Novel Bis(indole) Alkaloid Dragmacidin D: Synthetic Quest for the Last 13 Years

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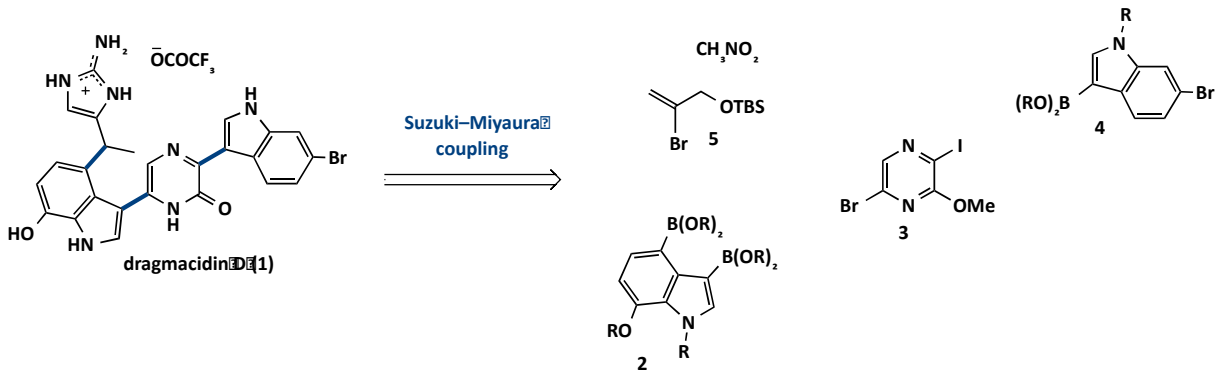
Abstract
Dragmacidin D, a bis(indole) alkaloid was isolated from deep water marine sponge in 1992 and 1998. The structural feature consists of two unsymmetrically substituted indole moiety connected through a pyrazinone linker and has a polar aminoimidazole moiety. Due to remarkable structural features 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.[1] 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.[2] 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 (±)-dragamcidin D was reported by Brian M. Stoltz in 2002 using Suzuki–Miyaura cross-coupling reactions as key reactions,[3] by Itami in 2011 using direct C–H coupling reactions[5] and synthesis of key intermediate by Sasaki in 2011.[6,7] Asymmetric synthesis was reported by Capon and Jia in 2015.[8]

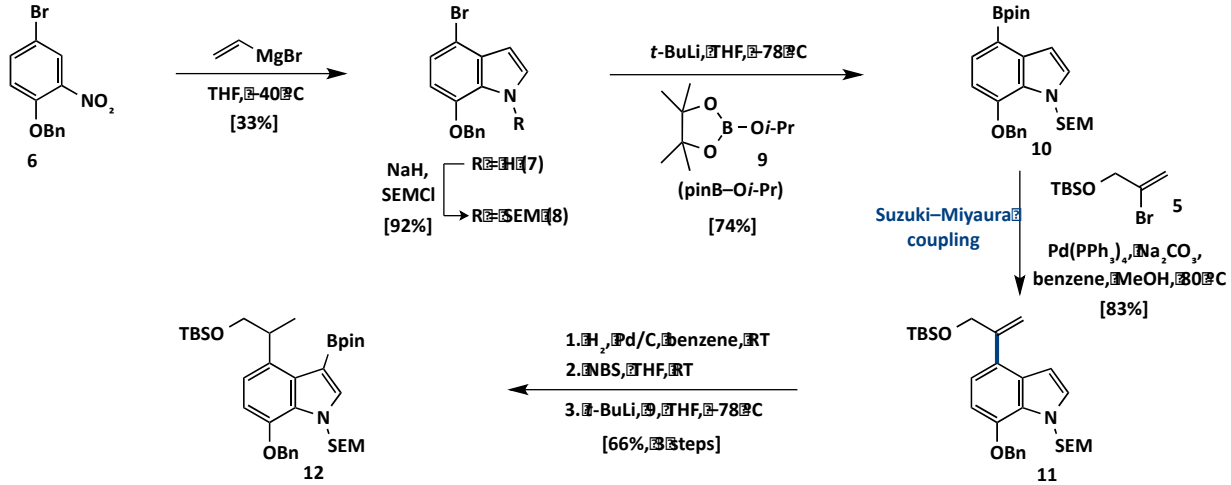
Brian M. Stoltz (2002)[3]

