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Asymmetric Total Synthesis of Brasilicardins

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Abstract: Brasilicardins are bacterial diterpenoid natural products that display highly potent immunosuppressive activity; therefore, they are considered to be promising immunosuppressant drug candidates. Structurally, they can be described as hybrids of terpenoids, amino acids, and saccharides, and share a characteristic highly strained *anti-syn-anti*-fused perhydrophenanthrene terpenoid scaffold (ABC-ring system) with two quaternary asymmetric carbon atoms. Herein, we describe our design of the unified and stereoselective total synthesis of all four brasilicardins based on the strategic use of an intramolecular conjugate addition. The ABC-ring system was initially constructed with high stereocontrol by novel intramolecular conjugate additions of Weinreb amides and in situ-generated (*Z*)-vinyl copper species. The late-stage common intermediate was subjected to stereoselective installation of the amino acid component, followed by introduction of the saccharide unit via glycosylation to accomplish the total synthesis of brasilicardins A–D. Our synthesis offers opportunities to synthesize various brasilicardin analogues for biological and pharmacological investigations.

Brasilicardins A–D (**1–4**) are bacterial diterpenoid natural products isolated from the cultured broth of the actinomycete *Nocardia brasiliensis* IFM 0406, which exhibit diverse biological activities (Figure 1).^[1–3] Among these congeners, brasilicardin A (**1**) displays potent immunosuppressive activity (IC₅₀, 0.05 nM). Although the mechanism of the immunosuppressive action of **1** has not been clarified in detail, it has been suggested that it is induced by amino acid deprivation via the inhibition of the amino acid transporter system L.^[4] Currently used immunosuppressive clinical agents such as tacrolimus and cyclosporin A often cause side effects such as nephrotoxicity and arterial hypertension; therefore, an alternative to them is desired. In this context, **1** is thus considered to be a promising drug candidate. Thus, **1** has been studied with keen interest, particularly in the context of the development of new immunosuppressive drugs.^[5,6] However, further biological and pharmacological studies of **1** have not been explored because of the limited availability of **1** from natural

sources; therefore, efficient chemical syntheses of **1** and its derivatives and simplified analogues are required to aid further studies.

Figure 1. Structures of brasilicardins.

Structurally, brasilicardins A–D (**1–4**) share a unique and highly strained *anti-syn-anti*-fused perhydrophenanthrene diterpenoid carbon scaffold (i.e., the ABC-ring) containing two angular methyl groups with the B-ring boat conformer (Figure 1). To this scaffold, different amino acid and saccharide units are attached.

The combination of their distinctive biological and pharmacological properties and the novel chemical structures has made brasilicardins extremely attractive targets for synthetic organic chemists.^[6–9] However, their complex and unique three-dimensional structure has hampered their chemical synthesis. Despite considerable synthetic efforts having been undertaken for over twenty years, the sole successful total synthesis was the *de novo* construction of **1** and **3** by Anada, Hashimoto, and co-workers in 2017^[10] which involved sequential functionalization of the Wieland–Miescher ketone derivative and a Diels–Alder reaction/reductive angular methylation sequence^[7] (Scheme 1a). Herein, we report a novel and unified approach that enables the total synthesis of all brasilicardins (**1–4**), including the first total synthesis of **2** and **4**.

From a synthetic perspective, the challenges posed by brasilicardins (**1–4**) are as follows: (1) development of a stereoselective synthetic methodology for the unique carbocyclic framework (the ABC-ring), which represents the most important issue in the synthesis, (2) construction of the amino acid

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Our first objective focused on the stereoselective synthesis of the crucial precursor **15** for the first intramolecular nitrile Michael addition (Scheme 2). Monosilylation of 2,2-dimethylpropane-1,3-diol (**16**) followed by Swern oxidation of the remaining alcohol afforded the corresponding aldehyde, which underwent one-pot Horner–Wadsworth–Emmons (HWE) olefination^[17] to furnish (*E*)- α,β -unsaturated ester **17** as the sole product. Asymmetric dihydroxylation of **17** by using the

