主論文

Synthesis of Pyrrole and Indole Alkaloids by Regioselective C–H Functionalization

位置選択的C–H結合官能基化を鍵とした
ピロール･インドールアルカロイドの合成

Atsushi Yamaguchi

山口　敦史

2015

Preface

The studies presented in this thesis have been carried out under the direction of Professor Kenichiro Itami at Department of Chemistry, Graduate School of Science, Nagoya University between April 2010 and March 2015. The studies are concerned with synthesis of pyrrole and indole alkaloids by regioselective C–H functionalization.

I would like to express my sincerest gratitude to Professor Kenichiro Itami for great support, valuable suggestions and hearty encouragement throughout this work. I would like to express my great appreciation to Associate Professor Junichiro Yamaguchi for his kind guidance, helpful discussions, technical assistance and enthusiasm during the course of this study. I appreciate to Dr. Yasutomo Segawa for his helpful suggestions and the measurement of X-ray crystallography. I also appreciate Associate Professor Shinya Hagihara, Assistant Professor Kei Murakami and Dr. Hideto Ito for their insightful comments and helpful discussions.

I would like to express my heartfelt appreciation to Professor Huw M. L. Davies for giving me an opportunity to visit Emory University as an exchange student, great support and valuable suggestions.

I would like to express my gratitude to Professor Shigehiro Yamaguchi and Associate Professor Susumu Saito for their helpful guidance and encouragement.

I must make special mention of Dr. Debashis Mandal and Ms. Kathryn M. Chepiga for their wonderful collaborations, valuable discussions and encouragement.

I heartily thank to Dr. Masakazu Nambo, Dr. Shuichi Yanagisawa, Dr. Kirika Ueda, Dr. Haruka Omachi, Dr. Katsuaki Kawasumi, Dr. Kazuya Yamaguchi, Dr. Eiji Yamaguchi, Dr. Shinpei Miyamoto, Dr. Kenji Mochida, Dr. Hua Zhang, Dr. Jiao Jiao, Dr. Asraa Ziadi, Mr. Shin Miyamura, Mr. Takeshi Kaneda, Ms. Hiromi Yamaguchi, Mr. Susumu Mori, Mr. Takuya Yamamoto, Ms. Akiko Katsura, Mr. Toshiki Kojima, Mr. Satoshi Tani, Mr. Kazuhiro Hata, Mr. Takehisa Maekawa, Ms. Sanae Matsuura, Mr. Kazuma Amaike, Mr. Hiroyuki Ishikawa, Mr. Kyohei Ozaki, Mr. Kazuki Kimura, Mr.

Kei Muto, Mr. Katsuma Matsui, Ms. Akiko Yagi, Ms. Hiromi Yoshida, Mr. Yuki Ishii, Mr. Takahiro Uehara, Mr. Tomonori Kajino, Ms. Keika Hattori, Ms. Yukari Mitamura, Mr. Tetsushi Yoshidomi, Mr. Takao Fujikawa, Mr. Hiroki Kondo, Mr. Kakishi Uno, Ms. Misaho Araki, Ms. Yuko Kamada, Ms. Natsumi Kubota, Mr. Yutaro Saito, Mr. Shin Suzuki, Mr. Ryosuke Takise, Mr. Masahiko Yoshimura. Mr. Tsuyoshi Oshima, Mr. Jun Orii, Mr. Kenta Kato, Ms. Mari Shibata, Ms. Kaho Maeda, Mr. Kiyotaka Mori, Mr. Shun Yamashita, Mr. Keishu Okada, Mr. Takahiro Kawakami, Ms. Chisa Kobayashi, Ms. Masako Fushimi, Mr. Keiichiro Murai, Ms. Manami Muraki, Mr. Shuya Yamada, Ms. Rika Kato, Ms. Yui Ueyama, Ms. Nanako Kato and all past members of Itami group for their enthusiasm and kind consideration.

I am grateful to the Japan Society for the Promotion of Science (JSPS) for the research fellowship for young scientists (DC1). I also thank to Integrative Graduate Education and Research Program in Green Natural Sciences (IGER) for the financial support.

Finally, I would like to express my deep appreciation to my family, especially her parents, Mr. Shoji Yamaguchi and Mrs. Fusae Yamaguchi for their constant assistance and encouragement.

Atsushi Yamaguchi

Department of Chemistry
Graduate School of Science
Nagoya University
2015

Contents

List of Abbreviations

Å	angström unit
Ac	acetyl
acac	acetylacetonate
Alk	alkyl
Ar	aryl
bipy	2,2′-bipyridyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
cat	catalytic
cod	1,5-cyclooctadiene
Cy	cyclohexyl
δ	chemical shift (NMR)
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5-dicyano-*p*-benzoquinone
DMAc	*N*,*N*-dimethylacetamide
DMAP	*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane
DMSO	dimethyl sulfoxide
dppf	1,1′-bis(diphenylphosphino) ferrocene
dppp	1,3- bis(diphenylphosphino) propane
dr	diastereomeric ratio
dtbpy	4,4′-di-*tert*-butyl-2,2′-bipyridine
equiv	equivalent(s)
Et	ethyl
EWG	electron withdrawing group
Fmoc	9-fluorenylmethyloxycarbonyl
h	hour(s)
hν	irradiation with light
Het	heteroaryl
Hex	hexyl
Ile	isoleucine
i-Pr	1-methyl-1-ethyl
J	coupling constant (NMR)
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
m	meta
Me	methyl
min	minute(s)
MOM	methoxymethyl
MS	molecular sieves
μW	microwave
MTAD	*N*-methyltriazolinedione
n-Bu	1-butyl
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
o	ortho
p	para
PEPPSI-IPr	[1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
pin	pinacolato

Ph	phenyl
Piv	pivaloyl
R	an organic group
rt	room temperature
SEN	[2-(trimethylsilyl)ethyl]methyl
SPhos	2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
t-Bu	1,1-dimethyl-1-ethyl
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
TfO	triflate
TosMIC	*p*-toluenesulfonylmethyl isocyanide
TPAP	tetrapropylammonium perruthenate
Trp	tryptophan
TsO	tosylate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	tosyl
UV	ultraviolet
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

General Introduction

Pyrrole and Indole Alkaloids

Pyrrole and indole alkaloids[1] are an important class of natural products that are widely found in nature and produced by various organisms including plants and marine species, *e.g.*, sponges, ascidian and symbiotic bacteria. These natural products show several different types of significant biological activities such as anticancer, anti-inflammatory and antimicrobial activities (Figure 1). For example, stephacidin B is a densely functionalized indole alkaloid isolated from the mitosporic fungus *Aspergillius ochraceus*, which is expected to be a novel antitumor agent because of its selective inhibition against testosterone-dependent prostate LNCaP cell line.[2] Dragmacidin D is a potent inhibitor of serine–threonine protein phosphatases, thereby receiving attention as a lead compound for treating Parkinson's, Alzheimer's, and Huntington's diseases.[3] Actinophyllic acid is a structurally unique indole alkaloid with potent inhibition of the coupled enzyme assay carboxypeptidase U(CPU)/hippuricase. Variolin B, which is a marine indole alkaloid isolated from an extremely rare Antarctic sponge, *Kirkpatrickia varialosa*, shows important antiproliferative activity against P388 leukaemia cells.[4] Rhazinilam is a both biologically and structurally unique pyrrole alkaloid that features a tetracyclic structure including a nine-membered lactam ring.[5] This compound interferes with microtubule assembly similar to taxol and vincristine, which are known as efficient anticancer agents.

Therefore, many pyrrole and indole alkaloids have applications in medicine and are promising leads in drug discovery. In addition to such notable biological activity, they have remarkable structural features, *e.g.* fused polycyclic frameworks and various highly polar functional groups. Because of the significant biological activities and unique structures, pyrrole and indole alkaloids have attracted the attention of synthetic organic chemists for a long time, and have also lead to a research campaign that is described by work presented in this thesis.

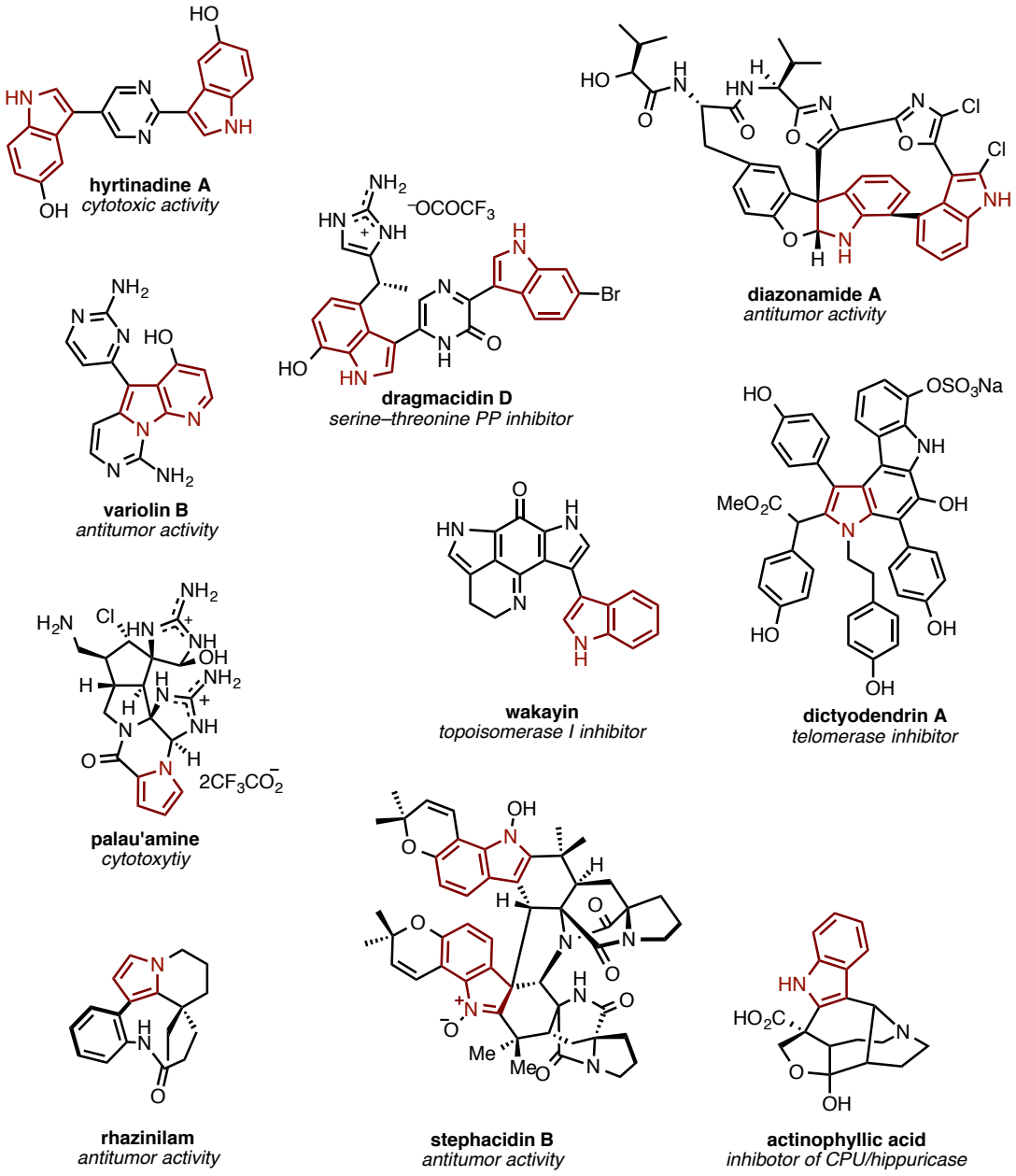


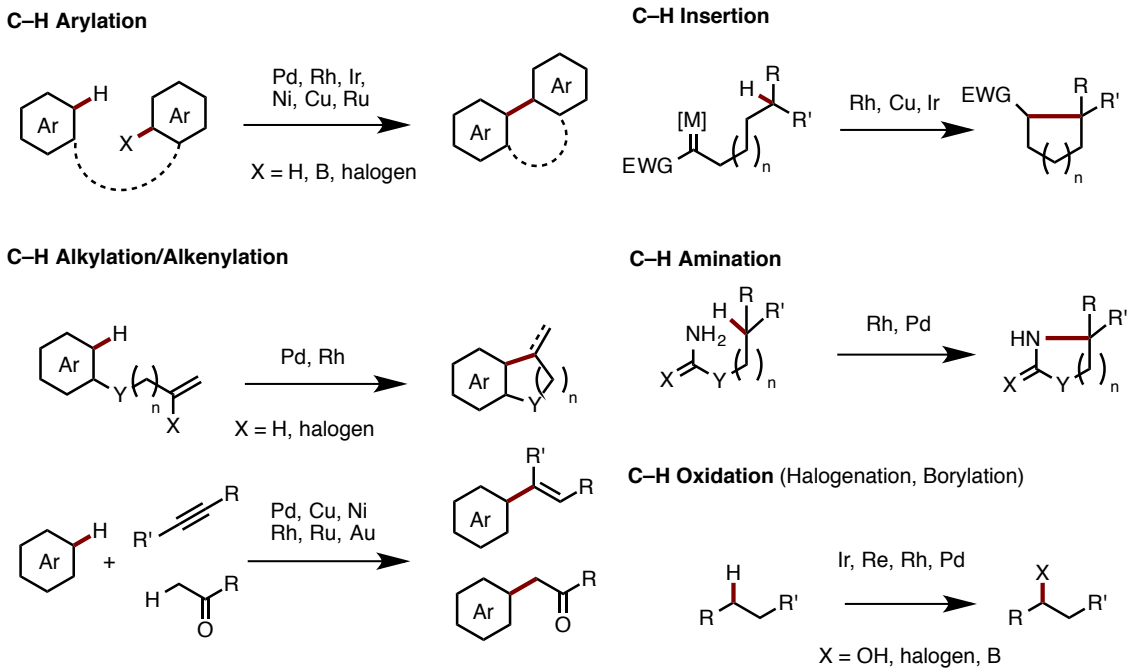
Figure 1. Bioactive pyrrole and indole alkaloids isolated from nature.

Natural Product Synthesis through C–H Functionalization

The total synthesis of natural products can result in great scientific discoveries of medicinal benefit. First, it can supply a large amount of biologically active compounds even though such compounds can only be obtained from nature on a small scale.

Second, total synthesis can provide various derivatives of natural products for structure-activity relationship studies. In addition, it can create chemical probes connecting with small molecules of biological interest. Such probes help identify protein structures that bind to these small molecules. Therefore, synthetic organic chemists continue to make an effort to develop various research fields as a joint objective alongside natural product synthesis.

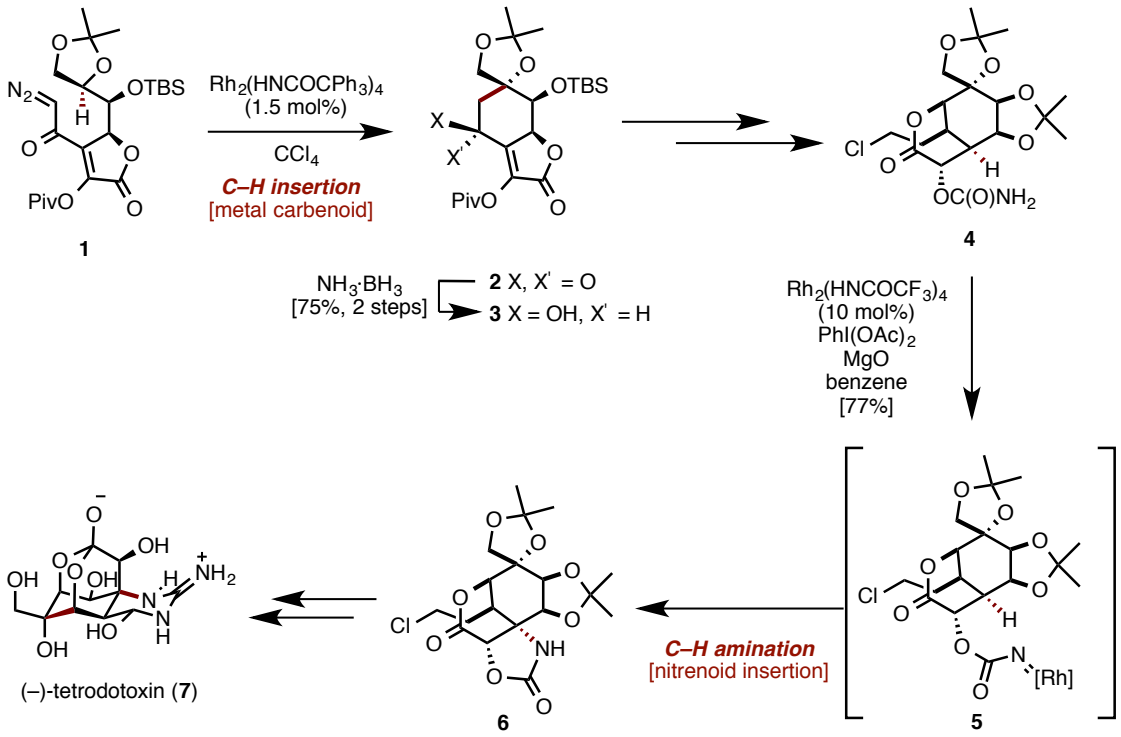
An equally exciting field of chemical research is the direct functionalization of ubiquitous carbon–hydrogen (C–H) bonds in organic compounds, which has been one of the most efficient methods to construct carbon–carbon (C–C) and carbon–heteroatom (C–X) bonds (Scheme 1). Since the discovery of the C–H alkenylation of benzene by Moritani and Fujiwara in 1967,[6] a number of C–H functionalization reactions catalyzed by transition metals have been developed. Intramolecular/intermolecular C–H arylation[7] is one of the most efficient methods for synthesizing bi(hetero)aryl frameworks. C–H alkylation[8] and C–H alkenylation[9] are also useful reactions for the construction of carbon–carbon bonds without pre-functionalization, in which alkenes, alkynes, alkenyl halides and carbonyl compounds with α-protons can be coupled with arenes and heteroarenes. C–H insertion[10] can give rise to a new $C(sp^3)$–$C(sp^3)$ bond *via* generation of metal carbenoid species, where dirhodium catalysts possessing chiral ligands can give the corresponding products with high enantioselectivity. C–H amination[11] is able to construct a carbon–nitrogen bond directly, whose utility has resulted in several reaction types including metal nitrenoid insertion and transition metal-catalyzed allylic C–H amination. C–H oxidation,[12] C–H halogenation[13] and C–H borylation[14] also enable the direct formation of carbon–heteroatom bonds, which has been facilitated by the advent of iridium-catalyzed borylation reactions pioneered by the Smith, Hartwig, Ishiyama and Miyaura groups.



Scheme 1. Methods for direct C–H bond transformation.

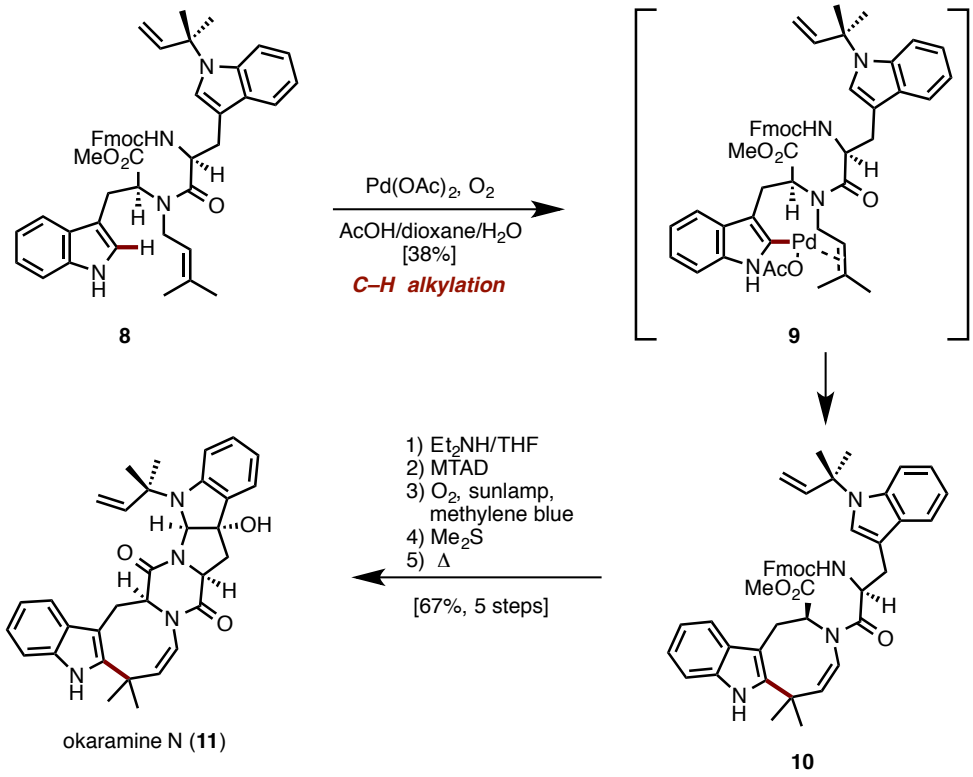
With the chemistry community's growing research interests in C–H functionalization, remarkable progress in the field of total synthesis *via* C–H functionalization (especially catalyzed by transition metals) has been made.[15] Examples of such syntheses will be classified below according to the type of key reactions that have been used.

In 2003, Hinman and Du Bois reported the total synthesis of (–)-tetrodotoxin (**7**) utilizing two different types of C–H functionalization: C–H insertion and C–H amination (Scheme 2).[16] A dirhodium-catalyzed intramolecular C–H insertion converted diazoketone **1** into cyclohexanone **2** in the presence of 1.5 mol% $Rh_2(HNCOCPh_3)_4$ *via* a rhodium carbenoid species generated from **1** *in situ*. Next, stereoselective reduction of ketone **2** with $NH_3{\cdot}BH_3$ furnished compound **3** in 75% yield over 2 steps. After a 14-step reaction sequence, **3** was converted into carbamate **4**. The key intramolecular C–H amination of **4** with $Rh_2(HNCOCF_3)_4$ (10 mol%) afforded **6** in 77% yield through the generation of rhodium nitrenoid **5**. Seven more steps from **6** were needed to complete the total synthesis of (–)-tetrodotoxin (**7**).



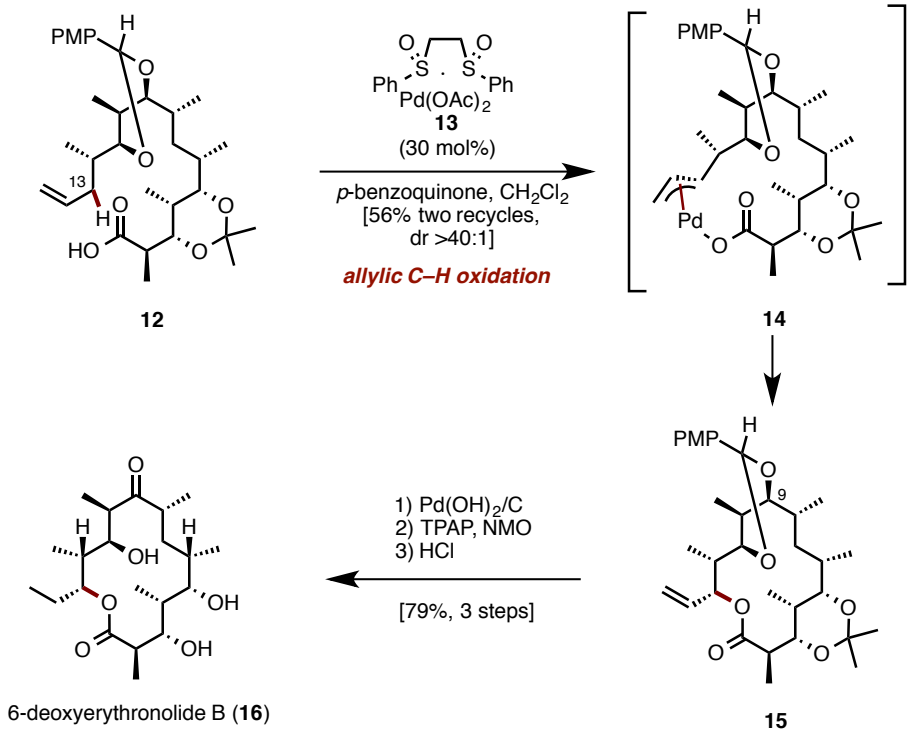
Scheme 2. Du Bois' synthesis of (–)-tetrodotoxin (**7**).[16]

In 2003, the group of Corey applied an intramolecular C–H alkylation to the total synthesis of okaramine N (**11**; Scheme 3).[17] The key C–H alkylation of bisindole **8** possessing a prenyl group in the presence of 1 equiv $Pd(OAc)_2$ in AcOH/dioxane/H_2O solution under O_2 atmosphere gave indoloazocine **10** in 38% yield. Compound **10** was converted into okaramine N (**11**) after five additional steps.



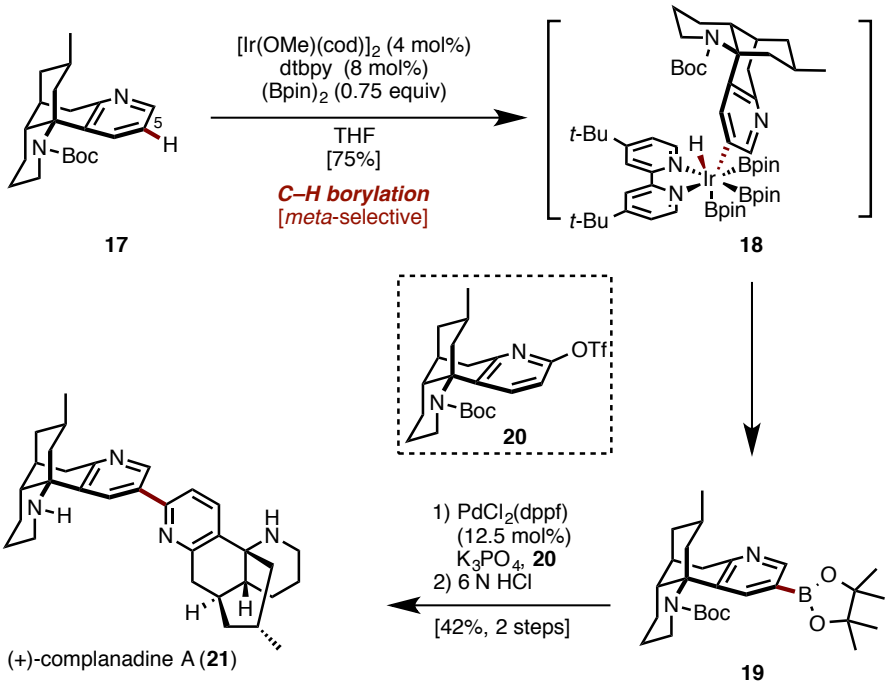
Scheme 3. Corey's synthesis of okaramine N (**11**).[17]

In 2009, Stang and White demonstrated the efficient synthesis of 6-deoxyerythronolide B (**16**) by means of an allylic C–H oxidation developed in their own group (Scheme 4).[18] Although several total syntheses of this family have been reported, a common method to construct its signature macrocycle is the lactonization of the corresponding hydroxycarboxylic acids. Meanwhile, the White group closed the macrocycle utilizing a late-stage intramolecular C–H oxidation of the alkenoic acid precursor. The intramolecular allylic C–H oxidation of carboxylic acid **12** containing a terminal olefin was catalyzed by palladium bis-sulfoxide complex **13**, proceeding through π-allylpalladium carboxylate **14** to provide 14-membered macrolide **15** in 56% yield with high diastereoselectivity after two recycled reactions. Treatment of resulting **15** with $Pd(OH)_2/C$ resulted in reduction of the terminal alkene and removal of the *p*-methoxyphenylmethyl acetal group. Then selective oxidation of the C9 alcohol and removal of the acetonide group completed the synthesis of (–)-6-deoxyerythronolide B (**16**) in a total of 22 steps.



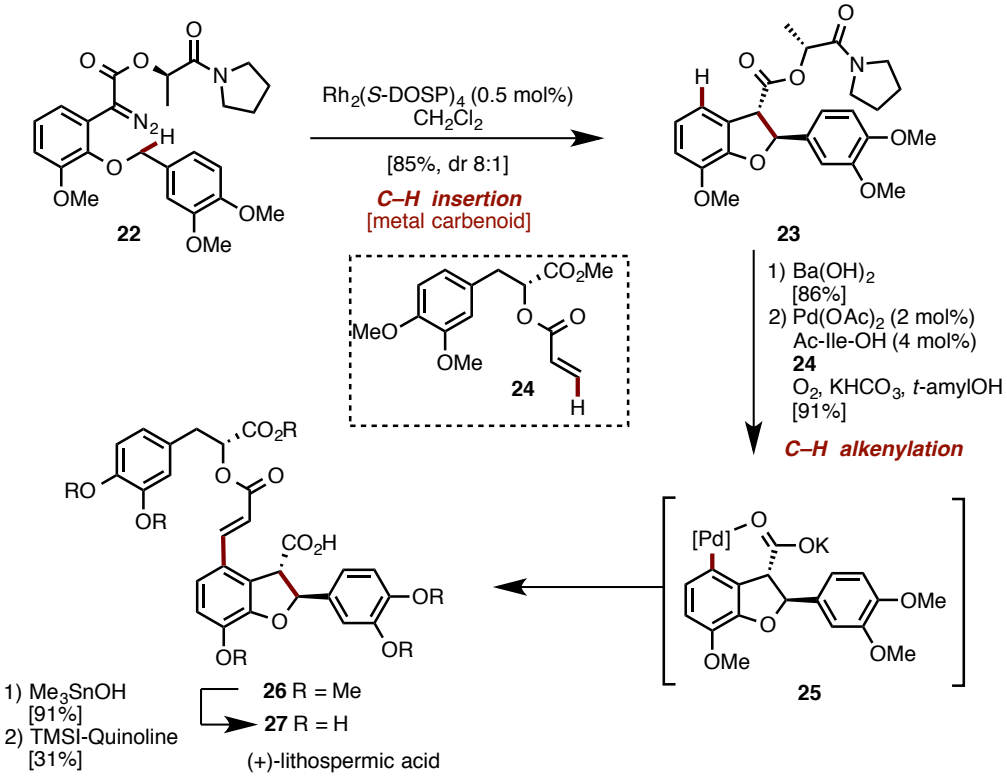
Scheme 4. White's synthesis of 6-deoxyerythronolide B (**16**).[18]

C–H borylation has also been applied to the total synthesis of natural products. The direct transformation has the benefit of the versatility in subsequent palladium-catalyzed Suzuki–Miyaura cross-coupling reactions, oxidative Mizoroki–Heck reactions, halogenations, etc. In 2010, Fischer and Sarpong achieved the use of C–H borylation for the total synthesis of (+)-complanadine A (**21**), an unsymmetrical lycodin dimer (Scheme 5).[19] The C–H borylation of pyridine derivative **17** prepared from **20** by removal of the triflate moiety proceeded smoothly at the C3-positon of the pyridine ring using a catalytic amount of $[Ir(OMe)(cod)]_2$/dtbpy and $(Bpin)_2$ to furnish boronate **19** in 75% yield. Then, Suzuki–Miyaura cross-coupling of **19** with triflate **20** followed by removal of the Boc groups afforded (+)-complanadine A (**21**) in 42% yield over two steps.



Scheme 5. Sarpong's synthesis (+)-complanadine A (**21**).[19]

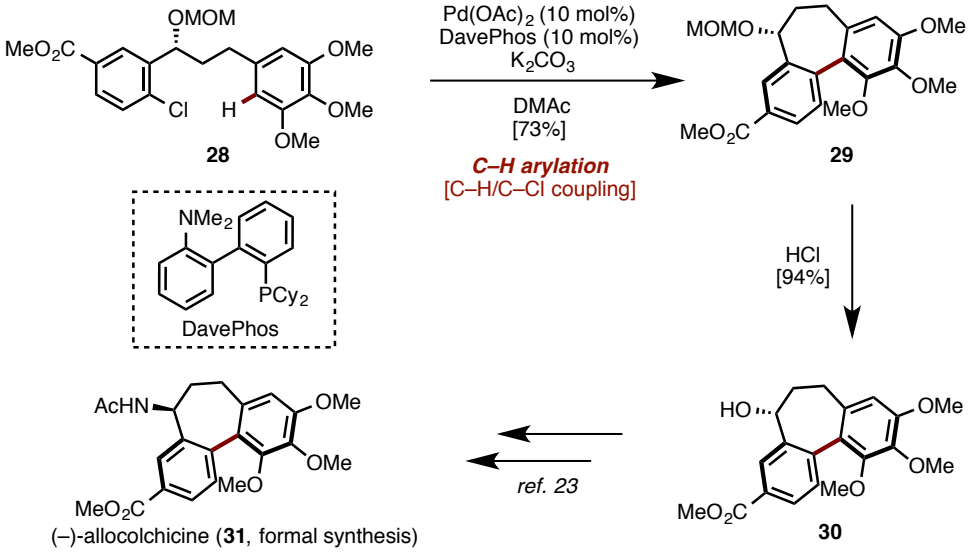
In 2011, the total synthesis of (+)-lithospermic acid (**27**) was achieved by Wang and Yu utilizing intramolecular C–H insertion and intermolecular C–H alkenylation (Scheme 6).[20] Treatment of diazoester **22** with Rh_2(*S*-DOSP)$_4$ in CH_2Cl_2 afforded *trans*-dihydrobenzofuran **23** in 85% yield as a result of the diastereoselective C–H insertion reaction. Removal of the chiral auxiliary group followed by a key intermolecular C–H alkenylation of the resulting carboxylic acid with acrylate **24** using a catalytic amount of $Pd(OAc)_2$/Ac-Ile-OH, $KHCO_3$ and O_2 gas gave alkenylated dihydrofuran **26** in excellent yield. The carboxylate unit in **25** served as a directing group presenting weak coordination. Finally, global demethylation completed the total synthesis of (–)-lithospermic acid (**27**).



Scheme 6. Yu's synthesis of (+)-lithospermic acid (**27**).[20]

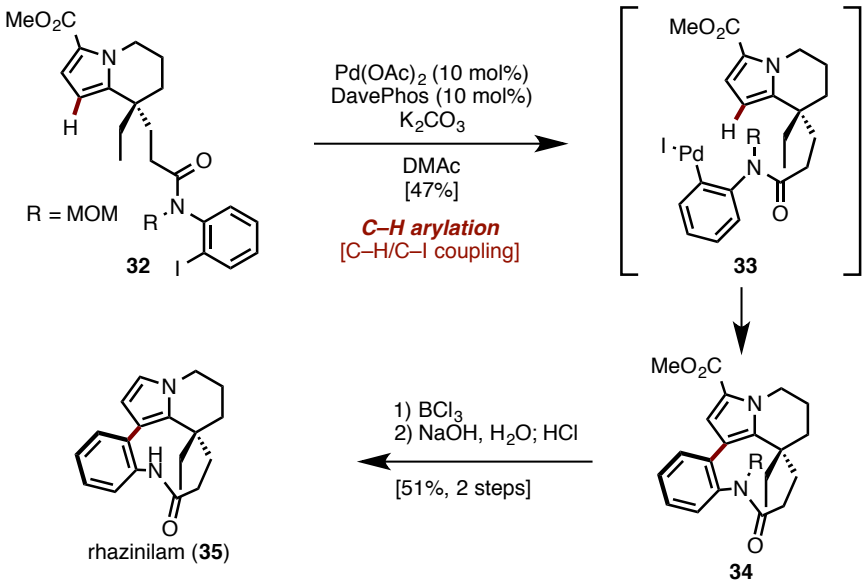
Application of C–H Arylation Reactions to Natural Product Synthesis

As shown in Schemes 2–6, notable applications of direct C–H functionalization to total synthesis of complex natural products have been achieved over the past decade.[21] However, few examples of total synthesis of structurally unique natural products featuring intramolecular or intermolecular C–H arylation (coupling) reactions have been reported. In 2005, Leblanc and Fagnou reported the formal synthesis of (–)-allocolchicine (**31**) by a palladium-catalyzed intramolecular C–H/C–Cl coupling reaction (Scheme 7).[22] Despite the difficulties involved in the formation of seven-membered rings, Fagnou developed reaction conditions to generate macrocycle **29**. The intramolecular biaryl coupling of diarylpropane **28** furnished **29** in 73% yield with a catalytic amount of $Pd(OAc)_2$/DavePhos and K_2CO_3 in DMAc. Treatment of resulting **29** with HCl in methanol gave deprotected product **30** as a known precursor[23] to (–)-allocolchicine (**31**).



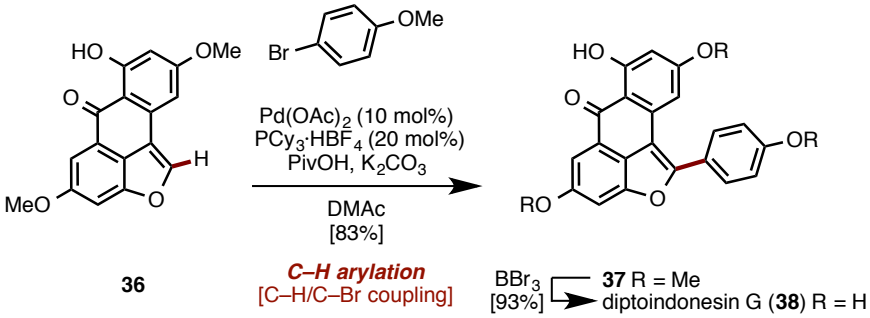
Scheme 7. Fagnou's formal synthesis of (–)-allocolchicine (**31**).[22]

In 2005, the group of Trauner achieved the total synthesis of rhazinilam (**35**) utilizing a palladium-catalyzed intramolecular C–H arylation of a pyrrole ring (Scheme 8).[24] The molecule contains a fused nine-membered lactam ring incorporating a biaryl moiety. This challenging structure was synthesized by applying similar reaction conditions reported by Fagnou to intramolecular C–H/C–I coupling of pyrrole **32**. This reaction gave the corresponding coupling product **34** in 47% yield, which was converted into rhazinilam (**35**) over two steps.



Scheme 8. Trauner's synthesis of rhazinilam (**35**).[24]

In addition to efficient syntheses using intramolecular C–H arylation, intermolecular C–H arylation was also applied to the synthesis of natural products. In 2010, the group of Kim reported the total synthesis of diptoindonesin G (**38**),[25] a novel oligostilbenoid possessing strong cytotoxic activity, isolated from the tree bark of *Hopea mengarawan* (Scheme 9). Fused benzofuran derivative **36** was arylated with *p*-bromoanisole in the presence of a catalytic amount of $Pd(OAc)_2/PCy_3{\cdot}HBF_4$, PivOH and K_2CO_3 in DMAc to give arylbenzofuran **37** in 83% yield. These reaction conditions tolerated the presence of methoxy, ketone, and unprotected hydroxy groups. Finally, demethylation of phenol groups completed the short synthesis of diptoindonesin G (**38**) in four linear steps.

