 (d, 2.7)	55.36	54.66
18			170.62	169.89
19	0.97 (s)	0.92 (s)	17.82	17.31
20	1.04 (s)	1.00 (s)	29.74	29.23
21	1.14 (s)	1.10 (s)	29.42	28.91
22	1.09 (s)	1.05 (s)	23.06	22.54
23	1.69 (s)	1.65 (s)	23.13	22.63
1'	5.06 (d, 1.1)	5.02 (br)	103.62	103.11
2'	4.46 (dd, 3.1, 1.1)	4.34 (br)	72.60	72.10
3'	4.12 (dd, 9.8, 3.1)	4.08 (dd, 9.6, 2.8)	80.35	79.86
4'	5.31 (t, 9.8)	5.27 (t, 9.7)	74.64	74.13
5'	4.05 (dq, 9.8, 6.2)	4.01 (dq, 9.6, 6.2)	68.58	68.07
6'	1.16 (d, 6.2)	1.12 (d, 6.2)	18.30	17.80
7'			167.50	167.01
8'			132.96	132.44
9'	7.51 (t, 1.4)	7.47 (br)	117.94	117.44
10'			159.50	158.99
11'	7.10 (dd, 7.6, 1.4)	7.06 (dd, 8.2, 2.0)	122.04	121.54
12'	7.38 (t, 7.6)	7.34 (t, 7.6)	131.38	130.88
13'	7.59 (dd, 7.6, 1.4)	7.55 (d, 7.6)	122.50	122.00
1"	4.58 (d, 8.5)	4.53 (d, 8.3)	104.54	104.05
2"	3.58 (dd, 10.0, 8.5)	3.55 (dd, 9.6, 8.9)	58.02	57.50
NHAc	1.54 (s)	1.49 (s)	23.42	22.89
			174.55	174.06
3"	3.41 (dd, 10.0, 8.1)	3.37 (dd, 9.6, 8.3)	75.80	75.31
4"	3.35 (m)	3.31 (m)	72.33	71.82
5"	3.33 (m)	3.28 (m)	78.30	77.78
6" (a)	3.73 (d, 11.6)	3.69 (d, 11.7)	63.07	62.56
6" (b)	3.93 (dd, 11.6, 1.6)	3.89 (dd, 12.4, 1.4)		

a) Reported in Kobayashi, J. *et al*. *J. Org. Chem.* **1998**, *63*, 6900. Internal reference was not indicated.

b) 600 MHz (CH_3OD, d_H 3.31).

c) 151 MHz (CD_3OD, d_c 49.0).

Table S2. Comparison of ^{1}H- and ^{13}C-NMR Spectra between Natural and Synthetic Brasilicardin B (**4**) in CD_3OD. [6]



Brasilicardin B (**4**)

