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HOKKAIDO UNIVERSITY
DISSERTATION

Asymmetric Total Synthesis of Brasilicardins
(ブラシリカルジン類の不斉全合成)

Ryusei Itoh

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. However, when neural functions of calcineurin are inhibited at the same time, various side effects such as nephrotoxicity and arterial hypertension are observed. Therefore, the development of novel immunosuppressive drugs without such side effects is one of the important clinical and social issues today.

![Figure 1. Representative immunosuppressive drugs](image)
Brasilicardin A (3) is a natural product, which was isolated from the cultured broth of the pathogenic actinomycete *Nocardia brasilensis* 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).\(^6,7\)

![Figure 2. Structures of brasilicardins A–D](image_url)
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](image)

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

<table>
<thead>
<tr>
<th>Compounds</th>
<th>R²</th>
<th>R³</th>
<th>MLR</th>
<th>L1210</th>
<th>MOLT4</th>
<th>Ball-1</th>
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<tbody>
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<td>NH₂</td>
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<tr>
<td>9</td>
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<th>DLD-1</th>
<th>Lu65</th>
<th>MOLT4</th>
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<tr>
<td>12</td>
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<td>NHCbz</td>
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<tr>
<td>17</td>
<td>NHEt</td>
<td>4.28</td>
<td>50</td>
<td>17.4</td>
<td>1.25</td>
</tr>
</tbody>
</table>

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

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). 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](image)

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). 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.
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.

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). 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). 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.
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 Danisefsky’s strategy (Scheme 5).\cite{Anada1990, Anada1992} 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.\textsuperscript{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,\textsuperscript{12} coupling of trichloroacetimidate 37 with the glycosyl donor 51 using boron trifluoride diethyl ether complex (BF\textsubscript{3}·OEt\textsubscript{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,\textsuperscript{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).\textsuperscript{16}

\begin{align*}
\text{Scheme 6. Total synthesis of brasilicardins A and C by the Anada and Hashimoto’s group}
\end{align*}

\textit{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.\textsuperscript{17}
Ireland and co-workers succeeded in the first chemical synthesis of the \textit{anti-syn-anti}-fused perhydrophenanthrene in their studies directed toward the total synthesis of fusidic acid (Scheme 7).\footnote{18} Thus, alkene 55, which was prepared via Robinson annulation, was oxidized with meta-chloroperoxybenzoic acid (mCPBA) to give epoxide 56. Subsequently, epoxide 56 was converted to the desired ketone 57 via the ring opening of epoxide induced by BF\textsubscript{3}·OEt\textsubscript{2} followed by hydride shift.

![Scheme 7. Approach by the Ireland’s group](image)

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

![Scheme 8. Approach by the Dauben’s group](image)

Corey and Virgil have synthesized alkene 63 containing the \textit{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).\footnote{20}
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).\textsuperscript{21} Initially, the trans-decalin skeleton 67 was constructed by polyene cyclization using stoichiometric use of \( \text{Hg(OTf)}_2 \) 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.
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). 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 °C 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](image)

Jung, Houk and co-workers constructed the anti-syn-anti-fused perhydrophenanthrene skeleton via a bicyclic transannular Diels–Alder reaction (Scheme 12). 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.
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 \(\alpha\)-methylidene ester \(79\) with lithium tri-sec-butylborohydride (L-Selectride\(^\circledR\)) in the presence of HMPA at \(-78\,^\circ\)C in THF afforded the six-membered 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-membered 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 \(0\,^\circ\)C 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 12.** Approach by the Jung and Houk’s group
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).\(^\text{25}\) Thus, \(\alpha,\beta\)-unsaturated lactone 87 possessing an alkanenitrile side chain, was prepared from (±)-\(\alpha\)-ionone (86). When 87 was treated with NaHMDS in the presence of HMPA at \(-78^\circ\text{C}\) in THF, 87 underwent the intramolecular Michael addition to give 88 having a quaternary carbon atom.\(^\text{26}\) Then, lactone 88 was converted to the \(\alpha,\beta\)-unsaturated ester 89 possessing exocyclic dibromoalkene. When 89 was treated with Me\(_2\)CuLi, the C-ring formation stereoselectively occurred to afford the tricyclic compound 91 in 39% yield.\(^\text{27}\) 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.
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 \( \alpha,\beta \)-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 \( \alpha,\beta \)-unsaturated ester 95 through a novel intramolecular Michael addition promoted by Me\(_2\)CuLi.\(^{27}\) 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 (\(Z\))-\(\alpha,\beta\)-unsaturated ester 97. Ester 97 would be derived from nitrile 98. The A-ring could be constructed by a similar Michael addition of acyclic (\(E\))-\(\alpha,\beta\)-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 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 quantitatively gave the optically active diol 103 with 95% ee. 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 chemocontrol, the author focused on N-methoxy-N-methylamides (commonly named Weinreb amides).³¹
The intramolecular Michael addition of $\alpha,\beta$-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., ($E$-$\alpha,\beta$-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 $-78^\circ$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.\textsuperscript{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 $\alpha,\beta$-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 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 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 \( \text{117} \) using \( N,O \)-dimethylhydroxylamine hydrochloride (MeONHMe·HCl) and isopropylmagnesium chloride.\(^{35}\)

![Synthesis Scheme 21](image)

**Scheme 21. Synthesis of the cyclization precursor \( \text{117} \)**

The second intramolecular nitrile Michael addition of \( \text{117} \) was the crucial factor in the present synthesis; thus, the author explored the optimal reaction conditions for this step (Scheme 22). Firstly, \((Z)\)-\(\alpha,\beta\)-unsaturated Weinreb amide \( \text{117} \) was treated with NaHMDS in the presence of TIPSCl and HMPA in THF at \(-78\) °C, which produced \( O \)-silyl \( N,O \)-ketene acetal \( \text{118} \) in situ. Upon addition of TBAF to \( \text{118} \) in situ, a mixture of the desired cyclization product \( \text{119} \) and its \( C8,9 \)-diastereomer \( \text{120} \) 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\(_2\)O as a solvent without addition of HMPA gave superior regioselectivity (\( \text{dr} = 80:20 \)). The stereochemistry of the desired product \( \text{119} \) was determined by the NOESY experiment.
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).\textsuperscript{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.

\textbf{Scheme 22.} Solvent effects in the second intramolecular Michael addition

![Scheme 22](image-url)
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. Similar to the cyclization of 117, the cyclization of 127 proceeded by the treatment of a mixture of 127 and TIPSCI with NaHMDS in Et₂O 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.

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 TIPSCI were all indispensable to achieve a high level of stereocontrol at the newly formed stereocenters of the B-ring product 129.

Scheme 24. Optimized conditions by using O-t-Bu substituted modified Weinreb amide
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. 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 Me₂CuLi 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 hindered 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 CBr₄ and PPh₃, 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). Thus, treating 95 with $\text{Me}_2\text{CuLi}$ (5 equiv.) in $\text{Et}_2\text{O}$ at $-78 \, ^\circ\text{C}$ for 30 min generated the (Z)-vinylcopper species 139 in situ. After the reaction mixture was warmed up to $-40 \, ^\circ\text{C}$ and then stirred at this temperature for 1 h, the subsequent conjugate addition of 139 to the $\alpha,\beta$-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 $\text{TS-139}$ over $\text{TS-139}'$ to avoid steric repulsion between the hydrogen at the $\alpha$ position of the unsaturated ester and the axial methyl group at the C8 position.

![Figure 4. Suggested transition state models of cyclization of 95](image)

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 $\alpha$-cyano carbanion to an acyclic ($E$)-$\alpha,\beta$-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 $\alpha,\beta$-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 (Et₂O) was distilled from sodium benzophenone ketyl. Anhydrous acetone, acetonitrile (MeCN), 1,2-dichloroethane ((CH₂Cl)₂), dichloromethane (CH₂Cl₂), N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), ethanol (EtOH), methanol (MeOH), pyridine, and toluene were purchased from Kanto Chemical Co. Diisopropylamine, diisopropylethylamine (i-Pr₂NEt) and triethylamine (Et₃N) was distilled from CaH₂ under argon and stored in the presence of NaOH (pellets). Hexamethylphosphoric triamide (HMPA) was distilled from CaH₂ under argon and stored in the presence of MS4Å. All other reagents and solvents were used as received from commercial sources without further purification.