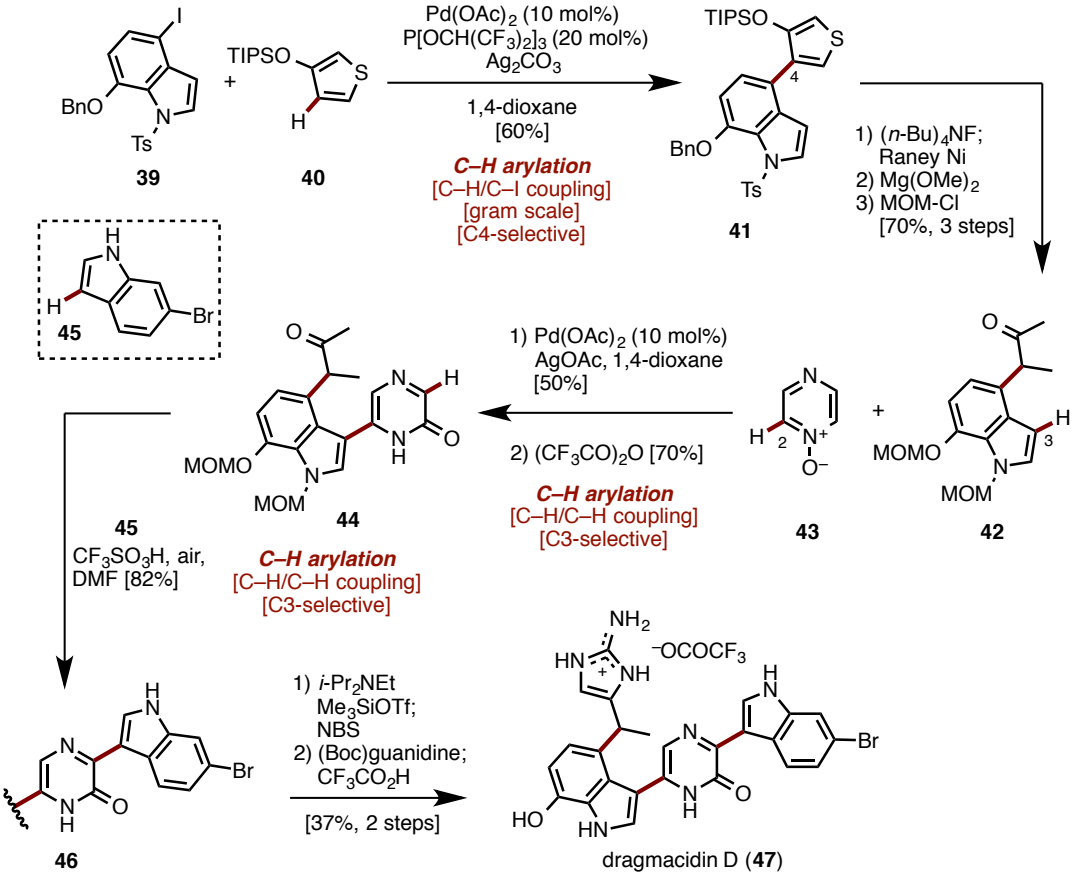


36

Scheme 9. Kim's synthesis of diptoindonesin G (**38**).[25]

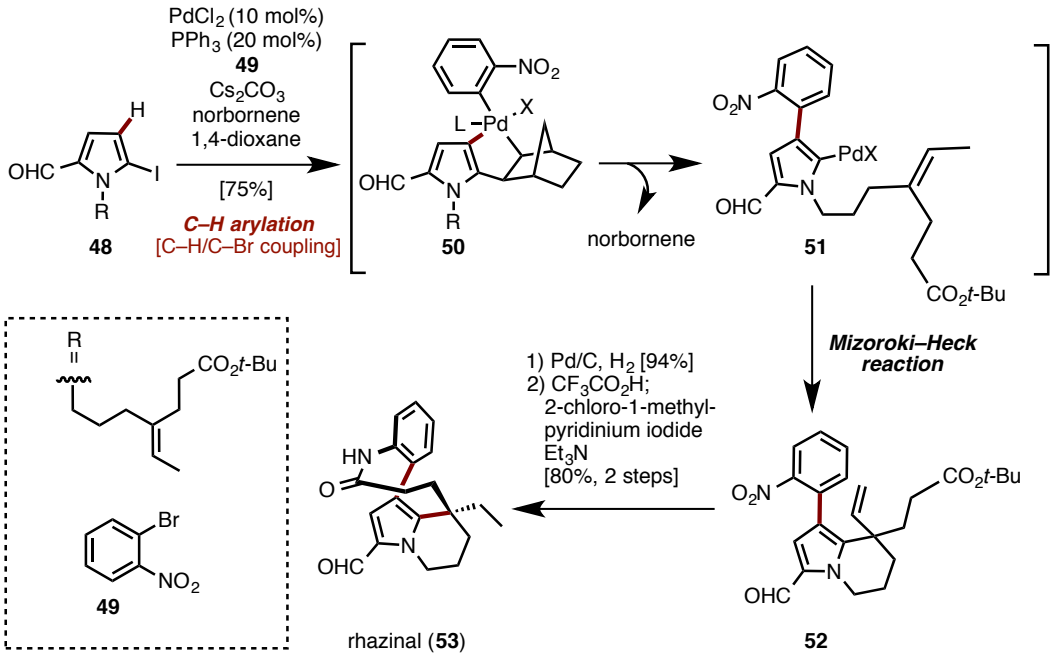
In 2012, Itami, Yamaguchi and co-workers demonstrated the concise total synthesis of complex marine alkaloid dragmacidin D (**47**) through direct C–H coupling reactions (Scheme 10).[26] The synthesis commenced with a β-selective C–H arylation of 3-triisopropylsilyloxythiophene (**40**) with iodoindole **39** using $Pd(OAc)_2/P[OCH(CF_3)_2]_3$ catalyst[27] to give the corresponding coupling product **41** in 60% yield. After the conversion of **41** into ketone **42** over three steps, the C–H/C–H coupling of **42** with pyrazine *N*-oxide (**43**) occurred in the presence of a catalytic amount of $Pd(OAc)_2$ and AgOAc in 1,4-dioxane to provide the heterobiaryl compound. Then tautomerization of resulting pyrazine *N*-oxide by treatment with trifluoroacetic anhydride afforded pyrazinone **44** in 70% yield. The second C–H/C–H coupling reaction of **44** with **45** proceeded in the presence of CF_3SO_3H under air to give bis(indolyl)pyrazinone **46** in 82% yield with concomitant removal of the two MOM groups. Finally, aminoimidazole formation followed by deprotection of the resulting guanidine compound completed the total synthesis of dragmacidin D (**47**). In this manner, the total synthesis of **47** was completed in 15 steps total, which is 10 steps

shorter than the previous total synthesis using Suzuki–Miyaura coupling reactions.[28]



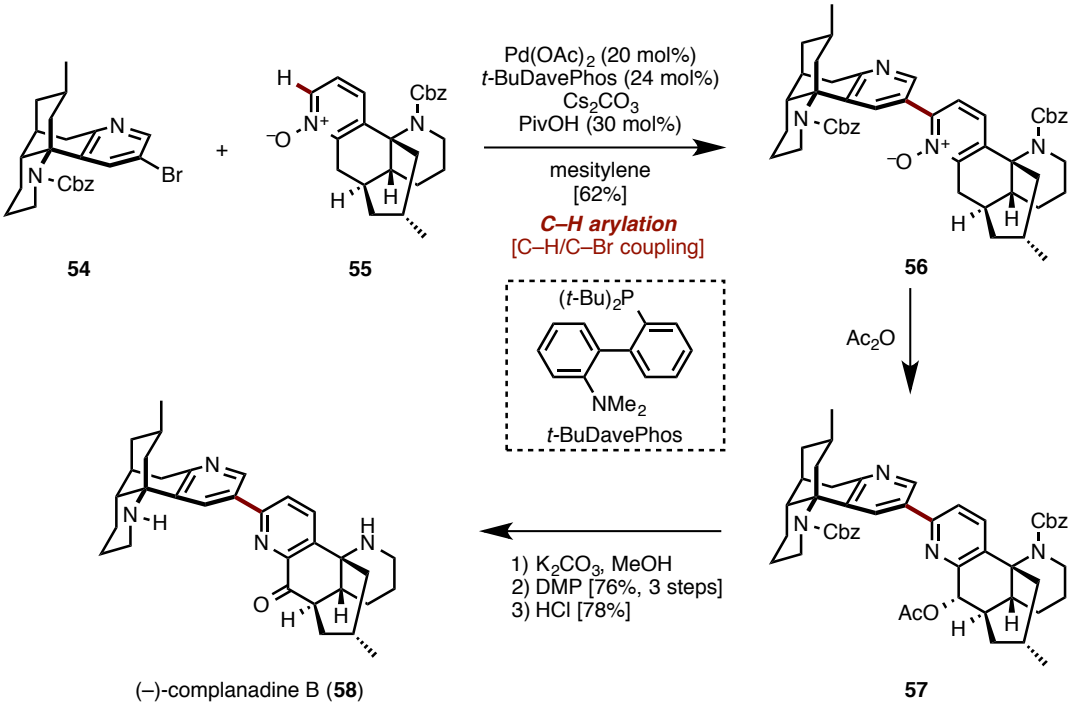
Scheme 10. Itami's synthesis of dragmacidin D (**47**).[26]

In 2013, Gu and co-workers applied a chemoselective Catellani reaction with two different aryl halides to the total synthesis of rhazinal (**53**: Scheme 11).[29] They planed to form both an aryl–pyrrole bond and a six-membered ring simultaneously using a norbornene-mediated reaction. *N*-Alkyl-2-iodopyrrole **48** and 1-bromo-2-nitrobenzene (**49**) were treated with a catalytic amount of $PdCl_2/PPh_3$, Cs_2CO_3 and norbornene which resulted in the intermolecular C–H arylation of the pyrrole ring followed by intramolecular Mizoroki–Heck reaction to provide the desired product **52** in 75% yield. The reaction proceeded *via* five-membered palladacycle **50** to give β-arylated pyrrole **51** selectively. Reduction of the terminal alkene and the nitro group of **52** followed by removal of *t*-butyl group by treatment with CF_3CO_2H and construction of the macrocycle completed the rapid synthesis of rhazinal (**53**).



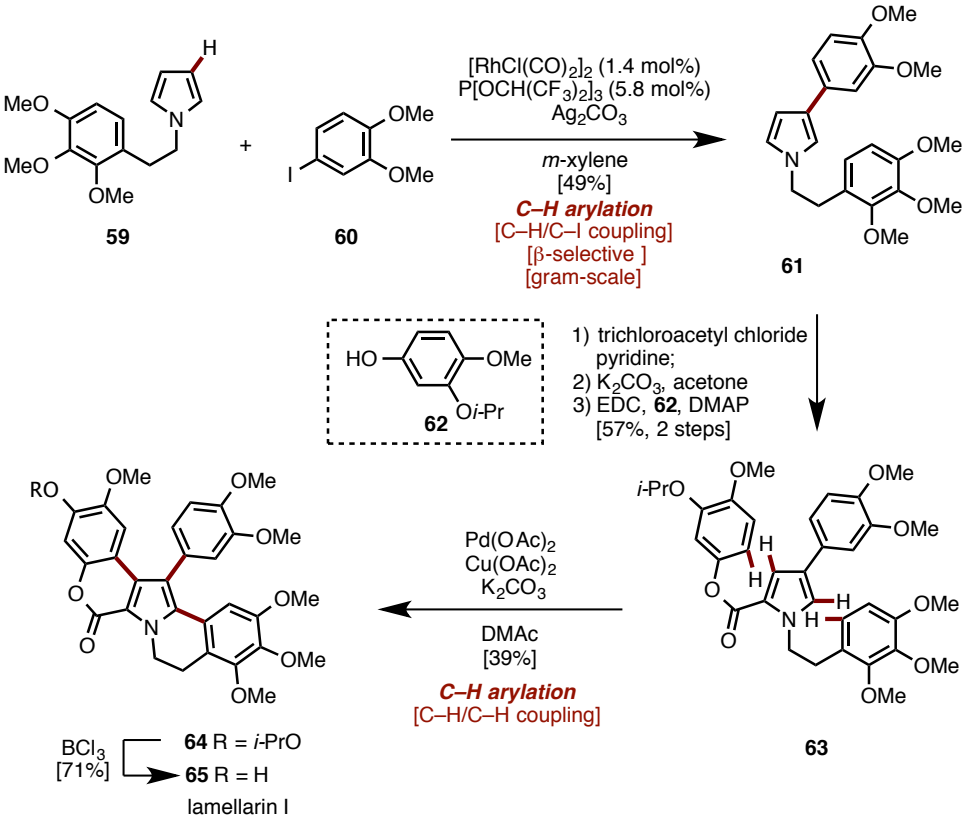
Scheme 11. Gu's synthesis of rhazinal (**53**).[29]

In the same year, Hirama, Tsukano and co-workers reported the total syntheses of (–)-complanadines A (**21**) and B (**58**) utilizing an intermolecular C–H coupling of two lycodine units (Scheme 12).[30] The intermolecular C–H coupling of *N*-oxide **55** with bromolycodine **54** successfully proceeded under the catalysis of $Pd(OAc)_2$/*t*-BuDavePhos/PivOH in the presence of Cs_2CO_3 and mesitylene to provide the corresponding coupling product **56** in 62% yield. Oxidation of the benzyl position of the pyridine *N*-oxide was carried out by proton transfer and subsequent Claisen-type rearrangement of *O*-acetylated pyridine *N*-oxide to afford acetate **57** as a 3:1 epimeric mixture. Removal of acetyl group in **57**, DMP oxidation of resulting alcohol and removal of the two Cbz groups were accomplished to complete the total synthesis of (–)-complanadine B (**58**).



Scheme 12. Hirama's synthesis of (–)-complanadine B (**58**).[30]

Very recently, Yamaguchi, Itami and co-workers developed a rhodium-catalyzed β-selective C–H arylation of pyrroles to accomplish the concise syntheses of lamellarins C and I.[31] The key C–H coupling of *N*-alkylpyrrole **59** with iodoarene **60** successfully proceeded in the presence of a catalytic amount of $[RhCl(CO)_2]_2$/$P[OCH(CF_3)_2]_3$ and Ag_2CO_3 in *m*-xylene to afford the 3-arylpyrrole **61** in 49% yield. Friedel–Crafts acylation of **61** with trichloroacetyl chloride, followed by hydrolysis and condensation of the resulting carboxylic acid with phenol derivative **62** provided trisubstituted pyrrole **63** in 57% yield. Another key reaction in this short synthesis was an intramolecular C–H/C–H coupling to construct two carbon–carbon bonds simultaneously. The double C–H/C–H coupling using stoichiometric amounts of $Pd(OAc)_2$, $Cu(OAc)_2$, and K_2CO_3 constructed the core structure of **64** in 39% yield. Finally, deprotection of the phenol group with BCl_3 completed the concise synthesis of lamellarine I (**65**) in 71% yield.



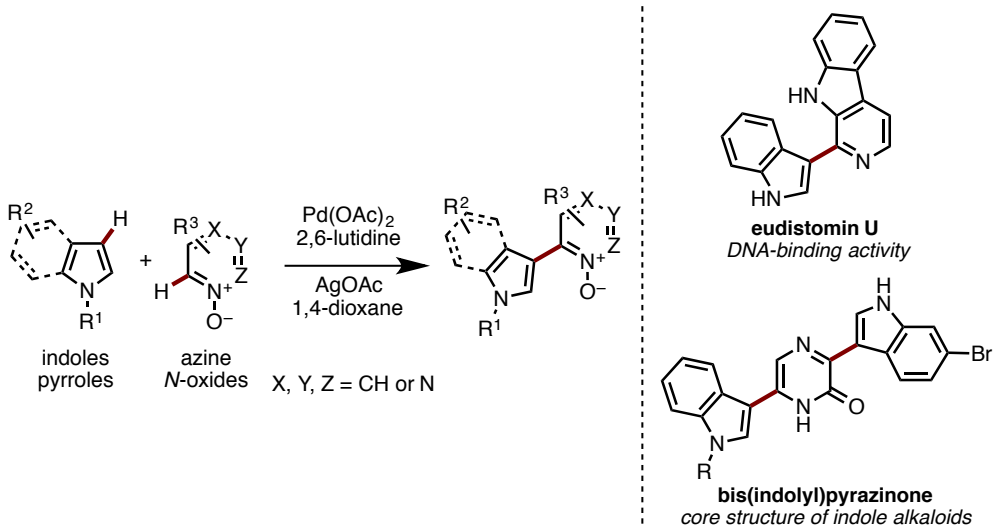
Scheme 13. Yamaguchi's synthesis of lamellarin I (**65**).[31]

To date, several total syntheses of complex natural products by intramolecular/intermolecular C–H coupling reactions have been achieved. These synthetic methods enable chemists to directly connect two heterocycles. As there are a great number of natural products containing (hetero)biaryl structures, further development and application of these fundamental methodologies toward total syntheses is in strong demand.

Survey of This Thesis

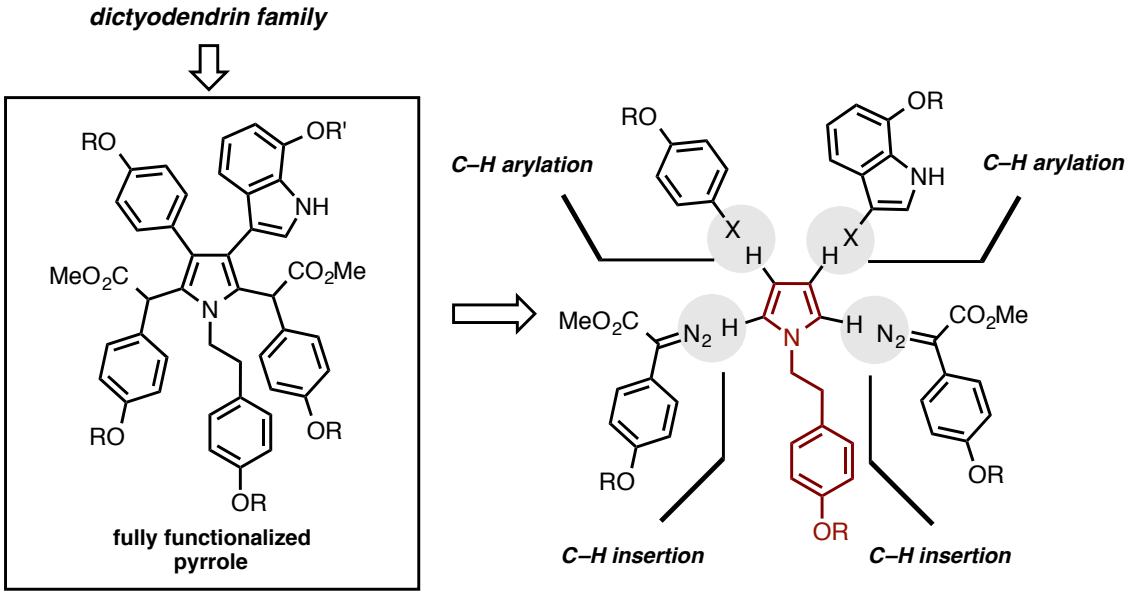
Chapter 1 describes the discovery of a palladium-catalyzed C–H/C–H coupling reaction of indoles/pyrroles with azine *N*-oxides (Scheme 14). This coupling reaction furnishes a C3-substituted indole/pyrrole with pyridine *N*-oxide with complete regioselectivity. Various substituted indoles and azine *N*-oxides such as pyrazine, pyrimidine, isoquinoline *N*-oxides can be used as coupling partners. In addition, by utilizing the developed direct coupling reaction, rapid syntheses of eudistomin U and a

bis(indolyl)pyrazinone framework have been achieved.[32]



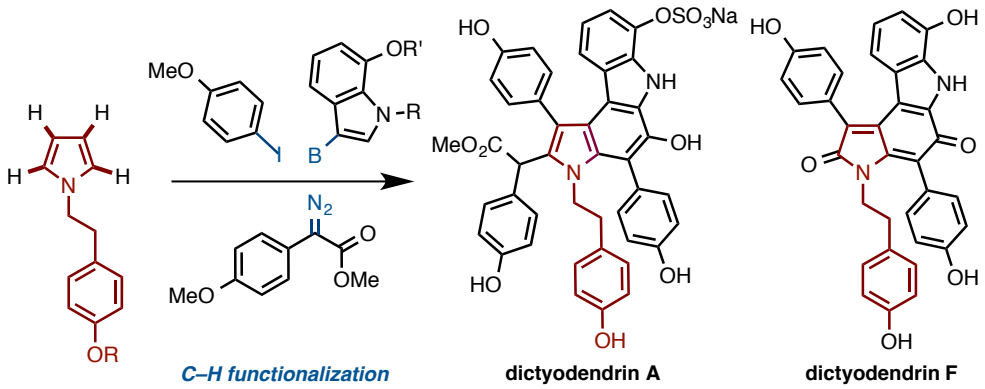
Scheme 14. Indole/pyrrole–azine C–H/C–H coupling reaction.

Chapter 2 describes the development of a synthetic methodology for the efficient synthesis of marine alkaloids dictyodendrins (Scheme 15). Previous reports for the total synthesis of dictyodendrins are summarized and a retrosynthetic analysis is proposed. The fully functionalized pyrrole, a key intermediate, could be prepared rapidly by means of the combination of C–H arylation and C–H insertion of a simple pyrrole ring.



Scheme 15. Synthetic strategy toward the synthesis of dictyodendrins.

Chapter 3 describes concise syntheses of dictyodendrins A and F by a sequential C–H functionalization strategy (Scheme 16). A Rh(I)-catalyzed regioselective C–H arylation and Rh(II)-catalyzed double C–H insertion, followed by a Suzuki–Miyaura cross-coupling reaction enables the construction of the fully functionalized pyrrole rapidly from a simple *N*-alkylpyrrole. Completion of the total syntheses was achieved by formal 6π electrocyclization of the resulting pentasubstituted pyrrole to form the key pyrrolo[2,3-*c*]carbazole core of the dictyodendrins.[33]



Scheme 16. Concise syntheses of dictyodendrins A and F.

References and Notes

1. Selected reviews of pyrrole and indole alkaloids: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582. (b) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532. (c) Young, I. S.; Thornton, P. D.; Thompson, A. *Nat. Prod. Rep.* **2010**, *27*, 1801.
2. Qian-Cutrone, J.; Huang, S.; Shu, Y.-Z.; Vyas, D.; Fairchild, C.; Menendez, A.; Krampitz, K.; Dalterio, R.; Klohr, S. E.; Gao, Q. *J. Am. Chem. Soc.* **2002**, *124*, 14556.
3. Capon, R. J.; Rooney, F.; Murray, L. M.; Collins, E.; Sim, A. T. R.; Rostas, J. A. P.; Butler, M. S.; Carroll, A. R. *J. Nat. Prod.* **1998**, *61*, 660.
4. Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron* **1994**, *50*, 3987.
5. (a) Banerji, A.; Majumder, P. L.; Chatterjee, A. *Phytochemistry* **1970**, *9*, 1491. (b) Abraham, D. J.; Rosenstein, R. D.; Lyon, R. L.; Fong, H. H. S. *Tetrahedron Lett.* **1972**, *13*, 909. (c) Décor, A.; Bellocq, D.; Thoison, O.; Lekieffre, N.; Chiaroni, A.; Ouazzani, J.; Cresteil, T.; Guéritte, F.; Baudoin, O. *Bioorg. Med. Chem.* **2006**, *14*, 1558.
6. (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119. (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.
7. (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (c) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (d) Chen, X.; Engle, K. M.; Wnag, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (e) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369.
8. (a) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (b) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866. (c) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (d) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74.
9. (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (b) Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, 6495. (c) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879.
10. (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (c) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704. (d) Herrmann, P.; Bach, T. *Chem. Soc. Rev.* **2011**,

40, 2022. (e) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev*. **2011**, *40*, 1857. (f) Davies, H. M. L.; Lian, Y. *Acc. Chem. Res.* **2012**, *45*, 923.

11. (a) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061. (b) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.* **2011**, *40*, 1926. (c) Ramirez, T. A.; Zhao, B.; Shi, Y. *Chem. Soc. Rev.* **2012**, *41*, 931.
12. (a) *Handbook of C–H transformations* (Ed.: Dyker, G.), Wiley-VCH, Weinheim, **2005**, pp. 497. (b) Ishihara, Y.; Baran, P. S. *Synlett* **2010**, *12*, 1733. (c) Liron, F.; Oble, J.; Lorion, M. M.; Poli, G. *Eur. J. Org. Chem.* **2014**, 5863.
13. Representative examples: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112. (c) Kakiuchi, F.; Kochi, T.; Mutsutani, H.; Kobayashi, N.; Urano, S.; Sato, M.; Nishiyama, S.; Tanabe, T. *J. Am. Chem. Soc.* **2009**, *131*, 11310. (d) Schröder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 8298. (e) Wang, X.-C.; Hu, Y.; Bonacorsi, S.; Hong, Y.; Burrell, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 10326.
14. (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (b) Hartwig, J. F. *Acc. Chem. Res.* **2012**, *45*, 864. (c) Ros, A.; Fernández, R.; Lassaletta, J. M. *Chem. Soc. Rev*. **2014**, *43*, 3229.
15. Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960.
16. Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510.
17. Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628.
18. Stang, E. M.; White, M. C. *Nat. Chem.* **2009**, *1*, 547.
19. Fischer, D. F.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 5926.
20. Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 5767.
21. (a) Zi, W.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2012**, *134*, 9126. (b) McMurray, L.; Beck, E. M.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9288. (c) Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563. (d) Cheng, H.-G.; Lu, L.-Q.; Wang, T.; Yang, Q.-Q.; Liu, X.-P.; Li, Y.; Deng, Q.-H.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2013**, *52*, 3250. (e) Meng, L.; Kamada, Y.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 10048. (f) Kieffer, M. E.; Chuang, K. V.; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 5557.
22. Leblanc, M.; Fagnou, K. *Org. Lett.* **2005**, *7*, 2849.

23. Vorogushin, A. V.; Predeus, A. V.; Wulff, W. D.; Hansen, H. J. *J. Org. Chem.* **2003**, *68*, 5826.
24. Bowie, A. L., Jr.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7*, 5207.
25. Kim, K.; Kim, I. *Org. Lett*. **2010**, *12*, 5314.
26. Mandal, D.; Yamaguchi, A. D.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2011**, *133*, 19660.
27. Ueda, K.; Yanagisawa, S. J.; Yamaguchi, K.; Itami. *Angew. Chem., Int. Ed.* **2010**, *49*, 8946.
28. Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179.
29. Sui, C.; Zhu, R.; Li, G.; Ma, X.; Gu, Z. *J. Am. Chem. Soc.* **2013**, *135*, 9318.
30. Zhao, L.; Tsukano, C.; Kwon, E.; Takemoto, Y.; Hirama, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 1722.
31. Ueda, K.; Amaike, K.; Maceiczyk, R. M.; Itami, K.; Yamaguchi, J. *J. Am. Chem. Soc.* **2014**, *136*, 13226.
32. Yamaguchi, A. D.; Mandal, D.; Yamaguchi, J.; Itami, K. *Chem. Lett.* **2011**, *40*, 555.
33. Yamaguchi, A. D.; Chepiga, K. M.; Yamaguchi, J.; Itami, K.; Davies, H. M. L. *J. Am. Chem. Soc.* **2015**, *137*, 644.

Chapter 1

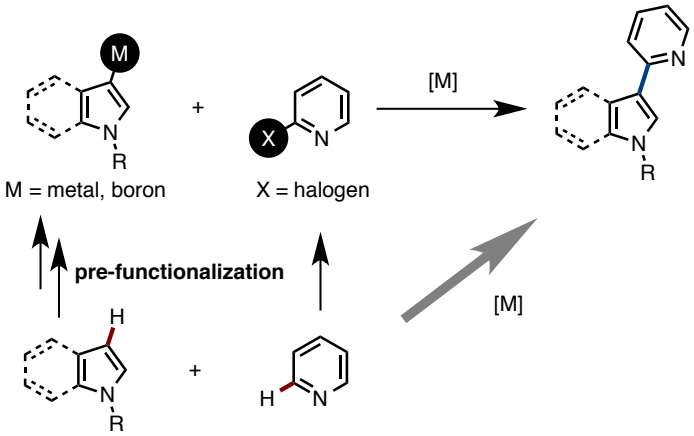
Oxidative C–H/C–H Coupling of Indole/Pyrrole and Azine Nuclei: Application to the Rapid Synthesis of Biologically Active Compounds

Abstract

A palladium-catalyzed C–H/C–H coupling reaction of indoles/pyrroles and azine *N*-oxides has been developed. The reaction proceeds in a virtually complete regioselective manner at the C3 position of indoles/pyrroles and at the C2 position of azine *N*-oxides, respectively. Furthermore, by using this newly developed C–H/C–H coupling reaction, concise syntheses of marine indole alkaloid eudistomin U and a bis(indolyl)pyrazinone framework have been accomplished.

1. Introduction

Organic molecules having indole–azine moieties can be seen in a number of natural products and bioactive molecules.[1] Thus, the development of efficient methods to build-up these frameworks has been a topic of considerable interest in organic chemistry. Furthermore, the field of medicinal chemistry and chemical biology would benefit from such a synthetic campaign because of the presence of the heterocyclic moieties as lead compounds in drug discovery. Currently, the most reliable synthetic method for synthesizing indole–azine compounds is by way of palladium-catalyzed cross-coupling reactions between indoles and azines.[2,3] However, each coupling partner has to be synthesized from their parent compound, which typically requires several steps. Therefore, the direct C–H/C–H coupling of heteroarenes and arenes holds significant synthetic potential as it eliminates the pre-activation of coupling components (Scheme 1).[4] In addition, to date, no total synthesis of biologically active compounds via C–H/C–H couplings of heteroarenes has been reported because of the great challenge to apply these reactions for natural product synthesis.



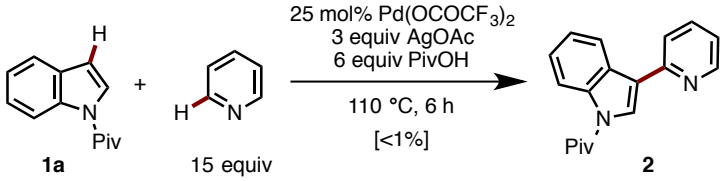
Scheme 1. Approach to indole/pyrrole–azine structure.

In this chapter, the development of a novel palladium-catalyzed C–H/C–H coupling reaction between indoles/pyrroles and azine *N*-oxides with high regioselectivity is described.[5] In addition, concise syntheses of marine indole alkaloid eudistomin U and a bis(indolyl)pyrazinone framework have been accomplished using this C–H/C–H coupling reaction.

2. Results and Discussion

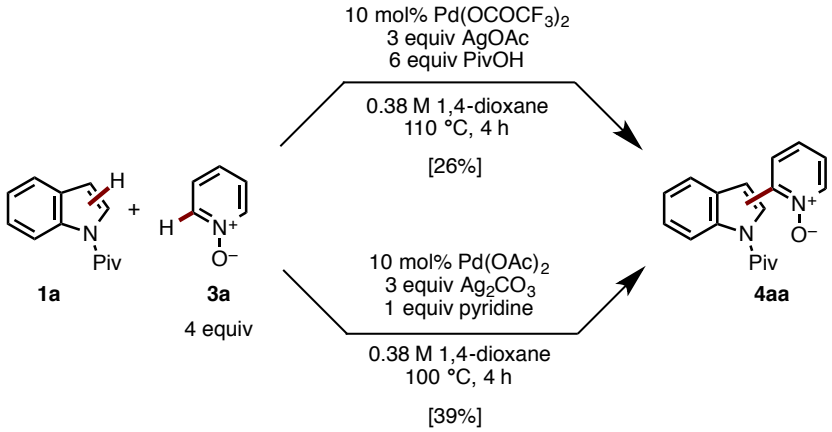
2-1. Discovery of an Indole/Azine C–H/C–H Coupling Reaction

First, the C–H/C–H coupling of *N*-pivaloylindole (**1a**) with unfunctionalized pyridine was examined (Scheme 2). Under palladium catalysis, only a trace amount of coupled product **2** was observed.



Scheme 2. C–H/C–H coupling reaction with unfunctionalized pyridine.

Recently, two research groups reported key findings related to our target reaction. The group of Fagnou reported a C–H/C–H coupling reaction that occurs between indole and benzene nuclei.[4a,b] The group of Chang reported a C–H/C–H coupling reaction that occurs between pyridine *N*-oxide and benzene nuclei.[4c] Inspired by these findings, the coupling reaction between *N*-pivaloylindole (**1a**) and pyridine *N*-oxide (**3a**) was attempted. The corresponding coupling product **4aa** was obtained using both Fagnou's and Chang's reaction conditions (Scheme 3).

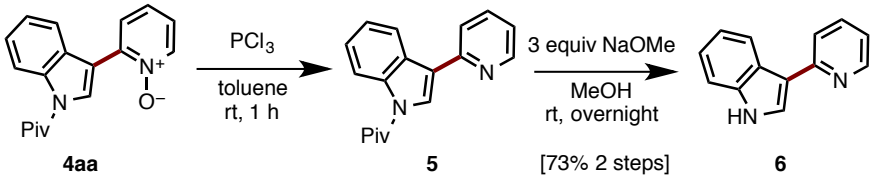


Scheme 3. Coupling of *N*-pivaloylindole (**1a**) with pyridine *N*-oxide (**3a**).

2-2. Determination of Regiochemistry of the Coupling Product

The regioselectivity of the coupling product **4aa** was determined by deriving it into known compound (Scheme 4). Treatment of **4aa** with PCl_3 gave the corresponding

reduced product **5**.[6] Removal of the pivaloyl group with NaOMe provided pyridylindole **6**. The ^{1}H and ^{13}C NMR spectra of **6** were in complete agreement with those previously reported.[7] As a result, it was found that the C–H/C–H coupling reaction occurred in a regioselective manner at the C3 position of the indole and at the C2 position of pyridine *N*-oxide, respectively.



Scheme 4. Determination of regiochemistry of the coupling product **4aa**.

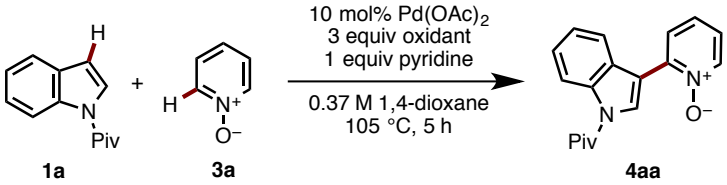
2-3. Optimization of Reaction Conditions

To find a new catalytic system for the C–H/C–H coupling of *N*-pivaloylindole (**1a**) with pyridine *N*-oxide (**3a**), various reaction conditions were screened.

2-3-1. Effect of Oxidant

Firstly, screening of different oxidants was tried. *N*-Pivaloylindole (**1a**) and pyridine *N*-oxide (**3a**) in 1,4-dioxane were stirred at 105 °C for 5 h in the presence of $Pd(OAc)_2$, pyridine and an oxidant (**1a**/**3a**/$Pd(OAc)_2$/oxidant/pyridine = 1.0 : 4.0 : 0.1 : 3.0 : 1.0 molar ratio). The results are shown in Table 1. Ag_2CO_3 and AgOAc were effective for the reaction (entries 1 and 2). In contrast, other Ag(I) salts were not effective (entries 3 and 4). Other oxidants $Cu(OAc)_2$, di-*tert*-butyl peroxide, *p*-benzoquinone, and (diacetoxyiodo)benzene turned out to be ineffective for the reaction (entries 5–8).

Table 1. Effect of oxidant on the indole–azine C–H/C–H coupling.



1a **3a** 4 equiv **4aa**

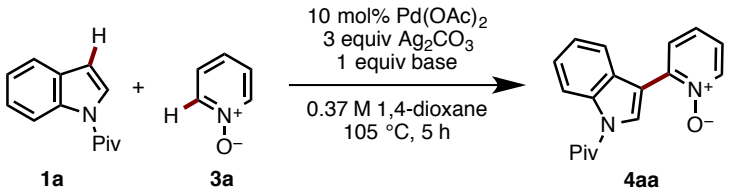
entry	oxidant	yield of **4aa** (%)[a]
1	Ag_2CO_3	48
2	AgOAc	66
3	Ag_2O	<1
4	AgOTf	<1
5	$Cu(OAc)_2$	<1
6	^{t}Bu-O-O-^{t}Bu	0
7	*p*-benzoquinone	<1
8	$PhI(OAc)_2$	<1

[a] Based on GC analysis with *n*-decane as an internal standard.

2-3-2. Effect of Base

At the early stages of this project, it was assumed that 1.0 equivalent of pyridine was consumed as a base in the reaction. Therefore, the screening of different bases was carried out (Table 2). A pyridine derivative, 2,6-lutidine, produced **4aa** in 62% yield (entry 2).[8] Inorganic bases K_2CO_3, MgO, CsOAc, Cs_2CO_3, and K_2HPO_4 only gave trace amounts of the coupling product **4aa** (entries 3–7). P(*o*-tolyl)$_3$ and Et_3N were not effective for the reaction (entries 8 and 9).

Table 2. Effect of base on the indole–azine C–H / C–H coupling.



1a **3a** 4 equiv **4aa**

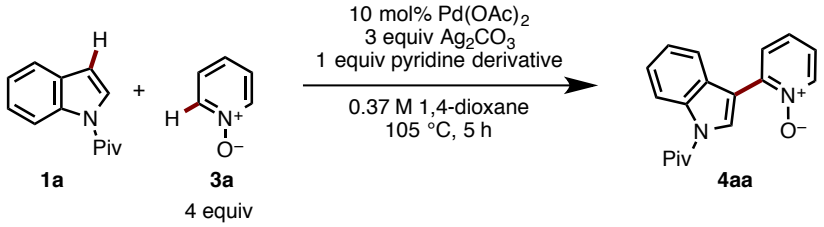
entry	base	yield of **4aa** (%)[a]
1	pyridine	48
2	2,6-lutidine	62
3	K_2CO_3	0
4	MgO	1
5	CsOAc	0
6	Cs_2CO_3	<1
7	K_2HPO_4	<1
8	P(*o*-tolyl)$_3$	4
9	Et_3N	0

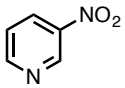
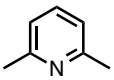
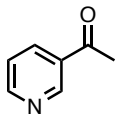
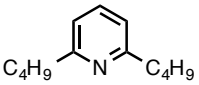
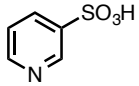
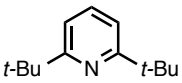
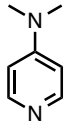
[a] Based on GC analysis with *n*-decane as an internal standard.

2-3-3. Effect of Pyridine Derivative

Various pyridine derivatives were screened (Table 3). It was found that 2,6-dialkylpyridines are most effective for the reaction (entries 2–4). In addition, 3-fluoropyridine and 3-nitropyridine provided **4aa**, while 3-acetylpyridine and 3-pyridinesulfonic acid were ineffective (entries 5–8). Furthermore, *N*,*N*-dimethyl-4-aminopyridine and piperidine showed poor reactivity (entries 9 and 10).

Table 3. Effect of pyridine derivative on the indole–azine C–H / C–H coupling.



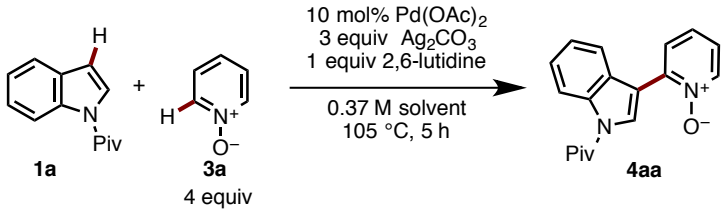
entry	pyridine derivative	yield of **4aa** (%)[a]	entry	pyridine derivative	yield of **4aa** (%)[a]
1		48	6		37
2		62	7		8
3		45	8		<1
4		54	9		<1
5		63	10		0

[a] Based on GC analysis with *n*-decane as an internal standard.

2-3-4. Effect of Solvent

Solvent screening for this reaction was conducted (Table 4). *N*-Pivaloylindole (**1a**) and pyridine *N*-oxide (**3a**) were stirred at 105 °C in the presence of $Pd(OAc)_2$, Ag_2CO_3 and 2,6-lutidine (**1a**/**3a**/$Pd(OAc)_2$/Ag_2CO_3/2,6-lutidine = 1.0 : 4.0 : 0.1 : 3.0 : 1.0 molar ratio) in various solvents. Aprotic polar solvents DMF and DMSO gave low yields of **4aa** (entries 1 and 2). The use of 1,2-dichloroethane cyclopentyl methyl ether (CPME), and *tert*-butyl methyl ether (*t*-BME) provided **4aa** in reasonable yields (entries 4–6), but 2-propanol and THF were not efficient for the reaction (entries 3 and 7).

Table 4. Effect of solvent on the indole–azine C–H/C–H coupling.



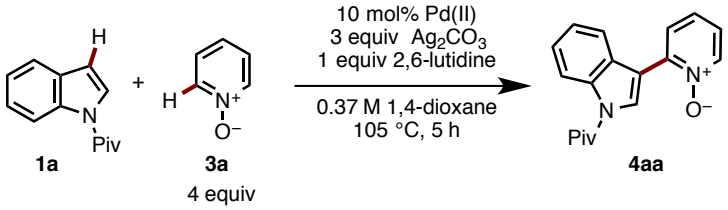
entry	solvent	yield of **4aa** (%)[a]
1	DMF	17
2	DMSO	4
3	2-propanol	1
4	1,2-dichloroethane	35
5	CPME	56
6	*t*-BME[b]	23
7	THF	3

[a] Based on GC analysis with *n*-decane as an internal standard.
[b] *t*-BME = *tert*-butyl methyl ether

2-3-5. Effect of Palladium Source

Various palladium(II) complexes were screened in place of $Pd(OAc)_2$. *N*-Pivaloylindole (**1a**) and pyridine *N*-oxide (**3a**) in 1,4-dioxane were stirred at 105 °C in the presence of a Pd catalyst, Ag_2CO_3 and 2,6-lutidine (**1a**/**3a**/Pd/Ag_2CO_3/2,6-lutidine = 1.0 : 4.0 : 0.1 : 3.0 : 1.0 molar ratio). The results are shown in Table 5. $Pd(OCOCF_3)_2$ gave a lower yield (entry 2). Palladium halides such as $PdCl_2$ and $PdBr_2$ were ineffective for the reaction (entries 4 and 5). Other Pd complexes provided trace amounts of **4aa** (entries 6 and 7). This result indicates that $Pd(OAc)_2$ is the best Pd source for the reaction.

Table 5. Effect of palladium source on the indole–azine C–H/C–H coupling.



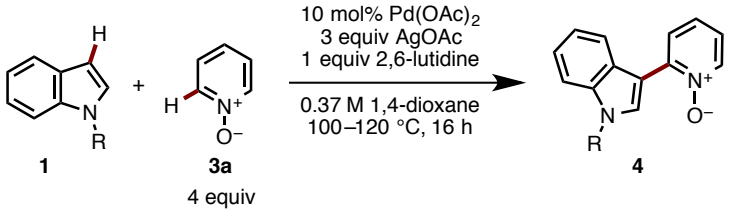
entry	Pd(II)	yield of **4aa** (%)[a]
1	$Pd(OAc)_2$	62
2	$Pd(OCOCF_3)_2$	20
3	$Pd(acac)_2$	7
4	$PdCl_2$	20
5	$PdBr_2$	8
6	$Pd(bipy)Cl_2$	1
7	$Pd(dppf)Cl_2$	0

[a] Based on GC analysis with *n*-decane as an internal standard.

2-3-6. Effect of *N*-Protecting Group on Indole

Various *N*-substituted indoles **1** were screened for the C–H/C–H coupling (Table 6). Unprotected indole (**1b**), *N*-TBS indole (**1c**), and *N*-trifluoroacetylindole (**1d**) provided no coupling product (entries 2–4). The tosyl group (entry 5) was effective for the reaction as well as the methyl group (entry 6). *N*-MOM indole (**1g**) gave the coupling product **4ga** in 73% yield (entry 7).