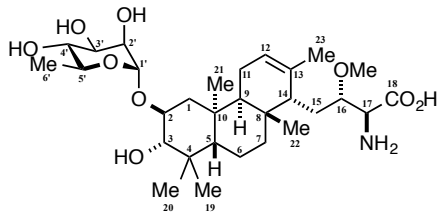
	^{1}H-NMR		^{13}C-NMR	
	Chemical shifts in ppm [multiplicity, *J* (Hz)]		Chemical shifts in ppm	
Carbon	Natural[a]	Synthetic[b]	Natural[a]	Synthetic[c]
1 (a)	1.85 (m)	1.82 (dd, 12.0, 4.0)	44.76	44.01
1 (b)	1.49 (m)	1.45 (m)		
2	3.76 (m)	3.70 (m)	80.60	79.87
3	3.06 (d, 9.3)	3.02 (d, 9.8)	84.15	83.36
4			41.89	41.17
5	1.67 (m)	1.63 (m)	45.49	44.65
6 (a)	1.77 (m)	1.75 (m)	19.62	18.85
6 (b)	1.67 (m)	1.65 (m)		
7 (a)	1.90 (m)	1.78 (m)	32.25	31.51
7 (b)	1.38 (m)	1.32 (m)		
8			38.89	38.25
9	1.43 (m)	1.35 (m)	48.15	47.62
10			38.56	37.85
11 (a)	1.94 (m)	1.91 (m)	27.71	26.86
11 (b)	1.94 (m)	1.90 (m)		
12	5.38 (m)	5.38 (br)	124.05	123.77
13			139.06	137.84
14	1.33 (m)	1.30 (m)	57.50	56.55
15 (a)	1.67 (m)	1.54 (m)	28.26	26.96
15 (b)	1.46 (m)	1.37 (m)		
16	1.99 (m)	2.00 (m)	34.64	32.82
OMe				
17	3.54 (t, 5.6)	3.99 (t, 5.7)	57.60	56.77
18			175.13	174.08
19	0.96 (s)	0.93 (s)	18.19	17.36
20	1.04 (s)	1.01 (s)	30.16	29.32
21	1.18 (s)	1.13 (s)	29.52	28.79
22	1.05 (s)	1.03 (s)	24.22	23.29
23	1.72 (s)	1.67 (s)	24.19	23.12
1'	5.08 (brs)	5.02 (br)	103.79	103.13
2'	4.39 (brd, 3.0)	4.34 (br)	72.71	71.83
3'	4.13 (dd, 9.6, 3.0)	4.07 (dd, 9.2, 2.3)	80.80	79.87
4'	5.31 (t, 9.6)	5.28 (t, 9.8)	74.83	74.14
5'	4.06 (dq, 9.6, 6.0)	4.00 (dq, 9.8, 6.3)	68.73	68.08
6'	1.17 (d, 6.0)	1.13 (d, 6.3)	18.59	17.81
7'			168.12	167.01
8'			132.94	132.44
9'	7.52 (t, 1.9)	7.47 (br)	118.31	117.44
10'			159.69	158.99
11'	7.11 (dd, 8.1, 1.9)	7.06 (dd, 8.0, 1.7)	122.56	121.54
12'	7.38 (t, 8.1)	7.34 (t, 8.1)	131.69	130.88
13'	7.59 (d, 8.1)	7.55 (d, 8.1)	122.84	122.00
1"	4.57 (d, 8.1)	4.53 (d, 8.0)	105.00	104.05
2"	3.61 (dd, 9.3, 8.1)	3.54 (dd, 9.8, 9.2)	57.86	57.50
NHAc	1.52 (s)	1.50 (s)	23.41	22.64
			175.00	174.04
3"	3.43 (dd, 9.3, 8.1)	3.43 (dd, 9.3, 8.1)	76.04	75.31
4"	3.36 (m)	3.36 (m)	72.71	72.10
5"	3.36 (m)	3.31 (m)	78.35	77.79
6" (a)	3.93 (d, 11.8)	3.89 (d, 10.9)	63.04	62.56
6" (b)	3.74 (m)	3.69 (dd, 11.5, 4.6)		

a) Reported in Kobayashi, J. *et al*. *Bioorg. Med. Chem.* **2004**, *12*, 5545.
The 3.35 ppm resonance of residual CH_3OH and 49.8 ppm of CD_3OD were used as internal references.

b) 500 MHz (CD_3OD, d_H 3.31).

c) 151 MHz (CD_3OD, d_c 49.0).

Table S3. Comparison of ^{1}H- and ^{13}C-NMR Spectra between Natural and Synthetic Brasilicardin C (**5**) in CD_3OD. [6]



Brasilicardin C (**5**)