¹H-NMR spectra were measured using a JEOL ECA-500 (500 MHz) or JEOL ECA-600 (600 MHz) in CDCl₃ (δH 7.26), CD₃OD (δH 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. ¹³C-NMR spectra were measured using a JEOL ECA-500 (125 MHz) or JEOL ECA-600 (151 MHz) in CDCl₃ (δC 77.0), CD₃OD (δC 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 (60F₂₅₄) plates. Preparative TLC (PTLC) was performed using 0.50 mm E. Merck silica gel (60F₂₅₄) 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\textsubscript{18}-PREP were used for flash column chromatography. High performance liquid chromatography (HPLC) was recorded on a Jasco PU-2089 \textit{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 (TBSCI) (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 NH₄Cl solution (300 mL) and water (100 mL). After the layers were separated, the aqueous layer was extracted with Et₂O (100 mL×3). The combined organic layers were washed with brine (100 mL), dried over MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~400 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; ¹H-NMR (500 MHz, CDCl₃): δ 3.46 (4H, s), 0.90 (9H, s), 0.88 (6H, s), 0.06 (6H, s); ¹³C-NMR (125 MHz, CDCl₃): δ 72.88, 72.37, 36.32, 25.81, 21.43, 18.14, −5.69; HRMS (FD): Calcd for C₁₁H₂₆O₂Si [M+H]⁺: 219.1780; found: 219.1767.
A solution of DMSO (9.0 mL, 125.3 mmol) in CH$_2$Cl$_2$ (19 mL) was added to a solution of oxalyl chloride (6.0 mL, 70.1 mmol) in CH$_2$Cl$_2$ (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$_2$Cl$_2$ (25 mL) was slowly added over 10 min. The mixture was stirred at −78 °C for 30 min, and then Et$_3$N (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$_4$Cl (100 mL) solution and water (50 mL). After the layers were separated, the aqueous layer was extracted with Et$_2$O (150 mL×3). The combined organic layers were washed with H$_2$O (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, 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$_3$Si [M+H]$^+$: 287.2043; found: 287.2091.
Compound 103

To a mixture of K$_3$Fe(CN)$_6$ (27.7 g, 84.0 mmol), K$_2$CO$_3$ (11.6 g, 84.0 mmol), MeSO$_2$NH$_2$ (2.66 g, 28.0 mmol), (DHQ)PHN (703.7 mg, 1.40 mmol) in t-BuOH–H$_2$O (1:1, 280 mL) was added K$_2$OsO$_2$(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$_2$S$_2$O$_3$ (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, $J = 9.8$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 173.88, 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$_5$Si [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 H₂O, 0.450 mmol), MeSO₂NH₂ (38.3 mg, 0.450 mmol) in acetone–H₂O (1:1, 1.0 mL) was added OsO₄ (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 Na₂S₂O₃ (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 H₂O (2 mL), after the aqueous phase was separated, and extracted with EtOAc (2 mL×3). The combined organic layers were dried over MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~5 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; ¹H-NMR (500 MHz, CDCl₃): 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); ¹³C-NMR (125 MHz, CDCl₃): 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 C₁₅H₃₅O₅Si [M+H]+: 321.2097; found: 321.2082.
To a solution of the optically active diol 103 (23.8 g, 74.3 mmol) in (CH$_2$Cl)$_2$ (74 mL) and i-Pr$_2$NEt (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$_2$O (100 mL x 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: [α]$_D^{23}$ +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$_3$Si [M+H]$^+$: 409.2622; found: 409.2635.
To a mixture of lithium aluminum hydride (LiAlH₄) (4.83 g, 127.2 mmol) in Et₂O (100 mL) was added dropwise a solution of ester 104 (26.0 g, 63.6 mmol) in Et₂O (100 mL) at 0 °C over 15 min. After being stirred at 0 °C for 1.5 h, the reaction mixture was diluted with Et₂O (200 mL). To the reaction mixture were added dropwise sequentially H₂O (5 mL), 15% aqueous NaOH solution (5 mL), and H₂O (15 mL) at 0 °C. Then, the resulting suspension was stirred at room temperature for 1 h, dried over MgSO₄ 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 (CH₂Cl)₂ (130 mL) were added I₂ (21.0 g, 82.7 mmol), PPh₃ (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 Et₂O (150 mL), and the reaction mixture was quenched with a saturated aqueous Na₂S₂O₃ solution (200 mL). After the layers were separated, the aqueous layer was extracted with Et₂O (100 mL×3). The combined organic layers were washed with a saturated aqueous Na₂S₂O₃ solution (50 mL×3) and brine (100 mL), dried over MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~300 g, n-hexane/EtOAc = 5:1) afforded iodide 105 (28.9 g, 60.7 mmol, 96% for 2 steps) as a colorless oil: [α]²⁴D –12.3 (c 1.46, CHCl₃); IR (ATR): ν 2953, 2928, 2886, 2856, 1471, 1361, 1252, 1148, 1093, 1022, 919, 835, 774 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃): 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), 0.94 (6H, s); ¹³C-NMR (125 MHz, CDCl₃): 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$_3$CHLiCN (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$_4$Cl solution (300 mL). After the layers were separated, the aqueous layer was extracted with Et$_2$O (150 mL×3). The combined organic layers were washed with H$_2$O (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$_4$Cl 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: [α]$_D^{25}$ −94.3 (c 1.06, CHCl$_3$); IR (ATR): ν 3487, 2980, 2887, 2359, 2341, 1473, 1463, 1382, 1148, 1097, 1016, 917
Compound 107

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 CH₂Cl₂–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 (SiO₂~200 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: [α]_27^20 = -39.7 (c 0.96, CHCl₃); IR (ATR): ν 2940, 2896, 2826, 1719, 1456, 1397, 1210, 1148, 1098, 1079, 920, 917 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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); 13C-NMR (125 MHz, CDCl3): 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 C14H25NO5 [M]+: 287.1733; found: 287.1731.

**Compound 99**

![Compound 99](image)

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 NH4Cl solution (10 mL) and H2O (10 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (5 mL×4). The combined organic layers were dried over MgSO4, and concentrated under reduced pressure. Purification by flash column chromatography (SiO2~30 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: [α]27D –124.0 (c 0.99, CHCl3); IR (ATR): ν 2978, 2940, 2894, 1714, 1648, 1465, 1388, 1366, 1309, 1294, 1269, 1149, 1098, 1042, 918, 866 cm⁻¹; 1H-NMR (500 MHz, CDCl3) 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),
to 28 °C. The reaction mixture was quenched with a saturated aqueous NH₄Cl solution (1 mL) and H₂O (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 MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~5 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: [α]D²⁸ = −45.6 (c 1.00, CHCl₃); IR (ATR): ν 2980, 2937, 2894, 2826, 1734, 1466, 1394, 1377, 1302, 1265, 1191, 1146, 1103, 1018, 915, 759 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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, 7.5 Hz), 3.81 (1H, ddd, J = 9.8, 6.9 Hz), 3.65 (1H, ddd, J = 12.1, 9.8, 6.9 Hz), 3.41 (3H, s), 3.38 (3H, s), 3.14 (1H, d, J = 9.8 Hz), 2.55 (1H, d, J = 17.8, 7.5 Hz), 2.46 (1H, d, J = 17.8, 4.6 Hz), 2.44 (1H, d, J = 11.5, 7.5 Hz), 2.32 (1H, d, 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); ¹³C-NMR (125 MHz, CDCl₃): 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 C₁₈H₃₁NO₆ [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 NH₄Cl solution (1 mL) and H₂O (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 MgSO₄, and concentrated under reduced pressure.
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); 13C-NMR (125 MHz, CDCl₃): 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 C₁₈H₃₁NO₆ [M]+: 357.2151; found: 357.2149.