Table 6. Effect of indole *N*-substituent on the indole–azine C–H/C–H coupling.



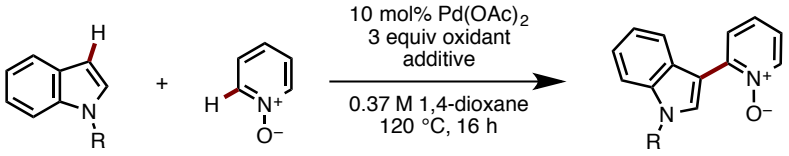
entry	**1**	R	yield of **4** (%)[a]	
1	**1a**	Piv	**4aa**	50
2	**1b**	H	**4ba**	0
3	**1c**	TBS	**4ca**	0
4	**1d**	$COCF_3$	**4da**	0
5	**1e**	Ts	**4ea**	67
6	**1f**	Me	**4fa**	50
7	**1g**	MOM	**4ga**	73

[a] Isolated yield

2-3-7. Further Experiments

Further experiments were carried out to complete the reaction optimization (Table 7). It was possible to decrease the catalyst loading to 2 mol% while maintaining reasonable yield (entry 1). Both an excessive amount of pyridine *N*-oxide and addition of 2,6-lutidine were essential for keeping the reactivity (entries 2 and 3). When 2,2′-bipyridyl was used as a chelating ligand, the yield diminished (entry 4). In contrast, an electron-deficient diene ligand, tetrafluorobenzobarrelene, gave the coupling product **4ga** in 55% yield (entry 5). In 2010, Hu, You and co-workers reported an oxidative C–H/C–H coupling reaction between two heteroarenes.[4h] Their reaction conditions were applied to a C–H/C–H coupling of **1g**/**1e** with **3a**. *N*-MOM indole (**1g**) was coupled with pyridine *N*-oxide in good yield (entry 6); on the other hand, *N*-tosylindole (**1e**) gave low yield (entry 7).

Table 7. Further experiments for the indole–azine C–H/C–H coupling.



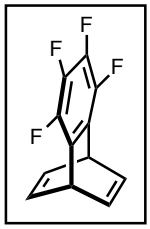
1g: R = MOM
1e: R = Ts

3a

X equiv

4

entry	**1**	X (equiv)	oxidant	additive	yield of **4** (%)[a]	
1[b]	**1g**	4	AgOAc	1 equiv 2,6-lutidine	**4ga**	53
2	**1g**	1	AgOAc	1 equiv 2,6-lutidine	**4ga**	27
3	**1g**	4	AgOAc	–	**4ga**	22
4	**1g**	4	AgOAc	10 mol% bipy	**4ga**	24
5	**1g**	4	AgOAc	20 mol% tfb	**4ga**	55
6[c]	**1g**	4	$Cu(OAc)_2 \cdot H_2O$	1 equiv pyridine	**4ga**	64
7[c]	**1e**	4	$Cu(OAc)_2 \cdot H_2O$	1 equiv pyridine	**4ea**	15



tetrafluoro-benzobarrelene (tfb)

[a] Isolated yield. [b] 2 mol% of $Pd(OAc)_2$ was used. The reaction time was 43 h.
[c] The reaction conditions were reported by Hu, You and co-workers.[4h]

2-4. Proposed Reaction Mechanism

As of yet, the precise mechanism of the coupling reaction is unknown. One possible scenario involves a catalytic Pd^{II}/Pd^{0} redox system (Figure 1): i) PdX_2 reacts with the acidic C2–H of pyridine *N*-oxide to produce a pyridylpalladium species; ii) the electrophilic organopalladium species is then attacked by the most nucleophilic C3 position of indole; iii) the coupling product and Pd^{0} species are generated via reductive elimination, followed by reoxidation of Pd^{0} to Pd^{II} by AgOAc, completing the catalytic cycle.

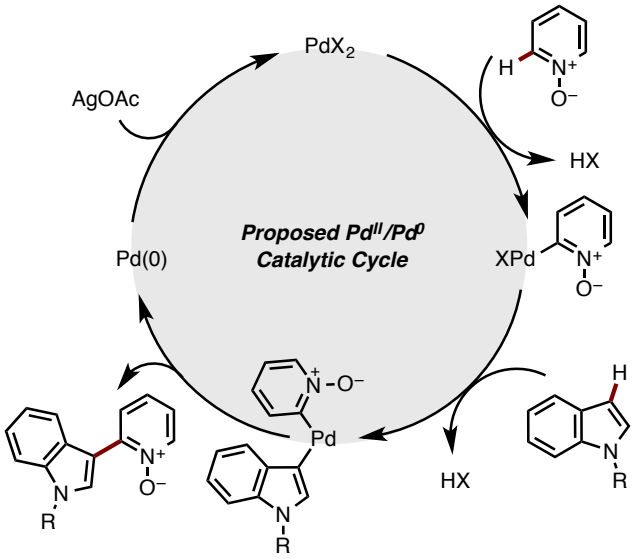
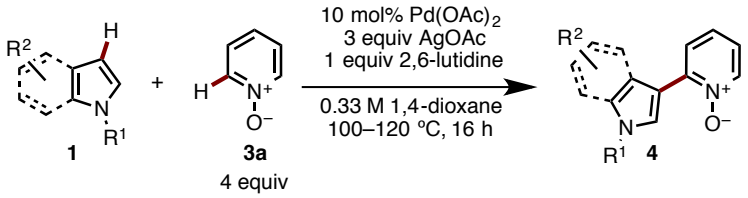


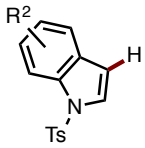
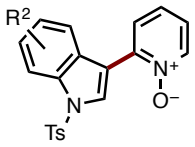
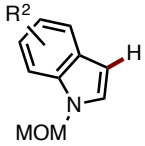
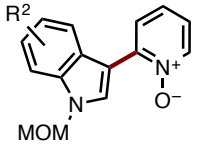
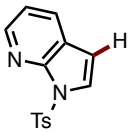
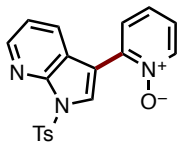
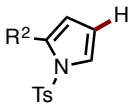
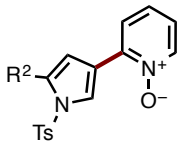
Figure 1. Proposed catalytic cycle.

2-5. Scope of Indoles and Pyrroles

The scope of the direct indole–azine *N*-oxide coupling was investigated using various indoles and pyridine *N*-oxide (Table 8). This reaction tolerated substitutions on the indole ring such as cyano (entry 1), methoxy (entry 2), nitro (entries 3 and 4), and ester (entry 5) groups. The coupling reaction proceeded even with 7-azaindole (entry 6), which is more electron-deficient. Furthermore, the C–H/C–H coupling of pyrroles with **3a** selectively gave 3-pyridinated pyrrole products in moderate yields (the same selectivity observed with indole).[9]

Table 8. Scope of indoles and pyrroles.



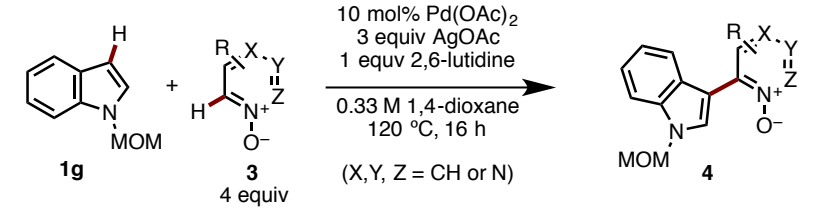
entry	1		yield of **4** (%)[a]	
1		**1h** R^2 = 5-CN		**4ha** 52
2		**1i** R^2 = 6-OMe		**4ia** 38
3		**1j** R^2 = 5-NO_2		**4ja** 56
4		**1k** R^2 = 6-NO_2		**4ka** 49
5		**1l** R^2 = 6-CO_2Me		**4la** 55
6		**1m**		**4ma** 46
7		**1n** R^2 = H		**4na** 42[b]
8		**1o** R^2 = Ac		**4oa** 47[b]
9		**1p** R^2 = CO_2Me		**4pa** 47[b]

[a] Isolated yield. [b] The reaction time was 48 h.

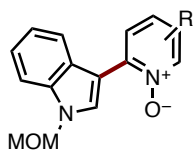
2-6. Scope of Azine *N*-Oxides

Finally, the scope of the coupling reaction with respect to azine *N*-oxides was examined. Representative results are shown in Table 9. Substitutions on the pyridine ring of pyridine *N*-oxide such as methyl, nitro, and cyano groups were well tolerated, providing the corresponding coupling products in moderate yields. When pyrazine *N*-oxide was used as a substrate, the expected coupling product 4ge was obtained in a good yield (70%) when acetic acid was added to the reaction mixture.[10] Notably, the use of quinoxaline *N*-oxide as a substrate gave coupling product **4gf** in higher yield than the parent indole–pyridine *N*-oxide coupling reaction. Furthermore, the coupling products derived from isoquinoline, phthalazine, and pyrimidine *N*-oxides were obtained, and their regioselective outcomes were consistent with the parent coupling reaction.

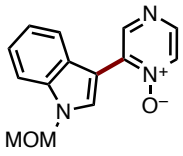
Table 9. Scope of azine *N*-oxides.



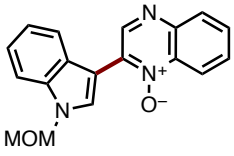
Product **4**: isolated yield



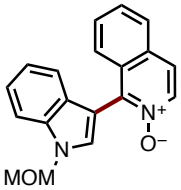
4gb (R = 2-Me) : 34%
4gc (R = 4-NO_2): 56%
4gd (R = 4-CN) : 57%



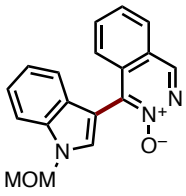
4ge: 70%[a]



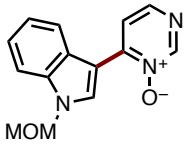
4gf: 86%



4gg: 57%



4gh: 44%

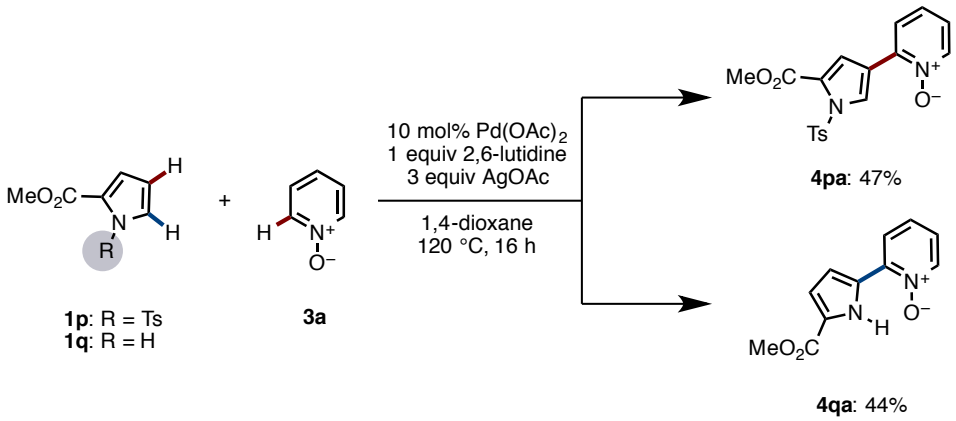


4gi: 32%

[a] AcOH was used instead of 2,6-lutidine.

2-7. Regioselectivity Control of Pyrrole Ring

While carrying out the coupling reactions of various pyrroles and pyridine *N*-oxide (**3a**), it was found that methyl pyrrole-2-carboxylate (**1q**) gave 2-pyridinated pyrrole **4qa** as an α-selective arylated product (Scheme 5). The selectivity was different from the coupling reaction of *N*–tosylpyrrole **1p** with pyridine *N*-oxide (**3a**). Although the precise mechanism of the regioselectivity switch of these pyrrole derivatives is currently unknown, a possibility exists whereby the formation of a hydrogen bond from the NH group of pyrrole helps achieve α-selectivity at the pyrrole by pre-organizing substrates together. In contrast, unsubstituted pyrrole produced no coupling product under the same reaction conditions.



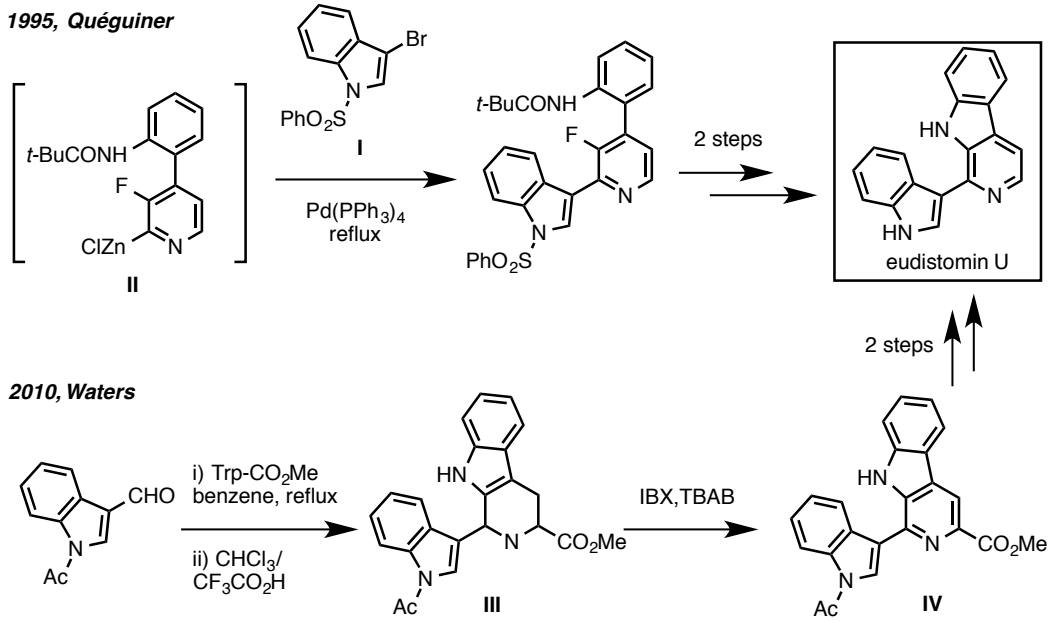
Scheme 5. Regioselectivity control of pyrrole ring.

2-8. Rapid Synthesis of Eudistomin U

Next the synthesis of eudistomin U, a marine indole alkaloid, was planned through a direct synthetic strategy using above the C–H/C–H coupling reaction as a key step.

2-8-1. Previous Reports Describing the Total Synthesis of Eudistomin U

Eudistomin U is a marine indole alkaloid that was isolated from the marine ascidian *Lissoclinum fragile* by Francisco and co-workers in 1994.[11a] Eudistomin U displays DNA-binding activity as well as strong antimicrobial properties and possesses a heterobiaryl structure. Although the total synthesis of eudistomin U has already been reported by some groups,[11b–d] the construction of its skeleton from two simple heteroarene units, indole and β-carboline, has not been achieved. Previous synthetic strategies for the core structure are shown in Scheme 6.

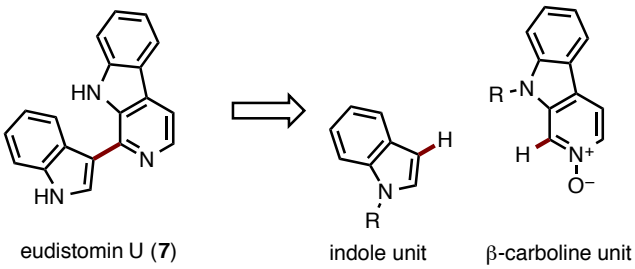


Scheme 6. Previous syntheses of eudistomin U.

In 1995, Quéguiner and co-workers synthesized the heterobiaryl structure of eudistomin U by palladium-catalyzed cross-coupling of 3-bromoindole **I** and *in situ* prepared organozinc compound **II,** followed by β-carboline ring formation.[11c] Recently in 2010, Waters and co-workers provided tetrahydro-β-carboline **III** by Pictet–Spengler condensation of *N*-acetyl indole-3-carboxaldehyde and tryptophan methyl ester. Then, dehydrogenation of **III** in the presence of 2-iodoxybenzoic acid (IBX) and tetra-*n*-butylammonium bromide (TBAB) gave the 1-(3-indolyl)-β-carboline derivative **IV**.[11d]

2-8-2. Retrosynthetic Strategy

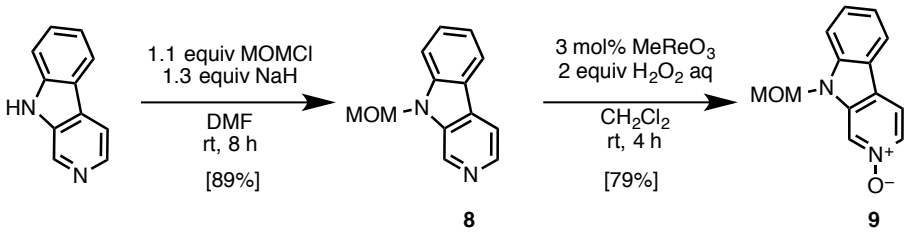
Retrosynthetic analysis of eudistomin U (**7**) is shown in Scheme 7. The heterobiaryl structure could be synthesized from indole and β-carboline units through a C–H/C–H coupling reaction.



Scheme 7. Retrosynthetic strategy.

2-8-3. Total Synthesis of Eudistomin U through C–H/C–H Coupling Reaction

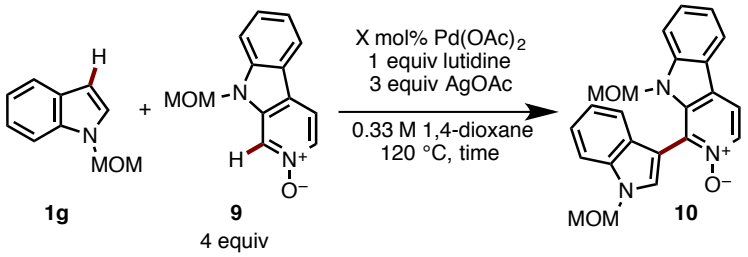
The short synthesis of eudistomin U began with a MOM protection of commercially available β-carboline to afford **8** in 89% yield. Then treatment of **8** with a catalytic amount of $MeReO_3$ and aqueous H_2O_2 provided the corresponding *N*-oxide **9** in 79% yield (Scheme 8).[12]



Scheme 8. Preparation of coupling precursor **9**.

Then the key C–H/C–H coupling reaction of *N*-MOM indole (**1g**) with β-carboline *N*-oxide **9** was tried (Table 10). *N*-MOM indole (**1g**) and *N*-oxide **9** were stirred at 120 °C for 16 h in the presence of 30 mol% $Pd(OAc)_2$, Ag_2CO_3 and 2,6-lutidine in 1,4-dioxane to afford the corresponding coupling product **10** in 35% yield (entry 1). It was found that **10** can be obtained in 41% yield in the presence of 10 mol% $Pd(OAc)_2$ by increasing the reaction time to 23 h (entry 3).

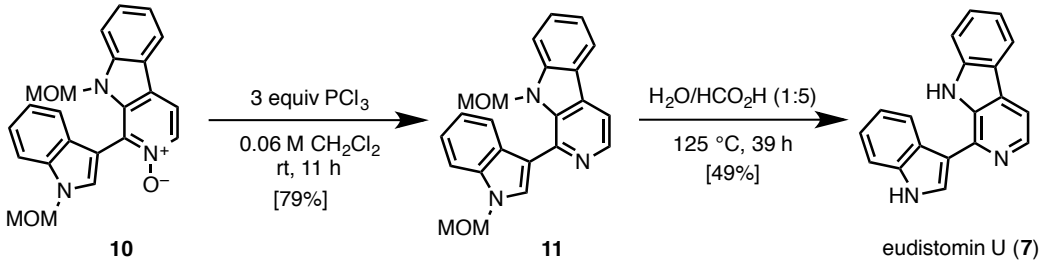
Table 10. C–H/C–H Coupling of indole derivative **1g** with β-carboline *N*-oxide **9**.



entry	X (mol%)	time (h)	yield of **10** (%)[a]
1	30	16	35
2	10	16	24
3	10	23	41

[a] Isolated yield.

To complete the total synthesis of eudistomin U, removal of an oxygen atom and *N*-MOM protecting group was carried out (Scheme 9). Reduction of *N*-oxide **10** proceeded by treatment of **10** with PCl_3 in CH_2Cl_2 to afford **11** in 79% yield.[6] Finally, removal of *N*-MOM groups using HCO_2H in water completed the synthesis of eudistomin U (**7**) in 49% yield.



Scheme 9. Completion of the total synthesis of eudistomin U.

2-9. Synthesis of Bis(indolyl)pyrazinone through C–H/C–H Coupling

Next, an investigation toward two sequential C–H/C–H coupling reactions to access the bis(indolyl)pyrazinone framework, which is present in various natural products such as dragmacidin[13] and hamacanthin[14] was commenced.

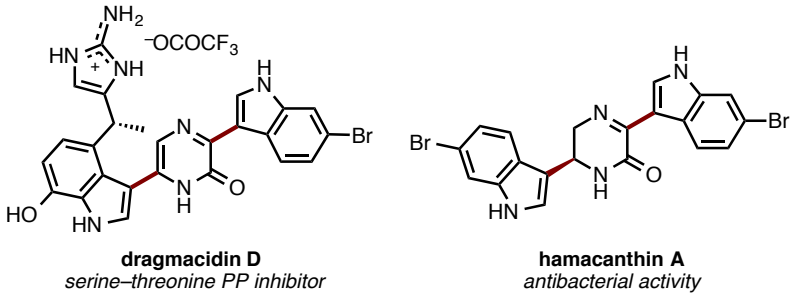
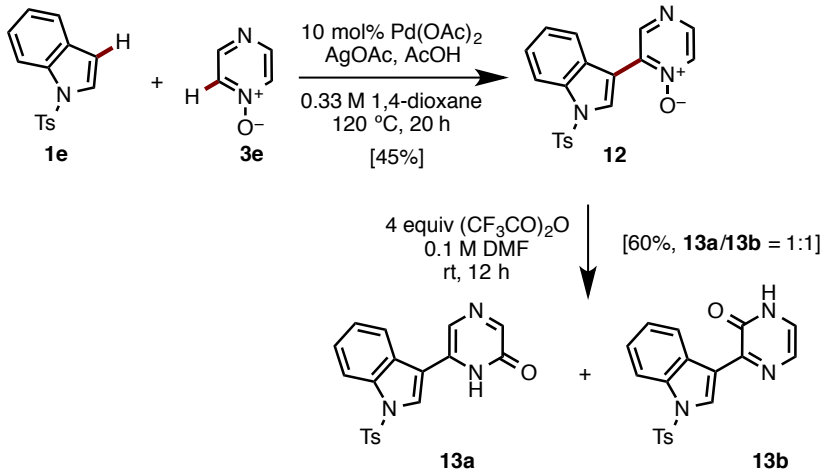


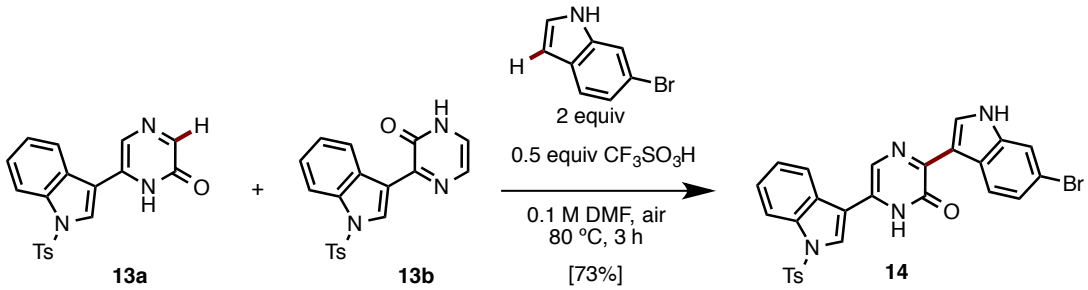
Figure 2. Natural products containing bis(indolyl)pyrazinone structure.

Initially, C–H/C–H coupling reaction of *N*-tosylindole (**1e**) with pyrazine *N*-oxide (**3e**) was conducted. Regioselective coupling of indole **1e** with pyrazine *N*-oxide (**3e**) proceeded to give the corresponding coupling product **12** by modifying the original conditions. Treatment of **12** with $(CF_3CO)_2O$ gave two pyrazinones **13a** and **13b** in 60% yield (**13a**/**13b** = 1:1) as an inseparable mixture (Scheme 10).[15]



Scheme 10. Formation of pyrazinones **13a** and **13b**.

Next, an acid-catalyzed Friedel–Crafts type oxidative pyrazinone/indole C–H/C–H coupling was carried out.[16] The inseparable mixture of **13a** and **13b** in DMF were stirred with 6-bromoindole at 80 °C with 0.5 equivalent of CF_3SO_3H in the presence of air. The C–H/C–H coupling reaction of pyrazinone **13a** and 6-bromoindole proceeded to give the desired bis(indolyl)pyrazinone **14** in 73% yield (Scheme 11) and unreacted pyrazinone **13b** was removed at this step.



Scheme 11. Acid-catalyzed C–H/C–H coupling.

The molecular structure of **14** was determined by single-crystal X-ray diffraction

analysis (Figure 3).

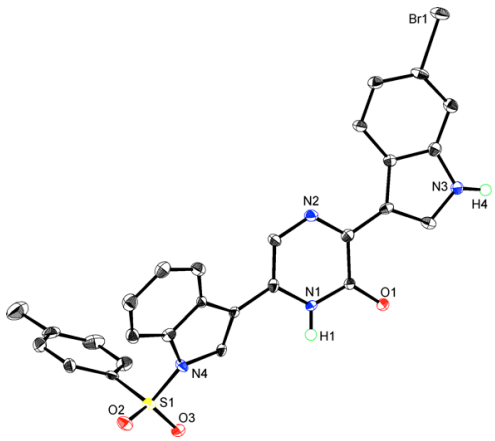
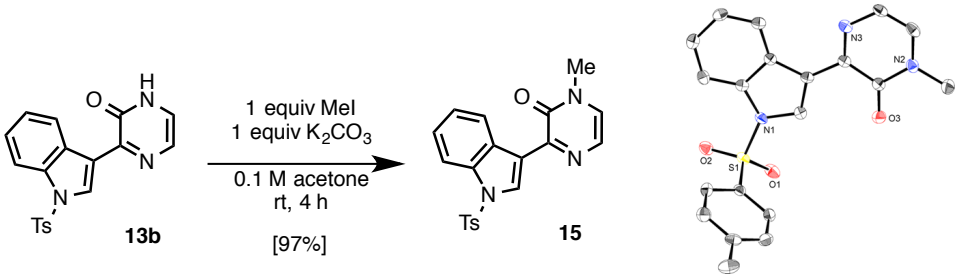


Figure 3. X-ray crystal structure of **14**·2THF.

The structure of **13b** was confirmed by single-crystal X-ray diffraction analysis after converting it to the corresponding *N*-methyl pyrazinone **15** (Scheme 12).



Scheme 12. X-ray crystal structure of **15**.

3. Conclusion

In this chapter, the C–H/C–H coupling reaction of indoles/pyrroles with azine *N*-oxides in the presence of $Pd(OAc)_2$/AgOAc/2,6-lutidine/1,4-dioxane system was described. The reaction proceeds in a virtually complete regioselective manner at the C3 position of indoles/pyrroles and at the C2 position of azine *N*-oxides, respectively. Various azine *N*-oxides such as pyrazine, pyrimidine, isoquinoline, phthalazine, and quinoxaline *N*-oxide can be used as coupling partners in the reaction. Furthermore, rapid syntheses of eudistomin U and bis(indolyl)pyrazinone framework through this C–H/C–H coupling reaction were described. The synthesis of eudistomin U from two

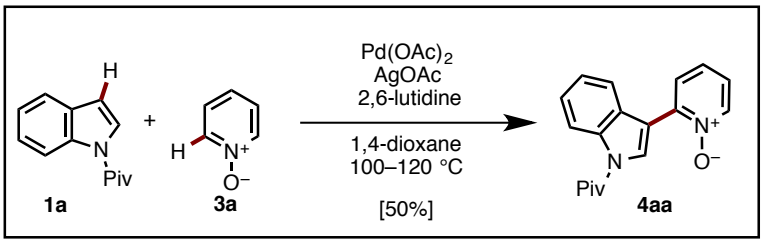
heteroaromatic fragments (indole and β-carboline units) was accomplished through the direct C–H/C–H coupling reaction in a total of five steps. Meanwhile, the methodology was developed further to access a bis(indolyl)pyrazinone structure. One of the indole–azine bonds was built by our Pd-catalyzed C–H/C–H coupling described above while the other bond was constructed through the rearrangement of pyrazine *N*-oxide to pyrazinone followed by an acid-catalyzed oxidative Friedel–Crafts-type reaction. It is of note that, simultaneously with our group, the groups of Zhang, Li and You independently reported the same transformation to access indole–azine frameworks.[17]

4. Experimental

4-1. General

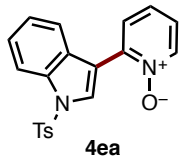
Unless otherwise noted, all materials including dry solvents were obtained from commercial suppliers and used without further purification. Unless otherwise noted, all reactions were performed with dry solvents under an atmosphere of argon in flame-dried glassware using standard vacuum-line techniques. All Coupling reactions were carried out in glass vessels equipped with J. Young® O-ring tap, heated in a 8-well reaction block (heater + magnetic stirrer). All work-up and purification procedures were carried out with reagent-grade solvents in air. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid/sulfuric acid. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh). Preparative thin-layer chromatography (PTLC) was performed using Wako-gel® B5-F silica coated plates (0.75 mm) prepared in our laboratory. Gas chromatography (GC) analysis was conducted on a Shimazu GC-2010 instrument equipped with a HP-5 column (30 m × 0.25 mm, Hewlett-Packard). GCMS analysis was conducted on a Shimazu GCMS-QP2010 instrument equipped with a HP-5 column (30 m × 0.25 mm, Hewlett-Packard). LCMS analysis was conducted on an *Agilent 6100* instrument. High-resolution mass spectra (HRMS) were obtained from a JMS-T100TD instrument (DART). Low-resolution mass spectra (LRMS) were obtained from an *Agilent 6100* instrument. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECA-600 (^{1}H 600 MHz, ^{13}C 150 MHz) spectrometer. Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.0 ppm) and $CDCl_3$ (7.26 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, brs = broad singlet), coupling constant (Hz), and integration. Compounds **1a**, **1c**, **1d**, **1e**, **1g**, **1n**, **1o** and **1q** were prepared using literature procedures.[18]

4-2. Typical Procedure for Pd-Catalyzed C–H/C–H Coupling of Indoles/Pyrroles with Azine *N*-Oxides

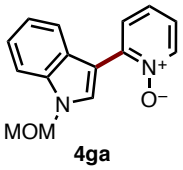


2-(1-Pivaloyl-1*H*-indol-3-yl)pyridine *N*-oxide (4aa): All coupling reactions were performed on a 0.40 mmol scale at 0.35 M unless otherwise stated. A 20-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vessel were added $Pd(OAc)_2$ (9 mg, 40 μmol), AgOAc (200 mg, 1.2 mmol), 1-pivaloylindole (80.5 mg, 0.4 mmol), pyridine *N*-oxide (152.2 mg, 1.6 mmol), dry 1,4-dioxane (1.2 mL), and 2,6-lutidine (47 μL, 0.4 mmol) under a stream of argon. The vessel was sealed with O-ring tap, and then heated at 120 °C for 16 h in a 8-well reaction block with stirring. After cooling the reaction mixture to room temperature, it was passed through a pad of Celite® (CH_2Cl_2) and the filtrate was concentrated under reduced pressure. The crude products were purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4aa** (58.9 mg, 50%) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.56 (s, 9H), 7.15 (td, *J* = 6.9, 2.0 Hz, 1H), 7.32–7.35 (m, 2H), 7.39 (t, *J* = 6.8 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 8.36 (d, *J* = 6.9 Hz, 1H), 8.60 (d, *J* = 8.2 Hz, 1H), 9.54 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 28.5, 41.5, 110.7, 117.4, 118.9, 122.5, 124.0, 125.3, 125.3, 125.5, 126.8, 130.4, 136.4, 140.5, 143.0, 177.3. HRMS *m*/*z* calcd for $C_{18}H_{19}N_2O_2$: 295.1447, found 295.1445.

2-(1-Tosyl-1*H*-indol-3-yl)pyridine 1-oxide (4ea): The title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4ea** in 67% yield as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.31 (s, 3H), 7.18–7.38 (m, 6H), 7.77 (m, 2H), 7.86 (d, *J* = 7.6 Hz, 2H), 8.08 (d, *J* = 8.3 Hz, 1H), 8.36 (d, *J* = 5.5 Hz, 1H), 8.95 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 112.6, 113.7, 120.5, 123.3, 123.7, 124.9, 125.1, 125.9, 127.0, 128.2, 129.7, 130.0, 134.4, 134.8, 140.5, 142.9, 145.3. HRMS *m*/*z* calcd for $C_{20}H_{17}N_2O_3S$: 365.0960, found 365.0959.

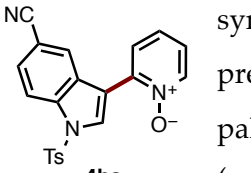


2-(1-(Methoxymethyl)-1*H*-indol-3-yl)pyridine 1-oxide (4ga): The title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4ga** in 73% yield as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.28 (s, 3H), 5.53 (s, 2H), 7.06 (td, *J* = 6.9, 2.0 Hz, 1H), 7.27–7.34 (m, 3H), 7.60 (d, *J* = 8.9 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 8.36 (d, *J* = 6.2 Hz, 1H), 9.00 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.7, 77.7, 106.2, 110.7, 119.4, 120.8, 121.4, 122.6, 124.3, 125.0, 126.4, 133.3, 135.7, 140.2, 144.1. HRMS *m*/*z* calcd for $C_{15}H_{15}N_2O_2$: 255.1134, found 255.1132.



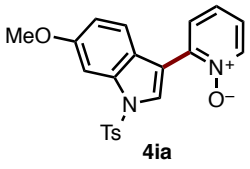
4ga

2-(5-Cyano-1-tosyl-1*H*-indol-3-yl)pyridine 1-oxide (4ha): The title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4ha** in 52% yield as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.28–7.30 (m, 3H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.63 (dd, *J* = 8.9, 1.4 Hz, 1H), 7,70 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 8.14 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 8.40 (d, *J* = 6.8 Hz, 1H), 8.83 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 107.3, 113.1, 114.5, 119.0, 124.2, 125.4, 126.2, 126.3, 127.0, 127.7, 128.3, 130.2, 130.8, 134.1, 136.1, 140.5, 141.9, 146.1. HRMS *m*/*z* calcd for $C_{21}H_{16}N_3O_3S$: 390.0912, found 390.0910.



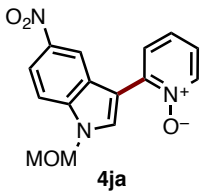
4ha

2-(6-Methoxy-1-tosyl-1*H*-indol-3-yl)pyridine 1-oxide (4ia): The title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4ia** in 38% yield as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.88 (s, 3H), 6.92 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.17 (td, *J* = 7.6, 2.0 Hz, 1H), 7.23 (d, *J* = 8.6 Hz, 2H), 7.30 (td, *J* = 7.6, 2.0 Hz, 1H), 7.60 (d, *J* = 2.8 Hz, 1H), 7.64 (d, *J* = 8.9 Hz, 1H), 7.75 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 8.35 (d, *J* = 6.9 Hz, 1H), 8.84 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 55.6, 97.9, 112.7, 112.7, 121.2, 121.9, 123.1, 125.1, 125.8, 126.9, 128.5, 129.9, 134.8, 135.5, 140.5, 143.0, 145.3, 157.9. HRMS *m*/*z* calcd for $C_{21}H_{19}N_2O_4S$: 395.1066, found 395.1067.



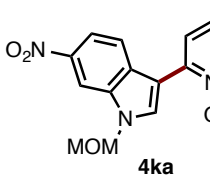
4ia

2-(1-(Methoxymethyl)-5-nitro-1*H*-indol-3-yl)pyridine 1-oxide (4ja): The title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4ja** in 56% yield as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.32 (s, 3H), 5.57 (s, 2H), 7.20 (td, *J* = 6.7, 2.0 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.66 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 8.23 (td, *J* = 8.9, 2.0 Hz, 1H), 8.40 (d, *J* = 6.2 Hz, 1H), 8.89 (s, 1H), 9.05 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.4, 78.4, 108.6, 111.2, 116.8, 118.4, 122.4, 124.9, 125.8, 126.3, 135.9, 138.9, 140.6, 143.0, 143.1. HRMS *m*/*z* calcd for $C_{15}H_{14}N_3O_4$: 300.0984, found 300.0983.



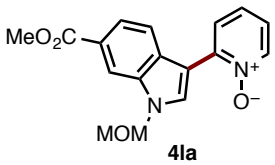
4ja

2-(1-(Methoxymethy)-6-nitro-1*H*-indol-3-yl)pyridine 1-oxide (4ka): The title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4ka** in 49% yield as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.35 (s, 3H), 5.62 (s, 2H), 7.15 (td, *J* = 6.8, 2.0 Hz, 1H), 7.40 (td, *J* = 8.3, 1.4 Hz, 1H), 7.91 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.99 (d, *J* = 8.9 Hz, 1H), 8.19 (dd, *J* = 8.9, 2.0 Hz, 1H), 8.41 (d, *J* = 6.8 Hz, 1H), 8.57 (d, *J* = 2.0 Hz, 1H), 9.10 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.4, 78.4, 107.6, 107.8, 116.8, 119.8, 122.4, 124.9, 125.5, 131.3, 134.6, 137.7, 140.5, 143.2, 143.6. HRMS *m*/*z* calcd for $C_{15}H_{14}N_3O_4$: 300.0984, found 300.0987.



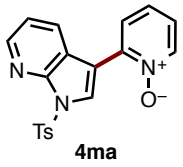
4ka

2-(6-(Methoxycarbonyl)-1-(methoxymethyl)-1*H*-indol-3-yl)pyridine 1-oxide (4la): The title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4la** in 55% yield as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.31 (s, 3H), 3.95 (s, 3H), 5.59 (s, 2H), 7.13 (td, *J* = 5.5, 2.1 Hz, 1H), 7.36 (td, *J* = 6.3, 1.4 Hz, 1H), 7.91–7.98 (m, 3H), 8.32 (s, 1H), 8.38 (d, *J* = 5.5 Hz, 1H), 9.07 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 51.9, 56.1, 78.0, 106.9, 112.9, 119.2, 121.6, 122.6, 124.5, 124.7, 125.4, 130.2, 135.3, 136.0, 140.4, 143.8, 167.3. HRMS *m*/*z* calcd for $C_{17}H_{17}N_2O_4$: 313.1188, found 313.1190.



4la

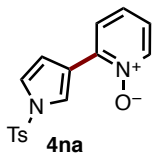
2-(1-Tosyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)pyridine 1-oxide (4ma): The title compound



4ma

was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4ma** in 46% yield as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.23–7.29 (m, 4H), 7.35 (td, *J* = 7.6, 1.4 Hz, 1H), 7.70 (dd, *J* = 8.3, 2.0 Hz, 1H), 8.14–8.16 (m, 3H), 7.88 (dd, *J* = 6.8, 1.4 Hz, 1H), 8.49 (dd, *J* = 4.9, 1.4 Hz, 1H), 8.85 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 110.5, 119.1, 120.8, 123.8, 125.4, 125.9, 128.3, 128.9, 129.7, 130.2, 134.9, 140.6, 142.9, 145.3, 145.5, 146.7. HRMS *m*/*z* calcd for $C_{19}H_{16}N_3O_3S$: 366.0912, found 366.0923.

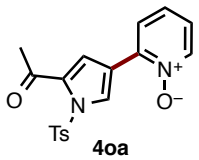
2-(1-Tosyl-1*H*-pyrrol-3-yl)pyridine 1-oxide (4na): The title compound was synthesized



4na

according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4na** in 42% yield as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.38 (s, 3H), 6.74 (dd, *J* = 3.4, 1.4 Hz, 1H), 7.08 (td, *J* = 6.8, 2.1 Hz, 1H), 7.22–7.29 (m, 4H), 7.58 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 8.27 (d, *J* = 6.9 Hz, 1H), 8.87 (t, *J* = 2.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 111.5, 119.2, 120.7, 122.3, 123.6, 124.0, 125.2, 127.1, 130.0, 135.4, 140.5, 142.8, 145.3. HRMS *m*/*z* calcd for $C_{16}H_{15}N_2O_3S$: 315.0803, found 315.0808.

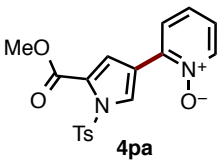
2-(5-Acetyl-1-tosyl-1*H*-pyrrol-3-yl)pyridine 1-oxide (4oa): The title compound was



4oa

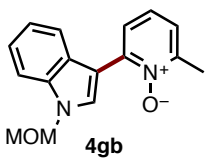
synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4oa** in 47% yield as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.41 (s, 3H), 7.16 (td, *J* = 7.2, 2.0 Hz, 1H), 7.28–7.30 (m, 3H), 7.66–7.65 (m, 2H), 7.95 (d, *J* = 8.3 Hz, 2H), 8.30 (d, *J* = 8.3 Hz, 1H), 9.15 (d, *J* = 1.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 27.1, 116.3, 122.3, 123.2, 123.7, 125.4, 128.5, 129.2, 131.7, 132.9, 135.2, 140.5, 141.9, 145.1, 186.0. HRMS *m*/*z* calcd for $C_{18}H_{17}N_2O_4S$: 357.0909, found 357.0902.