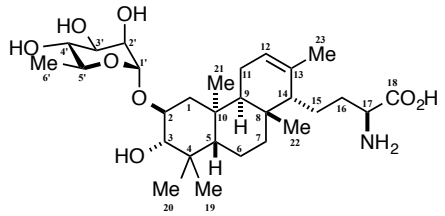
	^{1}H-NMR		^{13}C-NMR	
	Chemical shifts in ppm [multiplicity, *J* (Hz)]		Chemical shifts in ppm	
Carbon	Natural[a]	Synthetic[b]	Natural[a]	Synthetic[c]
1 (a)	1.82 (dd, 12.8, 4.4)	1.76 (dd, 12.6, 4.0)	44.78	44.11
1 (b)	1.46 (m)	1.39 (m)		
2	3.70 (m)	3.64 (m)	79.83	79.00
3	3.03 (d, 9.4)	2.97 (d, 9.8)	84.08	83.32
4			41.84	41.15
5	1.66 (m)	1.61 (m)	44.99	44.22
6 (a)	1.78 (m)	1.71 (m)	19.40	18.69
6 (b)	1.65 (m)	1.60 (m)		
7 (a)	1.78 (m)	1.71 (m)	31.98	31.24
7 (b)	1.38 (m)	1.33 (m)		
8			39.19	38.50
9	1.31 (m)	1.26 (m)	48.02	47.33
10			38.20	37.49
11 (a)	1.92 (m)	1.87 (br)	27.74	27.02
11 (b)	1.92 (m)	1.85 (br)		
12	5.38 (m)	5.33 (m)	124.22	123.51
13			139.26	138.55
14	1.61 (m)	1.55 (m)	53.00	52.23
15 (a)	1.57 (m)	1.50 (m)	32.71	31.93
15 (b)	1.46 (m)	1.35 (m)		
16	3.82 (dd, 10.8, 3.0)	3.77 (dd, 10.9, 2.9)	81.26	80.51
OMe	3.53 (s)	3.48 (s)	59.29	58.39
17	4.48 (d, 3.5)	4.43 (d, 2.9)	55.63	54.78
18			170.88	170.14
19	0.95 (s)	0.90 (s)	18.11	17.35
20	1.02 (s)	0.97 (s)	30.01	29.22
21	1.13 (s)	1.08 (s)	29.64	28.95
22	1.08 (s)	1.03 (s)	23.70	22.88
23	1.70 (s)	1.64 (s)	23.36	22.58
1'	4.99 (brs)	4.93 (brs)	104.18	103.56
2'	3.99 (m)	3.92 (dd, 2.9, 1.2)	72.93	72.21
3'	3.70 (m)	3.64 (dd, 9.2, 3.4)	73.22	72.47
4'	3.42 (t, 9.4)	3.37 (t, 9.7)	74.78	74.09
5'	3.75 (dq, 9.4, 6.4)	3.69 (dq, 9.2, 6.3)	70.58	69.85
6'	1.28 (d, 6.4)	1.23 (d, 6.3)	18.62	17.88

a) Reported in Kobayashi, J. *et al*. *Bioorg. Med. Chem.* **2004**, *12*, 5545.
The 3.35 ppm resonance of residual CH_3OH and 49.8 ppm of CD_3OD were used as internal references.

b) 500 MHz (CD_3OD, d_H 3.31).

c) 125 MHz (CD_3OD, d_c 49.0).

Table S4. Comparison of ^{1}H- and ^{13}C-NMR Spectra between Natural and Synthetic Brasilicardin D (**6**) in CD_3OD. [6]



Brasilicardin D (**6**)