**Compound 108 and 109**

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 MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~3 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**: [α]_D^25 −50.0 (c 1.09, CHCl₃); IR (ATR): ν 2940, 2893, 2824, 1726, 1471, 1391, 1365, 1147, 1104, 1055, 1032, 917, 771 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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): \(\nu\) 2339, 2953, 2890, 2824, 1455, 1395, 1218, 1148, 1103, 1029, 918, 776 cm\(^{-1}\); \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta\): 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**

![Chemical Structure](image.png)

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\(_4\)Cl 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\textsubscript{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: [\text{c}]\textsubscript{20}^\text{D}^\text{2} -61.8 (c 1.00, CHCl\textsubscript{3}); IR (ATR): ν 2980, 2889, 2359, 2341, 1659, 1626, 1463, 1380, 1149, 1098, 1021, 918, 735 cm\textsuperscript{-1}; 

\textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{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); \textsuperscript{13}C-NMR (125 MHz, CDCl\textsubscript{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\textsubscript{18}H\textsubscript{32}N\textsubscript{2}O\textsubscript{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\textsubscript{4}Cl 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 MgSO₄, 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 (SiO₂~100 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; [α]²⁸_D –51.9 (c 0.95, CHCl₃); IR (ATR): ν 2939, 2904, 2359, 2341, 2332, 1660, 1457, 1416, 1389, 1146, 1029, 915 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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, ddd, J = 16.6, 5.7 Hz), 2.63 (1H, dddd, J = 10.3, 5.7 Hz), 2.54 (1H, ddd, J = 16.1, 4.1 Hz), 2.31 (1H, ddd, 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); ¹³C-NMR (125 MHz, CDCl₃): 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 C₁₈H₃₂N₂O₆ [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 MgSO₄, 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 NH₄Cl 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 MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~300 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: [α]D²⁸ –66.4 (c 1.03, CHCl₃); IR (ATR): ν 2978, 2940, 2892, 2359, 1656, 1463, 1390, 1210, 1146, 1103, 1026, 916 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (125 MHz, CDCl₃): 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$_2$O (80:1, 223 mL) was added $p$-TsOH-H$_2$O (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 S$_3$ (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 S$_3$ (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$_4$Cl 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).
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$_2$Cl$_2$ (95 mL) was slowly added DIBAL (1.03 M in n-hexane, 41.6 mL, 42.8 mmol) at $-78$ °C for 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$_2$Cl$_2$ (95 mL) was slowly added DIBAL (1.03 M in $n$-hexane, 41.6 mL, 42.8 mmol) at $-78 \, ^\circ$C over 10 min, and the mixture was stirred at $-78 \, ^\circ$C for 1 h. The reaction was quenched by dropwise addition of EtOAc (50 mL) and the mixture was stirred at $-78 \, ^\circ$C for 15 min. Then, to the mixture was added a saturated aqueous sodium potassium tartrate solution (ca. 150 mL) at $-78 \, ^\circ$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$\times$3). The combined organic layers were washed with brine (100 mL), dried over MgSO$_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$\times$3). The combined organic layers were washed with brine (150 mL), dried over MgSO$_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): $\nu$ 3479, 2940, 2882, 2335, 2339, 1457, 1393, 1214, 1146, 1103, 1027, 916 cm$^{-1}$; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$: 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$_3$): $\delta$ 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\textsubscript{2}Cl\textsubscript{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\textsubscript{4}Cl 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\textsubscript{4}, and concentrated under reduced pressure. Purification by flash column chromatography (SiO\textsubscript{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: 

\([\alpha]_{D}^{25} -36.9 \text{ (c 1.04, CHCl}_3\); IR (ATR): \(\nu 2979, 2940, 2892, 2367, 2356, 2332, 1718, 1635, 1471, 1387, 1180, 1146, 1102, 1026, 916 \text{ cm}^{-1}; \) \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \(\delta: 5.71\) (1.5H, d, \(J = 12.1 \text{ Hz})
, 5.64 (0.5H, d, \(J = 13.2 \text{ Hz})
, 4.91 (1H, d, \(J = 6.9 \text{ Hz})
, 4.72 (1H, d, \(J = 6.9 \text{ Hz})
, 4.72 (1H, d, \(J = 6.3 \text{ Hz})
, 4.66 (1H, d, \(J = 6.3 \text{ Hz})
, 4.22-4.12 (2H, m), 3.70 (1H, ddd, \(J = 11.2, 9.2, 4.6 \text{ Hz})
, 3.42 (3H, s), 3.35 (3H, s), 3.13 (0.5H, d, \(J = 9.7 \text{ Hz})
, 3.10 (0.5H, d, \(J = 9.7 \text{ Hz})
, 2.60-2.49 (1H, m), 2.00 (0.5H, dd, \(J = 4.6, 4.0 \text{ Hz})
, 1.98 (0.5H, dd, \(J = 4.6, 4.1 \text{ Hz})
, 1.70 (0.5H, dd, \(J = 12.6, 12.0 \text{ Hz})
, 1.66-1.40 (5.5H, m), 1.29 (3H, d, \(J = 6.9 \text{ Hz})
, 1.29 (1.5H, t, \(J = 7.5 \text{ Hz})
, 1.29 (1.5H, t, \(J = 7.5 \text{ 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, 

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 \(\mu\)L, 1.34 mmol) at \(-78 \text{ °C}. \) After being stirred at \(-78 \text{ °C} \) for 20 h, the reaction mixture was quenched with a saturated aqueous NH\(_4\)Cl 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: $[\alpha]_{D}^{28}$ = -20.9 (c 1.05, CHCl$_3$); IR (ATR): $\nu$ 2939, 2888, 2820, 1653, 1459, 1426, 1387, 1363, 1147, 1104, 1031, 1147, 1104, 1031, 916, 774 cm$^{-1}$; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$: 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$_3$): $\delta$ 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$_2$O$_6$ [M]$^+$: 440.2886; found: 440.2877.

**Compound 119 and 120**

![Diagram of compounds 119 and 120]

To a mixture of (Z)-unsaturated Weinreb amide 117 (70.0 mg, 0.159 mmol) and triisopropylsilyl chloride (TIPSCI) (68 µL, 0.318 mmol) in Et$_2$O (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 NH₄Cl 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 Et₂O (2 mL×3). The combined organic layers were dried over MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~5 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:** [α]²⁶D −32.6 (c 0.36, CHCl₃); IR (ATR): ν 2947, 2883, 2823, 1661, 1464, 1416, 1388, 1362, 1337, 1149, 1101, 1030, 910, 726, 647, 617 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (125 MHz, CDCl₃): 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 C₂₃H₄₆N₂O₆ [M]+: 440.2886; found: 440.2893.

**Bicyclic compound 120:** [α]²⁸D −60.3 (c 0.94, CHCl₃); IR (ATR): ν 2948, 1666, 1445, 1417, 1388, 1341, 1211, 1147, 1106, 1028, 915, 735 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (125 MHz, CDCl₃): 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_{2}O_{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 mixture 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 KHSO₄ solution (200 mL). After the layers were separated, the aqueous layer was extracted with Et₂O (100 mL×5). The combined organic layers were washed with brine (200 mL), dried over MgSO₄, 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 CH₂Cl₂ (108 mL) was added Et₃N (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 H₂O (100 mL). After the layers were separated, the aqueous layer was extracted with Et₂O (100 mL×5). The combined organic layers were washed with brine (200 mL), dried over MgSO₄, 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): v 2979, 2938, 2887, 2368, 1652, 1456, 1389, 1365, 1330, 1146, 1102, 1028, 916, 860, 785 cm$^{-1}$; $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$: 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$_3$): $\delta$ 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$_2$O$_6$ [M]$^+$: 482.3356; found: 482.3353.

**Compound 129**

To a mixture of (Z)-unsaturated Weinreb amide 127 (8.42 g, 17.4 mmol) and TIPSCI (7.4 mL, 34.8 mmol) in Et$_2$O (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 NH₄Cl 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 Et₂O (60 mL×5). The combined organic layers were washed with brine (100 mL), dried over MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~300 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: [α]D₂₁ −11.2 (c 1.73, CHCl₃); IR (ATR): ν 2979, 2944, 2888, 2369, 2360, 2338, 2324, 1667, 1471, 1388, 1366, 1320, 1150, 1032, 917, 858 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (125 MHz, CDCl₃): 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 C₂₆H₄₆N₂O₆Na [M+Na]⁺: 505.3254; found: 505.3255.