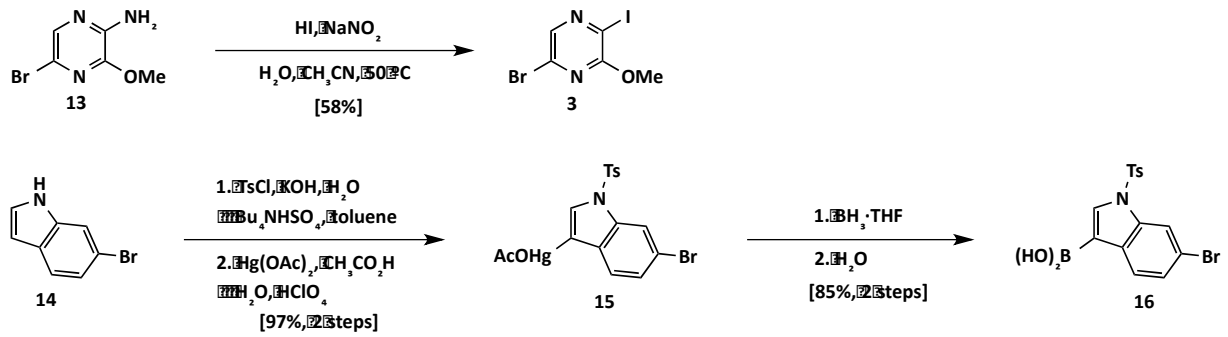
Brian M. Stoltz reported the first synthesis of (±)-dragmacidin D using halogen-selective Suzuki–Miyaura coupling reactions as key steps. The retrosynthetic sequences for the synthesis of dragmacidin D was using metal catalyzed cross-coupling approach: synthesis of the central bis(indolyl)pyrazine moiety using two sequential palladium catalyzed Suzuki–Miyaura couplings between metalated indole moieties **2**, **4** and 5-bromo-2-iodo-3 methoxypyrazine **3**. 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).