2-(5-(Methoxycarbonyl)-1-tosyl-1*H*-pyrrol-3-yl)pyridine 1-oxide (4pa): The above title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4pa** in 47% yield as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.78 (s, 3H), 7.16 (td, *J* = 6.2, 2.1 Hz, 1H), 7.29 (t, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.65 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 2H), 8.31 (d, *J* = 6.2 Hz, 1H), 9.31 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 51.9, 116.2, 121.0, 123.0, 123.6, 124.7, 125.3, 128.4, 129.4, 131.3, 135.1, 140.5, 142.0, 145.3, 158.8. HRMS *m*/*z* calcd for $C_{18}H_{17}N_2O_5S$: 373.0858, found 373.0853.



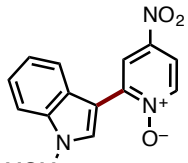
4pa

2-(1-(Methoxymethyl)-1*H*-indol-3-yl)-6-methylpyridine 1-oxide (4gb): The above title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4gb** in 34% yield as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.63 (s, 3H), 3.30 (s, 3H), 5.54 (s, 2H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.25–7.34 (m, 3H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.97 (d, *J* = 7.3 Hz, 1H), 9.03 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.8, 56.0, 78.1, 107.0, 110.9, 119.7, 121.7, 121.8, 122.4, 122.8, 124.7, 127.1, 133.6, 135.9, 144.4, 149.7. HRMS *m*/*z* calcd for $C_{16}H_{17}N_2O_2$: 269.1290, found 269.1297.



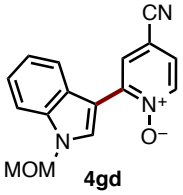
4gb

2-(1-(Methoxymethyl)-1*H*-indol-3-yl)-4-nitropyridine 1-oxide (4gc): The above title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4gc** in 56% yield as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.31 (s, 3H), 5.57 (s, 2H), 7.40–7.42 (m, 2H), 7.65–7.66 (m, 1H), 7.88 (dd, *J* = 6.8, 2.7 Hz, 1H), 8.62 (dd, *J* = 6.9, 2.8 Hz, 1H), 8.42 (d, *J* = 7.6 Hz, 1H), 8.90 (d, *J* = 2.8 Hz, 1H), 9.03 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.2, 78.2, 105.3, 111.4, 114.4, 118.3, 119.3, 122.6, 123.6, 126.1, 134.1, 136.1, 141.1, 142.2, 145.2. HRMS *m*/*z* calcd for $C_{15}H_{14}N_3O_4$: 300.0984, found 300.0980.



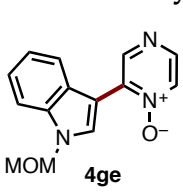
4gc

4-Cyano-2-(1-(methoxymethyl)-1*H*-indol-3-yl)pyridine 1-oxide (4gd): The title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4gd** in 57% yield as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.30 (s, 3H), 5.54 (s, 2H), 7.22 (dd, *J* = 6.9, 2.0 Hz, 1H), 7.35–7.40 (m, 2H), 7.63 (m, 1H), 7.92 (dd, *J* = 6.8, 1.4 Hz, 1H), 8.24 (d, *J* = 2.7 Hz, 1H), 8.36 (d, *J* = 6.6 Hz, 1H), 8.97 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.1, 78.1, 104.9, 107.5, 111.3, 116.5, 119.2, 122.3, 122.5, 123.5, 126.0, 127.0, 134.0, 136.0, 141.1, 145.5. HRMS *m*/*z* calcd for $C_{16}H_{14}N_3O_2$: 280.1086, found 280.1091.



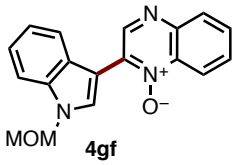
4gd

2-(1-(Methoxymethyl)-1*H*-indol-3-yl)pyrazine 1-oxide (4ge): The title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4ge** in 70% yield as a pale yellow solid except 1 equivalent of AcOH was used in place of 2,6-lutidine. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.29 (s, 3H), 5.53 (s, 2H), 7.32–7.37 (m, 2H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 1H), 8.22–8.23 (m, 2H), 8.90 (s, 1H), 9.24 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.0, 78.0, 103.7, 111.1, 119.7, 122.1, 123.3, 125.8, 133.7, 134.3, 136.0, 140.4, 141.6, 146.3. HRMS *m*/*z* calcd for $C_{14}H_{14}N_3O_2$: 256.1086, found 256.1081.



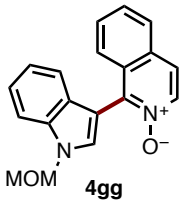
4ge

2-(1-(Methoxymethyl)-1*H*-indol-3-yl)quinoxaline 1-oxide (4gf): The title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4gf** in 86% yield as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.33 (s, 3H), 5.59 (s, 2H), 7.37–7.40 (m, 2H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.75–7.78 (m, 2H), 8.10–8.14 (m, 2H), 8.68 (dd, *J* = 8.3, 2.0 Hz, 1H), 9.20 (s, 1H), 9.57 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.2, 78.3, 105.2, 111.3, 118.6, 120.1, 122.3, 123.5, 126.3, 129.8, 130.3, 134.4, 135.9, 136.2, 137.4, 142.3, 146.2. HRMS *m*/*z* calcd for $C_{18}H_{16}N_3O_2$: 306.1243, found 306.1241.

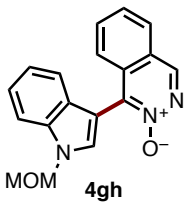


4gf

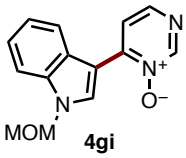
1-(1-(Methoxymethyl)-1*H*-indol-3-yl)isoquinoline 2-oxide (4gg): The title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4gg** in 57% yield as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.39 (s, 3H), 5.56 (d, *J* = 10.3 Hz, 1H), 5.64 (d, *J* = 11.0 Hz, 1H), 7.17 (t, *J* = 6.9 Hz, 1H), 7.31–7.33 (m, 2H), 7.49 (td, *J* = 8.9, 1.4 Hz, 1H), 7.56 (t, *J* = 6.8 Hz, 1H), 7.61–7.64 (m, 2H), 7.83 (t, *J* = 9.6 Hz, 2H), 7.90 (s, 1H), 8.32 (d, *J* = 6.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.2, 77.9, 105.4, 110.5, 121.1, 121.3, 122.3, 122.7, 126.6, 126.8, 128.0, 128.1, 128.6, 129.0, 129.5, 131.8, 136.1, 137.4, 141.3. HRMS *m*/*z* calcd for $C_{19}H_{17}N_2O_2$: 305.1290, found 305.1294.



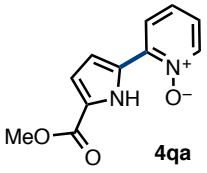
1-(1-(Methoxymethyl)-1*H*-indol-3-yl)phthalazine 2-oxide (4gh): The title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4gh** in 44% yield as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.38 (s, 3H), 5.59 (s, 2H), 7.18 (t, *J* = 6.9 Hz, 1H), 7.31–7.34 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.65 (td, *J* = 7.6, 1.4 Hz, 1H), 7.0 (td, *J* = 6.8, 1.4 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 7.6 Hz, 1H), 8.03 (s, 1H), 9.05 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.2, 77.9, 104.2, 110.6, 121.0, 121.1, 121.2, 122.8, 125.2, 127.1, 127.5, 128.6, 132.3, 132.4, 132.9, 133.1, 136.1, 150.4. HRMS *m*/*z* calcd for $C_{18}H_{16}N_3O_2$: 306.1243, found 306.1239.



6-(1-(Methoxymethyl)-1*H*-indol-3-yl)pyrimidine 1-oxide (4gi): The title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **4gi** in 32% yield as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.30 (s, 3H), 5.56 (s, 2H), 7.35–7.40 (m, 2H), 7.65 (dd, *J* = 6.9, 1.5 Hz, 1H), 8.00–8.01 (m, 2H), 8.21 (d, *J* = 5.5 Hz, 1H), 9.10 (s, 1H), 9.42 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.2, 78.4, 104.6, 111.6, 117.4, 119.7, 122.6, 123.6, 126.3, 136.2, 136.3, 142.6, 148.9, 150.9. HRMS *m*/*z* calcd for $C_{14}H_{14}N_3O_2$: 256.1086, found 256.1083.



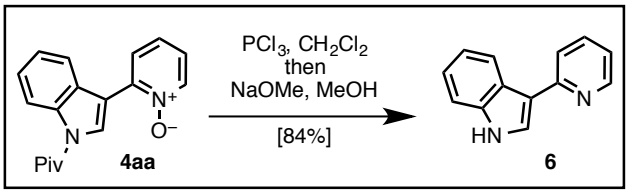
2-(5-(Methoxycarbonyl)-1*H*-pyrrol-2-yl)pyridine 1-oxide (3ba): The title compound was synthesized according to the general procedure and purified by preparative TLC ($CHCl_3$/MeOH = 20:1) to afford **3ba** in 44% yield as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.80 (dd, *J* = 3.7, 2.7 Hz, 1H), 6.98 (dd, *J* = 3.7, 3.4 Hz, 1H), 7.10 (td, *J* = 7.6, 1.9 Hz, 1H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.73 (dd, *J* = 8.2, 1.8 Hz, 1H), 8.22 (d, *J* = 6.4 Hz, 1H), 12.97 (brs, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 51.5, 110.9, 115.7, 122.4, 123.0, 123.1, 126.5, 128.1, 139.4, 140.5, 160.7. HRMS *m*/*z* calcd for $C_{11}H_{11}N_2O_3$: 219.0770, found 219.0770.



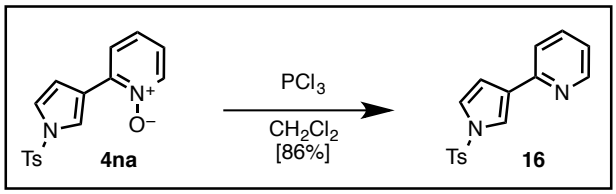
4qa

4-3. Determination of Regiochemistry

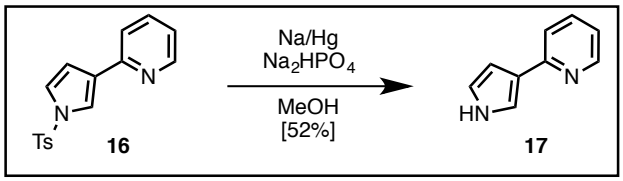
The regiochemistry of **4aa** and **4na** were determined by NMR spectra (^{1}H and ^{13}C) comparisons with **6**[7] and **17**[19].



3-(Pyridin-2-yl)-1*H*-indole (6):[7] To a stirred solution of **4aa** (88 mg, 0.30 mmol) in CH_2Cl_2 (1.5 mL) was added PCl_3 (78.3 μL, 0.90 mmol) dropwise. After stirring at room temperature for 1 h, the reaction mixture was concentrated under reduced pressure and dissolved in MeOH (1.5 mL). Then NaOMe (81 mg, 1.5 mmol) was added and the resultant mixture was stirred at room temperature for 3 h. After concentrating under reduced pressure, the residue was dissolved in CH_2Cl_2, filtered with cotton plug, and recrystallized with Et_2O/hexane (1:1) to afford **6** (48.8 mg, 84%) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.12 (td, *J* = 5.5, 2.1 Hz, 1H), 7.24–7.26 (m, 2H), 7.40 (m, 1H), 7.70–7.72 (m, 2H), 7.78 (d, *J* = 2.8 Hz, 1H), 8.31 (t, *J* = 5.5 Hz, 1H), 8.67 (d, *J* = 4.9 Hz, 1H), 8.68 (brs, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 111.5, 117.3, 120.3, 120.6, 120.8, 120.8, 122.4, 124.6, 125.3, 136.4, 136.9, 149.4, 155.0. HRMS *m*/*z* calcd for $C_{13}H_{11}N_2$: 195.0922, found 195.0922.

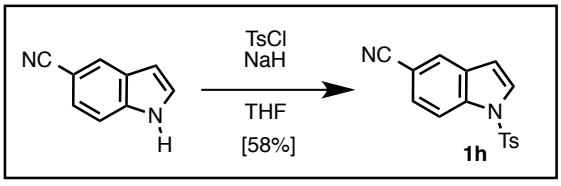


2-(1-Tosyl-1*H*-pyrrol-3-yl)pyridine (16): To a 30 mL round-bottom flask containing a magnetic stirring bar were added **4na** (83.6 mg, 0.27 mmol), CH_2Cl_2 (6 mL) and PCl_3 (67 μL, 0.80 mmol). The reaction mixture was stirred for 7 h and quenched with saturated aqueous $NaHCO_3$ solution (18 mL). The mixture was extracted with CH_2Cl_2 (20 mL × 3), dried over $MgSO_4$, and concentrated to give a solid. The crude mixture was purified by preparative TLC (hexane/EtOAc = 1:1) to afford compound **16** (67.9 mg, 86%) as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.38 (s, 3H), 6.80 (dd, *J* = 3.5, 2.1 Hz, 1H), 7.11 (dd, *J* = 6.8, 4.8 Hz, 1H), 7.22 (t, *J* = 2.8 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.63 (td, *J* = 7.6, 1.4 Hz, 1H), 7.74 (t, *J* = 2.1 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 2H), 8.55 (d, *J* = 4.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 111.7, 118.6, 119.6, 121.6, 126.9, 129.5, 129.9, 135.6, 136.4, 145.1, 149.4, 152.2. HRMS *m*/*z* calcd for $C_{16}H_{15}N_2O_2S$: 299.0854, found 299.0850.



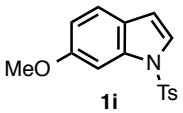
2-(1*H*-Pyrrol-3-yl)pyridine (17):[19, 20] To a 30 mL round-bottom flask containing a magnetic stirring bar were added **16** (67.9 mg, 0.23 mmol), MeOH (5 mL), Na_2HPO_4 (130 mg, 0.92 mmol) and Na/Hg (340 mg). The reaction mixture was stirred for 12 h and then quenched with saturated aqueous NH_4Cl solution (8 mL). The mixture was extracted wit EtOAc (10 mL × 3), dried over $MgSO_4$, filtered and concentrated to give a solid. The crude mixture was purified by preparative TLC (hexane/EtOAc = 1:1) to afford compound **17** (17.1 mg, 52%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.73 (d, *J* = 1.3 Hz, 1H), 6.83 (d, *J* = 2.0 Hz, 1H), 7.03–7.05 (m, 1H), 7.43 (d, *J* = 2.1 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.62 (td, *J* = 8.2, 2.0 Hz, 1H), 8.54 (d, *J* = 4.1 Hz, 1H), 9.21 (brs, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 106.7, 117.3, 119.2, 119.2, 120.2, 124.9, 130.4, 149.1, 154.7. HRMS *m*/*z* calcd for $C_9H_9N_2$: 145.0766, found 145.0767.

4-4. General Procedure for the Synthesis of *N*-Tosyl Indoles and Pyrroles



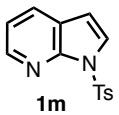
1-Tosyl-1*H*-indole-5-carbonitrile (1h): To a stirred solution of indole-5-carbonitrile (250 mg, 1.76 mmol) in anhydrous THF (17 mL) was added NaH (60% dispersion in mineral oil, 133 mg, 2.81 mmol) at 0 °C. The reaction mixture was allowed to warm to 23 °C and stirred for 30 min. After cooling to 0 °C, TsCl (401 mg, 2.11 mmol) was added to the reaction mixture and it was stirred at 23 °C for overnight. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (10 mL), extracted with EtOAc (10 mL × 2), washed with brine, dried over $MgSO_4$ and evaporated to dryness. The crude mixture was purified by flash column chromatography (hexane/EtOAc = 5:1) to afford **1h** (302.2 mg, 58%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.37 (s, 3H), 6.72 (d, *J* = 4.3 Hz, 1H), 7.27 (d, *J* = 8.9 Hz, 2H), 7.56 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.69 (d, *J* = 4.1 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.88 (s, 1H), 8.07 (d, *J* = 8.9 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 106.5, 108.3, 114.0, 119.0, 126.1, 126.6, 127.2, 128.2, 129.9, 130.4, 134.4, 136.1, 145.5. HRMS *m*/*z* calcd for $C_{16}H_{13}N_2O_2S$: 297.0698, found 297.0698.

6-Methoxy-1-tosyl-1*H*-indole (1i): The title compound was synthesized according to the above procedure and purified by flash column chromatography (hexane/EtOAc = 10: 1 to 3:1) to afford **1i** in 75% yield as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.87 (s, 3H), 6.57 (d, *J* = 3.5 Hz, 1H), 6.85 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 3.4 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.74 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 55.5, 97.8, 108.8, 112.2, 121.6, 124.3, 124.9, 129.5, 129.6, 135.0, 135.7, 144.8, 157.7. HRMS *m*/*z* calcd for $C_{16}H_{16}NO_3S$: 302.0851, found 302.0857



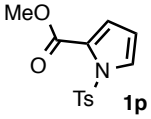
1i

1-Tosyl-1*H*-pyrrolo[2,3-*b*]pyridine (1m): The title compound was synthesized according to the above procedure and purified by preparative HPLC to afford **1m** in 88% yield as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.34 (s, 3H), 6.57 (d, *J* = 4.1 Hz, 1H), 7.15 (dd, *J* = 8.3, 4.8 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.71 (d, *J* = 4.1 Hz, 1H), 7.78 (dd, *J* = 7.6, 1.4 Hz, 1H), 8.07 (d, *J* = 8.9 Hz, 2H), 8.42 (dd, *J* = 4.8, 1.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 105.1, 118.6, 122.6, 127.7, 129.4, 135.1, 144.6, 144.9, 147.0. HRMS *m*/*z* calcd for $C_{14}H_{13}N_2O_2S$: 273.0698, found 273.0698.



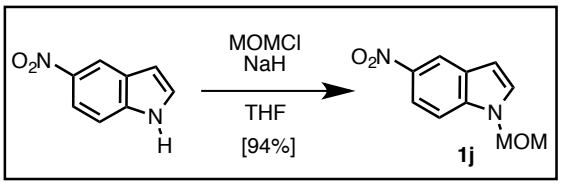
1m

Methyl 1-tosyl-1*H*-pyrrole-2-carboxylate (1p): The title compound was synthesized according to the above procedure and purified by flash column chromatography (hexane/CH_2Cl_2 = 1:3) followed by recrystallization with ether to afford **1p** in 47% yield as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.73 (s, 3H), 6.31 (t, *J* = 3.4 Hz, 1H), 7.05 (dd, *J* = 4.1, 1.9 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.72 (dd, *J* = 2.8, 2.1 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 51.3, 110.1, 123.0, 124.4, 127.8, 128.8, 129.1, 135.4, 144.7, 158.7. HRMS *m*/*z* calcd for $C_{13}H_{14}NO_4S$: 280.0644, found 280.0640.



1p

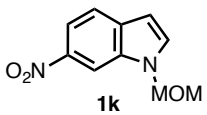
4-5. General Procedure for the Synthesis of *N*-MOM Indoles



1j

1-(Methoxymethyl)-5-nitro-1*H*-indole (1j): To a stirred solution of 5-nitroindole (332 mg, 2.11 mmol) in THF (20 mL) was added NaH (60% dispersion in mineral oil, 110 mg, 2.7 mmol) at 0 °C. The suspension was warmed to room temperature for 20 min and then cooled to 0 °C. At 0 °C chloromethyl methyl ether (142 μL, 2.5 mmol) was added to the reaction mixture and it was stirred for overnight. After completion of the reaction, it was quenched by the addition of saturated aqueous $NaHCO_3$ solution (15 mL). The reaction mixture was extracted with EtOAc (10 mL × 2), washed with brine, dried over Na_2SO_4 and evaporated to dryness. The crude mixture was purified by flash column chromatography (hexane/EtOAc = 3:1) to afford **1j** (408.7 mg, 94%) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.27 (s, 3H), 5.49 (s, 2H), 6.71 (d, *J* = 3.1 Hz, 1H), 7.34 (d, *J* = 3.0 Hz, 1H), 7.52 (d, *J* = 9.3 Hz, 1H), 8.13 (dd, *J* = 9.3, 2.1 Hz, 1H), 8.57 (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.1, 79.7, 104.7, 109.9, 117.6, 117.9, 128.4, 131.1, 139.1, 142.1. HRMS *m*/*z* calcd for $C_{10}H_{11}N_2O_3$: 207.0770, found 207.0769.

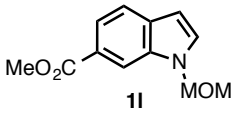
1-(Methoxymethyl)-6-nitro-1*H*-indole (1k): The title compound was synthesized according to the above procedure and purified by flash column chromatography (hexane/CH_2Cl_2 = 1:1) to afford **1k** in 86% yield as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.28 (s, 3H), 5.52 (s, 2H), 6.65 (d, *J* = 2.8 Hz, 1H), 7.47 (d, *J* = 2.8 Hz, 1H), 7.67 (d, *J* = 8.9 Hz, 1H), 8.05 (dd, *J* = 8.9,



1k

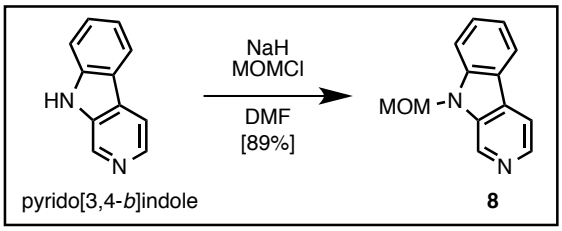
2.1 Hz, 1H), 8.45 (d, *J* = 2.1 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.8, 77.4, 102.9, 106.6, 115.2, 120.5, 133.6, 133.7, 134.4, 142.9. HRMS *m*/*z* calcd for $C_{10}H_{11}N_2O_3$: 207.0770, found 207.0771.

Methyl 1-(methoxymethyl)-1*H*-indole-6-carboxylate (1l): The title compound was synthesized according to the above procedure and purified by flash column chromatography (hexane/EtOAc = 5:1) to afford **1l** in 56% yield as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.26 (s, 3H), 3.94 (s, 3H), 5.51 (s, 2H), 6.59 (d, *J* = 2.8 Hz, 1H), 7.34 (d, *J* = 3.4 Hz, 1H), 7.65 (d, *J* = 8.9 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 8.25 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 51.7, 55.7, 77.2, 102.7, 112.0, 120.4, 121.1, 123.7, 131.1, 132.6, 135.5, 167.7. HRMS *m*/*z* calcd for $C_{12}H_{14}NO_3$: 220.0974, found 220.0979.



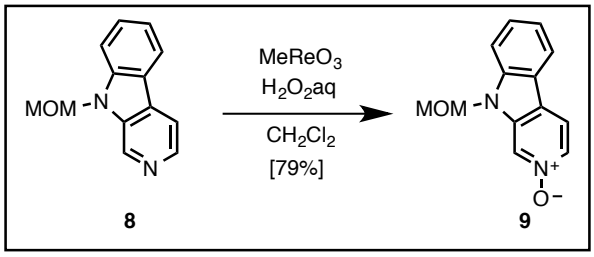
1l

4-6. Synthesis of Eudistomin U

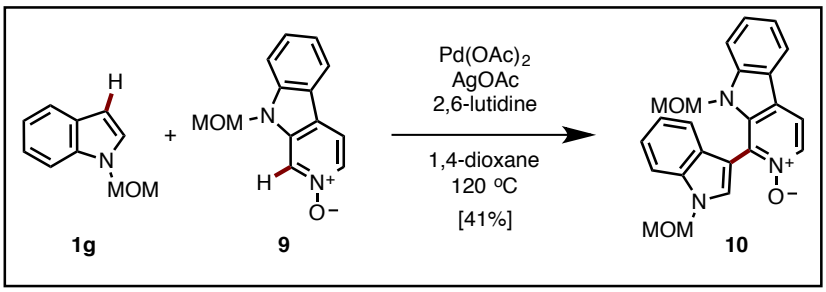


9-(Methoxymethyl)-9*H*-pyrido[3,4-*b*]indole (8): To a 200-mL round bottom flask containing a magnetic stirring bar was added pyrido[3,4-*b*]indole (1 g, 6.0 mmol). Then the flask was purged with argon and dry DMF (25 mL) was added to yield a clear solution. The flask was submerged into an ice-bath and cooled to 0 °C. Sodium hydride (Wako, ca. 60 % dispersion in mineral oil, 309 mg, 7.7 mmol) was added to the flask and the reaction mixture was allowed to stir at 0 °C for 15 min. Then chloromethyl methyl ether (497 μL, 6.5 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 8 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL), extracted with EtOAc (20 mL × 3), washed with brine (20 mL × 2), briefly dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexane/EtOAc = 1:1) to afford compound **8** (1.12 g, 89%) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.29 (s, 3H), 5.70 (s, 2H), 7.32 (td, *J* = 8.2, 2.0 Hz, 1H), 7.57–7.61 (m, 2H), 7.92 (d, *J* = 5.5 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 8.50 (d, *J* = 4.8 Hz, 1H), 9.00 (s, 1H). ^{13}C

NMR (150 MHz, $CDCl_3$) δ 56.3, 74.3, 109.93, 114.5, 120.6 121.5, 121.8, 128.6, 129.0, 132.5, 136.6, 140.0, 141.1. HRMS *m*/*z* calcd for $C_{13}H_{13}N_2O$: 213.1028, found 213.1027.

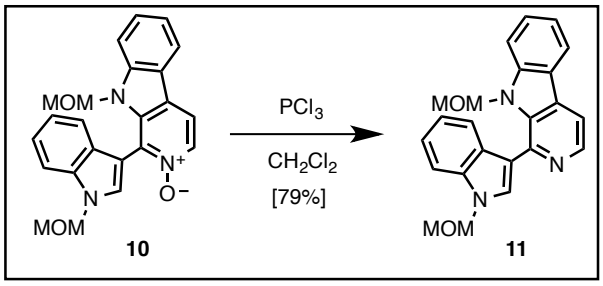


9-(Methoxymethyl)-9*H*-pyrido[3,4-*b*]indole 2-oxide (9): To a stirred solution of compound **5c** (500 mg, 2.4 mmol) in CH_2Cl_2 (15 mL), methyl rhenium trioxide (17.9 mg, 0.72 μmol) was added. Then the flask was cooled to 0 °C and 30% aqueous H_2O_2 solution (550 μL, 10.5 mmol) was added. After stirring the reaction mixture at room temperature for 14 h, catalytic amount of MnO_2 (5 mg) was added and stirred until oxygen evolution ceased (1 h). Following phase separation, the water phase was extracted with CH_2Cl_2 (10 mL × 3), and the combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc then $CHCl_3$/MeOH = 10:1) to afford compound **9** (434.4 mg, 79%) as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.31 (s, 3H), 5.60 (s, 2H), 7.35 (t, *J* = 8.3 Hz, 1H), 7.56–7.57 (m, 2H), 7.86 (d, *J* = 6.8 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 8.18 (dd, *J* = 6.9, 2.1 Hz, 1H), 8.66 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 56.5, 74.7, 110.1, 116.3, 121.1, 121.4, 121.6, 121.7, 123.3, 128.3, 132.4, 137.9, 142.2. HRMS *m*/*z* calcd for $C_{13}H_{13}N_2O_2$: 229.0977, found 229.0975.



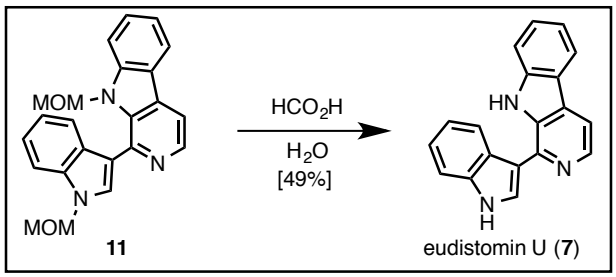
9-(Methoxymethyl)-1-(1-(methoxymethyl)-1*H*-indol-3-yl)-9*H*-pyrido[3,4-*b*]indole 2-oxide (10): A 20-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vessel were added $Pd(OAc)_2$ (9 mg, 40 μmol),

AgOAc (200 mg, 1.2 mmol), indole **1g** (64.5 mg, 0.4 mmol), *N*-oxide **9** (365.2 mg, 1.6 mmol), dry 1,4-dioxane (1.2 mL), and 2,6-lutidine (47 μL, 0.4 mmol) under a stream of argon. The vessel was sealed with O-ring tap, and then heated at 120 °C for 23 h in a 8-well reaction block with stirring. After cooling the reaction mixture to room temperature, it was passed through a pad of Celite® (CH_2Cl_2) and the filtrate was concentrated under reduced pressure. The crude residue was purified by preparative HPLC to afford compound **10** (61.9 mg, 41%) as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.77 (s, 3H), 3.39 (s, 3H), 5.04 (d, *J* = 10.3 Hz, 1H), 5.08 (d, *J* = 10.3 Hz, 1H), 5.55 (d, *J* = 11.0 Hz, 1H), 5.63 (d, *J* = 11.0 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.32 (t, *J* = 6.8 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.48–7.53 (m, 2H), 7.61 (d, *J* = 8.2 Hz, 1H), 7.76 (s, 1H), 7.87 (d, *J* = 6.9 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 8.39 (d, *J* = 6.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.5, 56.2, 74.2, 78.0, 104.8, 110.6, 111.0, 114.5, 120.1, 120.6, 121.5, 121.8, 121.8, 122.0, 123.1, 127.7, 128.2, 130.6, 130.7, 133.4, 136.2, 137.5, 143.0. HRMS *m*/*z* calcd for $C_{23}H_{22}N_3O_3$: 388.1661, found 388.1661.



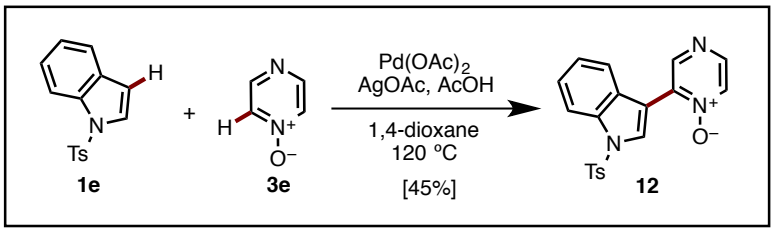
9-(Methoxymethyl)-1-(1-(methoxymethyl)-1*H*-indol-3-yl)-9*H*-pyrido[3,4-*b*]indole 2-oxide (11): To a 10-mL glass Schlenk tube containing a magnetic stirring bar were added compound **10** (45.3 mg, 0.12 mmol) and CH_2Cl_2 (2 mL). Then PCl_3 (30.6 μL, 0.35 mmol) was added dropwise to the solution. After stirring at room temperature for 11 h, saturated aqueous $NaHCO_3$ solution (8 mL) was added to the reaction mixture and it was stirred for 5 min. The reaction mixture was extracted with CH_2Cl_2 (8 mL × 3), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by preparative TLC (EtOAc) to afford compound **11** (34.5 mg, 79%) as a pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.82 (s, 3H), 3.37 (s, 3H), 5.36 (s, 2H), 5.59 (s, 2H), 7.16 (t, *J* = 8.3 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 6.8 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.56–7.62 (m, 3H), 7.67 (s, 1H), 7.97 (d, *J* = 4.8 Hz, 1H), 8.19 (d, *J* = 7.2 Hz, 1H), 8.61 (d, *J* = 4.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.3, 56.0, 74.4, 77.6, 110.2, 111.1, 113.2,

115.8, 120.3, 120.8, 121.1, 121.4, 122.1, 122.9, 127.8, 128.5, 128.5, 130.9, 135.6, 136.3, 138.5, 139.9, 142.1. HRMS *m*/*z* calcd for $C_{23}H_{22}N_3O_2$: 372.1712, found 372.1712.

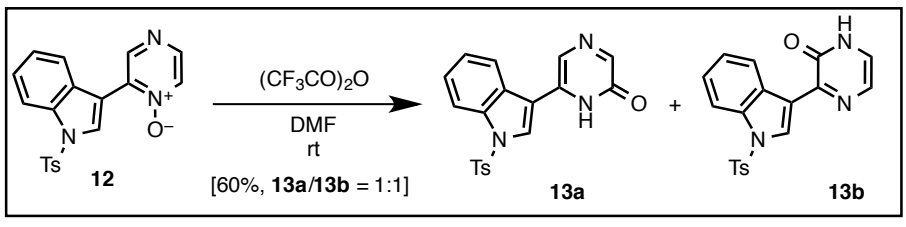


Eudistomin U (7): To a 20-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar were added compound **8** (25.8 mg, 70 μmol), H_2O (450 μL) and HCO_2H (750 μL). The vessel was sealed with O-ring tap, and then heated at 125 °C for 39 h in oil bath. After cooling to room temperature, saturated aqueous $NaHCO_3$ solution (30 mL) was added to the reaction mixture and it was stirred for further 5 min. The reaction mixture was extracted with CH_2Cl_2 (20 mL × 3), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by preparative TLC (EtOAc) to afford eudistomin U (**7**) (9.6 mg, 49%) as a yellow solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.15 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.52–7.56 (m, 2H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.97 (d, *J* = 4.8 Hz, 1H), 8.24 (d, *J* = 8.2 Hz, 1H), 8.31 (d, *J* = 1.4 Hz, 1H), 8.46 (d, *J* = 5.5 Hz, 1H), 8.55 (d, *J* = 7.6 Hz, 1H), 11.33 (s, 1H), 11.73 (s, 1H). ^{1}H NMR (600 MHz, CD_3OD) δ 7.13 (t, *J* = 6.8 Hz, 1H), 7.20–7.24 (m, 2H), 7.48–7.51 (m, 2H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.89 (s, 1H), 7.93–7.95 (m, 2H), 8.15 (d, *J* = 7.6 Hz, 1H), 8.34 (d, *J* = 4.8 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 112.5, 113.4, 114.0, 120.4, 120.7, 122.1, 122.3, 123.0, 123.2, 127.0, 127.1, 128.7, 129.2, 133.0, 137.5, 138.7, 141.2, 141.8. ^{13}C NMR (150 MHz, CD_3OD) δ 113.5, 114.0, 114.3, 115.2, 121.6, 122.0, 122.4, 123.3, 123.7, 124.2, 127.3, 128.4, 130.1, 131.5, 136.1, 139.2, 142.2, 143.6. HRMS *m*/*z* calcd for $C_{19}H_{14}N_3$: 284.1188, found 284.1192.

4-7. Synthesis of Bis(indolyl)pyrazinone

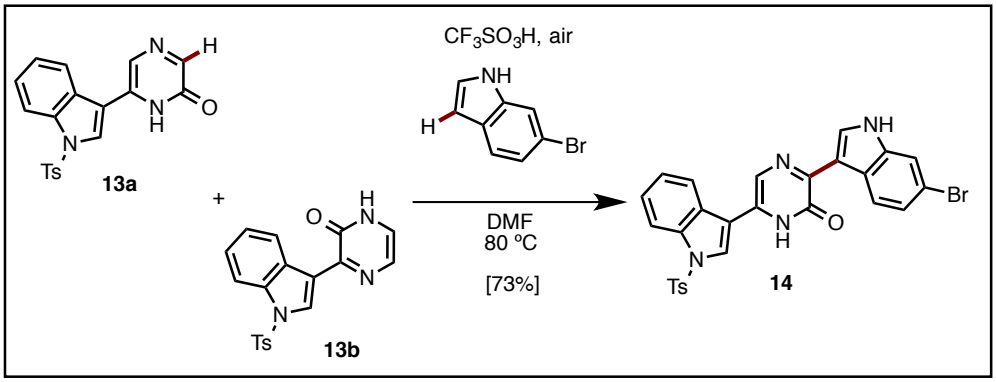


2-(1-Tosyl-1*H*-indol-3-yl)pyrazine 1-oxide (12): A 20-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vessel were added $Pd(OAc)_2$ (9.0 mg, 40 μmol, 0.1 equiv), AgOAc (200 mg, 1.20 mmol, 3.0 equiv), AcOH (24 mg, 0.40 mmol, 1.0 equiv), 1-tosylindole (**1e**: 108.5 mg, 0.40 mmol, 1.0 equiv), pyrazine *N*-oxide (**3e**: 153.7 mg, 1.6 mmol, 4.0 equiv) and anhydrous 1,4-dioxane (1.2 mL) under a stream of argon. The vessel was sealed with O-ring tap, and then heated at 120 °C for 16 h in a 8-well reaction block with stirring. After cooling the reaction mixture to room temperature, it was passed through a pad of Celite® ($CHCl_3$/MeOH = 9:1) and the filtrate was concentrated under reduced pressure. The crude product was purified by PTLC (ethyl acetate) to afford the desired product **12** in 45% yield (65.8 mg; 75% based on recovered starting material). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.35 (s, 3H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.35 (t, *J* = 8.2 Hz, 1H), 7.43 (t, *J* = 8.3 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 8.10 (d, *J* = 8.3 Hz, 1H), 8.26 (d, *J* = 4.1 Hz, 1H), 8.35 (d, *J* = 4.1 Hz, 1H), 8.92 (s, 1H), 9.04 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 109.6, 114.0, 120.5, 124.1, 125.4, 127.1, 127.5, 130.2, 134.5, 134.7, 139.2, 144.0, 145.6, 147.2. HRMS *m*/*z* calcd for $C_{19}H_{16}N_3O_3S$: 366.0912, found: 366.0911.



6-(1-tosyl-1*H*-indol-3-yl)pyrazin-2(1*H*)-one (13a):[15] To a stirred solution of compound **12** (65.8 mg, 0.18 mmol, 1.0 equiv) in anhydrous DMF (1.8 mL) at 0 °C, was added trifluoroacetic anhydride (151.2 mg, 0.72 mmol, 4.0 equiv). The reaction mixture was

stirred at 23 °C for 12 h. Then it was neutralized with saturated aqueous $NaHCO_3$ solution (1.0 mL) and stirred for 2 h. The reaction mixture was extracted with ethyl acetate (3 × 4 mL), washed with brine (3 × 2 mL), and dried over Na_2SO_4. The solvent was evaporated to give crude product. The crude was purified by flash column chromatography on silica gel (50% ethyl acetate in hexane as eluent) to yield the mixture of **13a** and **13b** (39.5 mg, 60%, **13a**/**13b** = 1:1). ^{1}H NMR of **13a** (600 MHz, $CDCl_3$) δ 2.37 (s, 3H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.97 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 2H), 8.09 (d, *J* = 8.3 Hz, 2H), 8.22 (s, 1H), 8.38 (s, 1H). ^{13}C NMR of **13a** (150 MHz, $CDCl_3$) δ 21.6, 113.1, 114.0, 120.2, 124.2, 124.3, 125.7, 126.9, 127.4, 127.7, 130.1, 133.1, 134.7, 135.3, 145.6, 145.8, 158.6. HRMS *m*/*z* calcd for $C_{19}H_{16}N_3O_3S$: 366.0912, found 366.0912.

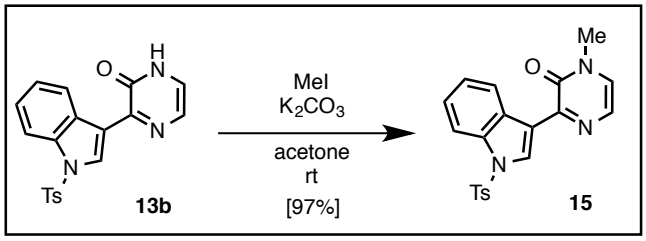


3-(6-Bromo-1*H*-indol-3-yl)-6-(1-tosyl-1*H*-indol-3-yl)pyrazin-2(1*H*)-one (14):[16] The mixture of two regioisomeric compound **13a** and **13b** (40 mg, 0.11 mmol, **13a**/**13b** = 1:1) was dissolved in anhydrous DMF (1.0 mL). To this solution of 6-bromoindole (21.6 mg, 0.11 mmol, 2.0 equiv to **13a**) was added CF_3SO_3H (4.5 mg, 0.03 mmol, 0.5 equiv to **13a**) in dark. The reaction mixture was stirred at 80 °C for 3 h in open air. After completion of the reaction, it was neutralized with saturated aqueous $NaHCO_3$ solution (0.5 mL), extracted with ethyl acetate (3 × 4 mL), washed with brine (3 × 2 mL), and dried over Na_2SO_4. The solvent was evaporated to give a crude, which was purified by PTLC (using 5% MeOH in $CHCl_3$ as eluent) and then by reverse-phase PTLC (using 10% H_2O in MeOH as eluent) to give the product **14** (22.4 mg, 73% yield from **13a**). At this stage the undesired pyrazinone isomer **13b** can be isolated. [The above reaction and work up has been done in dark because of the high light sensitivity

of the product in solution].

Compound **14:** ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.39 (s, 3H), 7.33 (d, J = 8.2 Hz, 1H), 7.42–7.50 (m, 4H), 7.72 (s, 1H), 7.98–8.11 (m, 5H), 8.50 (s, 1H), 8.65 (d, J = 8.2 Hz, 1H), 8.77 (brs, 1H), 11.55 (s, 1H), 12.16 (brs, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 21.4, 112.4, 113.9, 114.9, 115.4, 121.8, 123.7, 124.6, 124.8, 125.7, 125.9, 126.8, 127.4, 127.9, 130.8, 131.9, 134.8, 135.3, 137.9, 146.2, 155.7. HRMS *m*/*z* calcd for $C_{27}H_{20}BrN_4O_3S$: 559.0439, found 559.0432.