**Compound 132**

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 NH₄Cl solution (2 mL). After the layers were separated, the aqueous layer was
extracted with Et₂O (2 mL×3). The combined organic layers were dried over MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂ ~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, CHCl₃); IR (ATR): ν 2938, 2894, 1714, 1459, 1392, 1366, 1308, 1180, 1146, 1102, 1026, 916, 753, 665 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (125 MHz, CDCl₃): 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 C₂₃H₃₉NO₆ [M⁺]: 425.2777; found: 425.2780.

**Compound 133**

![Chemical structure of 133](image)

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 NH₄Cl 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 MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~5 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: [α]²⁵D –72.2 (c 0.80, CHCl₃); IR (ATR): ν 2941, 2891, 2821, 1660, 1627, 1462, 1412, 1379, 1146, 1103, 946, 916, 854 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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 = 9.8 Hz), 2.55-2.43 (1H, m), 1.79-1.61 (5H, m), 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); ¹³C-NMR (125 MHz, CDCl₃): 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 C₂₃H₄₀N₂O₆ [M]+: 440.2886; found: 440.2904.

Compound 120

To a mixture of (E)-unsaturated Weinreb amide 133 (13.5 mg, 30.6 µmol) and TIPSCI (13 µL, 61.2 µmol) in Et₂O (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 NH₄Cl 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 MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~5 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 MgSO₄, 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 CBr₄ (10.2 g, 30.8 mmol) in CH₂Cl₂ (40 mL) were added PPh₃ (16.2 g, 61.6 mmol) and Et₃N (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 CH₂Cl₂ (40 mL) at 0 °C. After being stirred for 2 h at room temperature, the reaction mixture was quenched with a saturated aqueous NaHCO₃ solution (100 mL). After the layers were separated, the aqueous layer was extracted with Et₂O (50 mL×3). The combined organic layers were washed with brine (100 mL), dried over MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~300 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); [α]D²⁵ +54.2 (c 1.02, CHCl₃); IR (ATR): ν 2948, 2882, 2822, 2364, 2229, 1465, 1388, 1364, 1304, 1213, 1148, 1102, 1029, 915, 803, 752 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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), 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); ¹³C-NMR (125 MHz, CDCl₃): 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 C₂₂H₂₃NO₄Br₂Na [M+Na]⁺: 558.0831; found: 558.0829.
To a solution of dibromoalkene 138 (6.29 g, 11.7 mmol) in CH₂Cl₂ (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 MgSO₄, 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 NH₄Cl 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 MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~150 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: [α]D²⁴ –8.70 (c 1.04, CHCl₃); IR (ATR): ν 2981, 2883, 1711, 1641, 1464, 1387, 1296, 1264, 1149, 1101, 1029, 916, 754 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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$_6$Br$_2$Na [M+Na]$^+$: 631.1246; found: 631.1238.

**Compound 94**

To a mixture of CuI (545.6 mg, 2.87 mmol, 99.0% purity, purchased from KANTO CHEMICAL CO., INC.) in Et$_2$O (0.73 mL) was slowly added MeLi (1.13 M in Et$_2$O, 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$_2$CuLi solution was slowly added a solution of (E)-unsaturated ester 95 (350.0 mg, 0.573 mmol) in Et$_2$O (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$_4$Cl 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 Et₂O (5 mL×3). The combined organic layers were dried over MgSO₄, and
concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~20 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); [α]D₂⁰ +64.6 (c 1.01, CHCl₃); IR (ATR): ν 2941,
2887, 1733, 1457, 1373, 1265, 1148, 1102, 1031, 916 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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, ddd, 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, ddd, J = 13.2, 4.6 Hz), 1.08 (3H, s), 1.00 (3H, s), 0.98 (3H, s), 0.91 (3H, s); ¹³C-NMR (125 MHz,
CDCl₃): 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,
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](image)

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 them is important for synthetic chemistry. Many methods for asymmetric synthesis of β-hydroxy-α-amino acids have been developed so far. 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-C2 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-Bu₂BOTf) and diisopropylethylamine (i-Pr₂NEt) with oxazolidinone 148, which afforded syn-α-chloro-β-hydroxy oxazolidinone 149 as a single isomer. However, this reaction was poor in reproducibility. Other Evans-type asymmetric aldol reactions by using oxazolidinethione and thiazolidinethione 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. Epoxy ester 151 would be a potential synthetic intermediate for the total synthesis (cf. azidolyisis of 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. Asymmetric epoxidation of 154 resulted in the formation of epoxy pyrrole amide 155 in moderate yield, however, the diastereomeric ratio of 154 varied between 10:1 and 1:1, and reproducibility could not be obtained.
Katsuki–Sharpless asymmetric epoxidation of an allyl alcohol is an asymmetric epoxidation reaction\(^\text{49}\) 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).\(^\text{50}\) Thus, treatment of \textit{trans}-epoxy alcohol 156 with sodium azide (\(\text{NaN}_3\)) in the presence of trimethoxy borate (\(\text{B(OMe)}_3\)) produced the C2 substitution product 157 with high regioselectivity (\(\text{dr} = 92:8\)). 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 31.** Asymmetric epoxidation of \(\alpha,\beta\)-unsaturated \(N\)-acylpyrrole 154

**Scheme 32.** Substitution reaction of \textit{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 \(\alpha,\beta\)-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.

\[
\begin{align*}
\text{1. DIBAL, CH}_2\text{Cl}_2 & \quad \text{THF} \quad \text{–90 °C} \\
\text{2. } (\text{EtO})_2\text{P}=\text{O} & \quad \text{NaNHMDS, THF} \quad 98\% \ (2 \text{ steps})
\end{align*}
\]

\[
\begin{align*}
\text{MOMO} & \quad \text{Me} \\
\text{MOMO} \quad \text{H} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{CO}_2\text{Et} & \quad \text{O} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

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.
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). 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. 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 (Me₃OBF₄) 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. 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 SnCl₂ gave methyl ester 170 of braslicardin A (3) and C (5) aglycon. Synthetic methyl ester 170 was identical to its derived from natural braslicardin A (3), including ¹H- and ¹³C-NMR, IR, and HRMS spectra and optical rotation.
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. 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 35. Synthesis of β-methoxy amino acid moiety
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). 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 NaN₃ 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).
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 \(p\text{-NsCl}\) produced monosylate 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\(_3\)OBF\(_4\) followed by reduction of azide 180 and protection of the resulting amine 181 with a 9-fluorenymethylxycarbonyl (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.

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).
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).

Thus, tricyclic compound 94 was converted to iodide 185 through lithium aluminum hydride (LiAlH₄) 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. 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 40. X-ray crystallographic analysis of 184
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 \(\Delta\delta\) values obtained for the MTPA amides \([\delta(S\text{-MTPA amide}) – \delta(R\text{-MTPA amide})]\) indicated that the absolute configuration at the C17 position of 192 was S.
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.
To a solution of tricyclic compound 94 (60.0 mg, 0.129 mmol) in CH$_2$Cl$_2$ (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: [α]$^2_1$D+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_{2}Cl_{2} (0.23 mL) were added i-Pr_{2}NEt (36 µL, 0.270 mmol), and dibutylboryl trifluoromethanesulfonate (n-Bu_{2}BOTf) (1.0 M in CH_{2}Cl_{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_{2}Cl_{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_{2}O_{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_{2}Cl_{2} (1 mL×3). The combined organic layers were washed with a saturated NH_{4}Cl 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: [α]_{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, \( J = 12.1 \) 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\(_3\)): \( \delta \) 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, 55.36, 50.45, 46.11, 43.08, 42.20, 40.10, 37.17, 37.13, 36.15, 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 \( \mu \)mol) in MeOH (0.3 mL) was added NaOMe (5.0 M in MeOH, 18 \( \mu \)L, 90.0 \( \mu \)mol) at 0 \( ^\circ \)C. After being stirred at 0 \( ^\circ \)C for 2 h, the reaction mixture was quenched with a saturated aqueous NH\(_4\)Cl solution (0.5 mL) at 0 \( ^\circ \)C. After the layers were separated, the aqueous layer was extracted with Et\(_2\)O (1 mL \( \times \)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 \( \mu \)mol, 98%) as a white amorphous foam: \([\alpha]^{27}_{D}\) +48.6 (c 0.72, CHCl\(_3\)); IR (ATR): \( \nu \) 2946, 2927, 2888, 2822, 1755, 1739, 1443, 1380, 1289, 1203, 1148, 1102, 1031, 917, 808, 742 cm\(^{-1}\); \(^1\)H-NMR (500 MHz, CDCl\(_3\)) \( \delta \): 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$_2$NEt (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$_2$O (1 mL). After the layers were separated, the aqueous layer was extracted with Et$_2$O (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: [α]$_D^{21}$ +89.7 (c 1.04, CHCl$_3$); IR (ATR): ν 2946, 2886, 1698, 1635, 1467, 1345, 1294, 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(Oi-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: [α]$_D^{25}$ +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**