Scheme 1. Retrosynthetic planning by Stoltz

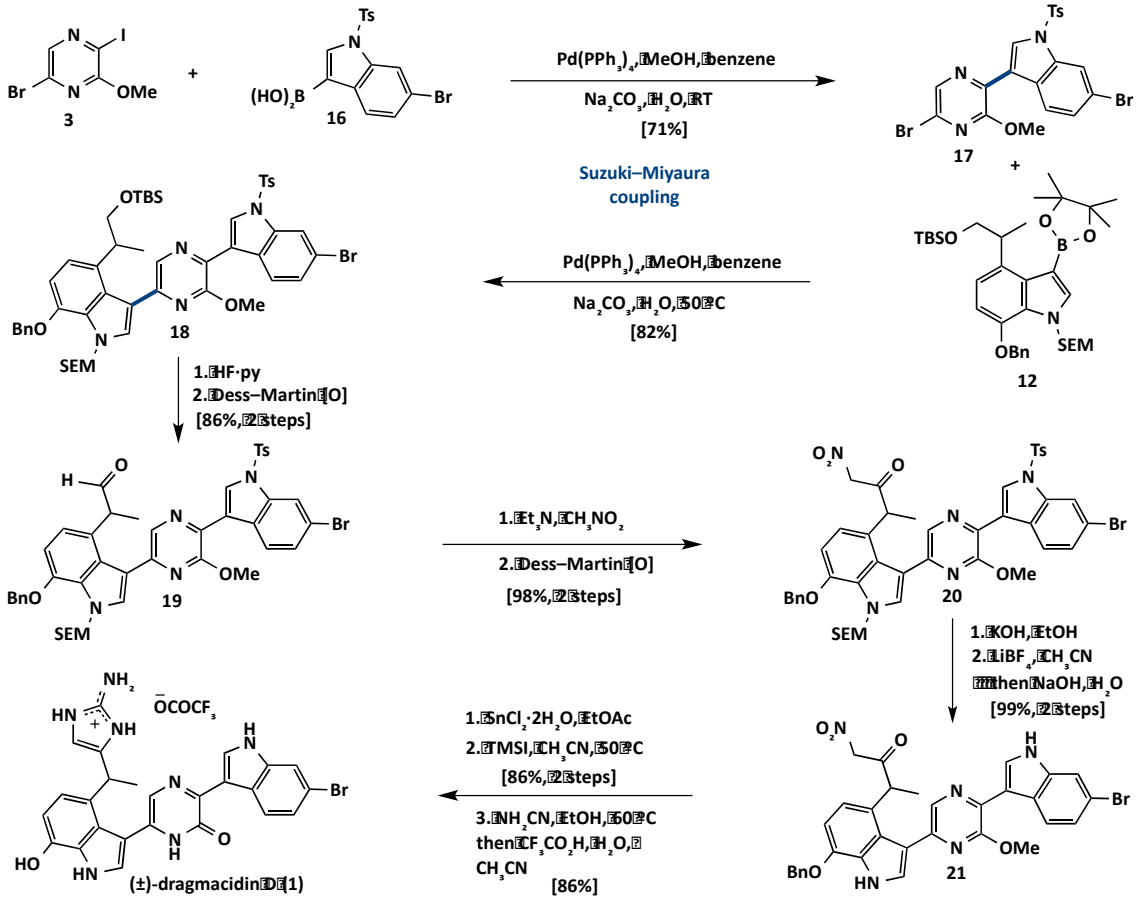
The Suzuki–Miyaura coupling approach for the construction of the bis(indolyl)pyrazinone framework of dragmacidin D is discussed below (Scheme 2). Firstly, the coupling partners were synthesized. The synthesis of 3,4,7-trisubstituted indole subunit **12** was commenced with 1-(benzyloxy)-4- bromo-2- nitrobenzene **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 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_3·THF/H_2O 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 **18**. The Suzuki coupling between 5-bromo-2-iodo-3-methozxy 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.

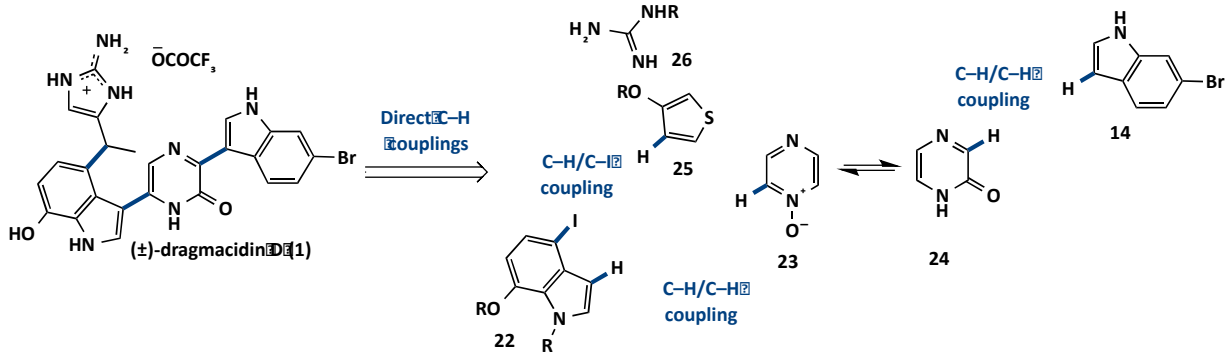


Scheme 3. Completion of (±)-dragmacidin D synthesis

Bis(indolyl)pyrazinone **18** was converted to aldehyde **19** through two step sequence. Aldehyde **19** was then transformed into α-nitroketone **20** using CH_3NO_2 folowed 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-aminoketone to an aminoimidazole moiety by the treatment with NH_2CN followed by CF_3CO_2H led the completion of (±)-dragmacidin D in 86% yield.

