Novel Bis(indole) Alkaloid Dragmacidin D: Synthetic Quest for the Last 13 Years
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Abstract
Dragmacidin D, a bis(indole) alkaloid was isolated from deep water marine sponge in 1992 and 1998. The structural feature consists of two unsymmetrically substituted indole moiety connected through a pyrazinone linker and has a polar aminoimidazole moiety. Due to remarkable structural features and diverse biological properties, dragmacidin D has attracted attention from synthetic community. In this review, the syntheses of dragmacidin D for the last 13 years are briefly summarized.

Keywords: Dragmacidin, alkaloid, marine sponge, pyrazinone.

Isolation and biological activities

Dragmacidin D, a novel bis(indole) alkaloid, was isolated from a deep-water marine sponge of the genus *Spongosorites* by Wright and co-workers in 1992. Subsequently, Capon and co-workers reported the isolation and structure determination of dragmacidin D from a *Spongosorites* collected during a trawling operation off the southern coast of Australia in 1998. It displays a broad array of biological activity including the growth inhibition of feline leukemia virus, fungal pathogens *Cryptococcus neoformans* and *Candida albicans*, and the P388 and A549 tumor cell lines. It is also a selective potent inhibitor of serine-threonine protein phosphatases PP1 and neutral nitric oxide synthase (bNOS) in the presence of inducible NOS (iNOS). The ability of selective bNOS growth inhibition may be useful in a variety of therapeutic areas including the treatment of Alzheimer’s, Parkinson’s, and Huntington’s diseases. Beyond its biological activities, dragmacidin D comprises two differentially substituted indoles connected through a pyrazinone linker and a polar aminoimidazole unit. Due to its unique chemical structure and promising biological activities, it has been selected as a synthetic target by many chemists. Syntheses of (±)-dragmacidin D was reported by Brian M. Stoltz in 2002 using Suzuki–Miyaura cross-coupling reactions as key reactions, by Itami in 2011 using direct C–H coupling reactions and synthesis of key intermediate by Sasaki in 2011. Asymmetric synthesis was reported by Capon and Jia in 2015.

Brian M. Stoltz (2002)

Brian M. Stoltz reported the first synthesis of (±)-dragmacidin D using halogen-selective Suzuki–Miyaura coupling reactions as key steps. The retrosynthetic sequences for the synthesis of dragmacidin D was using metal catalyzed cross-coupling approach: synthesis of the central bis(indolyl)pyrazine moiety using two sequential palladium catalyzed Suzuki–Miyaura couplings between metalated indole moieties and 5-bromo-2-iodo-3 methoxypyrazine. Formation of a polar, unstable aminoimidazole ring was planned at the late stage of the synthesis. Vinyl bromide derivative 5 and nitromethane could be viewed as four-carbon equivalent of the aminoimidazole moiety. The vinyl bromide could be connected to the indole moiety through another Suzuki coupling reaction followed by functionalization with nitromethane and the guanidine moiety would lead to the formation of the aminoimidazole unit (Scheme 1).
The Suzuki–Miyaura coupling approach for the construction of the bis(indolyl)pyrazinone framework of dragmacidin D is discussed below (Scheme 2). Firstly, the coupling partners were synthesized. The synthesis of 3,4,7-trisubstituted indole subunit 12 was commenced with 1-(benzyloxy)-4-bromo-2-nitrobenzene 6. Treatment of 6 with vinyl Grignard reagent gave indole 7 in 33% yield through the Bartoli indole synthesis. SEM protection of the indole nitrogen followed by the treatment with t-BuLi and dioxaborolane 9 produced dioxaborolanated indole 10 in 68% yield. Then Suzuki coupling between dioxaborolanated indole 10 and vinyl bromide 5 furnished coupling product 11 in 83% yield. Hydrogenation of the terminal olefin of 11 with \( \text{H}_2 \), Pd/C followed by C3-selective bromination, lithiation, treatment with dioxaborolane produced 3,4,7-trisubstituted indole derivative 12 in 66% yield. 5-Bromo-2-iodo-3-methoxypyrazine (3) was synthesized from 5-bromo-3-methoxypyrazin-2-amine (13) by the treatment with HI and NaNO\(_2\) in 58% yield. Bromoindole boronic acid derivative 16 was synthesized from 6-bromoindole (14) in three steps with good yield. N-tosyl protection of 6-bromoindole (14) followed by treatment with Hg(OAc)\(_2\) generated 15 in 97% yield. Reaction of 15 with BH\(_2\)-THF/H\(_2\)O provided bromoindole boronic acid derivative 16 in 85% yield.
Scheme 2. Synthesis of Suzuki–Miyaura coupling partners

After completion of the synthesis of Suzuki–Miyaura coupling partners, they were subjected to sequential Suzuki couplings for the formation of bis(indolyl)pyrazine 16. The Suzuki coupling between 5-bromo-2-iodo-3-methoxy pyrazine (3) and 6-bromo-N-tosylindole-3-yl boronic acid 16 proceeded smoothly to give the selective coupling product 17 in 71% yield. The next Suzuki coupling between bromopyrazine 17 and pinacol boronate 12 furnished the desired bis(indolyl)pyrazine 18 in 82% yield.