Scheme 2. Synthesis of the bicyclic intermediate **12**. TBS = *tert*-butyldimethylsilyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, MOM = methoxymethyl, LDA = lithium diisopropylamide, HMPA = hexamethylphosphoramide, TPAP = tetrapropylammonium perruthenate, NMO = *N*-methylmorpholine oxide, NaHMDS = sodium bis(trimethylsilyl)amide, DIBAL = diisobutylaluminum hydride, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, HOAt = 1-hydroxy-7-azabenzotriazole, TIPS = triisopropylsilyl, TBAF = tetrabutylammonium fluoride.

dihydroquinine-based 9'-phenanthryl ether ligand (DHQ)PHN^[18,19] quantitatively gave the optically active diol **18** with 95% ee. Protection of the diol in **18** with MOM groups, followed by reduction of the ethyl ester and iodination of the resulting alcohol, yielded alkyl iodide **19**. Alkylation of **19** with deprotonated propionitrile and the subsequent desilylation afforded alcohol **20**. This compound underwent oxidation with TPAP and HWE olefination to give (*E*)- α,β -unsaturated Weinreb amide **15** as the substrate for an intramolecular Michael addition.

We then focused on the crucial intramolecular Michael addition of **15** for the formation of the A-ring (Scheme 2). In an extensive screening of reaction conditions, it was found that when a THF solution of **15** was treated with NaHMDS at -78°C , intramolecular Michael addition proceeded stereoselectively to furnish the desired product **14** in 93% yield as a single isomer. The stereochemistry of **14** was unambiguously determined by nuclear Overhauser effect (NOE) experiments (Supporting Information, Figure S1). The observed complete stereocontrol for **14** was suggested to arise as a consequence of chelation control, wherein the keteniminate and α,β -unsaturated amide were both

oriented equatorially in an antiparallel dipolar arrangement in the transition state model (Supporting Information, Scheme S1).

The successful realization of an intramolecular nitrile Michael addition led us to the next phase of the synthesis: construction of the B-ring (Scheme 2). Thus, chemoselective reduction of the Weinreb amide over the cyano group in **14** with DIBAL followed by one-carbon homologation of the resulting aldehyde by a Wittig reagent produced enol methyl ether **21**. The product **21** was further converted to terminal alkene **23** in four steps. Introduction of the cyano group into **23** was achieved by cobalt-catalyzed hydrocyanation^[20] to give secondary nitrile **25** regioselectively. Oxidation of alcohol **25** with TPAP afforded the corresponding aldehyde, which underwent *Z*-selective HWE reaction^[21,22] to afford (*Z*)- α,β -unsaturated ester **26** (*Z/E* > 99:1). Saponification of **26** and the subsequent amidation produced the modified Weinreb amide,^[23] namely, *N-tert*-butoxy-*N*-methylamide **13**.

The second intramolecular nitrile Michael addition of **13** was the crucial factor in the present synthesis; therefore, we explored the optimal reaction conditions for this step, focusing on the solvent, additives, and reaction temperature. We found that this

Scheme 3. Stereoselective synthesis of the tricyclic compound **10**.

addition occurred upon the treatment of a mixture of **13** and TIPSCI^[15] with NaHMDs in Et₂O at -78°C , which produced *O*-silyl *N,O*-ketene acetal **27** in situ. Upon addition of TBAF to **27**, the desired cyclization product **12** was obtained as a 93:7 inseparable mixture of diastereomeric products (88% yield). Importantly, in this cyclization, 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 product (for comparison with the cyclization of other precursors, see Scheme S2 in the Supporting Information). The steric repulsions between the large substituents are likely to account for the stereochemical outcome (Supporting Information, Scheme S3). These key nitrile Michael additions (i.e., **15**→**14** and **13**→**12**) were reliably performed on a gram scale, which demonstrated the significant synthetic utility of this methodology.