Itami and Yamaguchi (2011)[5]

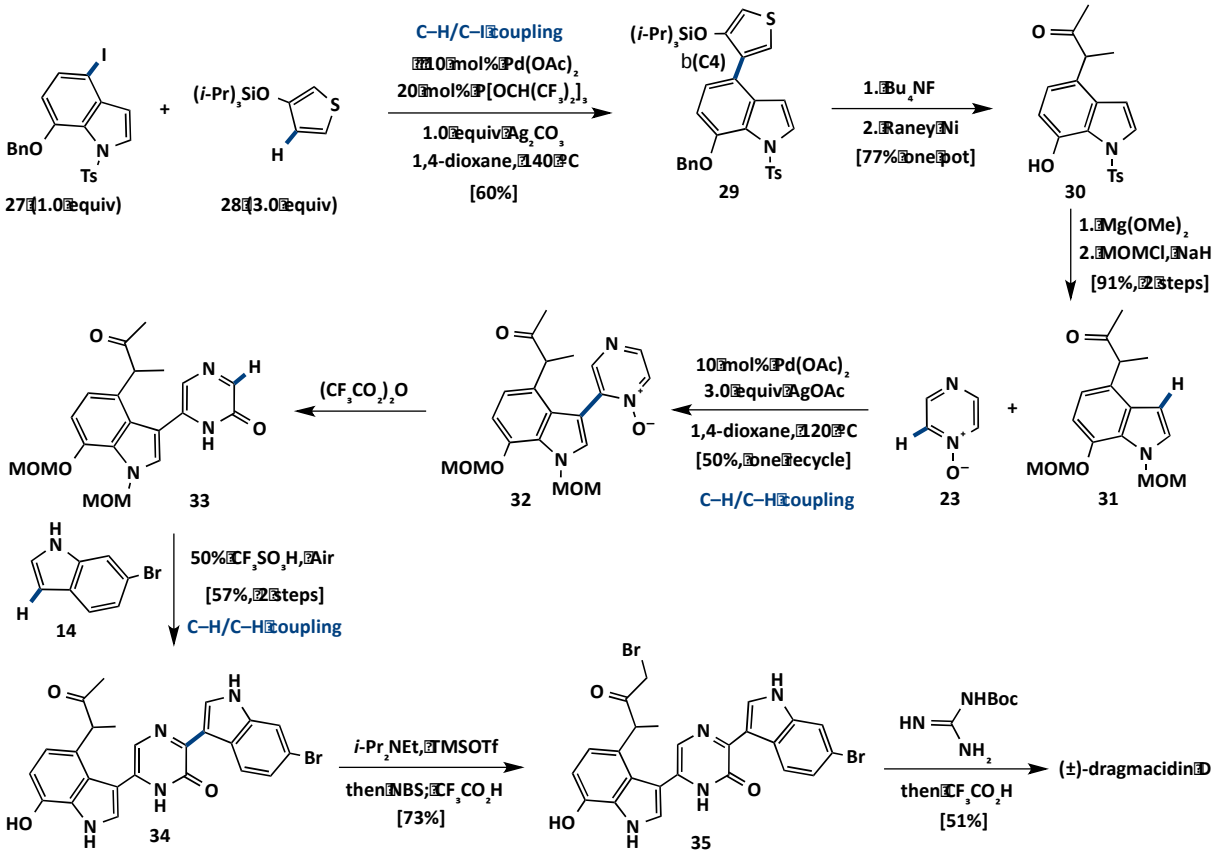
In the first synthesis of (±)-dragmacidin D, Stoltz used Pd(0)-catalyzed Suzuki–Miyaura cross-coupling reactions as the key reactions. It can be emphasized that the cross-coupling reaction is one of the most reliable method for the formation of C–C bonds in total synthesis as exemplified by Stoltz's 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 aminoimidazole moiety. The aminoimidazole 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 aminoimidazole 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.