	^{1}H-NMR		^{13}C-NMR	
	Chemical shifts in ppm [multiplicity, *J* (Hz)]		Chemical shifts in ppm	
Carbon	Natural[a]	Synthetic[b]	Natural[a]	Synthetic[c]
1 (a)	1.82 (dd, 12.8, 4.4)	1.76 (dd, 12.6, 4.0)	44.78	44.11
1 (b)	1.46 (m)	1.39 (m)		
2	3.70 (m)	3.64 (m)	79.83	79.00
3	3.03 (d, 9.4)	2.97 (d, 9.8)	84.08	83.32
4			41.84	41.15
5	1.66 (m)	1.61 (m)	44.99	44.22
6 (a)	1.78 (m)	1.71 (m)	19.40	18.69
6 (b)	1.65 (m)	1.60 (m)		
7 (a)	1.78 (m)	1.71 (m)	31.98	31.24
7 (b)	1.38 (m)	1.33 (m)		
8			39.19	38.50
9	1.31 (m)	1.26 (m)	48.02	47.33
10			38.20	37.49
11 (a)	1.92 (m)	1.87 (br)	27.74	27.02
11 (b)	1.92 (m)	1.85 (br)		
12	5.38 (m)	5.33 (m)	124.22	123.51
13			139.26	138.55
14	1.61 (m)	1.55 (m)	53.00	52.23
15 (a)	1.57 (m)	1.50 (m)	32.71	31.93
15 (b)	1.46 (m)	1.35 (m)		
16	3.82 (dd, 10.8, 3.0)	3.77 (dd, 10.9, 2.9)	81.26	80.51
OMe	3.53 (s)	3.48 (s)	59.29	58.39
17	4.48 (d, 3.5)	4.43 (d, 2.9)	55.63	54.78
18			170.88	170.14
19	0.95 (s)	0.90 (s)	18.11	17.35
20	1.02 (s)	0.97 (s)	30.01	29.22
21	1.13 (s)	1.08 (s)	29.64	28.95
22	1.08 (s)	1.03 (s)	23.70	22.88
23	1.70 (s)	1.64 (s)	23.36	22.58
1'	4.99 (brs)	4.93 (brs)	104.18	103.56
2'	3.99 (m)	3.92 (dd, 2.9, 1.2)	72.93	72.21
3'	3.70 (m)	3.64 (dd, 9.2, 3.4)	73.22	72.47
4'	3.42 (t, 9.4)	3.37 (t, 9.7)	74.78	74.09
5'	3.75 (dq, 9.4, 6.4)	3.69 (dq, 9.2, 6.3)	70.58	69.85
6'	1.28 (d, 6.4)	1.23 (d, 6.3)	18.62	17.88

a) Reported in Kobayashi, J. *et al*. *Bioorg. Med. Chem.* **2004**, *12*, 5545.
The 3.35 ppm resonance of residual CH_3OH and 49.8 ppm of CD_3OD were used as internal references.

b) 500 MHz (CD_3OD, d_H 3.31).

c) 125 MHz (CD_3OD, d_c 49.0).

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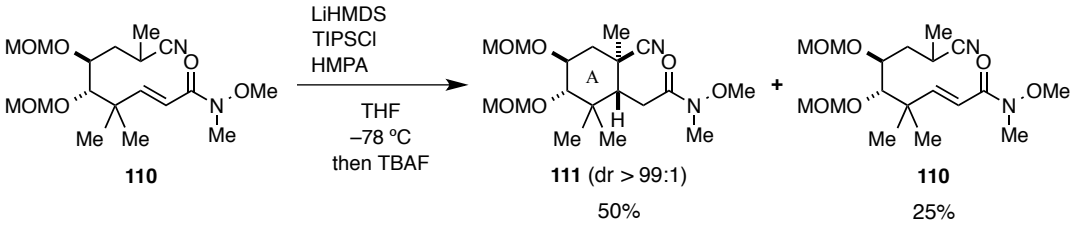

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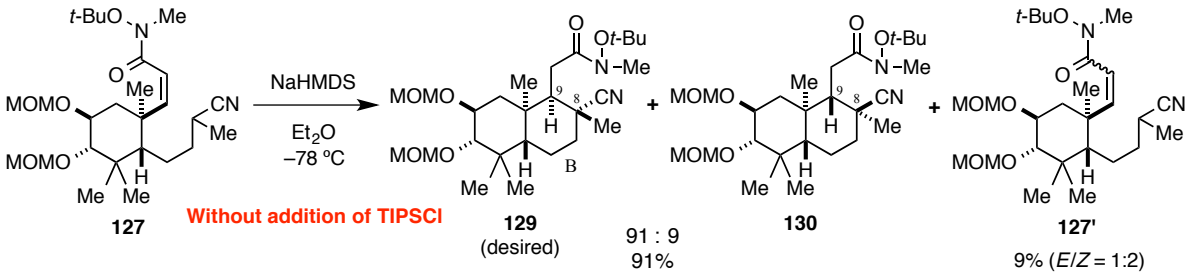