Having developed a method for the construction of the AB-ring including two quaternary asymmetric stereocenters based on the strategic nitrile Michael additions, we next focused on the third intramolecular Michael addition, which leads to the ABC-ring of brasilicardins (Scheme 3). To this end, Weinreb amide **12** was converted to 1,1-dibromoalkene **11**, the requisite cyclization precursor, in a four-step sequence: (1) chemoselective DIBAL reduction of the Weinreb amide moiety in **12** to an aldehyde, (2) Corey–Fuchs olefination, wherein the minor diastereomer of **12** was separated, (3) reduction of the cyano group to an aldehyde, and (4) HWE olefination of the resulting aldehyde.

The third intramolecular Michael addition for constructing the C-ring proceeded smoothly under the reaction conditions used^[16] (Scheme 3): treating **11** with Me₂CuLi (5 equiv) at -78°C in Et₂O for 30 min generated the (*Z*)-vinylcopper species **29** in situ. After the reaction mixture was warmed up to -40°C and then stirred at this temperature for 1 h, the subsequent conjugate addition of **29** to the α,β -unsaturated ester moiety proceeded smoothly in the one-pot system to furnish the tricyclic compound **10** with controlled stereochemistry at the C14 position (83% yield). The structure of **10** was verified by X-ray crystallographic analysis (Scheme 3). In this way, we established a novel method for the stereoselective construction of the *anti-syn-anti*-fused perhydrophenanthrene skeleton (the ABC-ring) by triple intramolecular Michael additions as the key steps.

On obtaining the tricyclic compound **10**, we directed our attention to installation of the appropriate amino acid portion to this skeleton (Scheme 4). Initially, we investigated installation of a β -methoxy amino acid for brasilicardins A and C, which was succeeded by application of Rama Rao's procedure^[24] (Scheme 4a). Half-reduction of **10** followed by HWE reaction of the resulting aldehyde yielded α,β -unsaturated *tert*-butyl ester **30**. Asymmetric dihydroxylation of **30** using (DHQ)PHN-ligand^[18] gave the desired diol **31** as a single diastereomer. Regioselective nosylation at the C17 alcohol of **31** produced mono-nosylate **32**, and subsequent treatment of **32** with NaN₃ afforded α -azide **33** with complete inversion of the configuration. *O*-Methylation of **33** followed by reduction of the azide and protection of the resulting amine with a Fmoc group resulted in the formation of the protected amino acid of brasilicardins A and C. Finally, removal of both MOM groups with HCl in methanol produced diol **8**. Stereochemistry of the amino acid component was verified by X-ray crystallographic analysis after the conversion to the corresponding *p*-bromobenzamide derivative of **8** (Supporting Information, Figure S2).

On the other hand, installation of the amino acid component of brasilicardins B and D was performed by asymmetric alkylation of the chiral Schiff base^[25] as the key step (Scheme 4b). Thus, ethyl ester **10** was converted to iodide **34** through LiAlH₄ reduction and iodination of the resulting alcohol. Alkylation of the readily available chiral Schiff base derived from glycine **35** with **34** proceeded smoothly when KHMDS was used as the base, providing the alkylation product **36** as the sole isomer. This compound was converted to diol **9** in three steps, i.e., removal of the chiral auxiliary group, Fmoc-protection of the resulting free-amine, and deprotection of the MOM groups. Stereochemistry of the amino acid portion was confirmed by the modified Mosher's method^[26] (Supporting Information, Scheme S4).

The final task in the synthesis was the challenging glycosylation of aglycons **8** and **9** (Scheme 5). First, the glycosylation of **8** toward brasilicardin A (**1**) was explored (Scheme 5a). Although Anada and Hashimoto's group succeeded in glycosylation of the C3-protected aglycon of **1** with the trichloroacetimidate donor of the disaccharide unit,^[8,10] this procedure could not be applicable to diol **8** because the formation of complex mixtures including the inseparable C3

Scheme 4. Stereoselective synthesis of the protected brasilicardin aglycons **8** and **9**. *p*-Ns = 4-nitrobenzenesulfonyl, Su = succinimidyl, Fmoc = 9-fluorenylmethyloxycarbonyl, KHMDS = potassium bis(trimethylsilyl)amide.