![](image.png)

To a solution of tricyclic compound 94 (100.0 mg, 0.214 mmol) in CH$_2$Cl$_2$ (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 MgSO₄, 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 NH₄Cl solution (2 mL) and H₂O (1 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (2 mL×3). The combined organic layers were dried over MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~10 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: [α]ᵢ₂⁰ +75.5 (c 0.87, CHCl₃); IR (ATR): ν 2939, 2883, 2844, 2820, 1718, 1651, 1443, 1367, 1305, 1264, 1207, 1147, 1101, 917, 755 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (125 MHz, CDCl₃): 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 C₂₉H₄₈O₆ [M⁺]: 492.3451; found: 492.3444.

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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 MgSO₄, 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 CH₂Cl₂ (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 CH₂Cl₂ (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\textsubscript{4}, and concentrated under reduced pressure. Purification by flash column chromatography (SiO\textsubscript{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\textsubscript{3}); IR (ATR): \(\nu\) 3445, 2947, 1442, 1380, 1148, 1102, 1032, 918, 805, 669 cm\textsuperscript{-1}; \(^1\)H-NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\): 5.37 (1H, br), 4.91 (1H, d, \(J = 6.3 \text{ Hz}\)), 4.74 (1H, d, \(J = 6.3 \text{ Hz}\)), 4.71 (1H, d, \(J = 6.3 \text{ Hz}\)), 4.68 (1H, d, \(J = 6.9 \text{ Hz}\)), 3.91 (1H, dd, \(J = 12.6, 2.9 \text{ Hz}\)), 3.72 (1H, dt, \(J = 11.5, 4.1 \text{ Hz}\)), 3.64 (1H, ddd, \(J = 15.5, 7.5, 4.0 \text{ Hz}\)), 3.42 (3H, s), 3.38 (3H, s), 3.00-2.94 (2H, m), 2.97 (1H, d, \(J = 9.8 \text{ Hz}\)), 1.92 (1H, br-dt), 1.85-1.80 (1H, m), 1.77 (1H, dd, \(J = 13.2, 4.6 \text{ Hz}\)), 1.72-1.67 (1H, m), 1.66 (3H, s), 1.63-1.54 (5H, m), 1.44 (1H, ddd, \(J = 14.9, 6.9, 3.5 \text{ Hz}\)), 1.38-1.25 (2H, m), 1.31 (1H, dd, \(J = 12.6, 4.6 \text{ Hz}\)), 1.09 (3H, s), 0.99 (3H, s), 0.99 (3H, s), 0.92 (3H, s); \(^{13}\)C-NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 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\textsubscript{27}H\textsubscript{46}O\textsubscript{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 \(\mu\)L, 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\textsubscript{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 H₂O (2 mL×2), dried over MgSO₄, 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–H₂O (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 NaHCO₃ 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 MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~5 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: [α]²⁷
+64.9 (c 1.44, CHCl₃); IR (ATR): ν 3447, 2941, 2895, 2102, 1457, 1376, 1270, 1147, 1101, 1032, 770 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (125 MHz, CDCl₃): 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 C₂₇H₄₆N₃O₆ [M+H]⁺: 510.3543; found: 510.3541.
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 H₂O (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 KHSO₄ solution (2 mL × 2), dried over MgSO₄, 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 CH₂Cl₂ (1.0 mL) was added trimethyloxonium tetrafluoroborate (Me₃OBF₄) (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 NaHCO₃ solution (10 mL × 2), 5% aqueous KHSO₄ solution (15 mL × 3), and dried over MgSO₄, 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$_2$Cl$_2$ (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$_2$S$_2$O$_3$ 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: [α]$_D^{26}$ +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, s), 1.06 (3H, s), 0.99 (3H, s), 0.91 (3H, s); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 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$_3$O$_5$Na [M+Na]$^+$: 486.2942; found: 486.2938.

**Compound 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 NaNHCO$_3$ 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$_3$) $\delta$: 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$_3$): $\delta$ 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$_{43}$N$_3$O$_5$ [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 CH₂Cl₂ (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 MgSO₄, 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) in THF (2.6 mL) was slowly added NaHMDS (1.14 M in THF, 541 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 NH₄Cl solution (5 mL) and H₂O (2 mL). After the layers were separated, the aqueous layer was extracted with EtOAc (3 mL×3). The combined organic layers were dried over MgSO₄, and concentrated under reduced pressure. Purification by flash column
chromatography (SiO₂~10 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: [α]D²⁶ +87.1 (c 0.79, CHCl₃); IR (ATR): ν 2971, 1715, 1366, 1149, 1035, 949 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (125 MHz, CDCl₃): 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 C₃₁H₅₂O₆ [M]⁺: 520.3764; found: 520.3777.

**Compound 177**

To a mixture of K₃Fe(CN)₆ (237.1 mg, 0.720 mmol), K₂CO₃ (99.5 mg, 0.720 mmol), DHQ-PHN (12.1 mg, 24.0 µmol) in t-BuOH–H₂O (1:1, 2.4 mL) was added K₂OsO₂(OH)₄ (1.8 mg, 4.80 µmol), and the mixture was stirred at room temperature for 1 h. To the mixture was added MeSO₂NH₂ (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 Na₂S₂O₃ (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 MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~10 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): $\nu$ 3472, 2946, 1732, 1446, 1369, 1289, 1251, 1149, 1103, 1032, 951, 917, 846 cm$^{-1}$; $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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$_2$Cl$_2$ (2.3 mL) were added Et$_3$N (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$_2$O (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 dimethylformamide (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$_2$O (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: [α]$_{D}^{26}$ +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$_{7}$O$_{7}$ [M+H]$^+$: 580.3962; found: 580.3956.
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$_2$Cl$_2$ (2.0 mL) was added trimethyloxonium tetrafluoroborate (Me$_3$OBF$_4$) (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$_2$O (3:1, 2.0 mL), NaHCO$_3$ (83.2 mg, 0.990 mmol), and N-(9-fluorenylethoxycarbonyloxy)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 MgSO₄, and concentrated under reduced pressure. The residue was filtered through a pad of silica gel (SiO₂~15 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 (SiO₂~10 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: [α]ᵢ²⁴D +89.8 (c 0.74, CHCl₃); IR (ATR): ν 3378, 2979, 2888, 1740, 1462, 1381, 1252, 1157, 952, 817 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (125 MHz, CDCl₃): 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 C₄₃H₅₀NO₇ [M]+: 701.4292; found: 701.4300.
Determination of the stereochemistry of 179

**Compound 184**

![Chemical structures and reactions]