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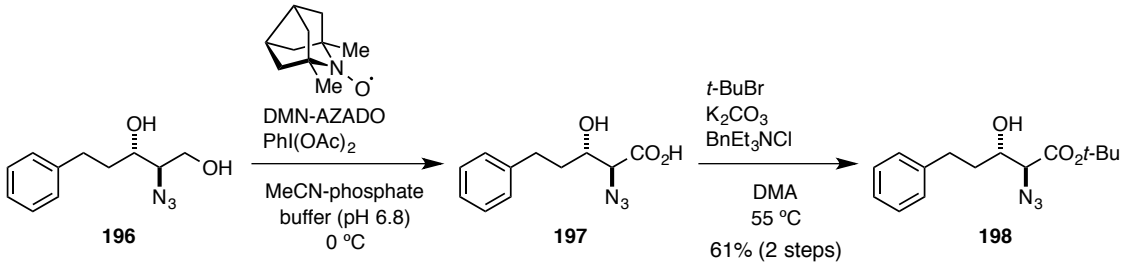
52) The model compound **196** was site-selectivly oxidized by DMN-AZADO catalyst to hydroxyl carboxylic acid **197** without affecting the secondary alcohol. The crude carboxylic acid **197** was esterified with *tert*-butyl bromide to give *t*-butyl ester **198** in good yield.



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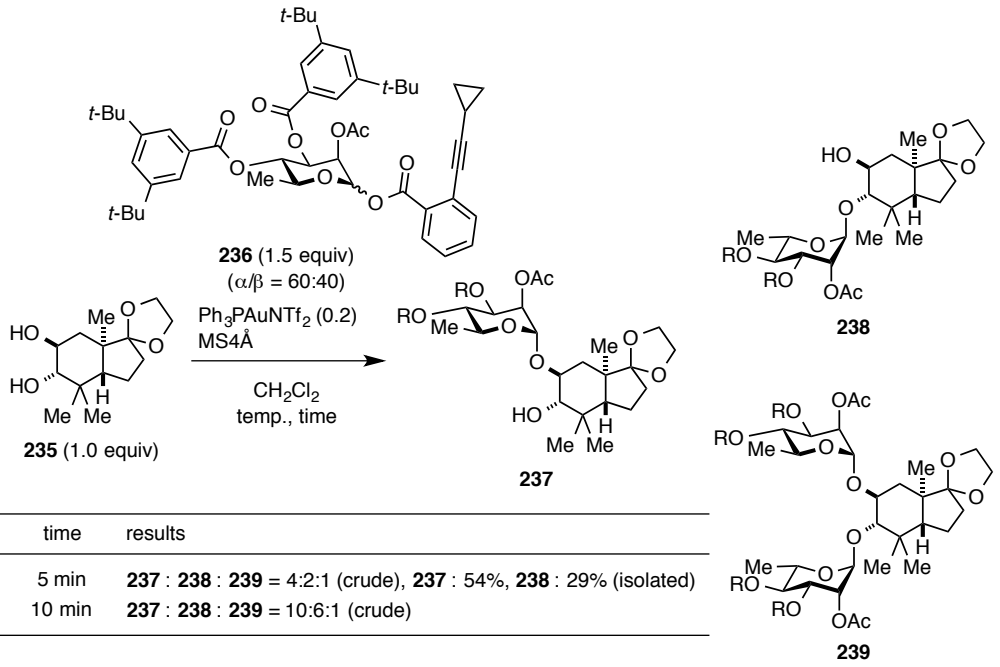
65) Given the successful regioselective glycosylation of disaccharide **209** (cf. Scheme 46), the author focused on the bulkiness of a glycosyl donor. Thus, the glycosylation with the rhamnose derivative **236** which possessed two bulky benzoates was attempted. Coupling of bulky *o*-cyclopropylethynylbenzoate **236** with the A-ring model diol **235** proceeded in good yields, however, the regioselectivity was not improved so much.



entry	temp.	time	results
1	rt	5 min	**237** : **238** : **239** = 4:2:1 (crude), **237** : 54%, **238** : 29% (isolated)
2	–40 °C	10 min	**237** : **238** : **239** = 10:6:1 (crude)

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68) As a note, it might be possible to use chloroacetyl group as a protecting group at the C3 alcohol, chloroactylation of the alcohol resulted in lower yield with several side products in the preliminary attempts using a model substrate.

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