Scheme 3. Completion of (±)-dragmacidin D synthesis
Bis(indolyl)pyrazinone 18 was converted to aldehyde 19 through two step sequence. Aldehyde 19 was then transformed into α-nitroketone 20 using CH$_3$NO$_2$ followed by Dess−Martin oxidation in 98% yield. Removal of the N-tosyl protecting group using ethanolic KOH followed by LiBF$_4$ promoted hydrolysis of N-SEM provided 21 in 99% yield. Reduction of the α-nitro to an α-amino group using SnCl$_2$ followed by iodotrimethylsilane (TMSI) mediated removal of the O-benzyl and methyl ethers were accomplished in 86% yield. Finally, the conversion of the α-amino ketone to an aminoisimazole moiety by the treatment with NH$_2$CN followed by CF$_3$CO$_2$H led the completion of (±)-dragmacidin D in 86% yield.

Itami and Yamaguchi (2011)$^5$

In the first synthesis of (±)-dragmacidin D, Stoltz used Pd(0)-catalyzed Suzuki–Miyaura cross-coupling reactions as the key reactions. It can be emphasized that the cross-coupling reaction is one of the most reliable method for the formation of C–C bonds in total synthesis as exemplified by Stoltz’s work. However, several steps are required for the activation of both coupling partners (organometalics and organic halides) prior to cross coupling. Recently, adapting the concept of “cross-coupling” into “direct-coupling” has shed new light in the field of organic synthesis.$^4$ Aiming for a step-

 economical synthesis of dragmacidin D, Itami et al have planned to convergently connect its building blocks using direct C–H couplings. The retrosynthetic planning is shown in Scheme 4. Dragmacidin D has a bis(indolyl)pyrazinone unit at its core and a polar aminoisimidazole moiety. The aminoisimidazole unit is connected to the C4 position through a sp$^3$ carbon bridge. The most direct way to install the two-indole moieties on to the central pyrazinone is C–H/C–H coupling reaction. To enhance the reactivity and to control the regioselectivity in the coupling, it was planned to capitalize on the tautomeric switch between pyrazinone and pyrazine N-oxide. Firstly, connecting the indole derivative 22 with the most acidic C2-carbon of pyrazine N-oxide 23 was planned through an indole–azine C–H/C–H coupling reaction. The installation of 6-bromoindole on the pyrazinone form could be envisioned through an oxidative Friedel–Crafts-type C–H/C–H coupling reaction. This sequence was designed so that the oxidation state of the central pyrazine moiety would remain unaltered throughout the synthesis. On the other hand, the thiophene moiety with an oxygen substituent at C3 position could be envisaged as a four-carbon unit equivalent of the aminoisimidazole side chain. Thiophene derivative 25 could be then connected to the indole moiety through a C4-selective thiophene–indole C–H/C–I coupling reaction.

Scheme 4. C–H coupling strategy for the synthesis of dragmacidin D

At the outset of the synthesis, the sequential key C–H couplings were planned: the indole–thiophene C–H/C–X coupling, the indole–azine C–H/C–H coupling, followed by the Friedel–
Crafts type C–H/C–H coupling. Synthesis began with the iodoindole derivative 27, which was easily synthesized through a known four steps from the commercially available 7-(benzyloxy)indole. Final sequence toward dragmacidin D synthesis is shown in Scheme 5.