Compound **13b:** ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.33 (s, 3H), 7.22 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 3.5 Hz, 1H), 7.33–7.38 (m, 2H), 7.70 (d, J = 4.1 Hz, 1H), 7.85 (d, J = 8.3 Hz, 2H), 8.03 (d, J = 7.6 Hz, 1H), 8.74 (d, J = 7.6 Hz, 1H), 9.21 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.6, 113.2, 117.2, 122.5, 123.9, 124.1, 124.8, 125.2, 127.0, 129.0, 130.0, 131.1, 134.7, 135.1, 145.2, 150.3, 156.6. HRMS *m*/*z* calcd for $C_{19}H_{16}N_3O_3S$: 366.0912, found 366.0912.



1-Methyl-3-(1-tosyl-1*H*-indol-3yl)pyrazin-2(1*H*)-one (15): To a stirred solution of compound **13b** (20 mg, 0.05 mmol, 1.0 equiv) in acetone (0.5 mL) was added potassium carbonate (6.9 mg, 0.05 mmol, 1.0 equiv) at 23 °C. The reaction mixture was cooled down to 0 °C and methyl iodide (7.0 mg, 0.05 mmol, 1.0 equiv) was added dropwise to the cooled solution. Then the reaction mixture was warmed to 23 °C and stirred for 4 h. After completion of the reaction, it was neutralized with saturated aqueous $NaHCO_3$ solution (0.5 mL) and then acetone was removed from the reaction mixture under reduced pressure. The residue was extracted with ethyl acetate (2 × 2 mL), washed with brine (1 × 1 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure to gave a crude that was purified by PTLC (5% ethyl acetate in CH_2Cl_2 as eluent) to give 1-methyl-3-(1-tosyl-1*H*-indol-3yl)pyrazin-2(1*H*)-one **15** (20.1 mg, 97%) as a light yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.63 (s, 3H), 7.08 (d, J =

4.1 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.31–7.37 (m, 2H), 7.47 (d, J = 4.1 Hz, 1H), 7.85 (d, J = 8.3 Hz, 2H), 8.05 (d, J = 8.3 Hz, 1H), 8.70 (d, J = 7.6 Hz, 1H), 9.21 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5, 37.6, 113.2, 117.2, 123.3, 123.8, 123.9, 125.0, 126.6, 127.0, 129.1, 129.9, 131.3, 134.8, 135.2, 145.1, 149.6, 155.3. HRMS m/z calcd for $C_{20}H_{18}N_3O_3S$: 380.1069, found 380.1064.

4-8. X-Ray Crystal Structure Analysis of 14 and 15

Details of the crystal data and a summary of the intensity data collection parameters for **14**·2THF and **15** are listed in Table 11. Co-crystallized THF molecules in **14**·2THF were determined by ^{1}H NMR spectroscopy shown below. Suitable crystals of **14**·2THF and **15** were mounted with mineral oil on a glass fiber and transferred to the goniometer of a Rigaku Saturn CCD diffractometer. Graphite-monochromated Mo Kα radiation (λ = 0.71070 Å) was used. The structures were solved by direct methods with (SIR-97)[21] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97).[22] The intensities were corrected for Lorentz and polarization effects. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using AFIX instructions.

Table 11. Crystallographic data and structure refinement details for **14** and **15**

	14·2THF	**15**
formula	$C_{35}H_{34}BrN_4O_5S$	$C_{20}H_{17}N_3O_3S$
fw	702.63	379.43
T (K)	103(2)	123(2)
λ (Å)	0.71070	0.71070
cryst syst	Triclinic	Monoclinic
space group	P-1	$P2_1/n$
a (Å)	9.588(4)	14.239(3)
b (Å)	10.753(4)	8.1646(17)
c (Å)	15.679(6)	15.033(3)
α (deg)	94.815(8)	90
β (deg)	95.074(4)	92.854(3)
γ (deg)	101.252(7)	90

V (Å^3)	1570.7(10)	1745.6(6)
Z	2	4
D_{calc}, (g / cm^3)	1.486	1.444
μ (mm^{-1})	1.426	0.213
F(000)	726	792
cryst size (mm)	0.20 × 0.05 × 0.02	0.15 × 0.10 × 0.05
2θ range, (deg)	3.10–25.00	3.15–25.00
reflns collected	10555	11262
indep reflns / R_{int}	5421 / 0.0454	3061 / 0.0395
params	416	246
GOF on F^2	1.106	1.050
R_1, wR_2 [I>2σ(I)]	0.0579, 0.1048	0.0418, 0.0994
R_1, wR_2 (all data)	0.0855, 0.1200	0.0514, 0.1059

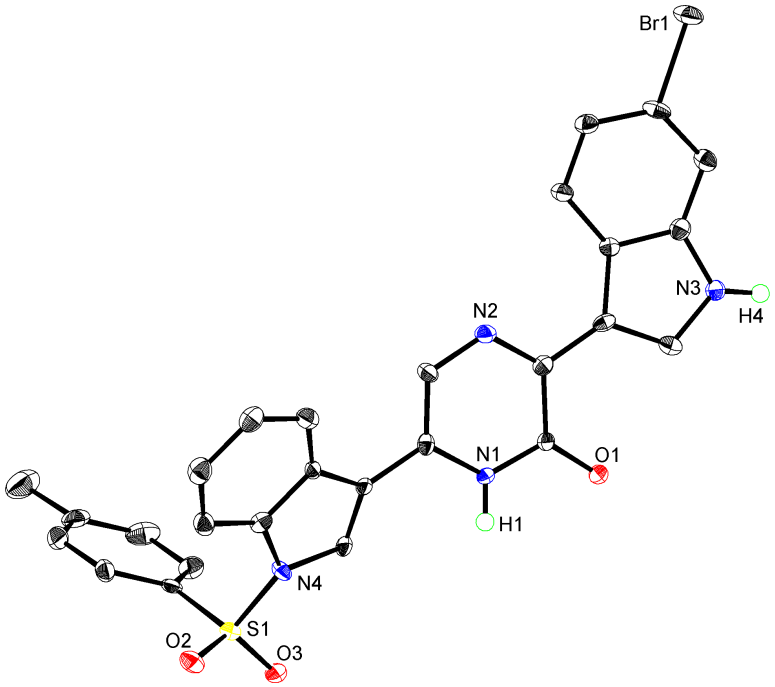


Figure 4. ORTEP drawing of **14**·2THF with 50% thermal ellipsoid. All hydrogen atoms except N–H and THF molecules are omitted for clarity.

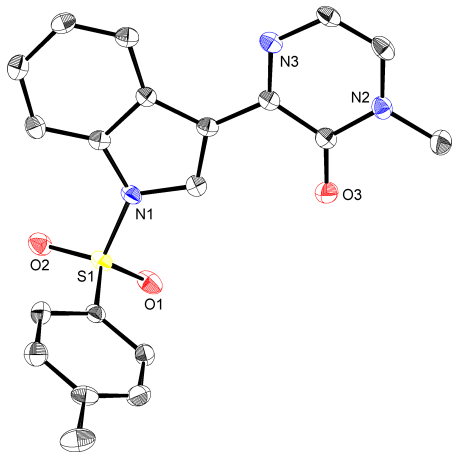


Figure 5. ORTEP drawing of **15** with 50% thermal ellipsoid. All hydrogen atoms are omitted for clarity.

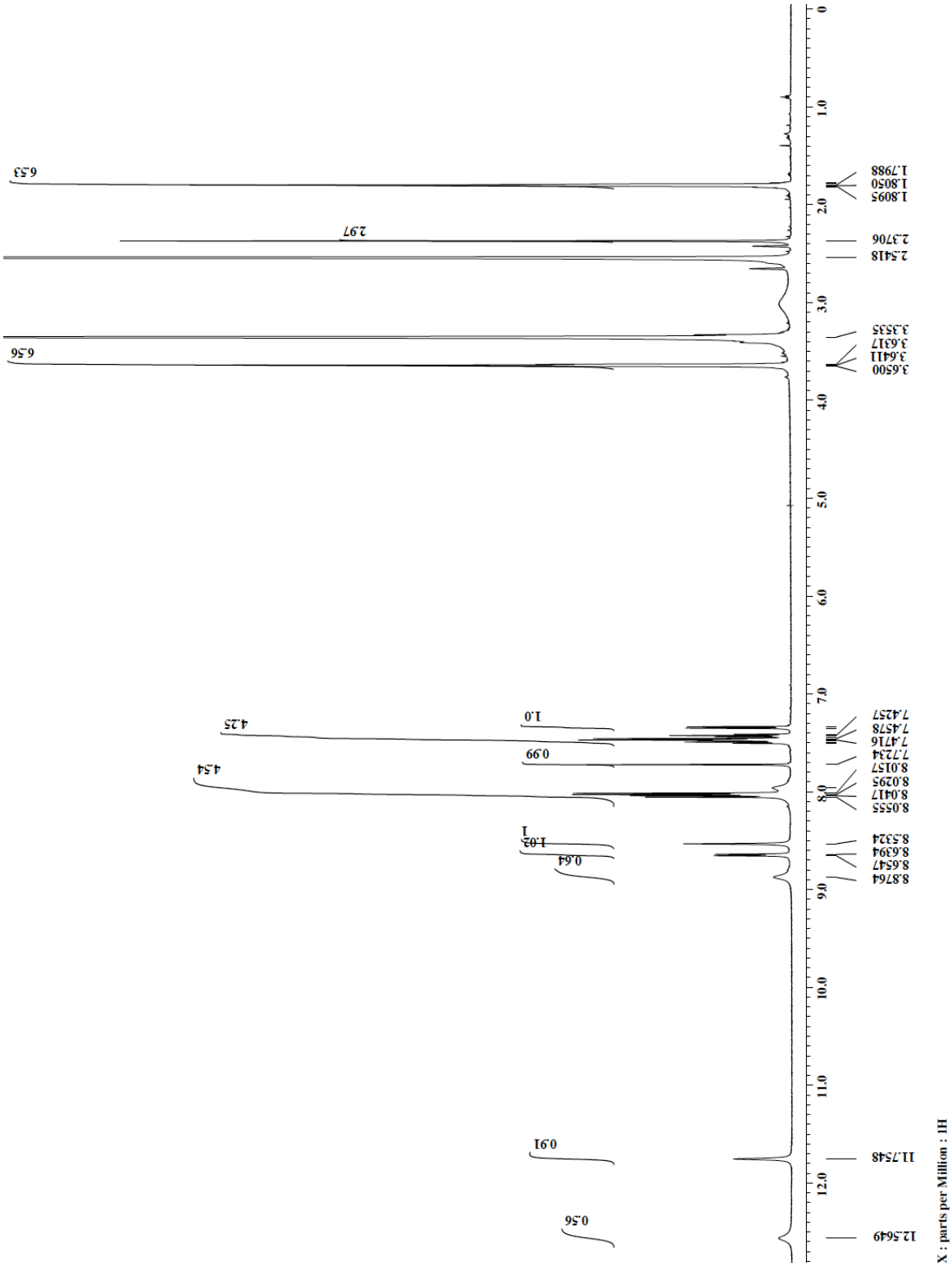


Figure 6. ^{1}H NMR (600 MHz, DMSO-d_6) of **14**·2THF.

References and Notes

1. Selected reviews of compounds containing indole–azine and indole–pyrrole moieties: (a) Jin, Z. *Nat. Prod. Rep.* **2009**, *26*, 382. (b) Young, I. S.; Thornton, P. D.; Thompson, A. *Nat. Prod. Rep.* **2010**, *27*, 1801.
2. Transition metal-catalyzed cross-coupling to synthesize indole/pyrrole–azine moieties: (a) Bourderioux, A.; Kassis, P.; Merour, J.; Routier, S. *Tetrahedron* **2008**, *64*, 11012. (b) Sakamoto, T.; Kondo, Y.; Takazawa, N.; Yamanaka, H. *Tetrahedron lett.* **1993**, *34*, 5955. (c) Bennacef, I.; Haile, C. N.; Schmidt, A.; Koren, A. O.; Seibyl, J. P.; Staley, J. K.; Bois, F.; Baldwin, R. M.; Tamagnan, G. *Bioorg. Med. Chem.* **2006**, *14*, 7582. (d) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358. (e) Dinsmore, A.; Billing, D. G.; Mandy, K.; Michael, J. P.; Mogano, D.; Patil, S. *Org. Lett.* **2004**, *6*, 293.
3. Total syntheses of natural products through transition metal-catalyzed cross-coupling reactoins: (a) Mosquera, A.; Riveiros, R.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **2008**, *10*, 3745. (b) Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179. (c) Ahaidar, A.; Fernández, D.; Danelón, G.; Cuevas, C.; Manzanares, I.; Alberico, F.; Joule, J. A.; Álvarez, M. *J. Org. Chem.* **2003**, *68*, 10020.
4. (a) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (b) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072. (c) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (d) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137. **(**e) Potavathri, S.; Dumas, A. S.; Dwight, T. A.; Naumiec, G. R.; Hammann, J. M.; DeBoef, B. *Tetrahedron Lett.* **2008**, *49*, 4050. (f) Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Pike, A.; LeBris, A. P.; DeBoef, B. *J. Am. Chem. Soc.* **2010**, *132*, 14676. (g) He, C.-Y.; Fan, S.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 12850. (h) Xi, P.; Yang, F.; Qin, S.; Zhao, D.; Lan, J.; Gao, G.; Hu, C.; You, J. *J. Am. Chem. Soc.* **2010**, *132*, 1822. (i) Hna, W.; Mayer, P.; Ofial, A. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 2178. (j) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 6993. (k) Kuhl, N.; Hopkinson, M. N.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 8230. (l) Wang, Z.; Song, F.; Zhao, Y.; Huang, Y.; Yang, L.; Zhao, D.; Lan, J.; You, J. *Chem. Eur. J.* **2012**, *18*, 16616. (m) Liu,

B.; Huang, Y.; Lan, J.; Song, F.; You, J. *Chem. Sci.* **2013**, *4*, 2163.

5. Yamaguchi, A. D.; Mandal, D.; Yamaguchi, J.; Itami, K. *Chem. Lett.* **2011**, *40*, 555.
6. Kanyiva, K. S.; Nakao, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8872.
7. Determination of regiochemistry of pyridylindole: Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3158.
8. It is assumed that 2,6-lutidine help stabilizing Pd species as a ligand.
9. β-selective arylations of five-membered heteroarenes: (a) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 14622. (b) Ueda, K.; Yanagisawa, S.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 8946. (c) Kirchberg, S.; Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2387. (d) Ueda, K.; Amaike, K.; Maceiczyk, R. M.; Itami, K.; Yamaguchi, J. *J. Am. Chem. Soc.* **2014**, *136*, 13226.
10. The yield of the coupling product was ca. 50% in the presence of 2,6-lutidine as an additive. The yield improved to 63% without 2,6-lutidine, and is of slightly higher yield (70%) in the presence of acetic acid.
11. Isolation of eudistomin U: (a) Badre, A.; Boulanger, A.; Abou-Mansour, E.; Banaigs, B.; Combaut, G.; Francisco, C. *J. Nat. Prod.* **1994**, *57*, 528. Previous report of total synthesis: (b) Molina, P.; Fresneda, P. M.; García-Zafra, S. *Tetrahedron Lett.* **1995**, *36*, 3581. (c) Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G.; Adams, L.; Alo, B. *Tetrahedron Lett.* **1995**, *36*, 7085. (d) Panarese, J. D.; Waters, S. P. *Org. Lett.* **2010**, *12*, 4086.
12. Copéret, C.; Adolfsson, A.; Khuong, T.-A. V.; Yudin, A. K.; Sharpless, K. B. *J. Org. Chem.* **1998**, *63*, 1740.
13. Isolation and biologically activity of dragmacidins (a) Kohmoto, S.; Kashman, Y.; McConnell, O. J.; Rinehart, K. L., Jr.; Wright, A.; Koehn, F. *J. Org. Chem.* **1988**, *53*, 3116. (b) Morris, S. A.; Andersen, R. J. *Tetrahedron* **1990**, *46*, 715. (c) Fahy, E.; Potts, B. C. M.; Faulkner, D. J.; Smith, K. *J. Nat. Prod.* **1991**, *54*, 564. (d) Wright, A. E.; Pomponi, S. A.; Cross, S. S.; McCarthy, P. *J. Org. Chem.* **1992**, *57*, 4772. (e) Murray, L. M.; Lim, T. K.; Hooper, J. N. A.; Capon, R. J. *Aust. J. Chem.* **1995**, *48*, 2053. (f) Capon, R. J.; Rooney, F.; Murray, L. M.; Collins, E.; Sim, A. T. R.; Rostas, J. A. P.; Butler, M. S.; Carrol, A. R. *J. Nat. Prod.* **1998**, *61*, 660. (g) Cutignano, A.; Bifulco,

G.; Bruno, I.; Casapullo, A.; Gomez-Paloma, L.; Riccio, R. *Tetrahedron* **2000**, *56*, 3743.

14. Isolation and biological activity of hamcanthins: (a) Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M. *J. Nat. Prod.* **1994**, *57*, 1437. (b) Casapullo, A.; Bifulco, G.; Bruno, I.; Riccio, R. *J. Nat. Prod.* **2000**, *63*, 447.
15. Konno, K.; Hashimoto, K.; Shirahama, H.; Matsumoto, T. *Heterocycles* **1986**, *24*, 2169.
16. Although there has been no report using pyrazinone as substrate, the coupling of indole-quinoxalin-2-ones was previously reported. See, (a) Aoki, K.; Obata, T.; Yamazaki, Y.; Mori, Y.; Hirokawa, H.; Koseki, J.; Hattori, T.; Niitsu, K.; Takeda, S.; Aburada, M.; Miyamoto, K. *Chem. Pharm. Bull.* **2007**, *55*, 255. (b) Aoki, K.; Koseki, J.; Takeda, S.; Aburada, M.; Miyamoto, K. *Chem. Pharm. Bull*. **2007**, *55*, 922. (c) Han, Y.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron Lett*. **2010**, *51*, 2023.
17. (a) Gong, X.; Song, G.; Zhang, H.; Li, X. *Org. Lett.* **2011**, *13*, 1766. (b) Wang, Z.; Li, K.; Zhao, D.; Lan, J.; You, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5365.
18. Preparation of **1a:** (a) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc*. **2007**, *129*, 12072. Preparation of **1c:** (b) Dhanak, D.; Reese, C. B. *J. Chem. Soc. Perkin Trans. 1* **1986**, 2181. Preparation of **1d:** (c) Cipiciani, A.; Clementi, S.; Linda, P.; Savelli, G.; Sebastiani, G. V. *Tetrahedron* **1976**, *32*, 2995. Preparation of **1e:** (d) Schoenebeck, F.; Murphy, J. A.; Zhou, S.; Uenoyama, Y.; Miclo, Y.; Tuttle, T. *J. Am. Chem. Soc*. **2007**, *129*, 13368. Preparation of **1g:** (e) Adams, D. R.; Abraham, A.; Asano, J.; Breslin, C.; Dick, C. A. J.; Ixkes, U.; Johnston, B. F.; Johnston, D.; Kewnay, J.; Mackay, S. P.; MacKenzie, S. J.; McFarlane, M.; Mitchell, L.; Spinks, D.; Takano, Y. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 6579. (f) Buttery, C. D.; Jones, R. G.; Knight, D. W. *J. Chem. Soc*. **1993**, *13*, 1425. Preparation of **1n:** (g) Zonta, C.; Fabris, F.; Lucchi, O. D. *Org. Lett*. **2005**, *7*, 1003. Preparation of **1o:** (h) Muratake, H.; Natsume, M. *Heterocycles* **1990**, *31*, 683. Preparation of **1q:** Schmuck, C.; Bickert, V.; Merschky, M.; Geiger, L.; Rupprecht, D.; Dudaczek, J.; Wich, P.; Rehm, T.; Machon, U. *Eur. J. Org. Chem.* **2008**, 324.
19. Determination of regiochemistry of pyridylpyrrole: Roppe, J.; Smith, N. D.; Huang, D.; Tehrani, L.; Wang, B.; Anderson, J.; Brodkin, J.; Chung, J.; Jiang, X.;

King, C.; Munoz, B.; Varney, M. A.; Prasit, P.; Cosford, N. D. P. *J. Med. Chem.* **2004**, *47*, 4645.

20. Deprotection of tosyl group: Boyles, D. A.; Nichols, D. E. *J. Org. Chem.* **1988**, *53*, 5128.
21. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115.
22. Sheldrick, G. M.; University of Göttingen; Göttingen, Germany, **1997**.

Chapter 2

Strategy for an Ideal Synthesis of Pyrrole and Indole Alkaloids

Abstract

A synthetic strategy for the total synthesis of marine alkaloids called the dictyodendrins has been proposed. Dictyodendrins possess unique structures as well as notable biological activities, thus attracting broad interest from synthetic chemists. In this chapter, previous reports for the total synthesis of dictyodendrins are summarized and a new synthetic strategy utilizing regioselective C–H functionalization is described. The synthetic approach features a combination of C–H arylation and C–H insertion of the pyrrole ring in order to overcome the problem of regioselectivity control and to realize a short synthesis.

1. Introduction

Synthetic studies for structurally and biologically unique natural products enable chemists to develop practical synthetic methodologies toward these compounds and to generate drug candidates. With advances in the field of synthetic organic chemistry, numerous total syntheses of natural products possessing complex structures have been reported, which can further benefit various scientific fields including medicinal chemistry and chemical biology. One of the most essential components regarding natural product synthesis is how carbon–carbon (C–C) bonds, which form the very basis of most molecular frameworks, are constructed. Although a number of total syntheses of complex natural products have been reported to date, most synthetic methodologies require many reaction steps and have limitations for applicable classes of natural products. Therefore, an efficient and universal synthetic strategy toward a broad class of complex biologically active compounds has been sought by synthetic organic chemists.

Dictyodendrins A–E were isolated in 2003 from a Japanese marine sponge, *Dictyodendrilla verongiformis* by Fusetani, Matsunaga and co-workers. (Figure 1).[1] These are the first marine alkaloids found to inhibit telomerase,[2] giving them potential as targets for cancer chemotherapy. In 2012, dictyodendrins F–J were isolated from a southern Australian marine sponge, an *Ianthella* sp. by Capon and co-workers.[3] These new examples of a rare class of marine alkaloids exhibited significant β-secretase (β-site APP cleaving enzyme: BACE) inhibitory activity (IC_{50} 1–2 μM). In addition to these significant biological activities, dictyodendrins have unique structural features including a highly substituted pyrrolo[2,3-*c*]carbazole core.[4] Because of the atypical molecular architecture and the remarkable biological activities, the development of a new synthetic method for the synthesis of dictyodendrins would benefit not only the field of synthetic chemistry but also that of medicinal chemistry and biology.

In this chapter, a strategy toward the efficient synthesis of marine alkaloids dictyodendrins is described. Previous reports detailing the total synthesis of dictyodendrins are summarized on the basis of their key reaction steps. The proposed synthetic route contains two types of C–H functionalization to rapidly access the fully functionalized intermediate.

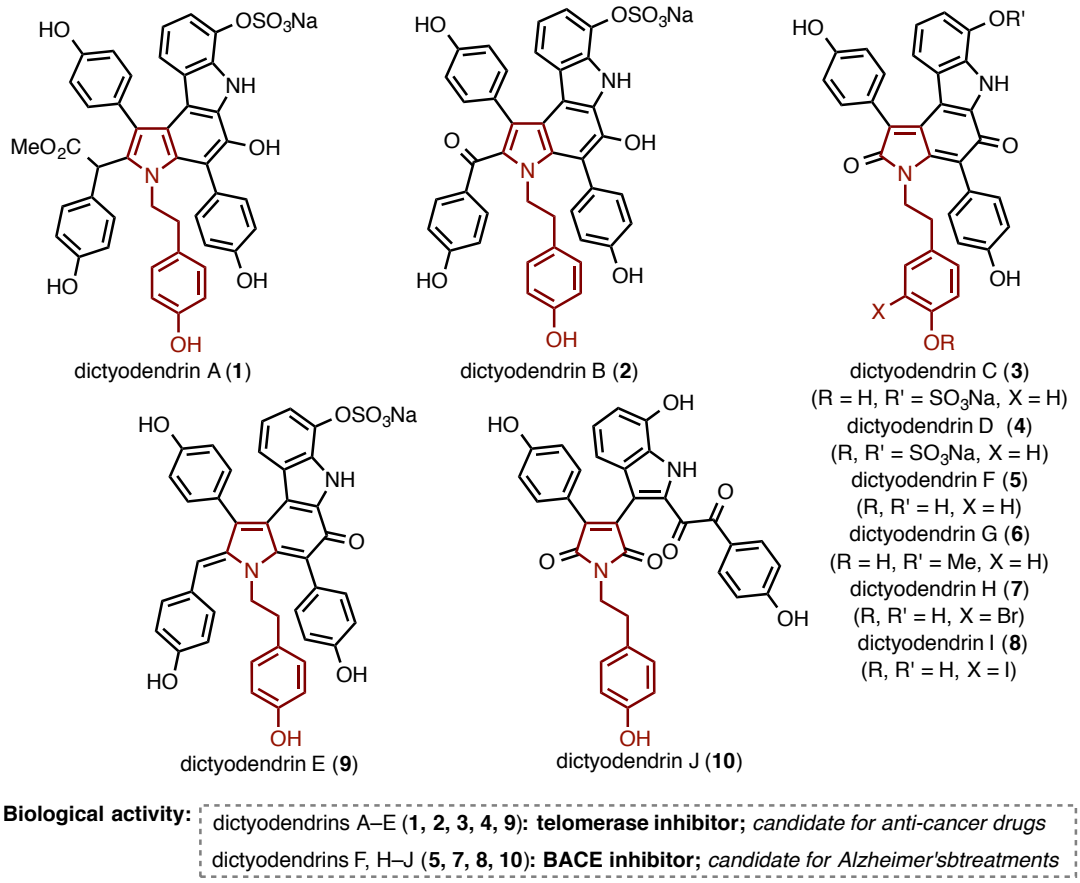


Figure 1. A summary of the structure and biological activities of dictyodendrins.

2. Results and Discussion

2-1. Previous Total Syntheses of Dictyodendrins

To date, four research groups have achieved the total synthesis of the dictyodendrin family (Figure 2). In 2005 and 2006, Fürstner and co-workers reported the first total synthesis of dictyodendrins B, C, E, and F, which featured a titanium-mediated reductive coupling reaction for the construction of the indole ring, followed by pyrrolo[2,3-*c*]carbazole core synthesis via 6π-electrocyclization.[5] In 2010, Iwao, Ishibashi and co-workers achieved an efficient synthesis of dictyodendrin B by use of a Suzuki–Miyaura cross-coupling reaction to introduce two aromatic rings to the pyrrole core.[6] In 2010 and 2011, Tokuyama and co-workers accomplished the total synthesis of dictyodendrins A–E utilizing an indoline formation by *in situ* generation of benzyne and a Pd-catalyzed cross-coupling.[7] In 2013 and 2014, Jia and co-workers reported the total synthesis of dictyodendrins B, C and E using a one-pot reaction of a Buchwald–

Hartwig amination and an intramolecular C–H coupling reaction.[8] As shown in Figure 2, Fürstner and Ishibashi selected a pyrrole ring for the core structure (drawn with red lines) then introduced other substituents. In contrast, the Tokuyama and Jia groups chose an indole ring for the core structure.

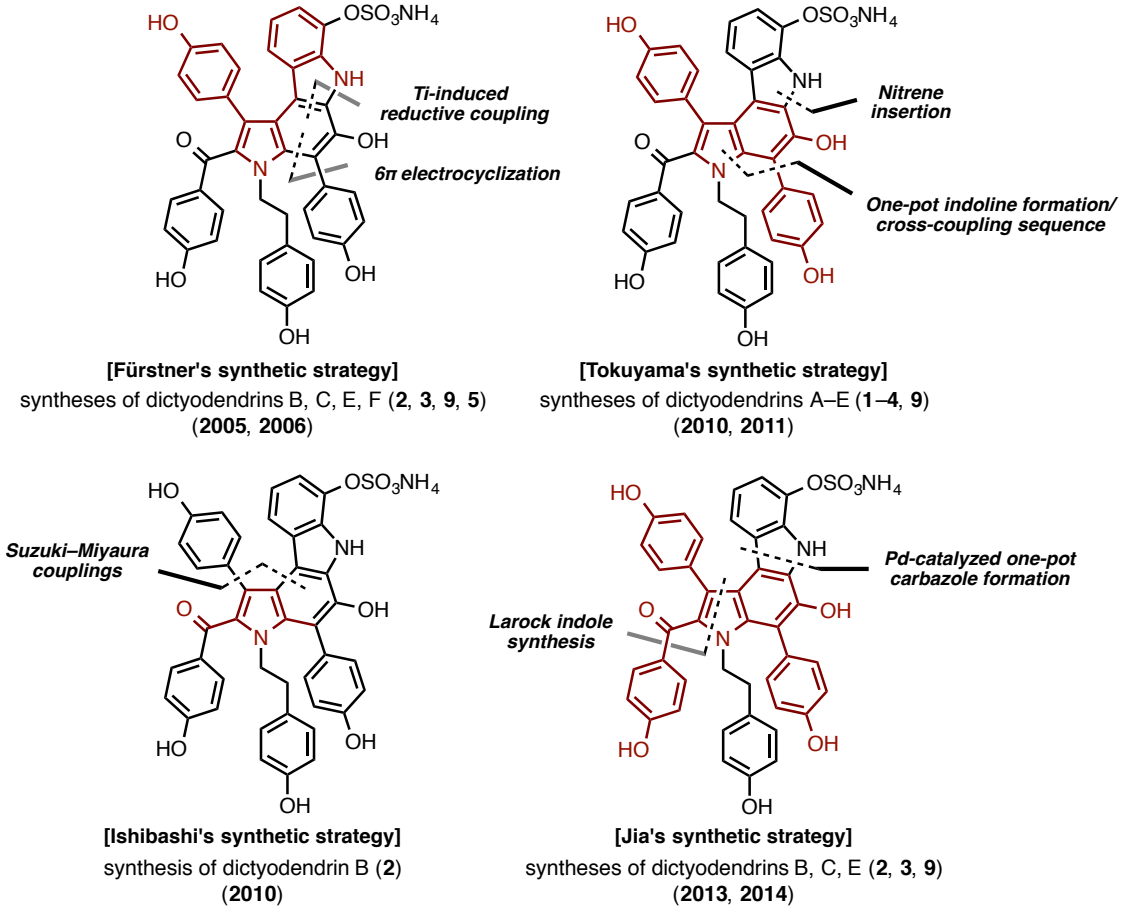


Figure 2. Previous total syntheses of dictyodendrins.

2-1-1. Fürstner's Synthesis (2005, 2006)

Fürstner and co-workers achieved the first total synthesis of dictyodendrins B, C and E. They noted that dictyodendrins A–E differ in their oxidation state and the substituent on the C2 position of the central pyrrole ring, and therefore pyrrolocarbazole **I** would be a common intermediate for the preparation of the entire dictyodendrin family (Figure 3).

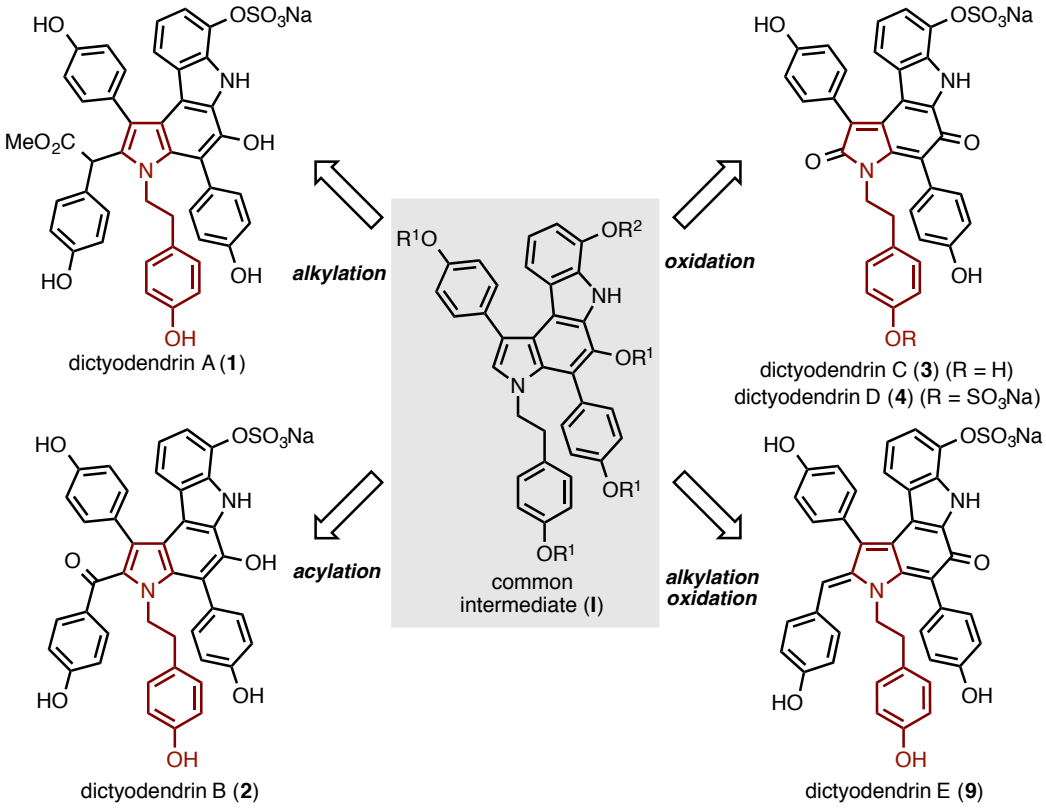
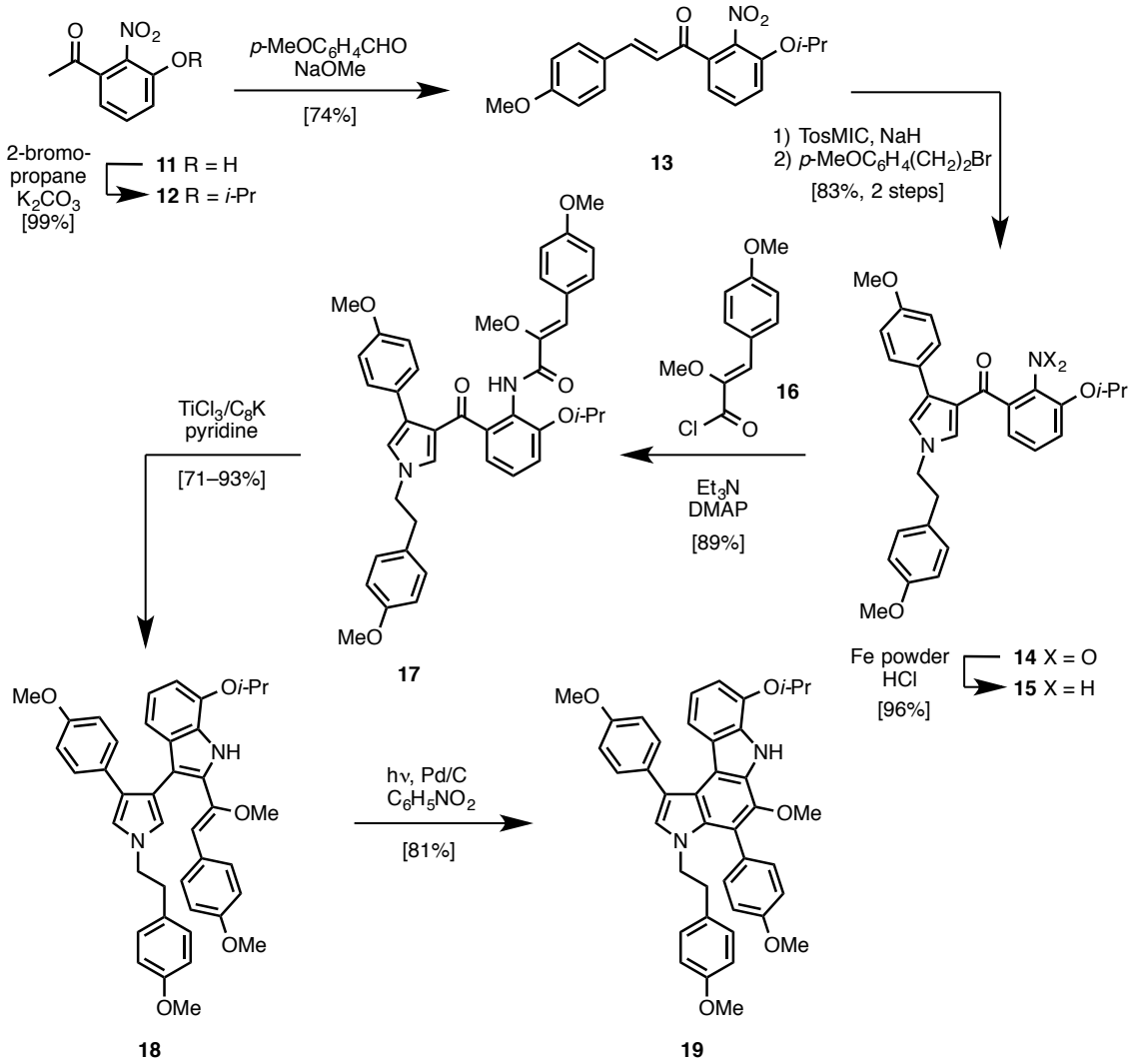


Figure 3. Fürstner's intermediate for the synthesis of dictyodendrins.

In 2005, Fürstner and co-workers accomplished the first total synthesis of dictyodendrin B (Schemes 1 and 2).[5a] At first, common intermediate **19** was synthesized from nitroacetophenone **11** prepared by nitration of commercially available 3-hydroxyacetophenone (Scheme 1). Alkylation of the phenol group on **11** followed by condensation with *p*-$MeOC_6H_4CHO$ afforded α,β-unsaturated ketone **13**. Treatment of **13** with toluenesulfonylmethyl isocyanide (TosMIC) and NaH at low temperature resulted in pyrrole ring construction,[9] followed by *N*-alkylation with *p*-$MeOC_6H_4(CH_2)_2Br$ to provide **14** in 83% yield over two steps. Reduction of the nitro group with Fe/HCl generated aniline **15** in 96% yield, which was condensed with acid chloride **16** to afford amide **17** as the precursor for the following indole synthesis. Intramolecular reductive coupling proceeded by refluxing **17** in the presence of $TiCl_3$ and graphite-potassium intercalate C_8K to afford indol-3-ylpyrrole **18** in 71–93% yield.[10] Next, they moved on to the key reaction step for the synthesis of dictyodendrin B (**2**). Construction of the dictyodendrin core was achieved by 6π-electrocyclization upon irradiation of **18** with UV light in CH_3CN. It was found that addition of Pd/C

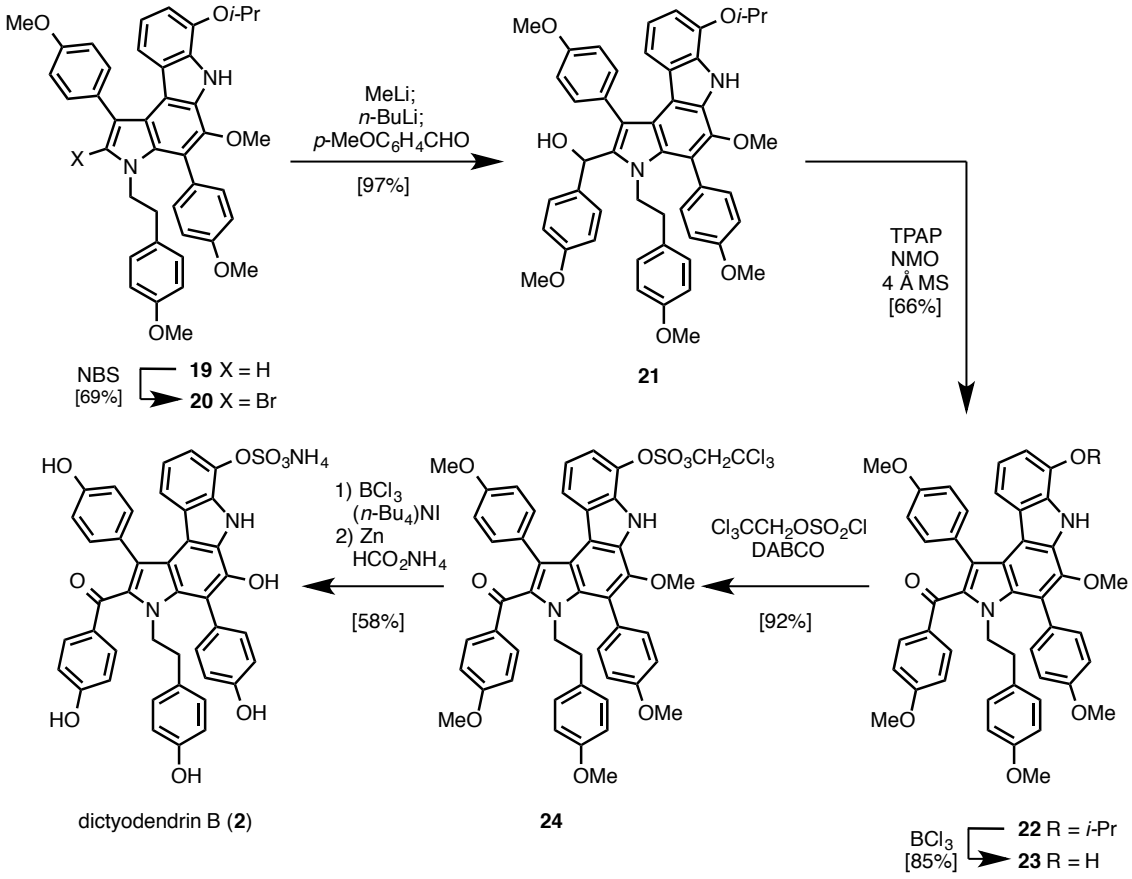
and nitrobenzene[11] results in concomitant aromatization of the product initially formed to give pyrrolocarbazole **19** in 81% yield, which is a common intermediate to access the dictyodendrin family.