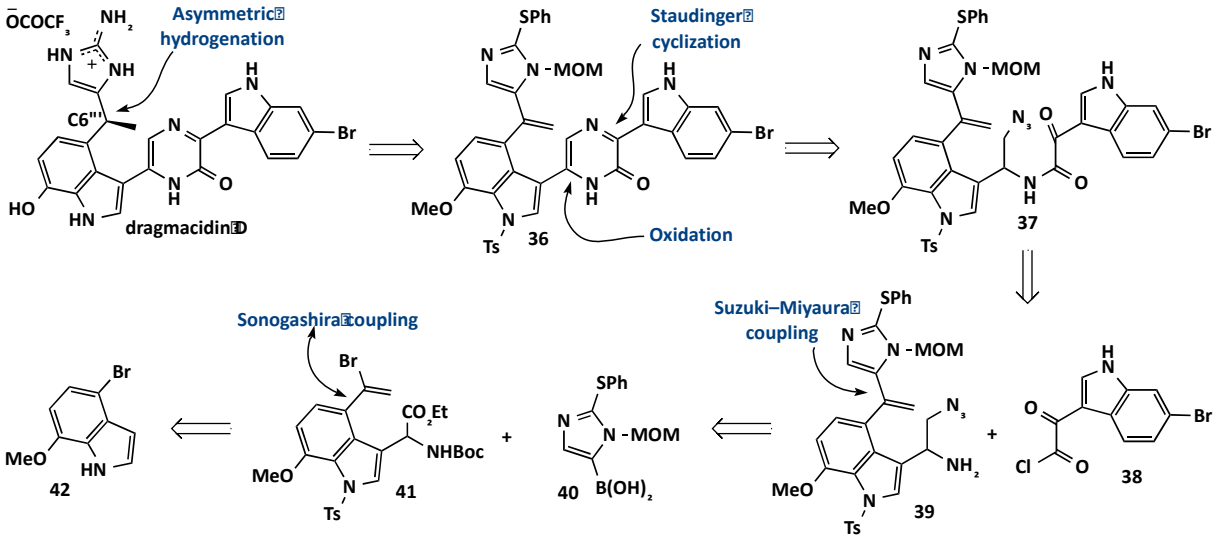
Scheme 5. Synthesis of (±)-dragmacidin D

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% $P[OCH(CF_3)_2]_3$, and 1.0 equiv Ag_2CO_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_4NF/CH_3CO_2H followed by the treatment with Raney Ni, allowed for concomitant reduction of the thiophene and debenzylation 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 CF_3SO_3H and air at 80 ºC 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 aminoimidazole 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*-Pr_2NEt to produce the corresponding silyl enol ether. The silyl enol ether was then selectively brominated using *N*-bromosuccinimide in the presence of CF_3CO_2H to provide α-bromoketone **35**. Finally, the transformation of a α-bromoketone to *N*-Boc aminoimidazole moiety using (Boc)guanidine followed by CF_3CO_2H 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 (2008, 2011)[6,7]