Scheme 5. Synthesis of (±)-dragmacidin D

The iodoindole derivative 27 was treated with the 3-(triisopropylsilyloxy) thiophene 28 in the presence of a catalytic system 10 mol% Pd(OAc)$_2$, 20 mol% P[OCH(CF$_3$)$_2$], and 1.0 equiv Ag$_2$CO$_3$ in 1,4-dioxane at 140 ºC to give the desired C4 coupling product 29 in 60% yield. Although 3.0 equiv of thiophene 28 was used but 86% of unreacted thiophene was recovered after the reaction. Removal of the triisopropylsilyl group using Bu$_3$NF/CH$_3$CO$_2$H followed by the treatment with Raney Ni, allowed for concomitant reduction of the thiophene and debenzoylation to afford the corresponding methyl ketone 30 in a one-pot process in 77% yield. Deprotection of N-tosyl group followed by methoxymethyl (MOM) protection delivered the bis-MOM protected indole 31 in 91% yield after two steps. Then the bis-MOM indole was coupled with pyrazine N-oxide in the presence of 10 mol% Pd(OAc)$_2$, and 3.0 equiv AgOAc in 1,4-dioxane at 120 ºC to produce the C3 selective indole–azine C–H/C–H coupling product in 50% yield after one recycle. The low yield in the indole–azine C–H/C–H coupling reaction could be
accounted from the low reactivity of indole 31 at C3 position. The low reactivity of indole 31 at C3 position could be explained on the basis that the C4 ketomethyl moiety sterically and electronically opposed the functionalization at the C3 position of indole. However, the starting materials, indole and pyrazine N-oxide were recovered quantitatively, and can be resubjected for the C–H/C–H coupling reaction to furnish the coupling product in 50% yield. Despite the moderate yield, the reaction produced the coupling product regioselectively. Treatment of the coupling product with trifluoroacetic anhydride furnished the C2-pyrazinone 33. Notably, the ratio of desired pyrazinone 33 over the undesired regioisomeric pyrazinone was 5:1. The Friedel–Crafts type oxidative C–H/C–H coupling reaction between (indolyl)pyrazinone 33 and 6-bromoindole in the presence of CF₃SO₂H and air at 80 °C afforded the coupling product bis(indolyl)pyrazinone 34 with concomitant removal of the two MOM groups in 57% yield after two steps. The next aim was to install a polar aminimidazole moiety to complete the synthesis of dragmacidin D (Scheme 5). For this purpose, firstly the α-bromination of ketone moiety of 34 gave α-bromo ketone 35. Indole 34 was treated with excess of TMSOTf in the presence of i-Pr₂NEt to produce the corresponding silyl enol ether. The silyl enol ether was then selectively brominated using N-bromosuccinimide in the presence of CF₃CO₂H to provide α-bromoketone 35. Finally, the transformation of a α-bromoketone to N-Boc aminimidazole moiety using (Boc)guanidine followed by CF₃CO₂H mediated deprotection of the Boc group led to the completion of (±)-dragmacidin D synthesis efficiently and step-economically in a total of 15 synthetic operations.


Makoto Sasaki reported the synthesis of the left-hand fragment of dragmacidin D followed by the synthesis of key advanced intermediate toward the synthesis of dragmacidin D using sequential Sonogashira and Suzuki–Miyaura coupling reactions in 2008 followed by 2011.

![Scheme 6. Sasaki’s synthetic strategy for dragmacidin D](image-url)
The synthetic strategy is comprised of a final stage asymmetric hydrogenation of the alkene moiety of intermediate 36 for the incorporation of an asymmetric carbon center at C6” in dragmacidin D (Scheme 6). The central pyrazinone ring in 36 could be formed via Staudinger/aza-Wittig reaction followed by oxidation of 37. Aylation of azidoamine 39 with oxoacetylchloride 38 could lead to the formation of 37. Azidoamine 39 could be formed via Suzuki coupling between imidazolylboronic acid 40 and indolylvinyl bromide 41, which in turn could be synthesized from 4-bromo-7-methoxy indole through Sonogashira coupling followed by Mannich-type Friedel–Crafts reaction.

For the synthesis of advanced intermediate 37, Suzuki–Miyaura coupling partners 40 and 41 were synthesized (Scheme 7). The imidazole nitrogen was protected using methoxymethyl chloride to give the N-MOM imidazole 44 in 99% yield. Treatment of N-MOM imidazole with n-BuLi followed by diphenyldisulfide at –78 °C produced the phenylsulfide imidazole 45 in 62% yield. Next, reaction of phenylsulfide imidazole with n-BuLi followed by trimethyl borate and acidic work-up furnished imidazole boronic acid derivative 40 in 77% yield. In the synthesis of indolylglycine fragment 46, 4-bromo-7-methoxyindole (42) was reacted with p-anisidine and ethyl glyoxylate in CH₂Cl₂ to produce 46 in 83% yield. Tosyl protection of the indole nitrogen followed by removal of the amine protecting group using cerium ammonium nitrate (CAN) furnished amine 48. Then, the free amine group was protected as an N-Boc group using Boc₂O.