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 CH₂Cl₂ (0.12 mL) in a test tube with screw cap was added Me₃OBF₄ (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 H₂O (2 mL), after the aqueous phase was separated, and extracted with EtOAc (1 mL×3). The organic layers were washed with 5% aqueous KHSO₄ solution (1 mL×3), and dried over MgSO₄, and concentrated under reduced pressure. The residue was filtered through a pad of silica gel (SiO₂–5 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 SnCl₂ (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 NaHCO₃ solution (1.5 mL). After the layers were separated, the aqueous layer was extracted with CHCl₃–MeOH (9:1 v/v, 1 mL×5). The combined organic layers were washed with brine (1 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was filtered through a pad of silica gel (SiO₂~5 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 CH₂Cl₂ (0.4 mL) was added N,N'-dicyclohexylcarbodiimide (DCC) (0.5 M in CH₂Cl₂, 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 (SiO₂, 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 powder from EtOH afforded colorless needles, which were analyzed by X-ray: M.p. 284-285 °C (EtOH) [lit.³ M.p. 286-287 °C]; [α]D²⁹ +118 (c 0.14, CHCl₃) [lit.³ [α]D²⁷ +118 (c 0.32, CHCl₃)]; IR (ATR): ν 3357, 2970, 2932, 2884, 1653, 1466, 1379, 1307, 1160, 1128, 950, 816, 772 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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); ¹³C-NMR (125 MHz, CDCl₃): 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 C₃₂H₄₆BrNO₆ [M]⁺: 619.2509; found: 619.2515.
To a solution of tricyclic compound 94 (65.0 mg, 0.139 mmol) in Et₂O (1.4 mL) was added LiAlH₄ (10.6 mg, 0.278 mmol) at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was diluted with Et₂O (3 mL). To the reaction mixture were added dropwise sequentially H₂O (15 µL), 15% aqueous NaOH solution (15 µL), and H₂O (45 µL) at 0 °C. Then, the suspension was stirred at room temperature for 10 min, and dried over MgSO₄ for 1 h, and filtered through a pad of Celite®, which was rinsed with Et₂O (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 CH₂Cl₂ (1.4 mL) were added I₂ (45.9 mg, 0.181 mmol), PPh₃ (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 Et₂O (2 mL), and quenched with a saturated aqueous Na₂S₂O₃ solution (3 mL). After the layers were separated, the aqueous layer was extracted with Et₂O (2 mL×3). The combined organic layers were dried over MgSO₄, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂~10 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: [α]D²⁷ +171.3 (c 1.06, CHCl₃); IR (ATR): ν 2942, 2884, 1445, 1379, 1214, 1146, 1102, 1027, 989, 916, 812 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃): 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).
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\(_3\)): \( \delta \) 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$_2$O (10 mL). After the aqueous layer was extracted with Et$_2$O (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$_2$CO$_3$ (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$_2$O (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$_2$O (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: [α]$_D^{23}$ +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$_2$Cl$_2$ (0.3 mL) was added DCC (0.50 M in CH$_2$Cl$_2$, 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$_3$NO$_6$ [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$_2$Cl$_2$ (0.3 mL) was added DCC (0.50 M in CH$_2$Cl$_2$, 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 regioselective 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.

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.

Figure 6. Saccharide units of brasilicardins A–D
Anada, Hashimoto, and co-workers accomplished the installation of the brasiliocardin A (3) saccharide moiety using the Jung’s procedure (Scheme 43c). Thus, the glycosylation of the C3 protected aglycon 51 with trichloroacetimidate 37 using BF₃·OEt₂ 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 brasiliocardin 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$_3$·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. 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 Cp₂HfCl₂/AgOTf 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, thiosugar 211, and glycosyl sulfoxide 212 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 1H-NMR spectrum of the compound proved highly dependent on the concentration and pH. However, its identification was finally achieved using 1H-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
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 brasiliardin A (3)

Brasiliardin B (4) was also synthesized from 190 using the similar sequence as those used for brasiliardin A (3) (Scheme 48).
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\(_3\)·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).
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 regiochemical outcome.55

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

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<th>result</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl₃C[O][NH]</td>
<td>54 : 23% (29% brsm), 216 : 45%</td>
<td>2</td>
<td>NTsPh[O][Ph]</td>
<td>54 : 45% (82% brsm), 216 : 8%</td>
</tr>
</tbody>
</table>
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 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 brasilcardins A (3) and B (4), but the C3 acetate remained intact contrary to expectation. Thus, acetate 227 was treated with sodium methoxide at 60 °C 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\textsuperscript{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.\textsuperscript{68}

![Scheme 52. Synthesis of the C3 protected alcohol 230](image)

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\textsuperscript{1}-catalyzed glycosylation of alcohol 230 with \textit{o}-cyclopropylethynylbenzoate 224 proceeded smoothly to afford glycoside 231 in good yield. Finally, glycoside 231 was successfully converted to brasilicardin C (5) via TFA-mediated removal of \textit{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).
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).
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 brasiliardin 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.\textsuperscript{11} To a solution of hemiacetal S10 (697.6 mg, 1.00 mmol, α-anomer exclusively) in CH$_2$Cl$_2$ (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$_2$Cl$_2$ (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$_2$Cl$_2$ (30 mL), to the mixture was added n-hexane (20 mL) at 0 °C. The resulting white precipitate 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; [α]$_D^{24}$ +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; [$\alpha$]$^\text{23}$$^\text{D}$ +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, d, $J = 10.3, 9.8$ 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.
The promoter was prepared by stirring a mixture of hafnocene dichloride (Cp₂HfCl₂) (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 CH₂Cl₂ (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 CH₂Cl₂ (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 NaHCO₃ 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 MgSO₄, and concentrated under reduced pressure. Purification by preparative TLC (SiO₂, 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 CH₂Cl₂ (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 brasiliocardin 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]; [α]D 25 +14.9 (c 0.40, MeOH) [lit.³ [α]D 25 +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; ¹H-NMR (600 MHz, CD₃OD): 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$_3$OD): $\delta$ 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$_2$O$_{16}$ [M–H]$^+$: 891.4496; found: 891.4510.

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´, $J_{C,H} = 171.1$ Hz; lit. $J_{C,H} = 171.0$ Hz) 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 mmø, MMS-005J).
The promoter was prepared by stirring a mixture of Cp₂HfCl₂ (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 CH₂Cl₂ (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 CH₂Cl₂ (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 NaHCO₃ 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 MgSO₄, and concentrated under reduced pressure. Purification by preparative TLC (SiO₂, 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 CH₂Cl₂ (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: [α]²⁷°D +16.9 (c 0.22, MeOH) [lit.⁶ [α]²³°D +17.0 (c 1.00, MeOH)]; IR (ATR): ν 3401, 2938, 1671, 1289, 1201, 1137, 1116, 1076, 1031, 669 cm⁻¹; ¹H-NMR (500 MHz, CD₃OD): 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); ¹³C-NMR (151 MHz, CD₃OD): 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, 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_{2}O_{15}Na [M+Na]^+: 885.4355; found: 885.4370.