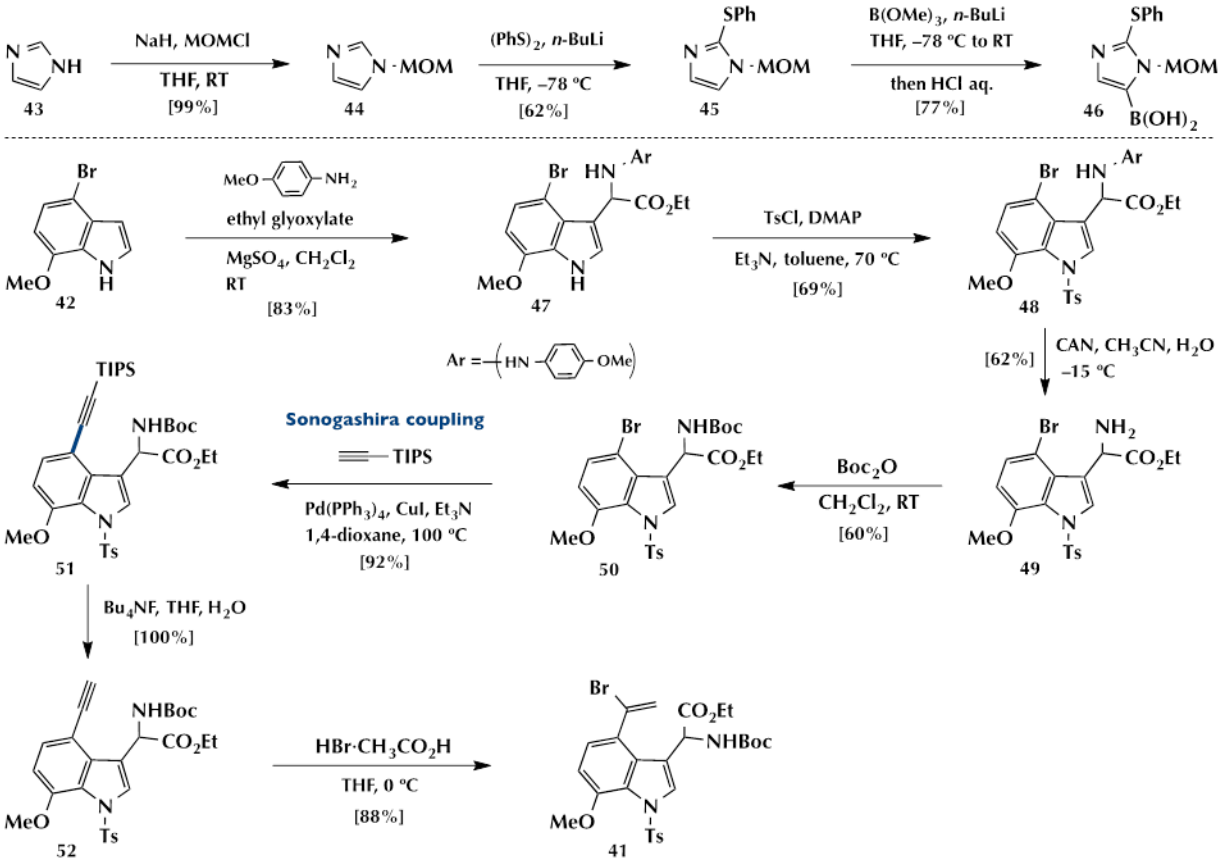
Makoto Sasaki reported the synthesis of the left-hand fragment of dragmacidin D followed by the synthesis of key advanced intermediate toward the synthesis of dragmacidin D using sequential Sonogashira and Suzuki–Miyaura coupling reactions in 2008 followed by 2011.



Scheme 6. Sasaki's synthetic strategy for dragmacidin D

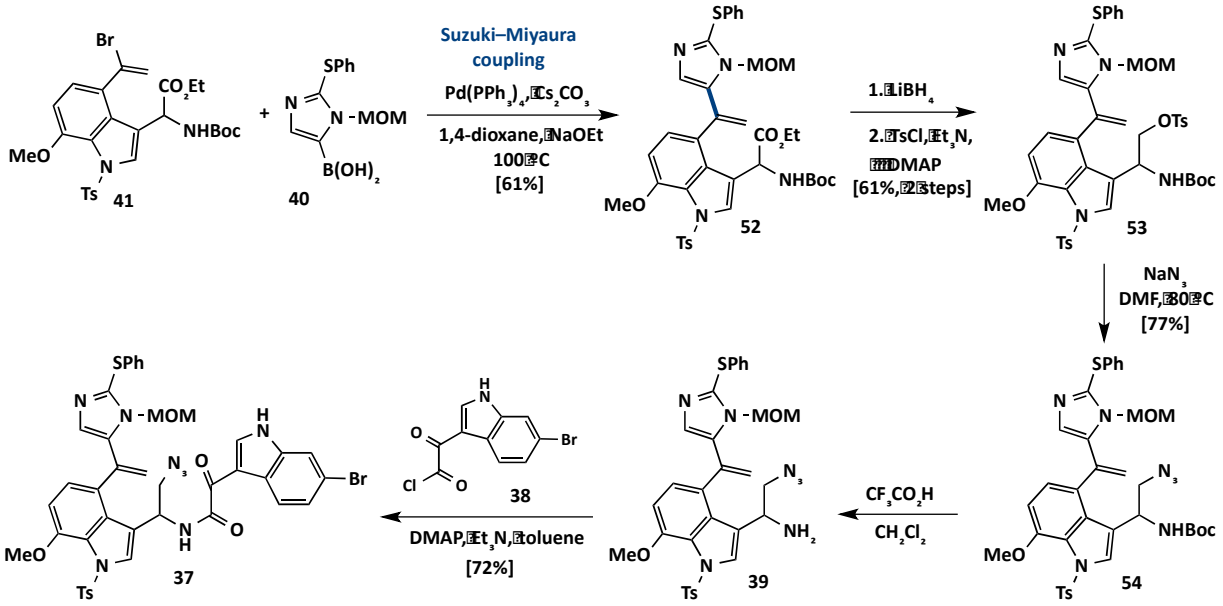
The synthetic strategy is comprised of a final stage asymmetric hydrogenation of the alkene moiety of intermediate **36** for the incorporation of an asymmetric carbon center at C6"' in dragmacidin D (Scheme 6). The central pyrazinone ring in **36** could be formed via Staudinger/aza-Wittig reaction followed by oxidation of **37**. Acylation of azidoamine **39** with oxaacetylchloride **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 ºC 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-methoxy-indole (**42**) was reacted with *p*-anisidine and ethyl glyoxylate in CH_2Cl_2 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 Boc_2O.