Scheme 7. Synthesis of Suzuki–Miyaura coupling fragments
The Suzuki–Miyaura coupling between 4-bromoindole derivative 49 and ethynyltriisopropylsilane delivered the coupling product 50 in 92% yield. Tetra-butyrammonium fluoride-facilitated deprotection of triisopropylsilyl group followed by bromination of the alkyne moiety using HBr·CH₂CO₂H afforded vinyl bromide 41, the precursor of the subsequent Suzuki–Miyaura coupling reaction. The Suzuki–Miyaura coupling reaction between vinyl bromide 41 and imidazole boronic acid 40 delivered the coupling product 52 in 61% yield. Then, the carboxylic ester of 52 was reduced to primary alcohol using LiBH₄ followed by tosylation protection of alcohol in 61% yield. Replacement of OTs group by azide using NaN₃ delivered azide 54. CF₃CO₂H facilitated N-Boc deprotection followed by condensation with oxoacetylchloride led the synthesis of advanced intermediate 37.

Scheme 8. Synthesis of an advanced intermediate toward the synthesis of dragmacidin D

**Asymmetric Synthesis: Capon and Jia (2015)**

During the isolation and structure elucidation of dragmacidin D by Capon and co-workers in 1998, the optical rotation [α]₀ was determined +12°. However, the absolute stereochemistry at C₆‴ of dragmacidin D remained unresolved still 2015. Robert J. Capon and Yanxing Jia reported the first asymmetric total synthesis of (+)-dragmacidin D and established the R absolute configuration at C₆‴. The retrosynthetic analysis comprised: installment of aminimidazole moiety at the final stage of synthesis from bis(indolyl)pyrazinone 55. The central pyrazinone unit of compound 55 was planned to synthesize through the condensation between indole moiety 56 and 6-bromoindole acid chloride 38 followed by oxidative aromatization. Compound 56 could be synthesized from 57 using known chemistry. The installment of stereogenic center of indole 57 was envisioned using Evan’s chiral auxiliary. Compound 58 was planned to synthesize from 59 which could be synthesize through Heck coupling of ortho-idoaniline 60 and butaldehyde 61.
Asymmetric synthesis is commenced with the reaction between 2-iodo-6-benzoxyaniline 61 and butaldehyde 60 in the presence of Pd(OAc)$_2$ to give indole 62 in 70% yield. N-Boc protection of indole N-H using (Boc)$_2$O followed by chemoselective iodination at C-4 position of indole using NIS in the presence of AcOH produced 4-iodoindole 63 in 88% yield. Heck reaction between 63 and Evan’s chiral auxiliary derivative 64 in presence of Pd(OAc)$_2$, Ag$_2$CO$_3$ under ligand-free conditions gave 58 in 82% yield (E/Z 7:2, which are not separable using flash column chromatography). Reaction of 58 with methyl cuprate generated from MeMgBr and CuBr$_2$:SMe$_2$ followed by removal of Evan’s chiral auxiliary using MeOMgBr generated the desired methyl ester 57 in 90% yield. The newly stereogenic center is formed in this reaction and the configuration was confirmed S. Compound 57 was converted to amine 56 in seven step sequence in 63% yield. Compound 57 was treated with HF-pyr to deprotect the OTBDPS group followed by Mitsunobu reaction with PPh$_3$ and diphenylphosphoryl azide (DPPA) generated the corresponding azide. Staudinger reduction of azide using PPh$_3$, deprotection of indole N-Boc using TFA, selective Boc protection of primary amine using (Boc)$_2$O followed by reaction with DDQ/TMSN$_3$ and reduction of azide using NaBH$_4$/NiCl$_2$ generated amine 56. Condensation of amine 56 with 6-bromoindole oxalyl chloride 38 followed by dprotection of NHBoc using TFA and DDQ promoted oxidative aromatization generated (bisindolyl)pyrazinone 55 in 50% yield. For the installment of aminomidazole moiety final three-step sequence was followed. Pyrazinone 55 was reacted with pyrazole-1-carboxamidine 66 in presence of Et$_3$N, DMAP to generate 67 in 80% yield. Reduction of methyl ester using DIBAL-H generated aza-hemiacetal, which in presence of TFA formed the aminomidazole ring followed by removal of SEM protection produced pyrazinone moiety. Finally, deprotection of OBn group using BBr$_3$ completed the asymmetric synthesis of (+)-dragmacidin D in 20% yield.

**Conclusion**

During last 13 years, the synthetic road for the synthesis of novel bis(indole) alkaloid dragmacidin D was garnished by various kinds of exciting chemistry. Since the first isolation of dragmacidin D in 1992, first synthesis of (±)dragmacidin D by Stoltz in 2002, efficient 15 step synthesis of (±)dragmacidin D by Itami in
2011. In 2015, Capon and Jia confirmed the absolute configuration of stereogenic center of dragmacidin D to be R via the completion of asymmetric synthesis of dragmacidin, which would lead to the detailed study of biological properties in future.

![Scheme 10. Asymmetric Synthesis of Dragmacidin D](image)

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