**Compound 217**

To a solution of hemiacetal S12 (300.0 mg, 1.03 mmol, α-anomer exclusively) in CH$_2$Cl$_2$ (21 mL) was added DAST (270 µL, 2.06 mmol) at 0 ºC, and the mixture was stirred at 0 ºC for 1.5 h. The reaction mixture was diluted with CH$_2$Cl$_2$ (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, $^3$J(C,F) = 215.8 Hz], 69.74, 68.74 [d, $^2$J(C,F) = 3.6 Hz], 68.00 [d, $^1$J(C,F) = 14.3 Hz], 67.62, 20.55, 20.45, 17.13 (one peak missing); HRMS (FD): Calcd for C$_{12}$H$_7$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$_3$): $\delta$ 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, $^3J(C,F) = 19.1$ 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**

```
  183  |  TBSOTf  |  2,6-lutidine  |  CH$_2$Cl$_2$  |  90 ºC  |
  183  |  TBSO   |  CO$_2$-t-Bu   |  NH$_2$Fmoc    |
  221  |  AcO$^-$ |  AcCl          |  pyridine      |
  222  |  TBSO   |  CO$_2$-t-Bu   |  NH$_2$Fmoc    |

To a solution of diol 183 (15.0 mg, 21.4 µmol) in CH$_2$Cl$_2$ (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 ºC. After being stirred at −90 ºC 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$_2$O (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$_2$Cl$_2$ (0.43 mL) were added pyridine (17 µL, 0.214 mmol) and acetyl chloride (7.6 µL, 0.107 mmol) at 0 ºC. 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$_2$O (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: $\left[\alpha\right]_{D}^{20} +78.3$ (c 0.85, CHCl$_3$); IR (ATR): $\nu$ 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$_3$) $\delta$: 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, d, $J = 8.6$ Hz), 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$_3$): $\delta$ 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$_8$Si $[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: $\left[\alpha\right]_{D}^{20} +90.5$ (c 0.44, CHCl$_3$); IR (ATR): $\nu$ 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$_3$) $\delta$: 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\(_3\)): \( \delta \) 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**

![Diagram of 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\(_2\)O (20 mL), and the aqueous phase was extracted with Et\(_2\)O (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\(_2\)O (20 mL×3). The combined organic layers were washed with H\(_2\)O (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\(_3\)): \( \delta \) 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-Pr2NET (780 µL, 4.48 mmol), and N,N’-dimethyl-4-aminopyridine (DMAP) (273.7 mg, 2.24 mmol) in CH2Cl2 (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 CH2Cl2 (100 mL). The organic layers were washed with brine (50 mL), and dried over MgSO4, and concentrated under reduced pressure. Purification by flash column chromatography (SiO2~25 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: [α]23D −36.4 (c 1.13, CHCl3); IR (ATR): ν 2970, 2931, 2897, 2857, 2359, 2341, 1735, 1718, 1507, 1457, 1369, 1246, 1155, 1083, 836, 775, 757, 741 cm−1; 1H-NMR (500 MHz, CDCl3): 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); 13C-NMR (125 MHz, CDCl3): 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 C28H36O9 [M]+: 458.1577; found: 458.1592.
To a solution of diol 183 (30.0 mg, 42.7 µmol) in CH₂Cl₂ (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 NaHCO₃ solution (1 mL). After the layers were separated, the aqueous layer was extracted with Et₂O (2 mL×3). The combined organic layers were washed with 5% aqueous KHSO₄ solution (2 mL), dried over MgSO₄, 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 CH₂Cl₂ (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 NaHCO₃ solution (2 mL). After the layers were separated, the aqueous layer was extracted with Et₂O (2 mL×3). The combined organic layers were washed with 5% aqueous KHSO₄ solution (2 mL), dried over MgSO₄, and concentrated under reduced pressure. Purification by preparative TLC (SiO₂, n-hexane/EtOAc = 3:1) afforded methoxyacetyl ester 229 (34.4 mg, 38.7 µmol, 91% for 2 steps) as a white amorphous foam: [α]⁰₂⁰° +79.4 (c 0.83, CHCl₃); 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; ¹H-NMR (500 MHz, CDCl₃) 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); \(^{13}\text{C}\)-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\(_9\)Si [M]\(^{+}\): 887.5368; found: 887.5378.

**Compound 230**

To a solution of methoxyacetyl ester 229 (32.0 mg, 36.0 \(\mu\)mol) 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 \(\mu\)mol, 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\(^{-1}\); \(^{1}\text{H}\)-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$_3$): $\delta$ 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, $\alpha/\beta = 40:60$), and freshly activated and powdered MS4Å (AW-300, 23.3 mg) in CH$_2$Cl$_2$ (1.9 mL) was added Ph$_3$PAuNTf$_2$ (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$_2$Cl$_2$ (10 mL). After the mixture was concentrated under reduced pressure. Purification by flash column
chromatography (SiO₂~10 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 CH₂Cl₂ (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 140C₁₈-PREP~5 g, H₂O/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: [α]²³ D +61.5 (c 0.71, MeOH) [lit.⁶ [α]²³ D +65.0 (c 1.00, MeOH)]; IR (ATR): ν 3373, 2944, 2834, 1671, 1448, 1395, 1200, 1143, 1097, 1021, 645 cm⁻¹; ¹H-NMR (500 MHz, CD₃OD): 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); ¹³C-NMR (125 MHz, CD₃OD): 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 C₃₀H₅₂NO₉ [M+H]⁺: 570.3637; found: 570.3647.
Compound S16

To a solution of diol 190 (30.0 mg, 44.6 µmol) in CH₂Cl₂ (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 NaHCO₃ solution (1 mL). After the layers were separated, the aqueous layer was extracted with Et₂O (2 mL×3). The combined organic layers were washed with 5% aqueous KHSO₄ solution (2 mL), dried over MgSO₄, 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 CH₂Cl₂ (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 NaHCO₃ solution (2 mL). After the layers were separated, the aqueous layer was extracted with Et₂O (2 mL×3). The combined organic layers were washed with 5% aqueous KHSO₄ solution (2 mL), dried over MgSO₄, and concentrated under reduced pressure. Purification by preparative TLC (SiO₂, n-hexane/EtOAc = 4:1) afforded methoxyacetyl ester S16 (34.6 mg, 40.3 µmol, 90% for 2 steps) as a white amorphous foam: [α]D²⁶ +90.9 (c 1.05, CHCl₃); IR (ATR): ν 2950, 2935, 2857, 2357, 2341, 2328, 1731, 1521, 1449, 1368, 1252, 1191, 1155, 1131, 1083, 837, 773, 760, 741 cm⁻¹; ¹H-NMR (500 MHz, CDCl₃) 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), 0.03 (3H, s), 0.01 (3H, s); \[^{13}\]C-NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 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\textsubscript{51}H\textsubscript{75}NO\textsubscript{8}Si [M]\(^+\): 857.5262; found: 857.5253.

**Compound 233**

![Chemical Structure](image)

To a solution of methoxyacetyl ester \(S16\) (31.5 mg, 36.7 \(\mu\)mol) 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\textsubscript{2}, \(n\)-hexane/EtOAc = 3:2) afforded alcohol \(233\) (26.5 mg, 35.6 \(\mu\)mol, 97%) as a white amorphous foam: \([\alpha]\)\text{D}\textsuperscript{26} +61.5 (c 0.71, CHCl\textsubscript{3}); IR (ATR): \(v\) 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\textsubscript{3}) \(\delta\): 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$_3$): $\delta$ 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$_2$Cl$_2$ (2.2 mL) was added Ph$_3$PAuNT$_2$ (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$_2$Cl$_2$ (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$_2$Cl$_2$ (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 140C18-PREP-5 g, H$_2$O/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: $\left[\alpha\right]_{D}^{27}$ +75.6 (c 0.56, MeOH) [lit. $\left[\alpha\right]_{D}^{20}$ +79.0 (c 0.50, MeOH)]; IR (ATR): $\nu$ 3401, 2935, 1674, 1533, 1437, 1437, 1200, 1142, 1053, 805, 668 cm$^{-1}$; $^1$H-NMR (500 MHz, CD$_3$OD): $\delta$ 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$_3$OD): $\delta$ 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.