Scheme 1. Fürstner's synthesis of common intermediate **19**.

Using intermediate **19** prepared above, Fürstner and co-workers accomplished the first synthesis of dictyodendrin B (**2**: Scheme 2). Acylation of the C2 position of **19** was needed to complete the synthesis of **2**. Treatment of **19** with NBS furnished brominated pyrrolocarbazole **20**, which was exposed to MeLi followed by *n*-BuLi to result in metal–halogen exchange. This metallated intermediate was quenched with *p*-$MeOC_6H_4CHO$ to give secondary alcohol **21** in 97% yield. Oxidation of the resulting alcohol with TPAP and NMO afforded the desired ketone **22**. Selective cleavage of the

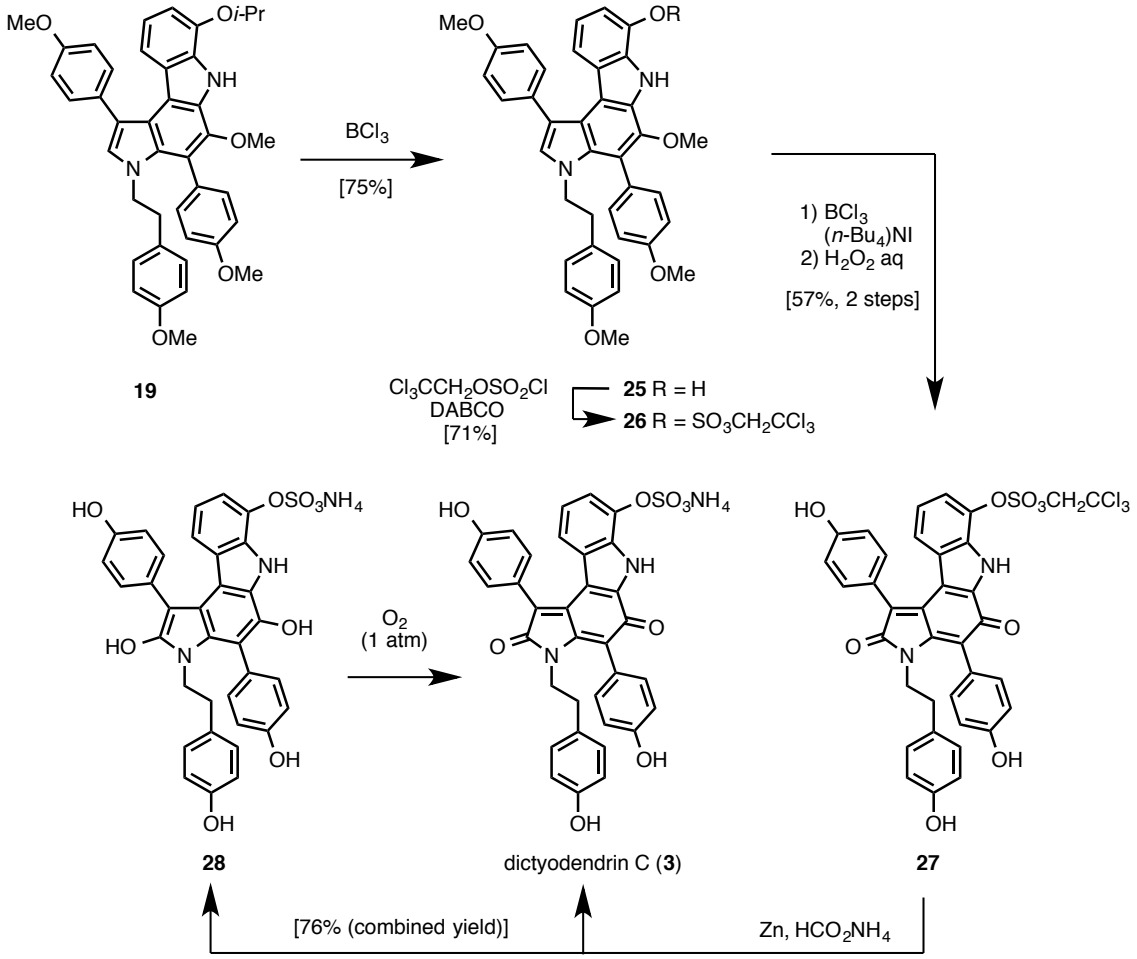
isopropyl ether in **22** with BCl_3, followed by treatment of the resulting phenol **23** with trichloroethyl chlorosulfate, provided arylsulfate **24** in 92% yield. Exhaustive demethylation of **24** proceeded smoothly by treatment with $BCl_3/(n\text{-}Bu)_4NI$.[12] Notably, the sulfate group was tolerated under these reaction conditions. Finally, reductive cleavage of the trichloroethyl sulfate with Zn/HCO_2NH_4 proceeded, making the completion of the synthesis of dictyodendrin B (**2**).[5a]



Scheme 2. Synthesis of dictyodendrin B (**2**) reported by Fürstner.[5a]

Meanwhile, dictyodendrin C (**3**) was also synthesized from common intermediate **19** (Scheme 3). Treatment of intermediate **19** with BCl_3 resulted in the selective removal of the isopropyl group to give phenol **25** in 75% yield. Phenol **25** was converted into arylsulfate **26** in 71% yield by reaction with trichloroethyl chlorosulfate. Removal of other methyl groups followed by oxidation with H_2O_2 in CH_3CN provided quinone **27** in 57% yield over two steps. Then, **27** was treated with MeOH to induce reductive cleavage of the trichloroethyl moiety to give dictyodendrin C (**3**). Even though generation of phenol derivative **28** was observed under the reductive reaction

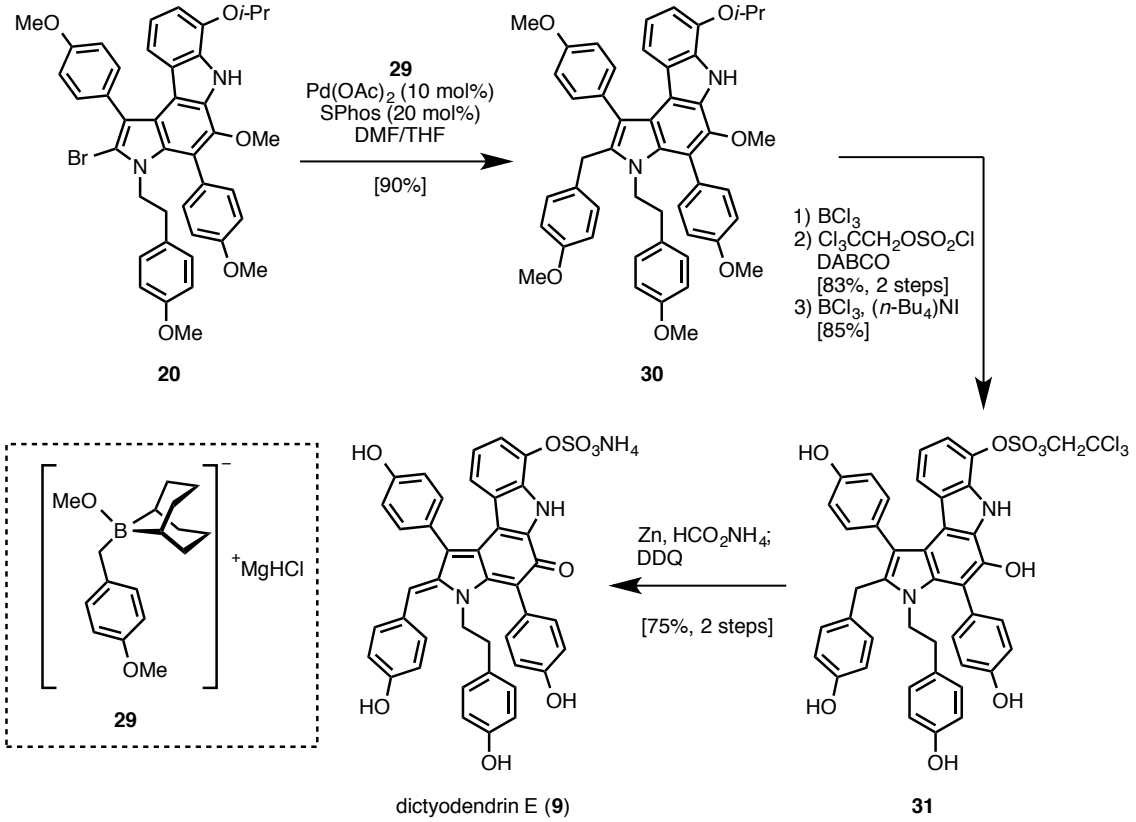
conditions, removal of the excess zinc dust followed by treatment of the crude mixture under an oxygen atmosphere afforded dictyodendrin C (**3**) as a single product in 76% yield over two steps (Scheme 3).[5b]



Scheme 3. Synthesis of dictyodendrin C (**3**) reported by Fürstner.[5b]

Furthermore, the synthesis of dictyodendrin E (**9**) was also completed from the same intermediate (Scheme 4). Fürstner and co-workers found that introduction of the substituent to the C2 position was achieved by use of borate complex **29** generated *in situ* from 9-MeO-9-BBN and *p*-methoxybenzylmagnesium chloride. Suzuki–Miyaura cross-coupling of bromopyrrolecarbazole **20** (prepared from bromination of **19**) with reactive intermediate **29**[13] afforded benzylated product **30** in 90% yield. Selective removal of the isopropyl group by BCl_3, followed by treatment with trichloroethyl chlorosulfate, gave an arylsulfate intermediate in 83% yield over two steps. The resulting arylsulfate was globally deprotected with BBr_3 to afford **31**, which was

immediately subjected to Zn/HCO_2NH_4 for the removal of the trichloroethyl group, followed by oxidation with DDQ. This reaction sequence afforded dictyodendrin E (**9**) in 75% yield over two steps.[5b]

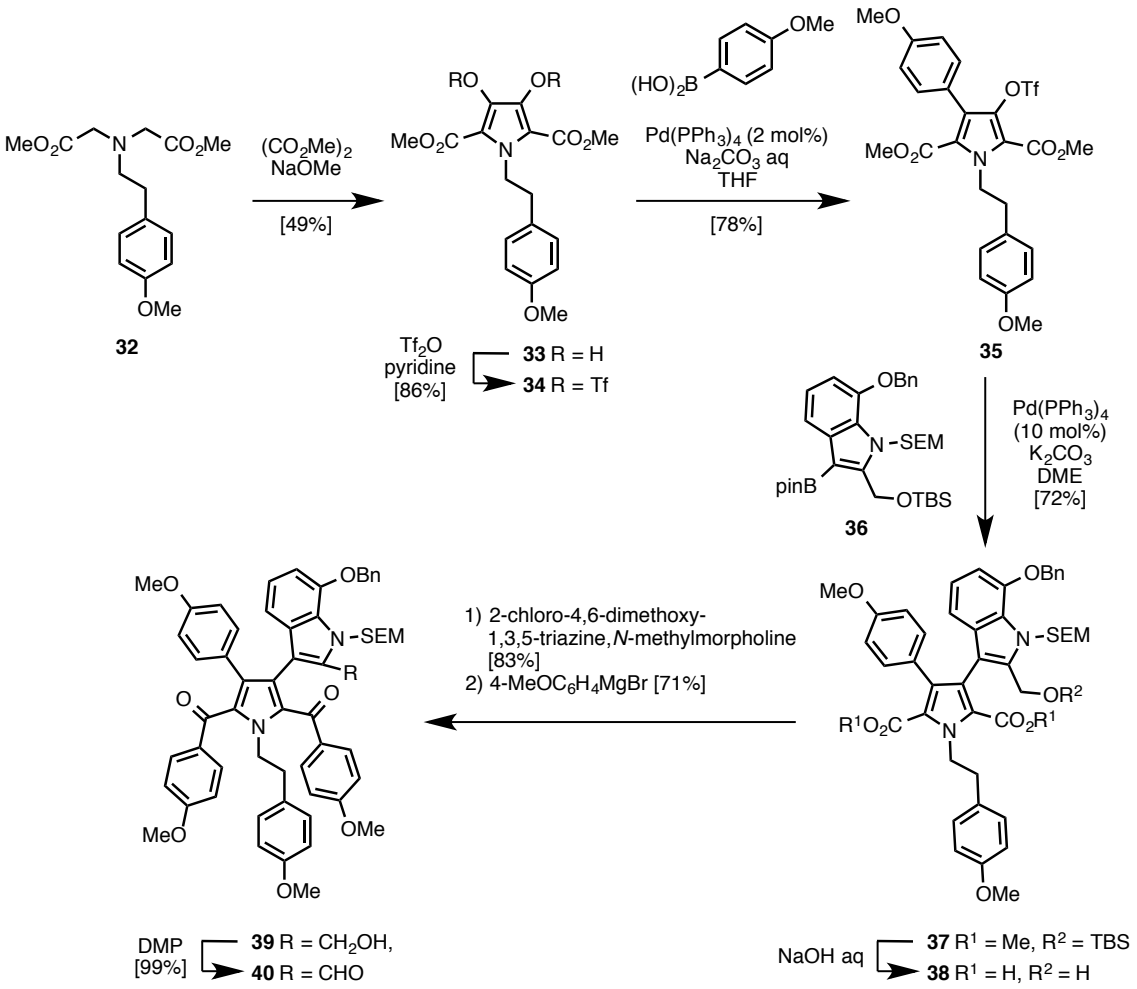


Scheme 4. Synthesis of dictyodendrin E (**9**) reported by Fürstner.[5b]

2-1-2. Ishibashi's Synthesis (2010)

In 2010, Ishibashi and co-workers reported the formal synthesis of dictyodendrin B (**2**), which features a Suzuki–Miyaura cross-coupling reaction to introduce two aromatic rings to the pyrrole core (Schemes 5 and 6).[6a] The preparation of the fully functionalized pyrrole **40**, which is the precursor for the reductive cyclization was conducted (Scheme 5). The initial iminodiacetate **32** was prepared by dialkylation of *p*-methoxyphenylethylamine with methyl bromoacetate.[14] Hinsberg-type condensation of **32** with methyl oxalate, followed by treatment of the resulting 3,4-dihydroxypyrrole-2,5-dicarboxylate **33** with $(CF_3SO_2)_2O$ and pyridine afforded bis-triflate **34**. Next, palladium-catalyzed cross-coupling of bis-triflate **34** with *p*-methoxyphenylboronic acid was conducted. In the presence of 2 mol% $Pd(PPh_3)_4$ and aqueous Na_2CO_3 in THF, the cross-coupling of **34** and *p*-methoxyphenylboronic acid

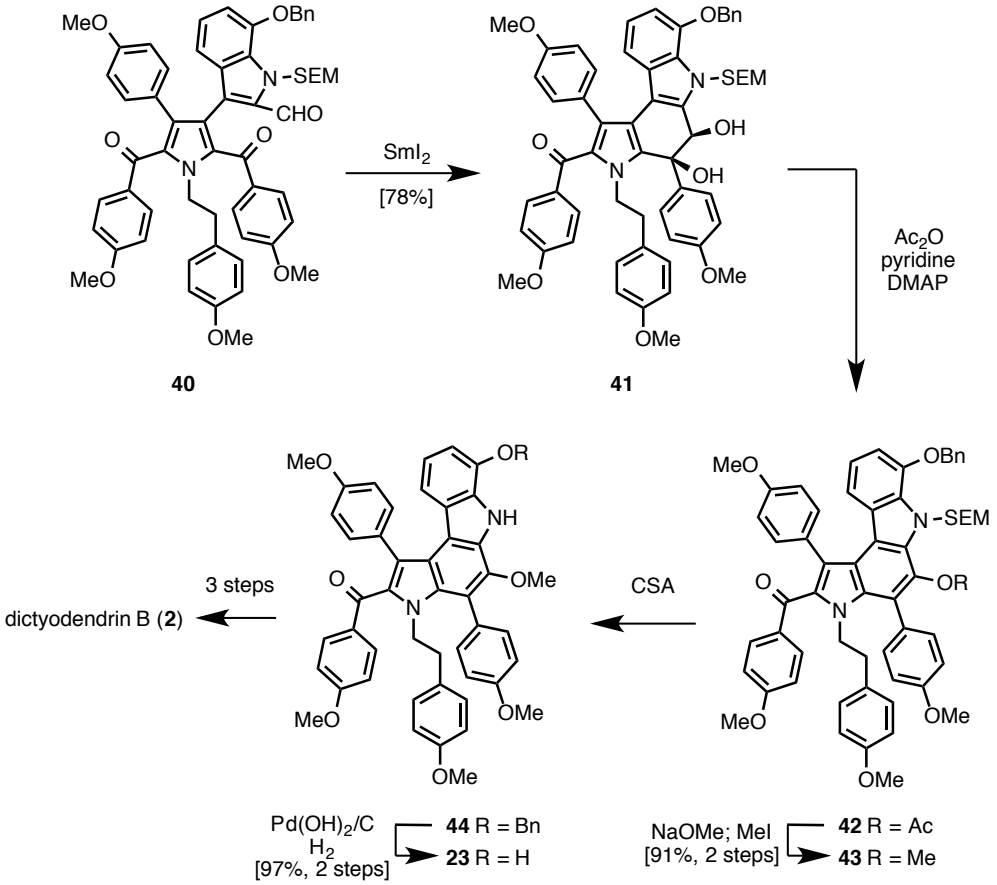
proceeded to produce mono-arylated pyrrole **35** in 78% yield. The resulting 3-arylpyrrole **35** was further arylated with indole-3-boronic acid pinacol ester **36** in the presence of $Pd(PPh_3)_4$ and K_2CO_3 to provide the corresponding coupling product **37** in 72% yield. Hydrolysis of diester **37** proceeded with concomitant removal of the TBS protecting group to give dicarboxylic acid **38**, which was converted into diketone **39** *via* esterification with 2-chloro-4,6-dimethoxy-1,3,5-triazine, followed by addition of *p*-methoxyphenylmagnesium bromide. Then, Dess–Martin oxidation of **39** provided aldehyde **40** in quantitative yield.



Scheme 5. Preparation of cyclization precursor **40**.

The pyrrolo[2,3-*c*]carbazole core of **42** was constructed by SmI_2-induced intramolecular pinacol coupling[15] of **40**, followed by treatment of diol **41** with Ac_2O, pyridine and DMAP. Deacylation of **42** followed by methylation of the resulting phenol group gave pyrrolocarbazole **43** in 91% yield (Scheme 6). Lastly, removal of the

SEM protecting group and benzyl ether converted **43** to known intermediate **23**[5] in 97% yield. Dictyodendrin B (**2**) could be synthesized from **23** in three steps by the procedure reported by Fürstner.[5]

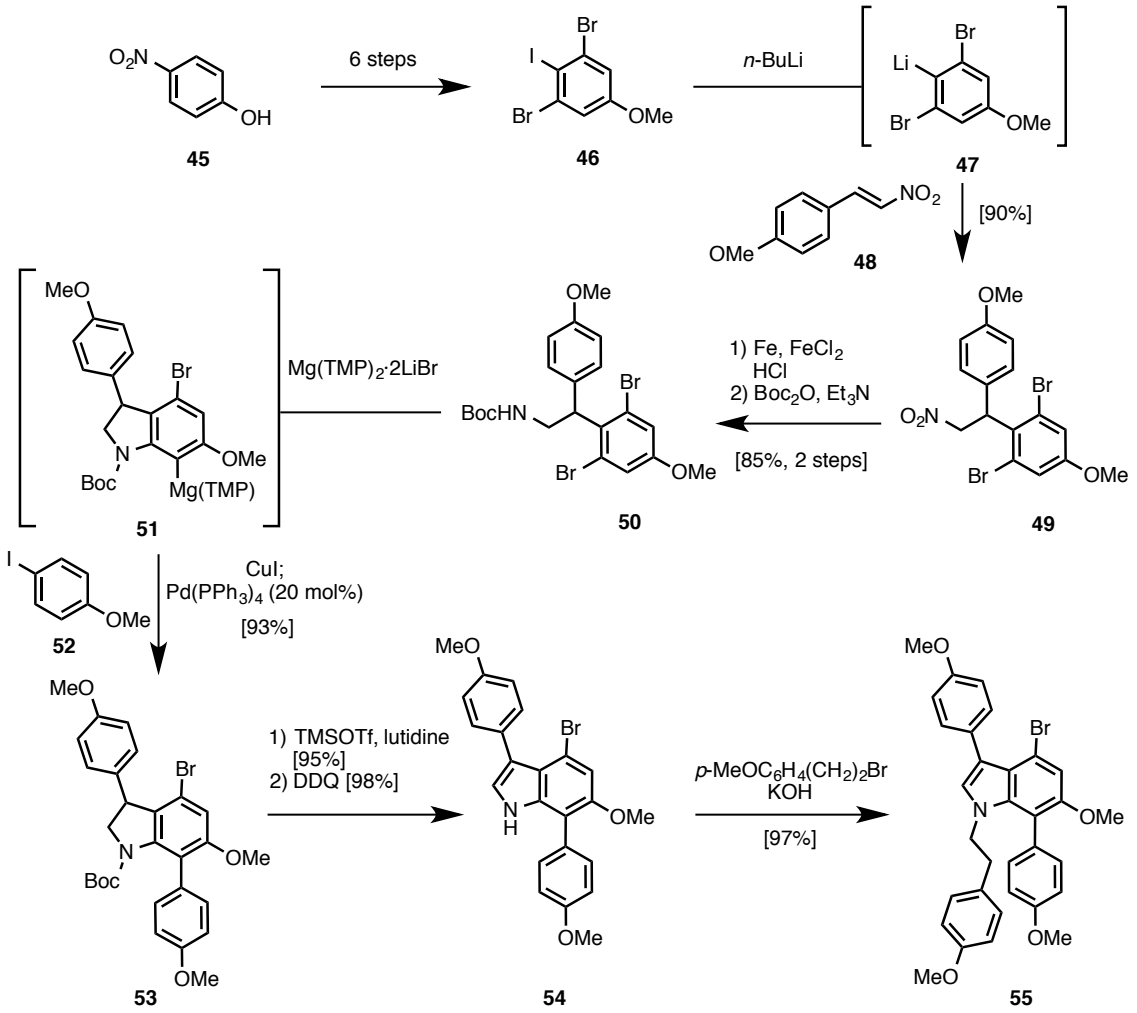


Scheme 6. Ishibashi's formal synthesis of dictyodendrin B (**2**).[6a]

2-1-3. Tokuyama's Synthesis (2010, 2011)

In 2010, Tokuyama and co-workers reported the total synthesis of dictyodendrin B (**2**) and the first total synthesis of dictyodendrin A (**1**), which features an efficient indoline formation through a benzyne species, followed by cross-coupling to prepare a highly functionalized 5-bromoindole derivative (Schemes 7 and 8).[7a] The synthesis commenced with the preparation of 2,6-dibromo-iodobenzene derivative **46** from *p*-nitrophenol (**45**) over six steps (Scheme 7).[16] Treatment of **46** with *n*-BuLi in toluene at –78 °C resulted in halogen–lithium exchange, and then addition to nitroolefin **48** provided diarylethane **49** in 90% yield. Then, reduction of the nitro group proceeded selectively and the resulting primary amine was Boc-protected to afford desired product **50** in 85% yield. After the preparation of **50**, the key indoline formation *via*

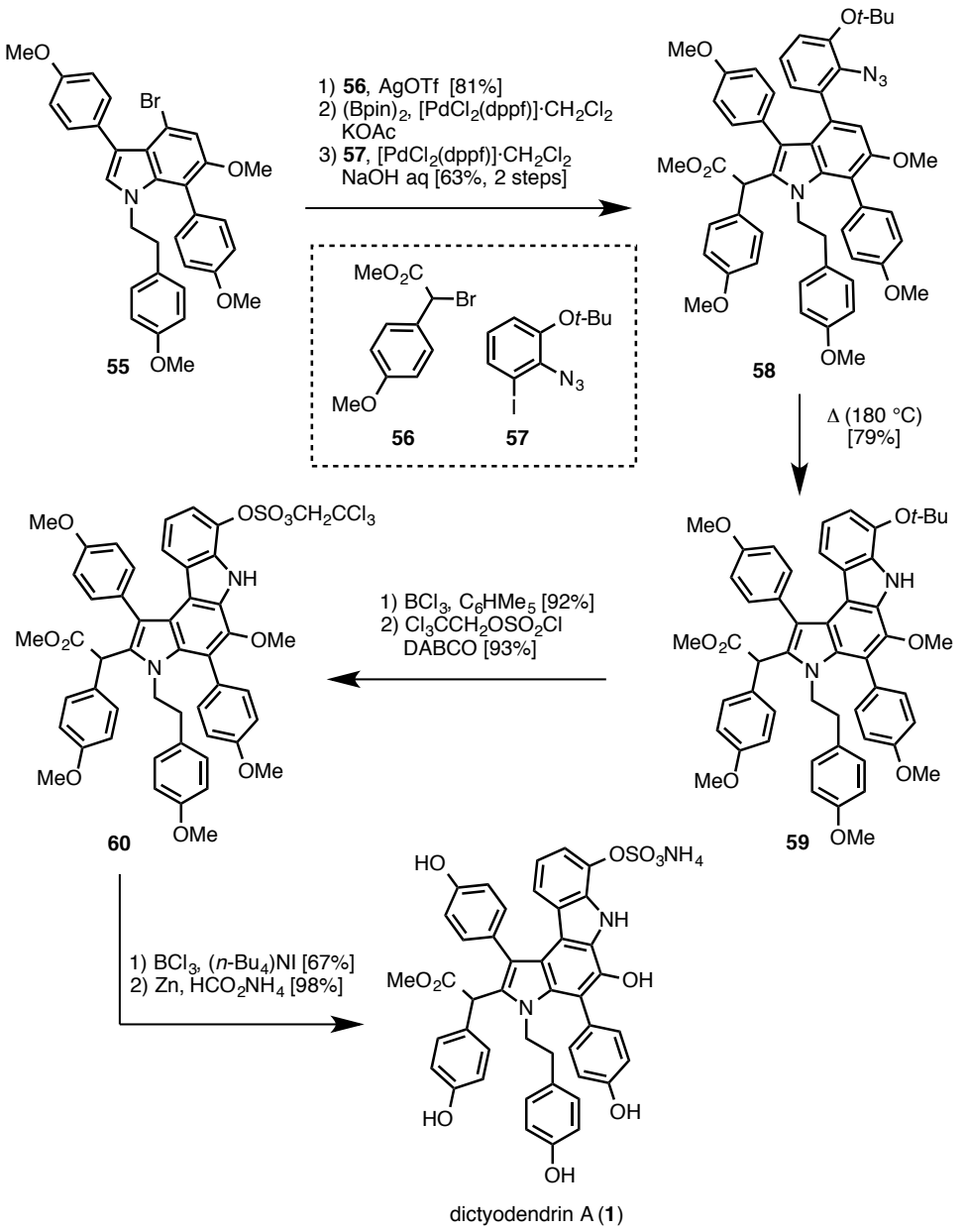
tandem generation of a benzyne species and arylation sequence was conducted. Treatment of **50** with $Mg(TMP)_2{\cdot}2LiBr$[17] promoted the benzyne formation/cyclization to form 7-magnesiospecies **51** *in situ*. After formation of the indoline, Kumada–Tamao coupling with *p*-iodoanisole (**52**) using CuI and $Pd(PPh_3)_4$ afforded the corresponding cross-coupling product **53** up to 93% yield. The reaction can also be conducted on a gram scale, giving **53** in 89% yield. Boc removal with the combination of TMSOTf and lutidine, followed by oxidation with DDQ, afforded indole **54**. Indole **54** was alkylated with *p*-methoxyphenylethyl bromide to provide *N*-substituted 4-bromoindole **55** in 97% yield.



Scheme 7. Preparation of highly functionalized indole **55**.

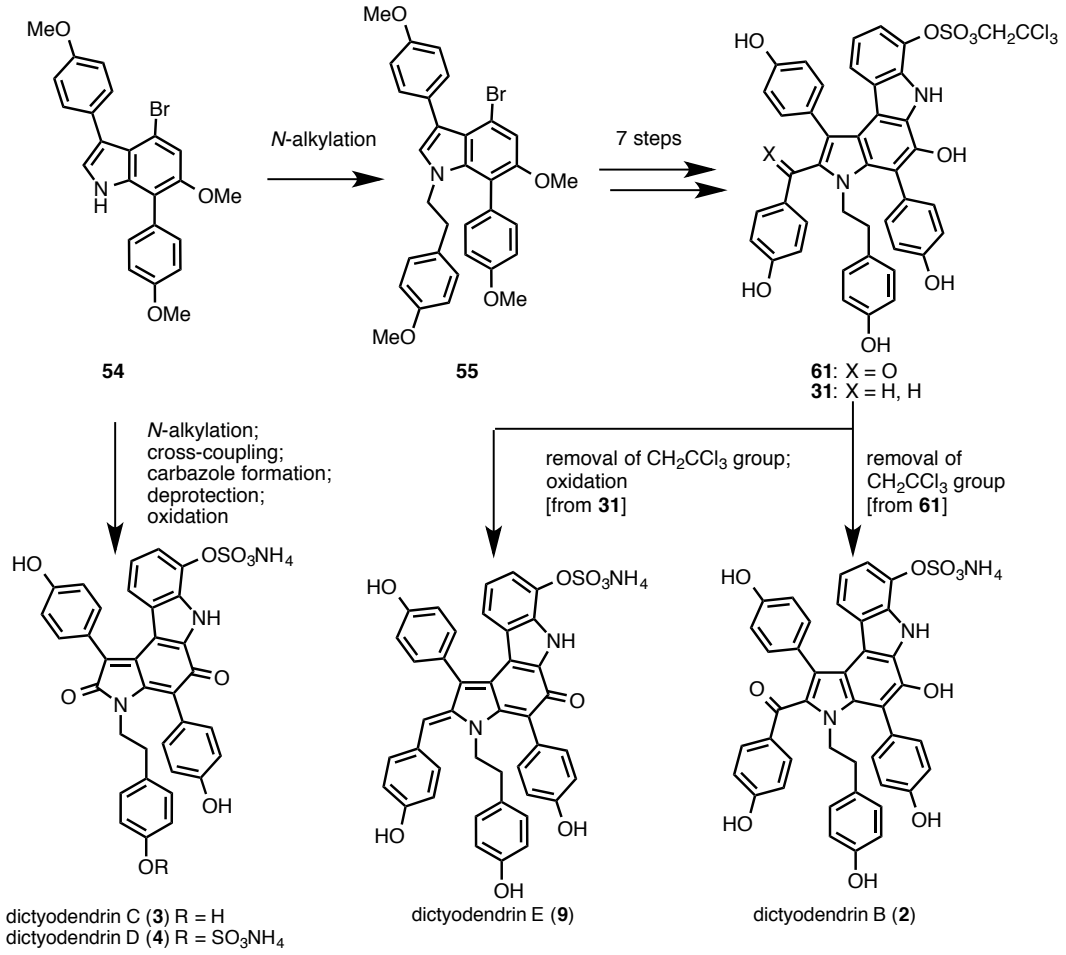
Friedel–Crafts alkylation of **55** with alkyl bromide **56** proceeded under mild conditions using AgOTf at –78 °C (Scheme 8). After the conversion of the bromide into a boryl group with $(Bpin)_2$, the azidophenyl group was introduced by Suzuki–Miyaura

cross-coupling with **57** to afford **58** in 63% yield over two steps. Then, thermolysis of azide **58** at 180 °C resulted in the generation of a nitrene, which inserted to the C–H bond on the C6 position of the indole core to give pyrrolocarbazole **59** in 79% yield.[18] The *tert*-butyl group was removed using BCl_3 in the presence of pentamethylbenzene as a non-Lewis-basic cation scavenger. Exposure of the resulting phenol to trichloroethyl chlorosulfate furnished arylsulfate **60** in 93% yield. Then, removal of the methyl groups, followed by removal of the trichloroethyl group accomplished the synthesis of dictyodendrin A (**1**).[7a]



Scheme 8. Synthesis of dictyodendrin A (**1**) reported by Tokuyama.[7a]

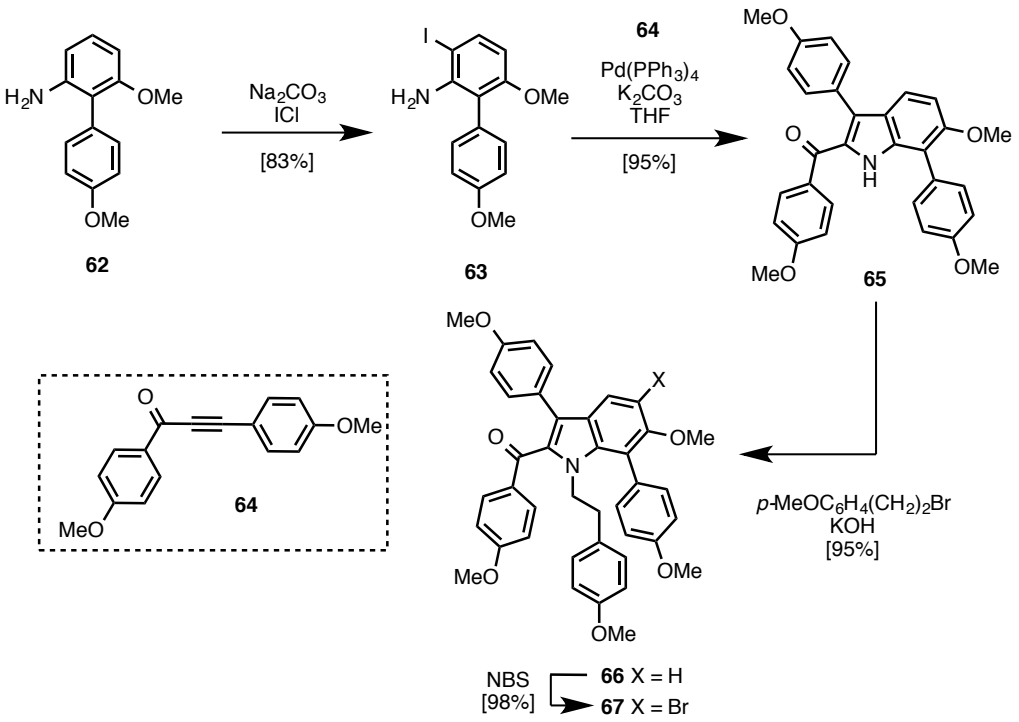
In 2011, Tokuyama and co-workers reported the divergent synthesis of dictyodendrins A–E (Scheme 9).[5b] After the preparation of **54** by a benzyne-mediated cyclization/arylation sequence, the dictyodendrin family was synthesized from this intermediate. The total synthesis of dictyodendrins C (**3**) and D (**4**) was accomplished from **54** through several transformations including *N*-alkylation, introduction of aryl azide moiety by use of a cross-coupling reaction, carbazole formation, deprotection and oxidation. On the other hand, the total synthesis of dictyodendrins B (**2**) and E (**9**) was completed from alkylindole **55** by a method similar to that used in the total synthesis of dictyodendrin A (**1**). 2-Substituted pyrrolocarbazoles **61** and **31** were synthesized from **55** over seven steps. Dictyodendrin B (**2**) was obtained by the removal of the trichloroethyl group of **61** with zinc dust and ammonium formate. Dictyodendrin E (**9**) was synthesized from **31** by the reductive cleavage of the trichloroethyl group, followed by oxidation of the core structure.[7b]



Scheme 9. Synthesis of dictyodendrins B–E reported by Tokuyama.[7b]

2-1-4. Jia's Synthesis (2013, 2014)

In 2013, Jia and co-workers reported the concise synthesis of dictyodendrin B (**2**) utilizing a C–H functionalization strategy (Schemes 10 and 11).[8a] Their synthesis features a sequential Pd-catalyzed Buchwald–Hartwig amination and intramolecular C–H/C–Cl coupling reaction. Preparation of the precursor of the key sequential reaction is shown in Scheme 10. The synthesis commenced with aniline **62** prepared from 1,3-dinitrobenzene and iodoanisole over three steps (condensation, mono-methoxylation and reduction of the remaining nitro group).[19] Iodination of **62** using ICl provided *o*-iodoaniline **63** in 83% yield. The Larock indole annulation of **63** with alkynylketone **64** using $Pd(PPh_3)_4$ and K_2CO_3 in THF gave the desired indole **65** in 95% yield as a single regioisomer. *N*-Alkylation of **65** with *p*-$MeOC_6H_4(CH_2)_2Br$ afforded the alkylindole **66** in 95% yield. Bromination at the 5-position of indole **66** with NBS gave **67** in 98% yield. In this manner, rapid access to intermediate **67** could be achieved on a multigram scale.

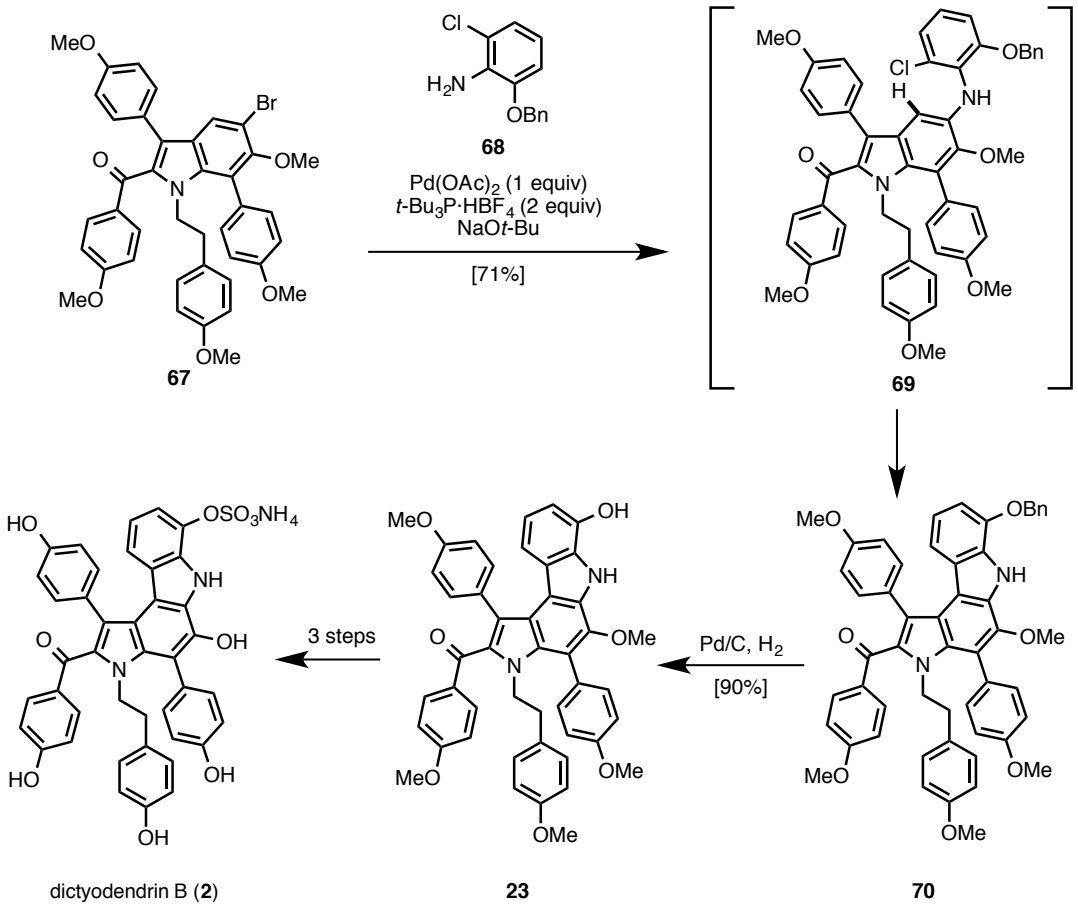


Scheme 10. Jia's synthesis of intermediate **67**.

After the synthesis of key intermediate **67**, carbazole formation was conducted by a sequential one-pot palladium-catalyzed Buchwald–Hartwig amination and intramolecular C–H/C–Cl coupling reaction using a single catalyst (Scheme 11). The

sequential reaction of bromoindole **67** with 2-chloroaniline **68** proceeded in the presence of 1 equiv $Pd(OAc)_2$, 2 equiv *t*-$Bu_3P{\cdot}HBF_4$ and 5 equiv NaO*t*-Bu in DMSO at 160 °C *via* key intermediate **69** to afford desired pyrrolocarbazole **70** in 71% yield. Then, removal of the benzyl ether with Pd/C catalyst under H_2 atmosphere provided the previously reported intermediate **23** in 90% yield, which could be readily converted to dictyodendrin B (**2**) over three steps following the procedure reported by Fürstner and Tokuyama.[5,7]

In 2014, Jia and co-workers also reported the synthesis of dictyodendrins C and E utilizing a same synthetic strategy.[8b]



Scheme 11. Jia's formal synthesis of dictyodendrin B (**2**).[8a]

2-2. New Synthetic Strategy for the Total Synthesis of Dictyodendrins

Dictyodendrins possessing a pyrrolocarbazole core can be classified into four types (**types I–IV**) according to their oxidation state and the substituent on the C2 position of the central pyrrole ring (Figure 4). It was envisioned that the fully functionalized pyrrole could lead to all the types of dictyodendrin derivatives. The carbazole core

would be synthesized from the pyrrole through the connection between the C2 position of the indole ring and the carbonyl group by only a single transformation. The C2 substituent of **type I** would be transformed into an acyl group (**type II**) or a benzyl group (**type III**) *via* hydrolysis of the ester group followed by decarboxylation. In contrast, fragmentation of the substituent of **type I** is able to provide the core structure of **type IV**. One of the most efficient synthetic methods for the preparation of the fully functionalized pyrrole is the direct introduction of C2–C5 substituents to an unsubstituted pyrrole ring. The new synthetic strategy is shown in Figure 4. The introduction of the indole and *p*-alkoxyphenyl groups could be achieved by means of C–H arylation of the pyrrole with two different coupling partners. On the other hand, the alkyl groups need to be installed on the C2 and C5 positions. Over the past decade, dirhodium(II)-catalyzed C–H insertion reactions with aryldiazoesters have been reported.[20] This reaction would allow for the direct introduction of the desired substituents containing the methyl ester and *p*-alkoxyphenyl to the pyrrole ring.