glycosylation product and degradation of **8** were observed. To our delight, after extensive screening of glycosyl donors and their activation conditions, the metallocene-based activator Cp₂HfCl₂/AgOTf^[27] allowed the regio- and stereoselective coupling of peracetyl glycosyl fluoride **38** (2 equiv) with **8** to give the desired α -glycoside **39** (with 43% of **8** recovered). Because the prolonged reaction time caused an undesired reaction at the C3 alcohol, this coupling was carefully stopped before full consumption of **8**, with recovery of unreacted **8**. Finally, removal of the *tert*-butyl ester using TFA followed by global deprotection of the acetyl and Fmoc groups furnished brasilicardin A (**1**) (43% yield, three steps). Confirming the identity of our synthesized sample was challenging because the ¹H-NMR spectrum of the compound proved highly dependent on the concentration and pH. However, its identification was achieved using ¹H-NMR spectrum of a mixture of synthetic and natural brasilicardin A in a 1:1 ratio after both materials were purified by reverse phase semi-preparative HPLC (Capcell Pak C18 SG120). Further, the fact that the ¹³C-NMR, IR, and HRMS spectra and optical rotation results for the synthesized product matched those of the natural sample supported successful synthesis of our desired product, as did the narrow range obtained for the melting temperature of the mixture. Brasilicardin B (**2**) was also synthesized from **9** using the same conditions as those used for **1**.

Achievement of total synthesis of **1** and **2** prompted us to pursue the total synthesis of brasilicardins C (**3**) and D (**4**) (Scheme 5b). Unlike the glycosylation with disaccharide **38**, glycosylation of the glycosyl fluoride donor derived from rhamnose with diols **8** or **9** did not show any regioselectivity at the C2 alcohol. Attempted use of other donors also failed.

Consequently, the C3 alcohol was temporary protected as an easily removable methoxyacetate,^[28] and the requisite mono-alcohols **41** and **42** were synthesized from **8** and **9**, respectively, through a three-step conversion. Toward the synthesis of total synthesis of brasilicardin C, we found that gold-catalyzed coupling^[29] of glycosyl *o*-cyclopropylethynylbenzoate **43** with **41** proved to be the most effective method for stereoselective installation of a rhamnose, providing the glycosylation product **44**. This compound was successfully converted to brasilicardin C (**3**) via TFA-mediated removal of *tert*-butyl ester and the subsequent global deprotection of the remaining acetyl, methoxyacetyl, and Fmoc groups with aqueous lithium hydroxide solution. In addition, brasilicardin D (**4**) was obtained from **42** via a similar sequence as that described for **3**. Thus, we accomplished the first total synthesis of brasilicardin B (**2**) and brasilicardin D (**4**) in addition to the total synthesis of brasilicardin A (**1**) and brasilicardin C (**3**).

In conclusion, we have developed a stereoselective synthetic route to synthesize brasilicardins with potent immunosuppressive activity, utilizing which we 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 readily available commercial materials. The synthesis features (1) the development of 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, (2) a Michael addition-based strategy for the stereoselective formation of the highly strained

Scheme 5. Total synthesis of brasilicardins A–D. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, MS4A = molecular sieves 4A, TFA = trifluoroacetic acid. Tf = trifluoromethanesulfonyl.

anti-syn-anti-fused perhydrophenanthrene skeleton (the ABC-ring), (3) stereoselective installation of the amino acid component to the terpenoid core, and (4) regio- and stereoselective glycosylation using glycosyl fluoride or *o*-alkynylbenzoate as the glycosyl donor. Our strategy allowed the unified synthesis of all brasilicardins from the common late-stage intermediate utilizing the appropriate installation methods for an amino acid and glycosylation. The novel synthetic route developed here would accelerate the synthesis and biological studies of brasilicardins 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.

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**Asymmetric Total Synthesis of
Brasilicardins**

The asymmetric total synthesis of brasilicardin A, a hybrid natural product with highly potent immunosuppressive activity, has been developed. The synthesis features a Michael addition-based strategy for the stereoselective formation of the highly strained *anti-syn-anti*-fused perhydrophenanthrene skeleton, and brasilicardins B–D are also synthesized based on the unified approach.