Scheme 7. Synthesis of Suzuki–Miyaura coupling fragments

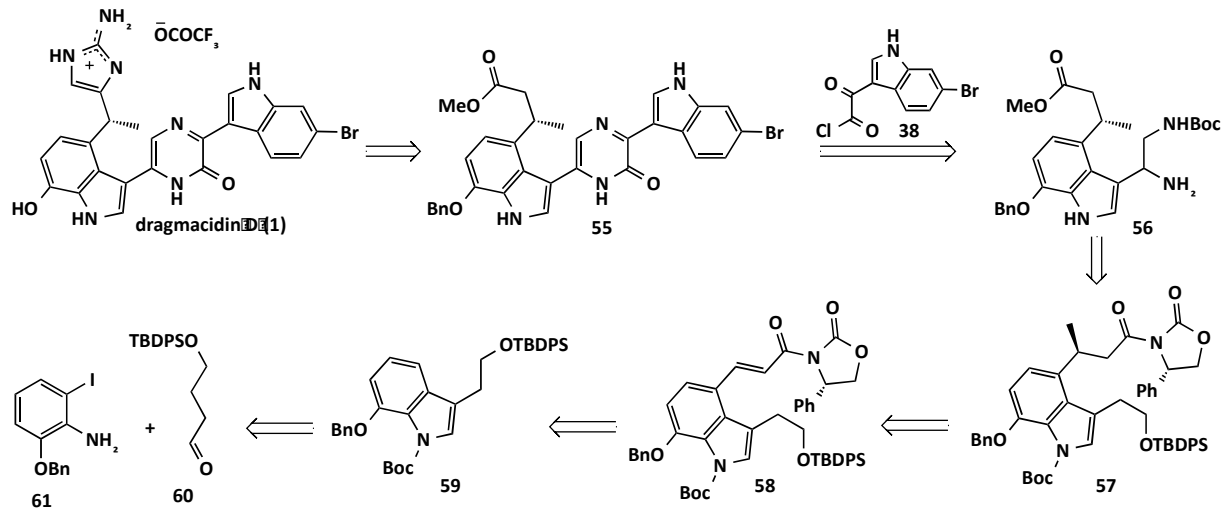
The Sonogashira coupling between 4-bromoindole derivative **49** and ethynyltriisopropylsilane delivered the coupling product **50** in 92% yield. Tetra-butylammonium fluoride-facilitated deprotection of triisopropylsilyl group followed by bromination of the alkyne moiety using $HBr{\cdot}CH_3CO_2H$ 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 $LiBH_4$ followed by tosyl protection of alcohol in 61% yield. Replacement of OTs group by azide using NaN_3 delivered azide **54**. CF_3CO_2H facilitated *N*-Boc deprotection followed by condensation with oxaacetylchloride 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)[8]

During the isolation and structure elucidation of dragmacidin D by Capon and co-workers in 1998, the optical rotation $[\alpha]_D$ was determined +12º. 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 aminoimidazole 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-indoaniline **60** and butaldehyde **61**.