This synthetic strategy faces a serious challenge regarding the regioselectivity control for the introduction of various substituents to the pyrrole ring. The sequence for the C–H functionalization reactions plays a key role to overcome the problem. Experimental studies for the completion of the concise synthesis of dictyodendrins are described in Chapter 3.

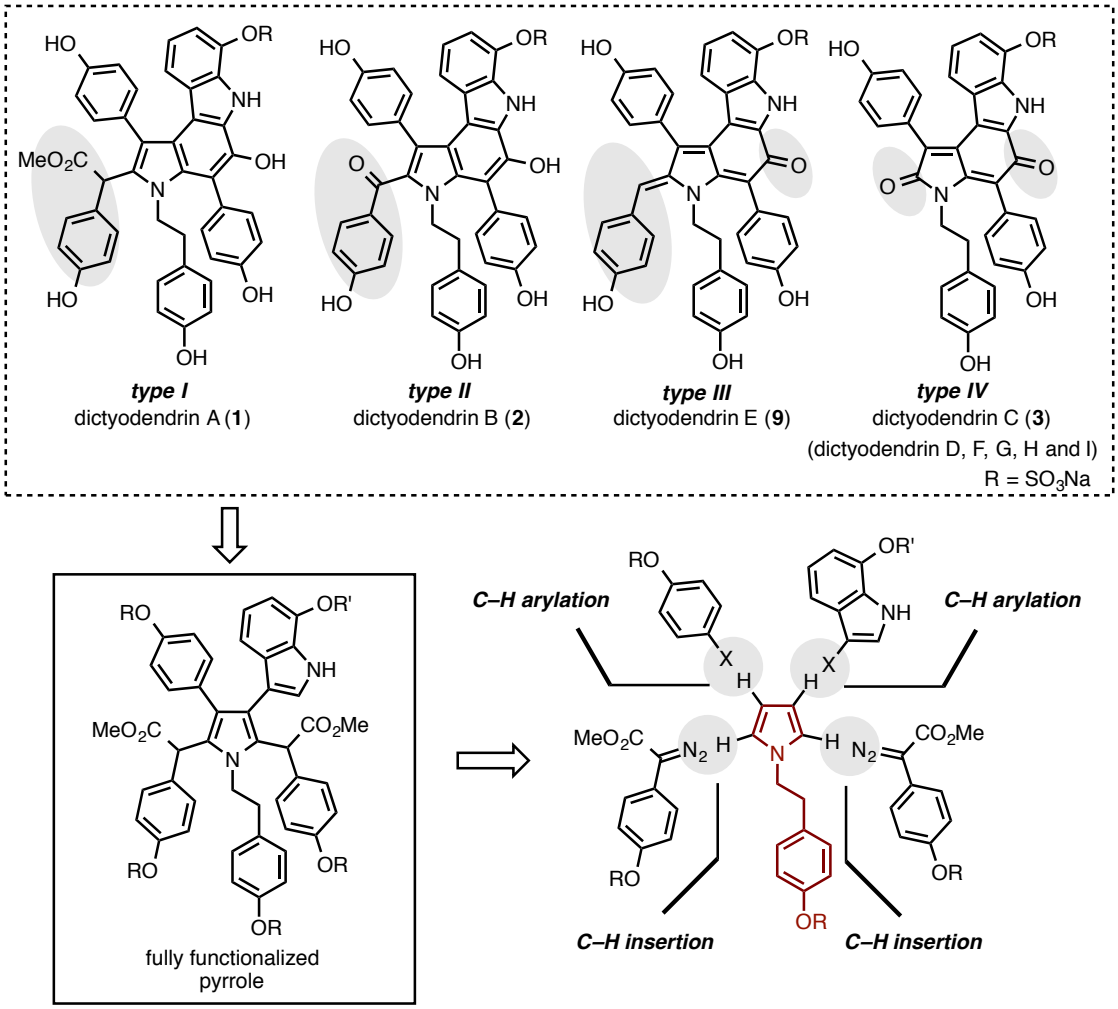


Figure 4. A synthetic strategy that involves regioselective C–H functionalization.

3. Conclusion

In this chapter, a synthetic strategy toward the efficient synthesis of marine alkaloids dictyodendrins, which exhibit notable biological activities and have unique structures, was described. Previous total syntheses of the dictyodendrin family by the groups of Fürstner, Ishibashi, Tokuyama and Jia were summarized with a focus on their key reaction steps. The proposed synthetic strategy targets the all members of the dictyodendrin family. It features a rapid access to the fully functionalized pyrrole core, which is a key intermediate for the synthetic strategy, by C–H functionalization. The combination of C–H arylation and C–H insertion would enable the construction of the key intermediate smoothly from a simple pyrrole as a starting material.

References and Notes

1. Warabi, K.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *J. Org. Chem.* **2003**, *68*, 2765.
2. Parkinson, E. K. *Ann. Med.* **2003**, *35*, 466.
3. Zhang, H.; Conte, M. M.; Khalil, Z.; Huang, X.-C.; Capon, R. J. *RSC Adv.* **2012**, *2*, 4209.
4. Ayats, C.; Soley, R.; Albericio, F.; Alvarez, M. *Org. Biomol. Chem.* **2009**, *7*, 860.
5. Syntheses of dictyodendrins B, C, E, and F: (a) Fürstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2005**, *127*, 11620. (b) Fürstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2006**, *128*, 8087. (c) Buchgraber, P.; Domostoj, M. M.; Scheiper, B.; Wirtz, C.; Mynott, R.; Rust, J.; Fürstner, A. *Tetrahedron* **2009**, *65*, 6519.
6. Synthesis of dictyodendrin B: (a) Hirao, S.; Yoshinaga, Y.; Iwao, M.; Ishibashi, F. *Tetrahedron Lett.* **2010**, *51*, 533. (b) Hirao, S.; Sugiyama, Y.; Iwao, M.; Ishibashi, F. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 1764.
7. Syntheses of dictyodendrins A–E: (a) Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5925. (b) Tokuyama, H.; Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T. *Chem. Asian J.* **2011**, *6*, 560.
8. (a) Liang, J.; Hu, W.; Tao, P.; Jia, Y. *J. Org. Chem.* **2013**, *78*, 5810. (b) Tao, P.; Liang, J.; Jia, Y. *Eur. J. Org. Chem.* **2014**, 5735.
9. van Leusen, A. M.; Siderius, H.; Hoogenboom, B. E.; van Leusen, D. *Tetrahedron Lett*. **1972**, *13*, 5337.
10. (a) Fürstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991. (b) Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem*. **1994**, *59*, 5215. (c) Fürstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2442. (d) McMurry, J. E. *Chem. Rev*. **1989**, *89*, 1513.
11. Rawal, V. H.; Jones, R. J.; Cava, M. P. *Tetrahedron Lett*. **1985**, *26*, 2423.
12. Brooks, P. R.; Wirtz, M. C.; Vetelino, M. G.; Rescek, D. M.; Woodworth, G. F.; Morgan, B. P.; Coe, J. W. *J. Org. Chem.* **1999**, *64*, 9719.
13. (a) Fürstner, A.; Seidel, G. *Tetrahedron* **1995**, *51*, 11165. (b) Fürstner, A.; Leitner, A. *Synlett* **2001**, 290. (c) Fürstner, A.; Nikolakis, K. *Liebigs Ann*. **1996**, 2107. (d) Soderquist, J. A.; Matos, K.; Rane, A.; Ramos, J. *Tetrahedron Lett*. **1995**, *36*, 2401.

14. Iwao, M.; Takeuchi, T.; Fujikawa, N.; Fukuda, T.; Ishibashi, F. *Tetrahedron Lett.* **2003**, *44*, 4443.
15. Namy, J. L.; Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765.
16. Yamada, K.; Kurokawa, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 6630.
17. $Mg(TMP)_2 \cdot 2LiBr$ as a deprotonating regent has been reported although it has not been used for benzyne generation. (a) Eaton, P. E.; Lee, C.-H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016. (b) Eaton, P. E.; Xiong, Y.; Gilardi, R. *J. Am. Chem. Soc.* **1993**, *115*, 10195. (c) Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Org. Chem.* **2003**, *68*, 4576.
18. (a) Pudlo, M.; Csányi, D.; Moreau, F.; Hajós, G.; Riedl, Z.; Sapi, J. *Tetrahedron* **2007**, *63*, 10320.
19. Cornforth, J.; Sierakowski, A. F.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2299.
20. (a) Davies, H. M. L.; Hodges, M. L.; Matasi, J. J.; Hansen, T.; Stafford, D. G. *Tetrahedron Lett.* **1998**, *39*, 4417. (b) Davies, H. M. L.; Loe, O. *Synthesis* **2004**, 2595.

Chapter 3

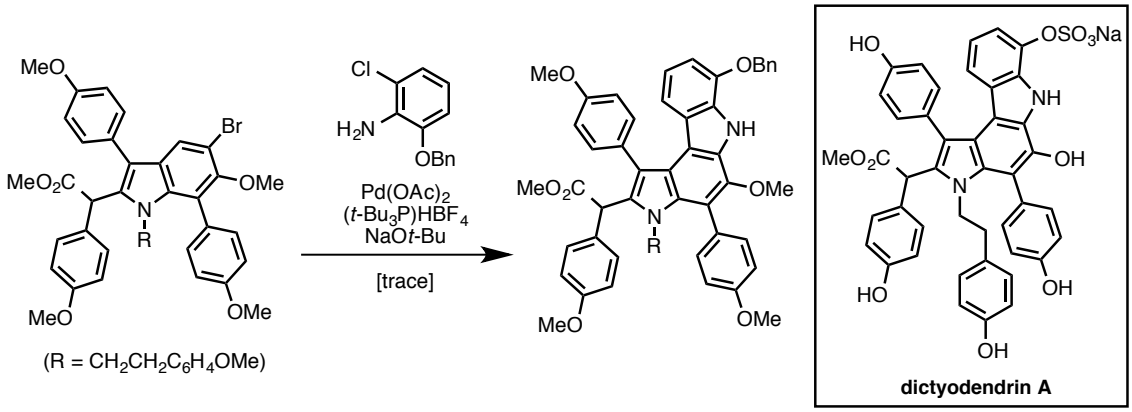
Concise Synthesis of Dictyodendrins A and F through Regioselective C–H Functionalizations

Abstract

Total syntheses of dictyodendrins A and F have been accomplished utilizing regioselective C–H functionalizations. A Rh(I)-catalyzed β-selective C–H arylation, a Rh(II)-catalyzed regioselective C–H insertion and a Suzuki–Miyaura cross-coupling at a sterically hindered position allowed for rapid construction of the fully functionalized pyrrole core. Completion of the total synthesis was achieved by formal 6π-electrocyclization of the highly substituted pyrrole intermediate to form the key pyrrolo[2,3-*c*]carbazole core of dictyodendrins.

1. Introduction

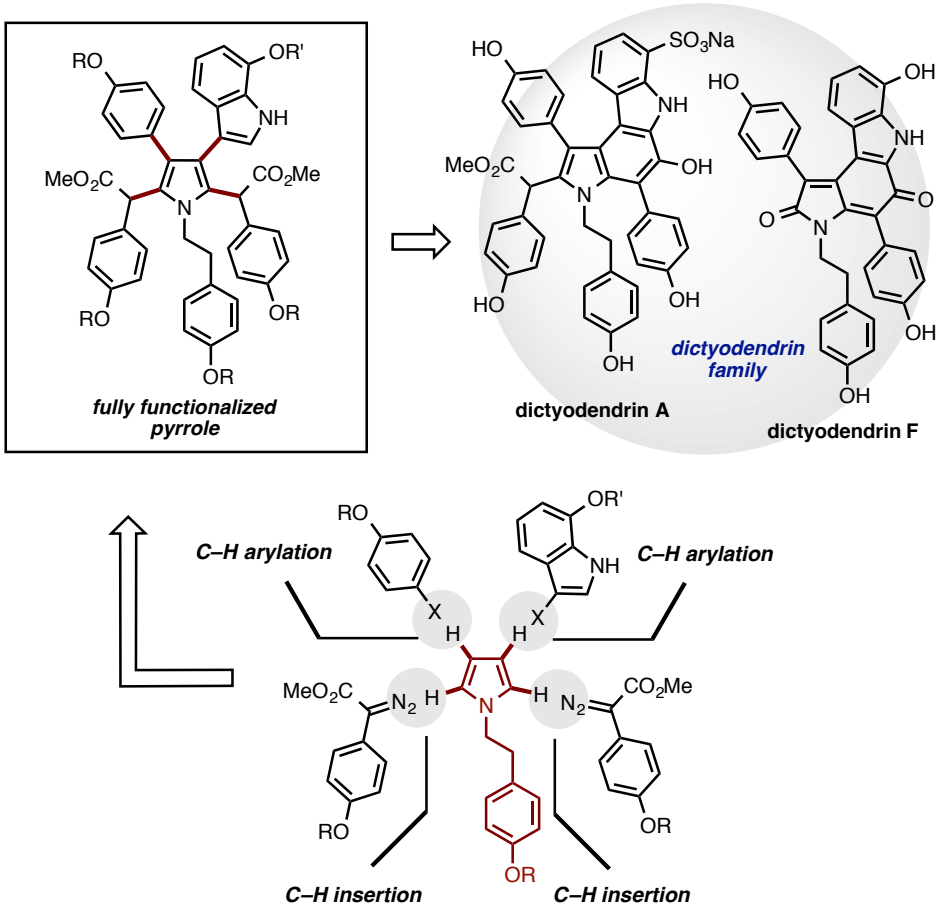
Dictyodendrins[1,2] are marine alkaloids that have unique structures and display various biological activities. Therefore, many research groups have made great efforts to synthesize this alkaloid family and several groups have successfully reported the total synthesis of dictyodendrins.[3] Although efficient synthesis of dictyodendrin B have been reported by four research groups, there has only been one synthesis of dictyodendrin A, which was accomplished by the Tokuyama group.[3f,g] Although Tokuyama and co-workers accomplished divergent synthesis of dictyodendrins A–E, the synthesis of dictyodendrin A required a longest linear sequence of 21 steps. Meanwhile, Jia and co-workers, who achieved the synthesis of dictyodendrins B, C and E through a C–H activation strategy, reported synthetic studies toward the total synthesis of dictyodendrin A.[3i] Their key one-pot reaction of Buchwald–Hartwig amination/intramolecular C–H coupling reaction gave a trace amount of the desired product when a substrate possessing the same substituents as those of dictyodendrin A was used (Scheme 1). They also failed to convert the intermediate of the synthesis of dictyodendrin B into dictyodendrin A by means of the transformation of the C2 substituent.



Scheme 1. Synthetic studies toward the synthesis of dictyodendrin A by Jia group.

In light of the above considerations, dictyodendrin A is seemingly a more challenging and attractive member of the dictyodendrin family and therefore it was chosen as the first synthetic target. As described in Chapter 2, it was envisioned that all dictyodendrin family including dictyodendrin A would be synthesized from the fully substituted pyrrole, that could be constructed from a *N*-alkylpyrrole utilizing a direct

C–H functionalization strategy as shown in Scheme 2.



Scheme 2. A synthetic strategy toward concise synthesis of dictyodendrins.

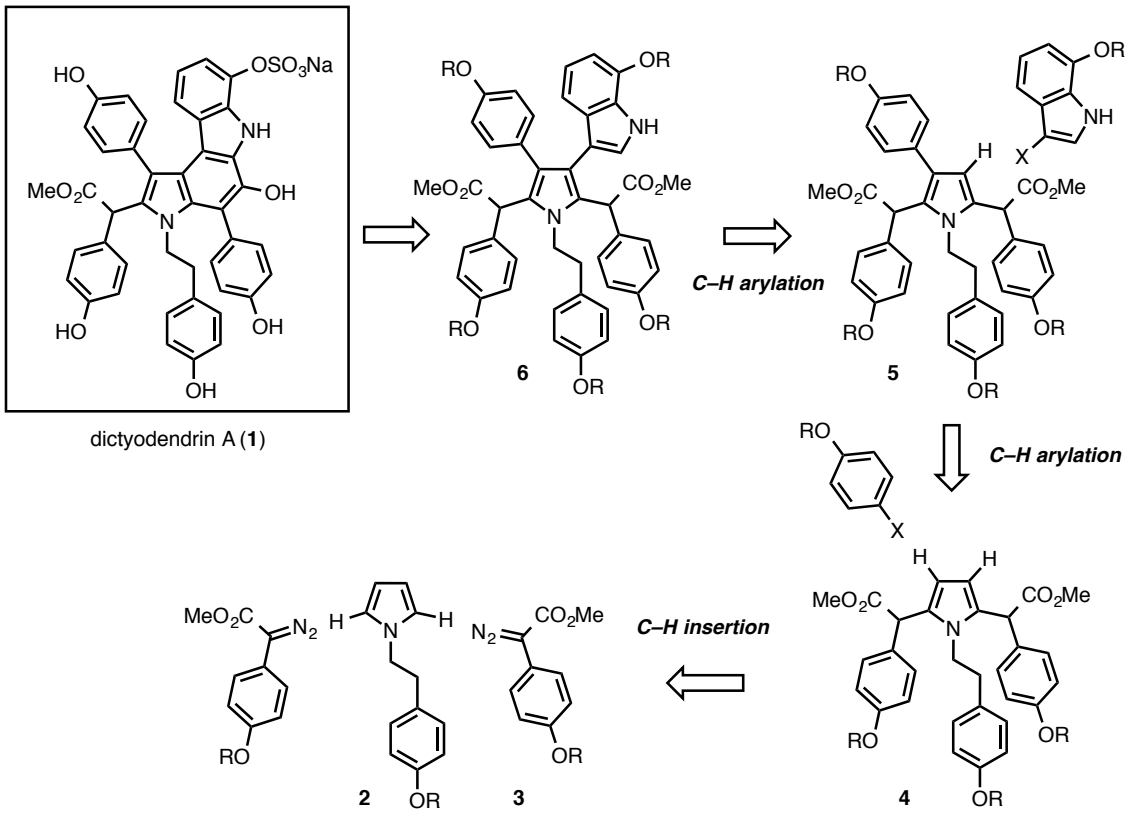
In this chapter, a new synthetic route toward a marine alkaloid dictyodendrin A through regioselective C–H functionalizations is described.[4] Regioselective C–H arylation and C–H insertion allow for the introduction of suitable substituents without substrate prefunctionalization, thus shortening the overall reaction sequence. The concise synthesis of dictyodendrin F was also accomplished from a common intermediate.

2. Results and Discussion

2-1. Initial Approach to the Total Synthesis of Dictyodendrin A

In most cases, C–H arylation of pyrroles proceeds at the α position of pyrrole rings.[5] Meanwhile, although C–H insertion of pyrroles has not been investigated widely, the

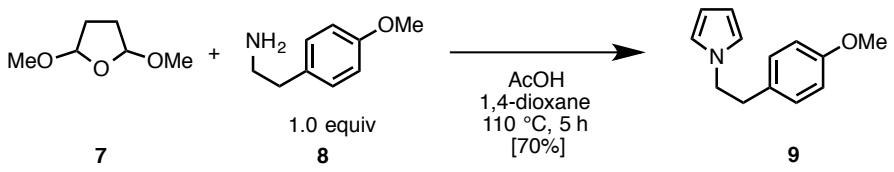
reaction tends to provide α-substituted pyrroles.[6] Based on the known regioselectivities of pyrrole functionalization chemistry, an initial approach toward dictyodendrins A (**1**) was proposed (Scheme 3). At first, double C–H insertion of *N*-alkylpyrrole **2** with aryldiazoester **3** would provide 2,5-disubstituted pyrrole **4**. Then C–H arylation would be able to introduce two different aryl moieties to afford the fully functionalized pyrrole **6**. The reaction is expected to proceed at the β position of the pyrrole because the two α positions are blocked by the alkyl groups. Finally, dictyodendrin A (**1**) would be prepared from fully functionalized pyrrole **6** by construction of the six-membered ring.



Scheme 3. An initial approach toward dictyodendrin A.

2-2. First Trial for the Total Synthesis of Dictyodendrin A

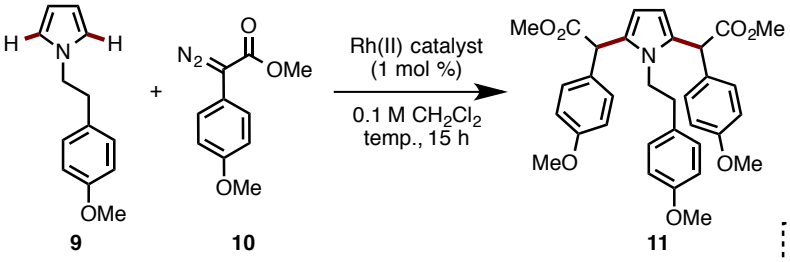
The synthesis was commenced with the preparation of *N*-alkylpyrrole **9** by the use of a Paal–Knorr pyrrole synthesis (Scheme 4). Heating 2,5-dimethoxytetrahydrofuran (**7**) and 2-(4-methoxyphenyl)ethylamine (**8**) in AcOH/1,4-dioxane at 100 °C provided pyrrole **9** in 70% yield.



Scheme 4. Preparation of **9** by a Paal–Knorr pyrrole synthesis.

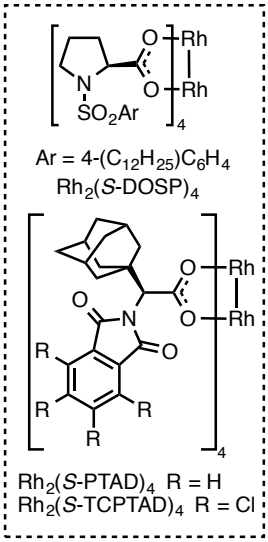
Next, the double C–H insertion of **9** with diazoester **10** was investigated (Table 1). Unfortunately, $Rh_2(OAc)_4$ did not provide any alkylated pyrrole product (entry 1). A more efficient catalyst for the reaction with diazoesters, Rh_2(*S*-DOSP)$_4$, gave the desired product **11** in less than 10% yield along with the 3,4-difunctionalized isomer (entry 2). Rh_2(*S*-PTAD)$_4$ or the tetrachlorinated derivative, a sterically hindered rhodium dimer, was effective for the reaction albeit in moderate yields (entries 4 and 5). It was found that the reaction temperature did not affect reactivity (entries 6 and 7).

Table 1. Double C–H insertion of **9** with diazoester **10**.



entry	Rh cat.	ratio of **9**/**10**	temperature	**11**[a]
1	$Rh_2(OAc)_4$	1:3	rt	<1%
2	Rh_2(*S*-DOSP)$_4$	1:3	rt	10%[b]
3	Rh_2(*S*-PTAD)$_4$	1:3	rt	11%
4	Rh_2(*S*-PTAD)$_4$	1:2	rt	30%
5	Rh_2(*S*-TCPTAD)$_4$	1:2	rt	26%
6	Rh_2(*S*-PTAD)$_4$	1:2	–10 °C to rt	22%
7	Rh_2(*S*-PTAD)$_4$	1:2	60 °C	19%

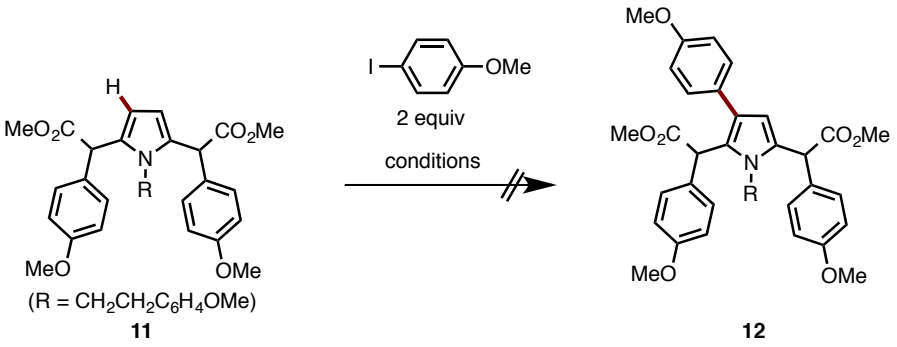
[a] Isolated yield. [b] 6% of 3,4-difunctionalized isomer was obtained as an inseparable mixture with **11**.



After 2,5-disubstituted pyrrole **11** was obtained, introduction of an aryl group to the C3 position of **11** was the next challenge in the total synthesis. Several reaction

conditions for direct C–H arylation of electron-rich heteroarenes previously developed in the Itami group were screened (Table 2). $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ has shown a high reactivity for the C–H arylation of thiophenes and pyrroles,[7] whereas a $PdCl_2/P[OCH(CF_3)_2]_3$ catalyst system has enabled a β-selective direct arylation of thiophenes.[8] On the other hand, $PdCl_2$/bipy catalyzes efficient C–H arylation of thiophenes to provide α-arylated thiophenes regioselectively.[9] Novel catalytic conditions [$Pd(OAc)_2$/bipy/TEMPO] have also shown β-selectivity in the direct arylation of thiophenes with arylboronic acids.[10] After screening these reaction conditions, unfortunately, no coupling product was furnished. One of the challenges seems to be steric hindrance at the C3 position of **11** as well as the electronic influence of ester groups and α-protons adjacent to carbonyl groups.

Table 2. Screening of reaction conditions for the direct C–H arylation of pyrrole **11**.

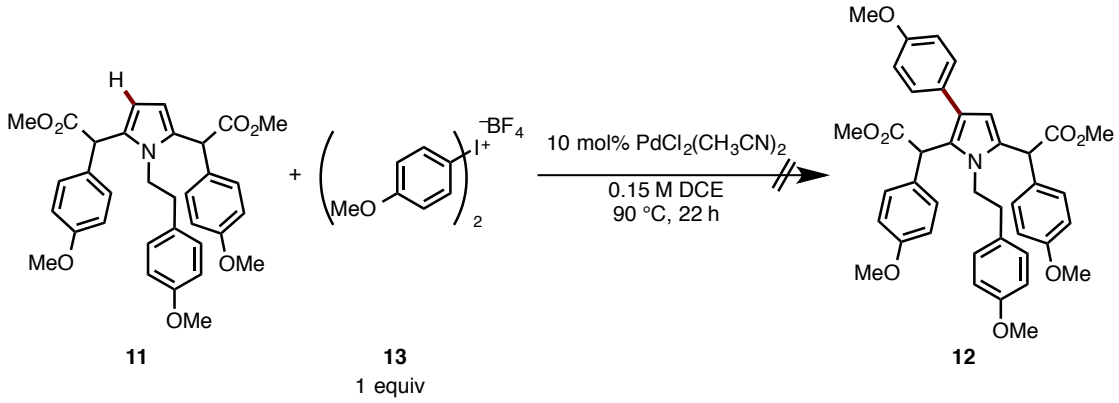


11 **12**

entry	reaction conditions	results
1	3 mol% $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ 1 equiv Ag_2CO_3 1 equiv DME 0.15 M *m*-xylene 150 °C, 22 h	nd
2	5 mol% $PdCl_2$ 10 mol% $P[OCH(CF_3)_2]_3$ 1 equiv Ag_2CO_3 0.15 M *m*-xylene 120 °C, 22 h	nd
3	5 mol% $PdCl_2$ 10 mol% bipy 2 equiv Ag_2CO_3 0.15 M *m*-xylene 120 °C, 22 h	nd
4[a]	10 mol% $Pd(OAc)_2$ 10 mol% bipy 4 equiv TEMPO 0.15 M $C_6H_5CF_3$ 80 °C, 22 h	nd

[a] 4 equiv of *p*-methoxyphenylboronic acid was used instead of iodoarene.

In 2011, Wagner and Sanford reported a palladium-catalyzed direct arylation of 2,5-disubstituted pyrroles with diaryliodonium salts.[11] Their reaction conditions were applied to 2,5-disubstituted pyrrole **11** and diaryliodonium salt **13**, but arylated product **12** was not obtained (Scheme 5).

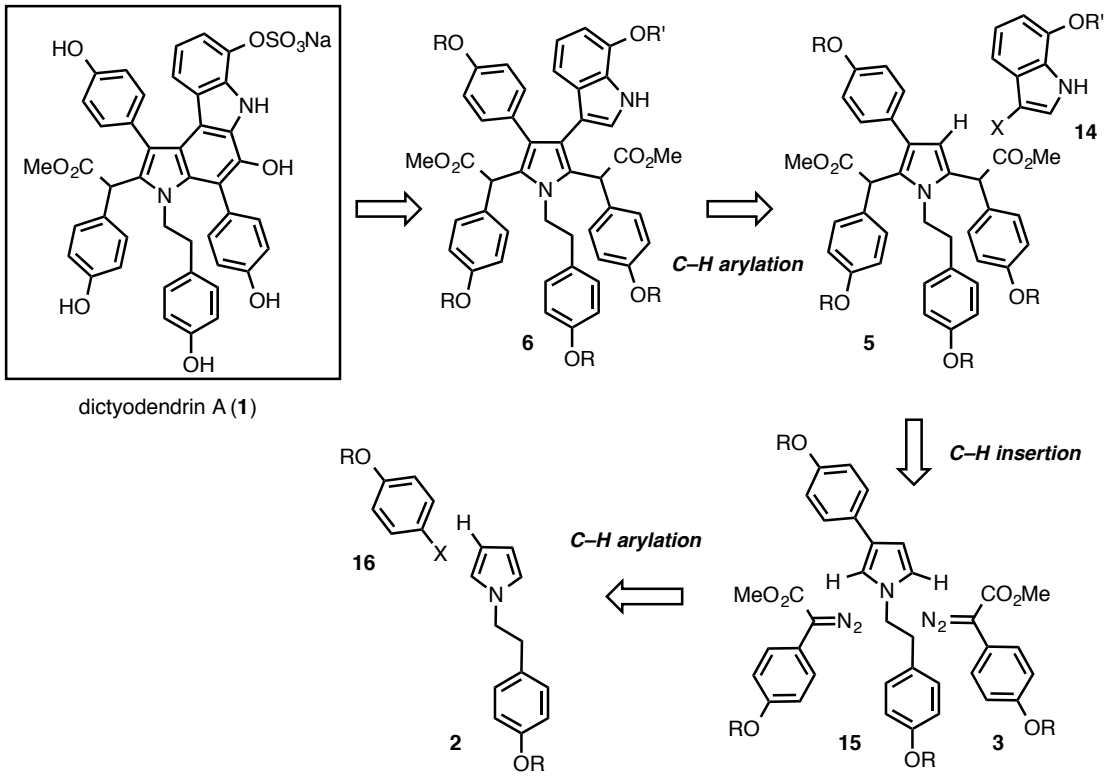


Scheme 5. Pd-catalyzed C–H arylation of **11** with diaryliodonium salt **13**.

Owing the difficulty in introducing aryl groups into sterically hindered pyrrole rings, another synthetic route that commences with β-selective direct arylation of pyrroles was chosen.

2-3. Another Synthetic Route for the Total Synthesis of Dictyodendrin A

Another synthetic approach toward the synthesis of dictyodendrin A (**1**) is shown in Scheme 6. Fully functionalized pyrrole **6** could be a key intermediate prepared form 2,3,4-trisubstituted pyrrole **5** by installing indole unit **14**. Alkylated pyrrole **5** would be obtained by double C–H insertion of 3-arylpyrrole **15** with diazoester **3**. β-Selective C–H arylation of *N*-alkylpyrrole **2** with aryl halide **16** should then give rise to **15** with high regioselectivity.

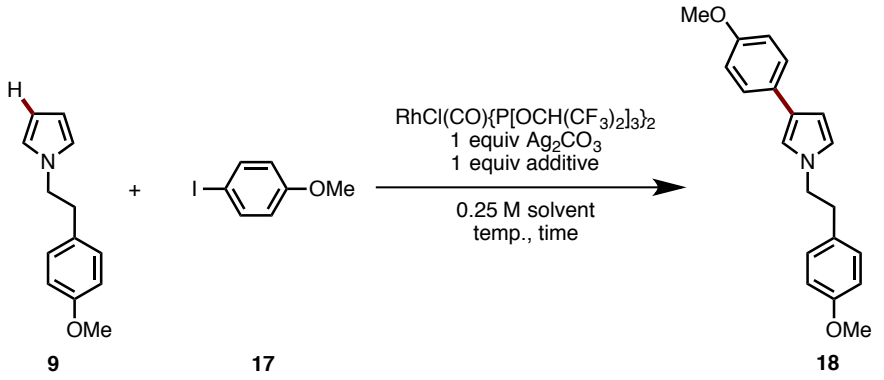


Scheme 6. Another synthetic approach toward dictyodendrin A (**1**).

2-4. β-Selective C–H Arylation of an *N*-Alkylpyrrole

As the first step, β-selective C–H arylation of pyrrole **9** was carried out (Table 3). In recent years, the direct C–H arylation of pyrroles has been achieved under several reaction conditions. However, almost all of such reactions show α-selectivity.[5] In contrast, Itami group has developed a β-selective C–H arylation of pyrroles using a rhodium(I) catalyst.[7,12] A strongly electrophilic and bulky ligand $P[OCH(CF_3)_2]_3$ plays an important role in both reactivity and selectivity. The previously developed reaction conditions were applied to the C–H arylation of *N*-alkylpyrrole **9**. Heating **9** and *p*-iodoanisole (**17**) with microwave irradiation in the presence of a catalytic amount of $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$, Ag_2CO_3 and DME in *m*-xylene at 200 °C provided the coupling product **18** in 37% yield with high β-regioselectivity (entry 1). This direct arylation also proceeded in the absence of microwave irradiation when heated to 150 °C for 22 hours (entry 2). Scaling up the same reaction resulted in improvement of the yield of **18** from 34% to 52% (entry 3). A lower catalyst loading was tolerated if the reaction time was increased (entry 5).

Table 3. β-Selective C–H arylation of pyrrole **9**.



9 1.5 equiv

17 X mmol

18

entry	additive	solvent	catalyst loading/mol%	temp./°C	X	reaction time/h	yield of **18**/%[a]
1	DME	*m*-xylene	3	200, μW	0.4	0.5	37
2	DME	*m*-xylene	3	150	0.4	22	34
3	DME	*m*-xylene	3	150	9	40	52
4	–	*m*-xylene/ 1,4-dioxane = 2/3	3	150	9	40	25
5	DME	*m*-xylene	1	150	9	62	52

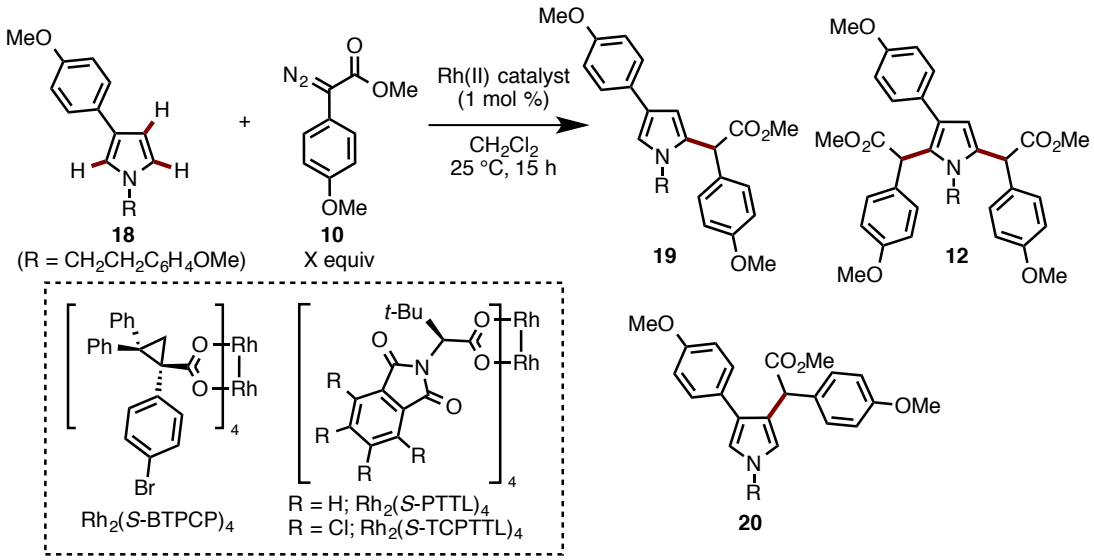
[a] Isolated yield.

2-5. Regioselective C–H Insertion of a 3-Arylpyrrole

Next, regioselective C–H insertion of the 3-arylpyrrole intermediate was investigated. This pyrrole possesses two electron-rich phenyl groups and an alkyl linker between the nitrogen atom and the benzene ring. These substituents seem to render the regiocontrol difficult. To overcome this challenge, screening of various dirhodium catalysts was conducted (Table 4). $Rh_2(OAc)_4$ and Rh_2(*S*-DOSP)$_4$ did not work at all in the reaction (entries 1 and 2). On the other hand, $Rh_2(esp)_2$, Rh_2(*S*-PTAD)$_4$, and Rh_2(*S*-PTTL)$_4$ gave the desired alkylated product **19** and undesired regioisomer **20** as an inseparable mixture with low to moderate selectivities (entries 3–5). To improve the regioselectivity, other rhodium catalysts possessing more sterically encumbered ligands, Rh_2(*S*-BTPCP)$_4$, Rh_2(*S*-TCPTTL)$_4$ and Rh_2(*S*-TCPTAD)$_4$ were screened. As a result, it was revealed that Rh_2(*S*-TCPTAD)$_4$ gives the high regioselectivity (ratio **19**:**20** = 90:10) (entries 6–8). Further optimization of the reaction conditions using Rh_2(*S*-TCPTAD)$_4$ allowed for the catalyst loading to be decreased by scaling up the reaction and reducing the number of equivalents of the diazoester. The optimized conditions

afforded the alkylated products in 78% yield with high regioselectivity (entry 9). In addition, it was also found that an excess amount of diazoester **10** (6.0 equiv) selectively gives 2,5-dialkylated product **12** as an inseparable diastereomeric mixture in 30% yield (entry 10). The moderate yield might be due to the further alkylation of **12** although by-products could not be identified.

Table 4. Regioselective C–H insertion of 3-arylpyrrole **18** with diazoester **10**.

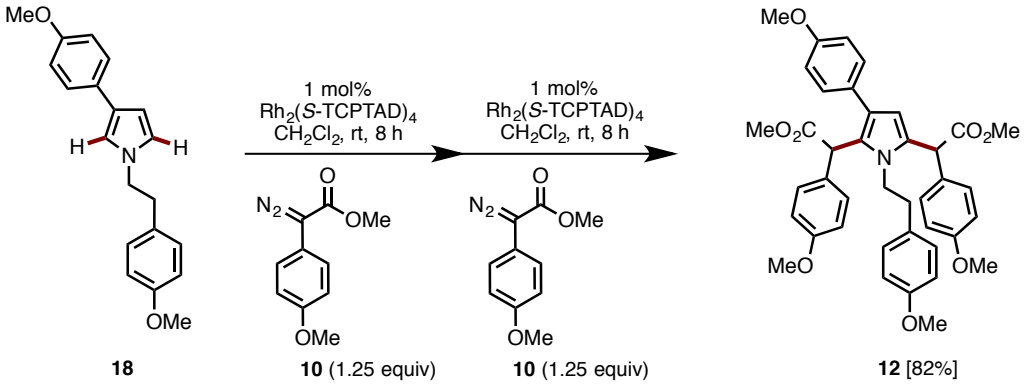


entry	Rh(II) catalyst	X/equiv	ratio[a] (**19**:**20**:**12**)	yield of **19** and **20**/%[b]	yield of **12**/%[b]
1	$Rh_2(OAc)_4$	2	–	<1	–
2	Rh_2(*S*-DOSP)$_4$	2	–	<1	–
3	$Rh_2(esp)_2$	2	76/24/<1	53	–
4	Rh_2(*S*-PTAD)$_4$	2	55/45/<1	33	–
5	Rh_2(*S*-PTTL)$_4$	2	61/39/<1	54	–
6	Rh_2(*S*-BTPCP)$_4$	2	53/47/<1	12	–
7	Rh_2(*S*-TCPTTL)$_4$	2	54/46/<1	23	–
8	Rh_2(*S*-TCPTAD)$_4$	2	90/10/<1	36	–
9[c]	Rh_2(*S*-TCPTAD)$_4$	1.3	92/8/<1	78	–
10	Rh_2(*S*-TCPTAD)$_4$	6	<1/7/93	2	30

[a] Determined by ^{1}H-NMR. [b] Isolated yield. [c] The reaction scale was changed from 0.1 to 3.0 mmol.