Synthetic brasilarcadin 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 NaHCO₃ solution (1 mL). After the aqueous layer was extracted with EtOAc (1 mL×3), the combined organic layers were dried over MgSO₄, 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 CH₂Cl₂, 83 µL, 83.4 µmol) in CH₂Cl₂ (0.15 mL) was added DCC (0.10 M in CH₂Cl₂, 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 (SiO₂, n-hexane/EtOAc = 1:2) afforded (S)-MTPA amide 194 (1.3 mg, 1.98 µmol, 71% for 2 steps) as a white powder.

¹H-NMR spectrum of synthetic methyl ester 192 was identical to its derived from natural brasilarcadin D (6) and ¹H-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$_3$OD. 3

![Brasilicardin A (3)](image)

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<th>$^{13}$C-NMR Chemical shifts in ppm</th>
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b) 600 MHz (CD$_3$OD, $d_3$-DMSO).
c) 151 MHz (CD$_3$OD, $d_4$-DMSO).
Table S2. Comparison of $^1$H- and $^{13}$C-NMR Spectra between Natural and Synthetic Brasilicardin B (4) in CD$_3$OD.  

![Brasilicardin B (4)](image)

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b) 500 MHz (CD$_3$OD, d$_3$).  
c) 151 MHz (CD$_3$OD, d. 49.0).  

The 3.35 ppm resonance of residual CH$_3$OH and 49.8 ppm of CD$_3$OD were used as internal references.
Table S3. Comparison of $^1$H- and $^{13}$C-NMR Spectra between Natural and Synthetic Brasilicardin C (5) in CD$_3$OD.  

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<td>13</td>
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<td>0.90 (s)</td>
</tr>
<tr>
<td>21</td>
<td>1.03 (s)</td>
<td>0.97 (s)</td>
</tr>
<tr>
<td>22</td>
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<td>1.03 (s)</td>
</tr>
<tr>
<td>23</td>
<td>23.70</td>
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</tr>
<tr>
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<td>49.8 ppm</td>
<td>4.99 (brs)</td>
</tr>
<tr>
<td>2'</td>
<td>3.99 (dd, 9.2, 1.2)</td>
<td>72.93</td>
</tr>
<tr>
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<td>73.22</td>
</tr>
<tr>
<td>4'</td>
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<td>3.77 (dd, 10.9, 2.9)</td>
</tr>
<tr>
<td>5'</td>
<td>3.35 ppm</td>
<td>3.35 ppm</td>
</tr>
<tr>
<td></td>
<td>OMe</td>
<td>3.35 ppm</td>
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</tbody>
</table>


The 3.35 ppm resonance of residual CH$_3$OH and 49.8 ppm of CD$_3$OD were used as internal references.

b) 500 MHz (CD$_3$OD, δ 3.31).

c) 125 MHz (CD$_3$OD, δ 49.0).
Table S4. Comparison of $^1$H- and $^{13}$C-NMR Spectra between Natural and Synthetic Brasilicardin D (6) in CD$_3$OD. 

<table>
<thead>
<tr>
<th>Carbon</th>
<th>$^1$H-NMR Chemical shifts in ppm [multiplicity, J (Hz)]</th>
<th>$^{13}$C-NMR Chemical shifts in ppm</th>
</tr>
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<tr>
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<td>Natural$^a$</td>
<td>Synthetic$^a$</td>
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<tr>
<td>1 (a)</td>
<td>1.82 (dd, 12.8, 4.4)</td>
<td>1.76 (dd, 12.6, 4.0)</td>
</tr>
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<td>1 (b)</td>
<td>3.46 (m)</td>
<td>1.39 (m)</td>
</tr>
<tr>
<td>2</td>
<td>3.70 (m)</td>
<td>3.64 (m)</td>
</tr>
<tr>
<td>3</td>
<td>3.03 (d, 9.4)</td>
<td>2.97 (d, 9.8)</td>
</tr>
<tr>
<td>4</td>
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<td></td>
</tr>
<tr>
<td>5 (a)</td>
<td>1.66 (m)</td>
<td>1.61 (m)</td>
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<tr>
<td>5 (b)</td>
<td>1.65 (m)</td>
<td>1.60 (m)</td>
</tr>
<tr>
<td>6 (a)</td>
<td>1.78 (m)</td>
<td>1.71 (m)</td>
</tr>
<tr>
<td>6 (b)</td>
<td>1.65 (m)</td>
<td>1.60 (m)</td>
</tr>
<tr>
<td>7 (a)</td>
<td>1.78 (m)</td>
<td>1.71 (m)</td>
</tr>
<tr>
<td>7 (b)</td>
<td>1.38 (m)</td>
<td>1.33 (m)</td>
</tr>
<tr>
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<td></td>
</tr>
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<td>9</td>
<td>3.11 (m)</td>
<td>1.26 (m)</td>
</tr>
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<td>11 (a)</td>
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<td>5.38 (m)</td>
<td>5.33 (m)</td>
</tr>
<tr>
<td>13</td>
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<td></td>
</tr>
<tr>
<td>14</td>
<td>1.61 (m)</td>
<td>1.55 (m)</td>
</tr>
<tr>
<td>15 (a)</td>
<td>1.57 (m)</td>
<td>1.50 (m)</td>
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<tr>
<td>15 (b)</td>
<td>1.46 (m)</td>
<td>1.35 (m)</td>
</tr>
<tr>
<td>16</td>
<td>3.82 (dd, 10.8, 4.0)</td>
<td>3.77 (dd, 10.9, 2.9)</td>
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<tr>
<td>OMe</td>
<td>3.53 (s)</td>
<td>3.48 (s)</td>
</tr>
<tr>
<td>17</td>
<td>4.48 (d, 3.5)</td>
<td>4.43 (d, 2.9)</td>
</tr>
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<td></td>
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<td>19</td>
<td>0.95 (s)</td>
<td>0.90 (s)</td>
</tr>
<tr>
<td>20</td>
<td>1.02 (s)</td>
<td>0.97 (s)</td>
</tr>
<tr>
<td>21</td>
<td>1.13 (s)</td>
<td>1.08 (s)</td>
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<td>1.03 (s)</td>
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<tr>
<td>23</td>
<td>1.70 (s)</td>
<td>1.64 (s)</td>
</tr>
<tr>
<td>1'</td>
<td>4.99 (bs)</td>
<td>4.93 (bs)</td>
</tr>
<tr>
<td>2'</td>
<td>3.99 (m)</td>
<td>3.22 (d, 2.9, 1.2)</td>
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<td>3.42 (t, 9.4)</td>
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<td>5'</td>
<td>3.75 (dq, 9.4, 6.4)</td>
<td>3.69 (dq, 9.2, 6.3)</td>
</tr>
<tr>
<td>6'</td>
<td>1.28 (d, 6.4)</td>
<td>1.23 (d, 6.3)</td>
</tr>
</tbody>
</table>

$^b$ The 3.35 ppm resonance of residual CH$_3$OH and 49.8 ppm of CD$_3$OD were used as internal references.
$b$) 500 MHz (CD$_3$OD, d, 3.31).
c) 125 MHz (CD$_3$OD, d, 49.0)
References and Notes


30) The use of standard AD-mix α resulted in the lower ee of 103 (94% yield, 83% ee).
32) The yield of 111 was decreased with recovery of 110 by the combined use of LiHMDS, HMPA, and TIPSCI.

\[
\begin{align*}
\text{MOMO} & \quad \text{LiHMDS} \quad \text{TIPSCI} \quad \text{HMPA} \\
\text{Me} & \quad \text{Me} \quad \text{CN} \\
\text{MOMO} & \quad \text{Me} \quad \text{Me} \\
\text{110} & \quad \text{THF} \quad \text{–78 ºC} \\
\text{MOMO} & \quad \text{Me} \quad \text{Me} \\
\text{OMe} & \quad \text{OMe} \\
\text{111 (dr > 99:1)} & \quad 50\% \\
\text{MOMO} & \quad \text{Me} \quad \text{Me} \\
\text{OMe} & \quad \text{OMe} \\
\text{110} & \quad 25\% \\
\end{align*}
\]

38) In the absence of TIPSCI, lower yield of the cyclization products and the retro-addition to form unsaturated amide 127' were observed.

\[
\begin{align*}
\text{t-BuO} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{MOMO} & \quad \text{Me} \quad \text{Me} \\
\text{127} & \quad \text{NaHMDS} \quad \text{Et}_2\text{O} \quad \text{–78 ºC} \\
\text{MOMO} & \quad \text{Me} \quad \text{Me} \\
\text{OMe} & \quad \text{OMe} \\
\text{CN} & \quad \text{CN} \\
\text{129} & \quad (\text{desired}) \quad 91:9 \quad 91\% \\
\text{MOMO} & \quad \text{Me} \quad \text{Me} \\
\text{OMe} & \quad \text{OMe} \\
\text{CN} & \quad \text{CN} \\
\text{130} & \quad \text{9\% (E/Z = 1:2)} \\
\end{align*}
\]


52) The model compound 196 was site-selectively 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.


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-cycloproplythynylbenzoate 236 with the A-ring model diol 235 proceeded in good yields, however, the regioselectivity was not improved so much.
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.

<table>
<thead>
<tr>
<th>entry</th>
<th>temp.</th>
<th>time</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt</td>
<td>5 min</td>
<td>237 : 238 : 239 = 4:2:1 (crude), 237 : 54% , 238 : 29% (isolated)</td>
</tr>
<tr>
<td>2</td>
<td>-40 °C</td>
<td>10 min</td>
<td>237 : 238 : 239 = 10:6:1 (crude)</td>
</tr>
</tbody>
</table>


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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