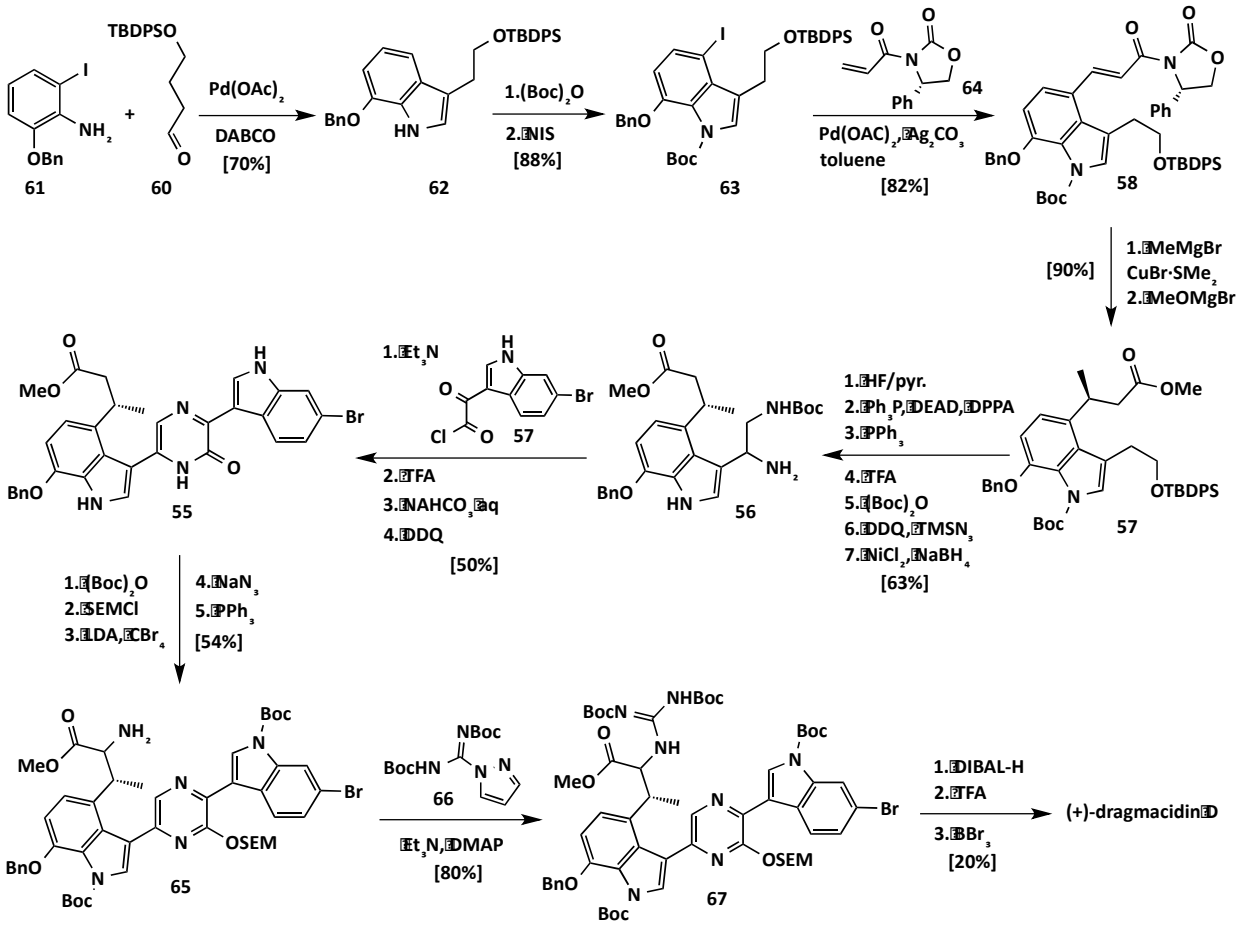
Scheme 9. Retrosynthetic Analysis for Asymmetric Synthesis

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 $(Boc)_2$ 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_2CO_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 $CuBr_2{\cdot}SMe_2$ 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 $(Boc)_2O$ 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 aminoimidazole moiety final three-step sequence was followed. Pyrazinone **55** was reacted with pyrazole-1-carboxamidine **66** in presence of Et_3N, DMAP to generate **67** in 80% yield. Reduction of methyl ester using DIBAL-H generated aza-hemiacetal, which in presence of TFA formed the aminoimidazole 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 dragamcidin 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 setereogenic 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

Acknowledgements

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