Fortunately, a modified sequential method increased the yield of **12** (Scheme 7). Treatment of **18** with 1 mol% of the rhodium catalyst and 1.25 equiv of diazoester **10** provided **19** initially. After 8 h, further treatment of the reaction mixture with an additional 1 mol% of the rhodium catalyst and 1.25 equiv of diazoester **10** resulted in

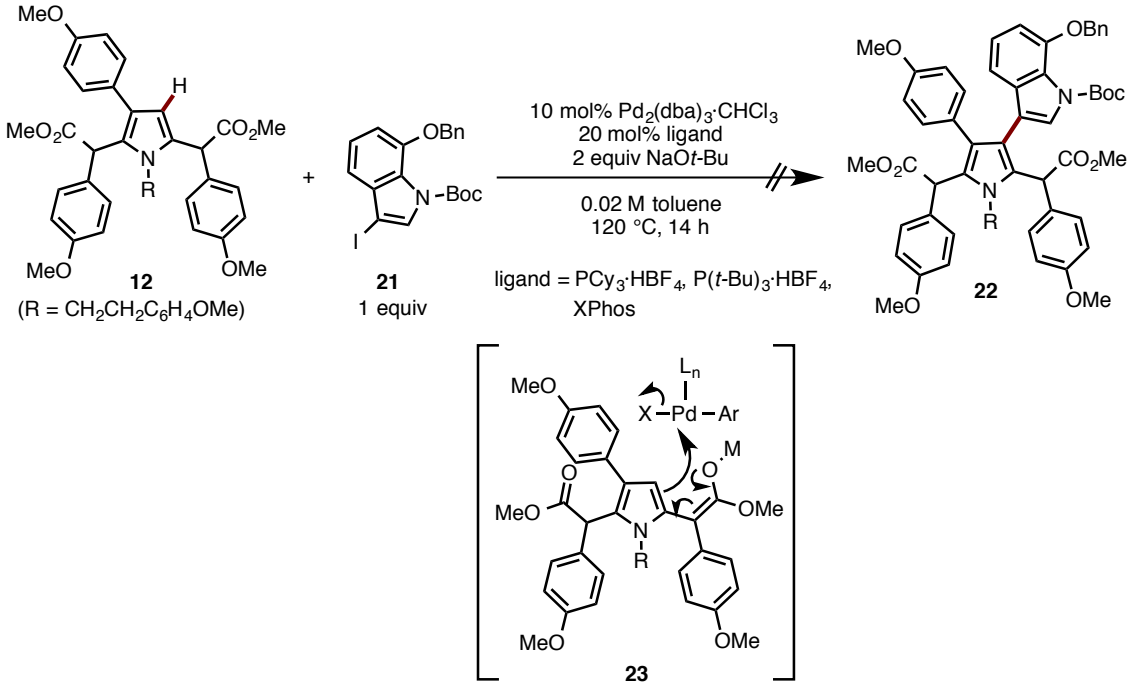
the production of **12** in 82% yield.



Scheme 7. A sequential method for the double C–H insertion.

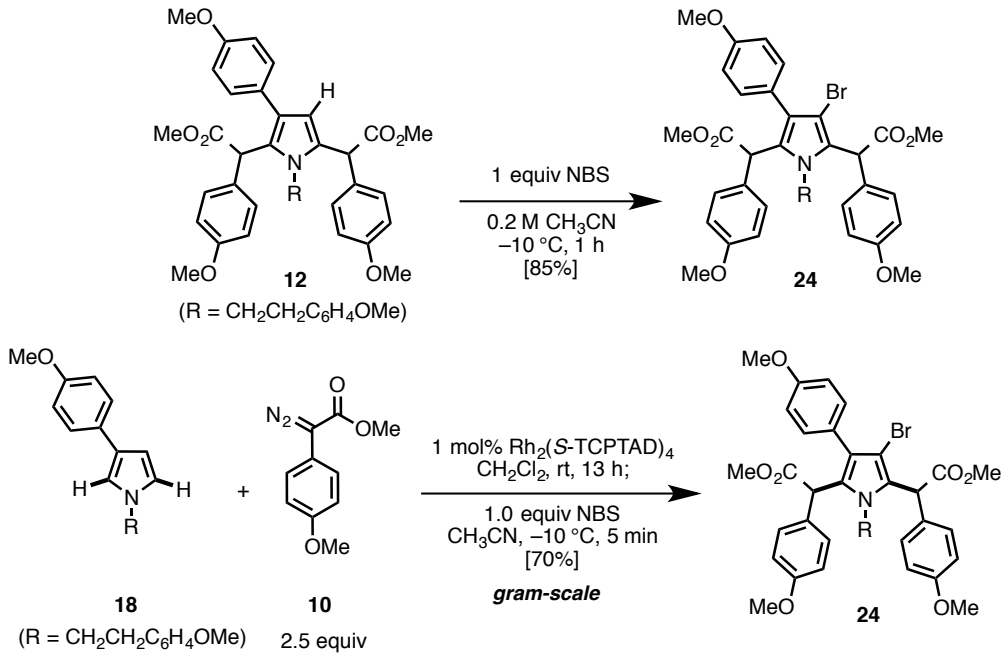
2-6. Introduction of an Indole Unit

The next step was the introduction of an indole moiety to the C4 position of the pyrrole ring. At first, a direct C–H coupling of **12** with 3-iodoindole **21** was investigated (Scheme 8). In the generation of the assumed intermediate **23**, NaO*t*-Bu, a strong base, was used. Screening of several ligands such as $PCy_3 \cdot HBF_4$, $P(t\text{-Bu})_3 \cdot HBF_4$ and XPhos was conducted in the presence of a catalytic amount of $Pd_2(dba)_3 \cdot CHCl_3$,[13] but unfortunately no coupling product was observed.



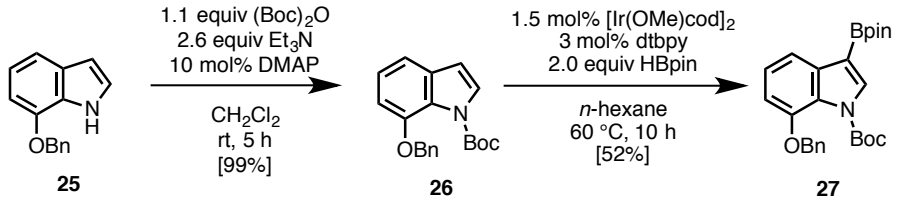
Scheme 8. Direct C–H coupling of **12** with iodoindole **21**.

At this juncture, introduction of the indole moiety through C4 bromination followed by a transition metal-catalyzed cross-coupling reaction was planned. Therefore, preparation of bromopyrrole **24** was carried out (Scheme 9). Treatment of **12** with NBS at –10 °C gave bromopyrrole **24** in 85% yield. A one-pot regioselective C–H insertion and bromination of 3-arylpyrrole **18** also successfully proceeded to provide **24** in 70% yield. The one-pot reaction can be performed on a gram-scale.



Scheme 9. Bromination of 2,3,5-trisubstituted pyrrole **12**.

In addition, indole-3-boronic acid pinacol ester **27** was synthesized from 7-benzyloxyindole (**25**) in good yield by Boc protection followed by direct C–H borylation of **26** at the C3 position (Scheme 10).[14]

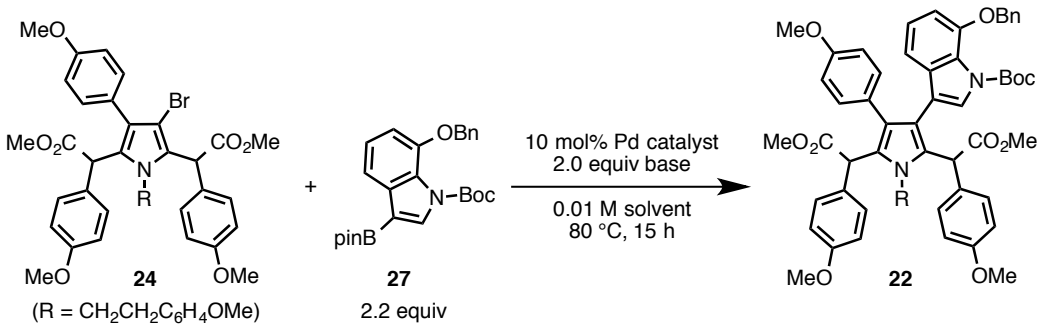


Scheme 10. Preparation of indole-3-boronic acid pinacol ester **27**.

After preparation of the coupling partners, the key Suzuki–Miyaura cross-coupling reaction of bromopyrrole **24** with pinacol ester **27** was investigated (Table 5). A mixture of bromopyrrole **24** and pinacol ester **27** in 1-butanol/H_2O was stirred at 80 °C in the

presence of a catalytic amount of $Pd(OAc)_2$/SPhos and K_3PO_4 to give the corresponding coupling product **22** in 13% yield (entry 1). Several bases such as Na_2CO_3, Cs_2CO_3, CsF, KF and $Ba(OH)_2$ were screened for this reaction condition but substantial improvement was not observed (entries 2–6). When 1,4-dioxane was used instead of 1-butanol, the yield was increased from 13% to 34% (entry 7). PEPPSI-IPr and $Pd(PPh_3)_4$, known as efficient palladium catalysts for various cross-coupling reactions, were not effective for this reaction (entries 8 and 9). In contrast, $Pd[P(t\text{-}Bu)_3]_2$, which possesses electron-rich ligands, gave coupling product **22** in 40% yield (entry 11). Further optimization (increasing the equivalents of boronic acid pinacol ester and base) resulted in the increase of yield to 47% (entry 12).

Table 5. Suzuki–Miyaura cross-coupling reaction of bromopyrrole **24** with **27**.



entry	Pd catalyst[b]	base	solvent	**22**/%[a]
1	$Pd(OAc)_2$/SPhos	K_3PO_4	1-butanol/H_2O = 10/1	13
2	$Pd(OAc)_2$/SPhos	$Ba(OH)_2$	1-butanol/H_2O = 10/1	10
3	$Pd(OAc)_2$/SPhos	CsF	1-butanol/H_2O = 10/1	23
4	$Pd(OAc)_2$/SPhos	Na_2CO_3	1-butanol/H_2O = 10/1	19
5	$Pd(OAc)_2$/SPhos	Cs_2CO_3	1-butanol/H_2O = 10/1	10
6	$Pd(OAc)_2$/SPhos	KF	1-butanol/H_2O = 10/1	19
7	$Pd(OAc)_2$/SPhos	K_3PO_4	1,4-dioxane/H_2O = 10/1	34
8	PEPPSI-IPr	K_3PO_4	1,4-dioxane/H_2O = 10/1	0
9	$Pd(PPh_3)_4$	K_3PO_4	DME	13
10	$Pd[P(t\text{-}Bu)_3]_2$	NaOH	1,4-dioxane/H_2O = 10/1	34
11	$Pd[P(t\text{-}Bu)_3]_2$	K_3PO_4	1,4-dioxane/H_2O = 10/1	40
12[c]	$Pd[P(t\text{-}Bu)_3]_2$	K_3PO_4	1,4-dioxane/H_2O = 10/1	47

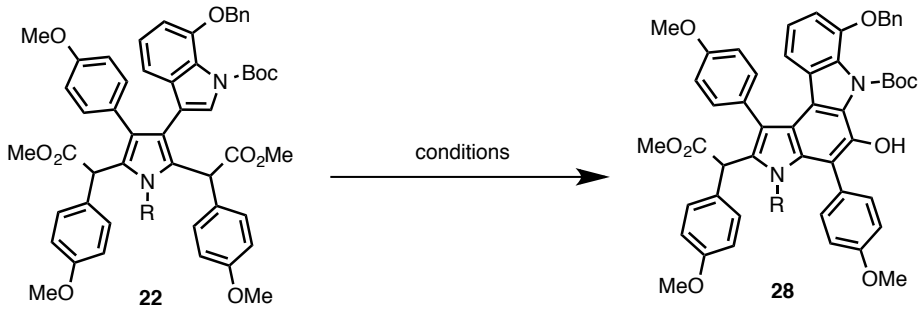
[a] Isolated yield. [b] Ratio of [Pd]/ligand = 1/2. [c] **27** (4.0 equiv), K_3PO_4 (4.0 equiv).

2-7. Completion of the Synthesis of Dictyodendrin A

The next reaction involved the formation of the key pyrrolo[2,3-*c*]carbazole core structure. Initially, a Friedel–Crafts type reaction promoted by Lewis acids[15] was tried but no C–C bond formation between the C2 position of the indole ring and the carbonyl group was observed. Next, the formation of the pyrrolocarbazole core by formal 6π-electrocyclization was investigated. To this end, a screening of bases was conducted (Table 6).[16] Treatment of **22** with LDA prepared *in situ* in THF at –78 °C gave the desired pyrrolocarbazole **28** in 47% yield (entry 1). In contrast, diethyl ether

and toluene gave lower yields of **28** (entries 2 and 3). Addition of hexamethylphosphoric triamide (HMPA) to enhance the reactivity of LDA did not improve the reaction. Interestingly, LHMDS, a bulkier and stronger base than LDA, afforded no cyclized product.

Table 6. Formal 6π-electrocyclization of **22**.

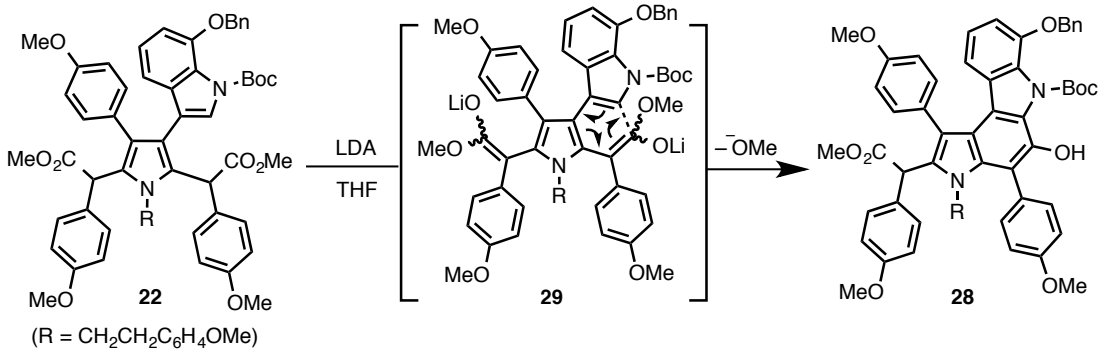


(R = $CH_2CH_2C_6H_4OMe$)

entry	conditions	results[a]
1	6 equiv diisopropylamine 6 equiv *n*-BuLi 32 mM THF –78 °C, 1.5 h	**28**: 47%
2	20 equiv diisopropylamine 20 equiv *n*-BuLi 5 mM Et_2O –78 °C to rt, 1 h	SM was decomposed.
3	20 equiv diisopropylamine 20 equiv *n*-BuLi 3 mM toluene –78 °C, 1 h	**28**: 17%
4	15 equiv diisopropylamine 15 equiv *n*-BuLi 7 equiv HMPA 8 mM THF –78 °C, 4 h	**28**: <10%
5	6 equiv LHMDS 17 mM THF –78 °C, 3 h	no reaction

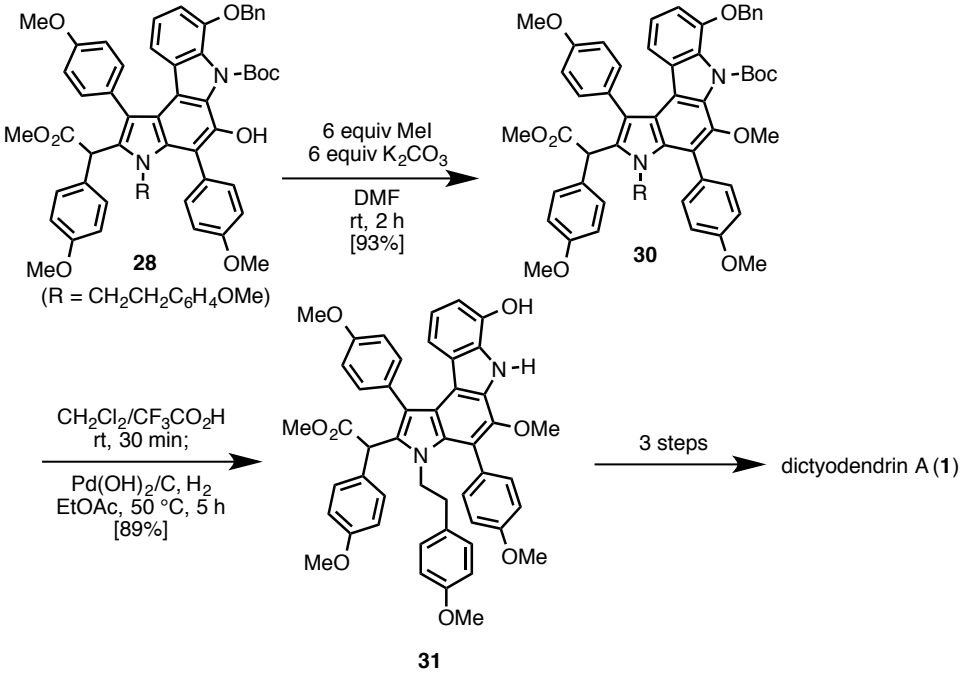
[a] Isolated yield.

The proposed reaction mechanism is shown in Scheme 11. The formal 6π-electrocyclization could proceed *via* enolate intermediate **29** formed by deprotonation of the α-protons adjacent to the carbonyl groups.



Scheme 11. Proposed mechanism for the formal 6π-electrocyclization of **22**.

In the final stages of the synthesis, methylation of the phenol group in pyrrolocarbazole **28** with MeI and K_2CO_3 furnished **30** in excellent yield. Thereafter, removal of the Boc group, followed by removal of the benzyl ether gave known intermediate **31** as reported by Tokuyama and co-workers (Scheme 12).[3f,g] This intermediate can be converted into dictyodendrin A (**1**) in three steps. This synthesis is accomplished by a longest linear sequence of 12 steps, which is significantly shorter than that reported by the Tokuyama group (21 linear steps).[3f,g]

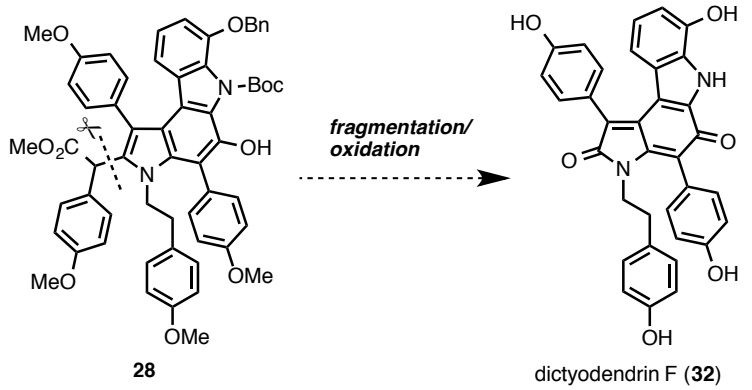


Scheme 12. Accomplishment of the total synthesis of dictyodendrin A (**1**).

2-8. Concise Synthesis of Dictyodendrin F

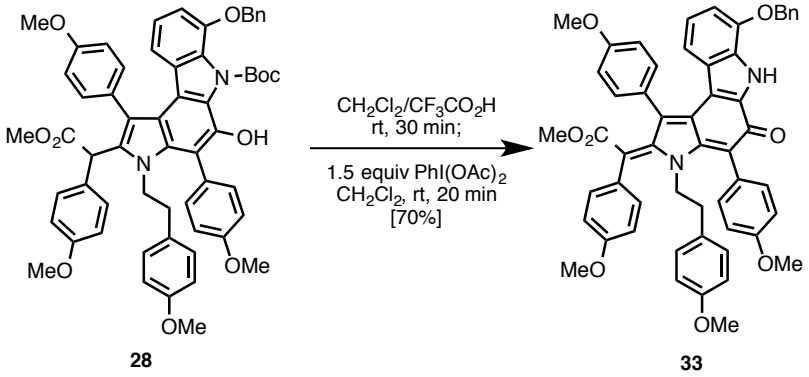
Following the completion of the concise synthesis of dictyodendrin A (**9**), it was

envisioned that another pyrrolocarbazole alkaloid, dictyodendrin F (**32**), could be synthesized from intermediate **28** by removal of the substituent on the "left" side and adjusting the oxidation state (Scheme 13).



Scheme 13. Synthetic approach to the synthesis of dictyodendrin F (**32**).

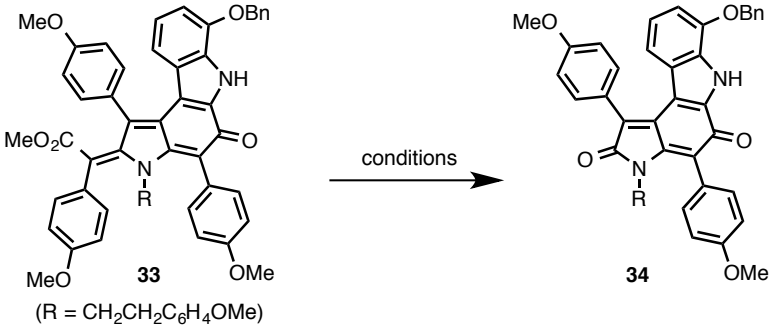
The removal of Boc group from **28** with CF_3CO_2H, followed by treatment with $PhI(OAc)_2$, provided quinone **33** in 70% yield through oxidation of the pyrrolocarbazole core (Scheme 14).



Scheme 14. Preparation of quinone-like intermediate **33**.

Next, hydrolysis for the cleavage of the "left" side chain was investigated (Table 7). Heating **33** in THF/1 M HCl at 100 °C provided a trace amount of diketone **34** (entry 1). In contrast, basic conditions using aqueous NaOH, was not effective for the cleavage (entry 2). When MeOH/4 M HCl was used, a trace amount of **34** was again obtained (entry 3). This low yield is due to the poor solubility of **33** to MeOH. In contrast, an acidic mixture with DMF afforded **34** in 26% yield by improving the solubility.

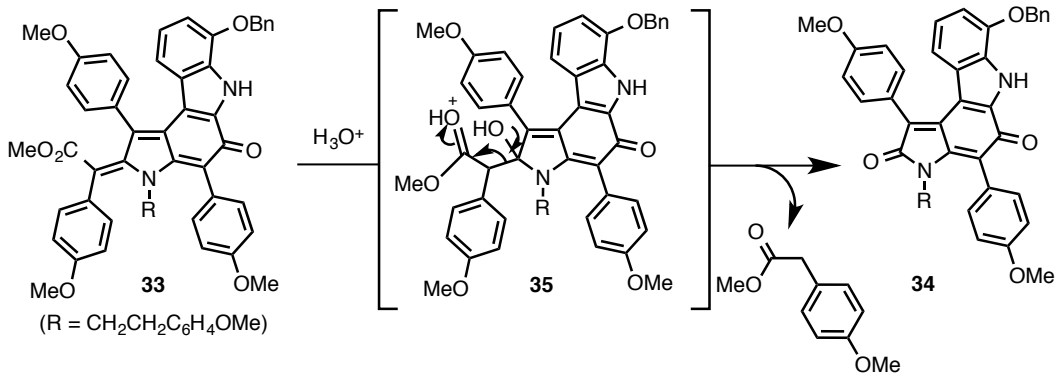
Table 7. Retro-aldol condensation of **33**.



entry	conditions	results
1	4 mM THF/HCl (1 M) = 1/2 100 °C, 2 h	trace
2	4 mM MeOH/40 wt% NaOH aq = 1/1 100 °C, 3 h	no reaction
3	4 mM MeOH/HCl (1 M) = 1/1 100 °C, 3 h	trace
4	4 mM DMF/HCl (4 M) = 1/1 100 °C, 2.5 h	**34**: 26%[a]

[a] Isolated yield.

The proposed mechanism of the formation of **34** is shown in Scheme 15. Hydration of **33** followed by the retro-aldol condensation of the resulting **35** gave diketone **34**.

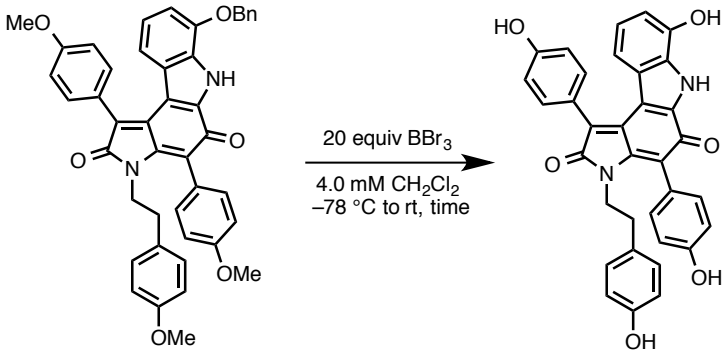


Scheme 15. Proposed mechanism of the formation of **34**.

Finally, removal of methyl and benzyl ethers completed the total synthesis of dictyodendrin F (**32**). Treatment of **34** with an excess amount of BBr_3 at –78 °C to room temperature furnished dictyodendrin F (**32**) in 68% yield (Table 8, entry 1). In the reaction, a longer reaction time seemed to cause the decomposition of the product

(entry 2). The synthetic route only needed 10 longest linear steps.

Table 8. Completion of the total synthesis of dictyodendrin F (**32**).



34 dictyodendrin F (**32**)

entry	time/h	yield of **32**/%[a]
1	1.5	68
2	3	28

[a] Isolated yield.

3. Conclusion

In this chapter, the concise synthesis of natural alkaloids dictyodendrins A and F is reported utilizing several direct C–H functionalization reactions of pyrroles. The reaction sequence of β-selective C–H arylation and double C–H insertion followed by Suzuki–Miyaura cross-coupling reaction commenced with a simple *N*-alkylpyrrole, to construct a fully functionalized pyrrole, which was the key intermediate toward both natural products. Completion of the total syntheses was achieved by direct pyrrolo[2,3-*c*]carbazole formation *via* formal 6π-electrocyclization of the highly substituted pyrrole. The synthesis of dictyodendrin A was accomplished by a longest linear sequence of 12 steps and the route for the synthesis of dictyodendrin F only needed 10 longest linear steps.

4. Experimental

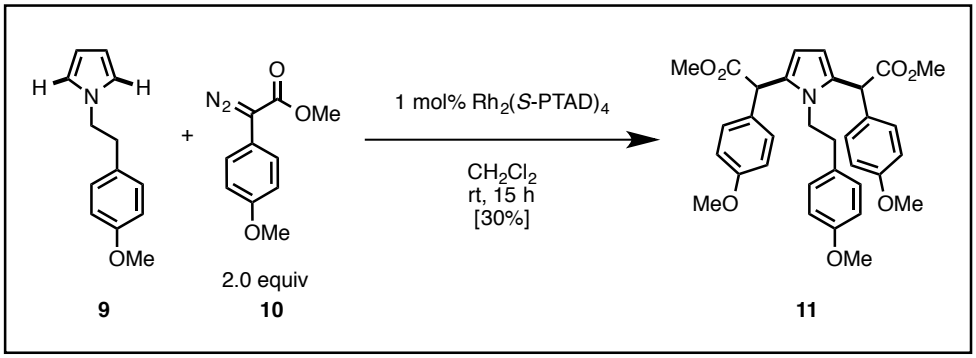
4-1. General

Unless otherwise noted, all materials including dry solvents were obtained from commercial suppliers and used without further purification. Diaryliodonium salt **8**,[17] $P[OCH(CF_3)_2]_3$,[18] $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$,[7a] Rh_2(*S*-TCPTAD)$_4$,[19] Rh_2(*S*-BTPCP)$_4$,[20] Rh_2(*S*-PTTL)$_4$,[21] Rh_2(*S*-TCPTTL)$_4$,[22] methyl 4-methoxyphenyldiazoacetate[23] were prepared according to procedures reported in the literature. Unless otherwise noted, all reactions were performed with dry solvents under an atmosphere of nitrogen in heat-gun-dried glassware using standard vacuum-line techniques. All work-up and purification procedures were carried out with reagent-grade solvents in air. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} pre-coated plates (0.25 mm). The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid/sulfuric acid. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh). Preparative high performance liquid chromatography (preparative HPLC) was performed with a Biotage Isolera One equipped with Biotage® SNAP Cartridge KP-C18-HS columns using acetonitrile/water as an eluent. Preparative recycling gel permeation chromatography (GPC) was performed with a JAI LC-9204 instrument equipped with JAIGEL-1H/JAIGEL-2H columns using chloroform as an eluent. The high-resolution mass spectra were conducted on Thermo Fisher Scientific Exactive. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECA-600 (^{1}H 600 MHz, ^{13}C 150 MHz) spectrometer. Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm), DMSO-d_6 (δ 2.50 ppm) or CD_3OD (δ 3.31 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm), DMSO-d_6 (δ 39.5 ppm) or CD_3OD (δ 49.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet, brs = broad singlet), coupling constant (Hz), and integration.

4-2. Regioselective C–H Insertion of Pyrroles

Dimethyl

2,2'-(1-(4-methoxyphenethyl)-1*H*-pyrrole-2,5-diyl)bis(2-(4-methoxyphenyl)acetate) (11)



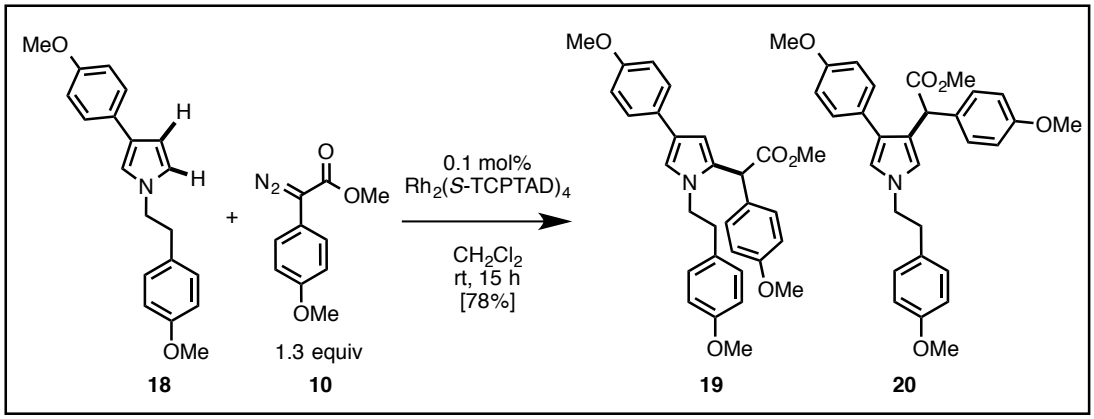
A 25-mL round-bottomed flask, containing a magnetic stirring bar, was dried and filled with nitrogen after cooling to 23 °C. To this vessel were added 1-[2-(4-methoxyphenyl)ethyl]pyrrole (**9**: 40.2 mg, 0.20 mmol, 1.0 equiv), Rh_2(*S*-PTAD)$_4$ (3.1 mg, 2.0 μmol, 1 mol%) and CH_2Cl_2 (500 μL). In a separate vial, diazoester **10** (82.5 mg, 0.40 mmol, 2.0 equiv) was dissolved in CH_2Cl_2 (1.5 mL) and then added to the reaction mixture by syringe pump over 1 h. After 14 h of additional stirring, CH_2Cl_2 was removed *in vacuo* and the remaining residue was purified by silica-gel flash column chromatography (hexane/EtOAc = 5:1) to afford **11** (mixture of diastereomers, 37.9 mg, 30% yield) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19–7.15 (m, 8H), 6.86–6.79 (m, 16H), 6.11 (s, 2H), 6.09 (s, 2H), 4.77 (s, 2H), 4.77 (s, 2H), 3.82–3.66 (m, 34H), 2.58–2.53 (m, 1H), 2.45 (t, J = 7.2 Hz, 2H), 2.27–2.22 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.17, 172.13, 159.1, 159.0, 158.5, 158.4, 130.0, 129.7, 129.6, 129.5, 129.42, 129.38, 114.07, 114.05, 114.03, 107.9, 107.8, 55.3, 55.2, 52.4, 49.2, 49.1, 45.71, 45.67, 36.33, 36.30; HRMS (ESI) m/z calcd for $C_{33}H_{34}NO_7$ $[M–H]^-$: 556.2330 found: 556.2322.

Methyl

2-(1-(4-methoxyphenethyl)-4-(4-methoxyphenyl)-1*H*-pyrrol-2-yl)-2-(4-methoxyphenyl)acetate (19)

Methyl

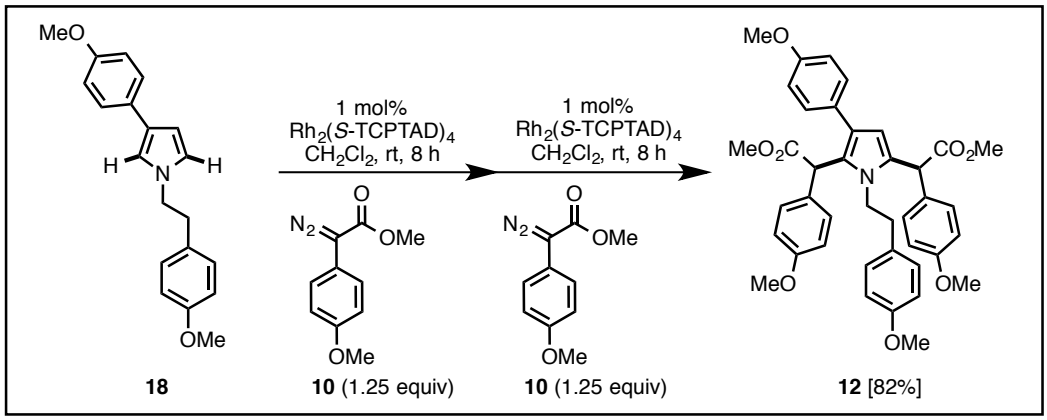
2-(1-(4-methoxyphenethyl)-4-(4-methoxyphenyl)-1*H*-pyrrol-3-yl)-2-(4-methoxyphenyl)acetate (20)



A 100-mL round-bottomed flask, containing a magnetic stirring bar, was dried and filled with nitrogen after cooling to 23 °C. To this vessel were added 3-arylpyrrole **18** (922 mg, 3.0 mmol, 1.0 equiv), Rh_2(*S*-TCPTAD)$_4$ (6.0 mg, 3.0 μmol, 0.1 mol%) and CH_2Cl_2 (7.4 mL). In a separate 50 mL round-bottomed flask, diazoester **10** (804 mg, 3.9 mmol, 1.3 equiv) was dissolved in CH_2Cl_2 (22.5 mL) and then added to the reaction mixture by syringe pump over 1 h. After 14 h of additional stirring, CH_2Cl_2 was removed *in vacuo* and the remaining residue was purified by silica-gel flash column chromatography (hexane/EtOAc = 4:1) to afford **19** and **20** (inseparable mixture of **19** and **20**, 1.10 g, 78% combined yield, **19**/**20** = 11.7:1 = 92:8) as a yellow solid. ^{1}H NMR of **19** (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.87–6.85 (m, 4H), 6.81 (s, 1H), 6.79 (d, *J* = 2.0 Hz, 2H), 6.32 (d, *J* = 1.4 Hz, 1H), 4.75 (s, 1H), 3.85 (t, *J* = 7.6 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 2.81–2.76 (m, 1H), 2.70–2.65 (m, 1H); ^{1}H NMR of **20** (600 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.83–6.79 (m, 6H), 6.62 (d, *J* = 2.5 Hz, 1H), 6.57 (d, *J* = 2.5 Hz, 1H), 4.91 (s, 1H), 4.06–3.97 (m, 2H), 3.78 (s, 3H), 3.78 (s, 6H), 3.57 (s, 3H), 2.99 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR of **19** (150 MHz, $CDCl_3$) δ 172.4, 159.2, 158.6, 157.8, 130.3, 129.94, 129.88, 129.85, 129.4, 128.7, 126.1, 123.5, 117.5, 114.3, 114.25, 114.20, 106.4, 55.48, 55.46, 55.44, 52.7, 49.0, 48.8, 37.4; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{31}NO_5Na$ $[M+Na]^+$: 508.2094 found: 508.2081.

Dimethyl

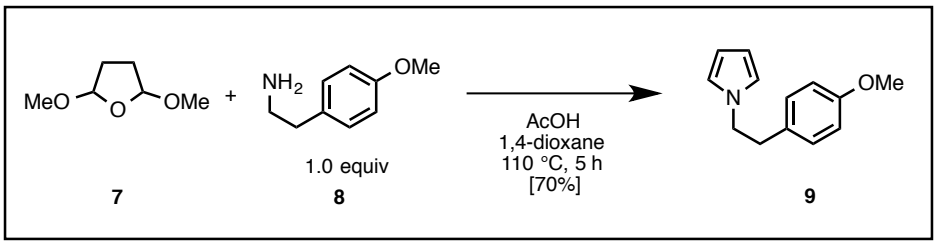
2,2'-(1-(4-methoxyphenethyl)-3-(4-methoxyphenyl)-1*H*-pyrrole-2,5-diyl)bis(2-(4-methoxyphenyl)acetate) (12)



A 50-mL round-bottomed flask, containing a magnetic stirring bar, was dried and filled with nitrogen after cooling to 23 °C. To this vessel were added 3-arylpyrrole **18** (615 mg, 2.0 mmol, 1.0 equiv), Rh_2(*S*-TCPTAD)$_4$ (42.2 mg, 20.0 μmol, 1 mol%) and CH_2Cl_2 (4.0 mL). In a separate vial, diazoester **10** (516 mg, 2.5 mmol, 1.25 equiv) was dissolved in CH_2Cl_2 (8.0 mL) and then added to the reaction mixture by syringe pump over 3 h. After 5 h of additional stirring, Rh_2(*S*-TCPTAD)$_4$ (42.2 mg, 20.0 μmol, 1 mol%) was added to the reaction mixture, and then CH_2Cl_2 solution of diazoester **10** (516 mg, 2.5 mmol, 1.25 equiv) was added by syringe pump over 3 h. After 5 h of additional stirring, CH_2Cl_2 was removed *in vacuo* and the remaining residue was purified by silica-gel flash column chromatography (hexane/EtOAc = 3:1) to afford **12** (mixture of diastereomers, 1.09 g, 82% yield) as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31–7.25 (m, 8H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.91–6.83 (m, 14H), 6.80–6.76 (m, 6H), 6.31 (s, 1H), 6.23 (s, 1H), 5.36 (s, 1H), 5.34 (s, 1H), 4.96 (s, 1H), 4.95 (s, 1H), 3.81–3.67 (m, 34H), 3.63 (s, 3H), 3.57 (s, 3H), 2.54–2.44 (m, 3H), 2.32–2.28 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.4, 172.3, 172.1, 172.0, 159.03, 159.01, 158.5, 158.4, 158.2, 158.0, 157.9, 130.0, 129.81, 129.76, 129.54, 129.48, 129.41, 129.33, 129.30, 129.2, 129.12, 129.06, 124.5, 124.3, 124.24, 124.20, 114.0, 113.9, 113.8, 113.7, 113.55, 113.52, 109.9, 109.7, 55.1, 52.4, 52.2, 52.1, 49.02, 49.00, 46.8, 46.7, 46.6, 36.2, 36.1; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{40}NO_8$ $[M–H]^-$: 662.2748 found: 662.2752.

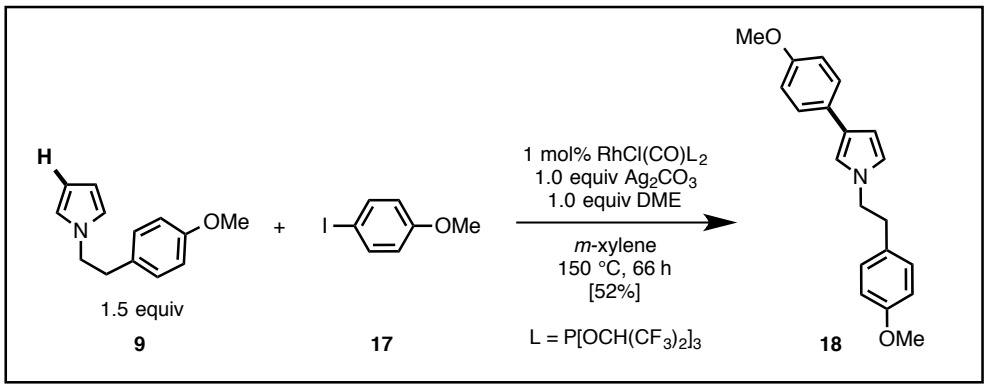
4-3. Syntheses of Dictyodendrins A and F

1-(4-Methoxyphenethyl)-1*H*-pyrrole (9)



To a solution of 2,5-dimethoxytetrahydrofuran (**7**: 12.9 mL, 100 mmol, 1.0 equiv) in AcOH (132 mL) and 1,4-dioxane (66.0 mL) was added 2-(4-methoxyphenyl)ethylamine (**8**: 14.6 mL, 100 mmol, 1.0 equiv). The reaction mixture was warmed to 110 °C and stirred for 5 h. After cooling to 23 °C, excess AcOH was removed *in vacuo*. The residue was purified by silica-gel flash column chromatography (hexane/EtOAc = 20:1) to afford pyrrole **9** (14.2 g, 70% yield) as colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.58 (t, *J* = 2.1 Hz, 2H), 6.11 (t, *J* = 2.1 Hz, 2H), 4.06 (t, *J* = 7.6 Hz, 2H), 3.78 (s, 3H), 2.98 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.2, 130.4, 129.5, 120.4, 113.8, 107.8, 55.1, 51.3, 37.4; HRMS (ESI) *m*/*z* calcd for $C_{13}H_{16}NO$ $[M+H]^+$: 202.1226 found: 202.1219.

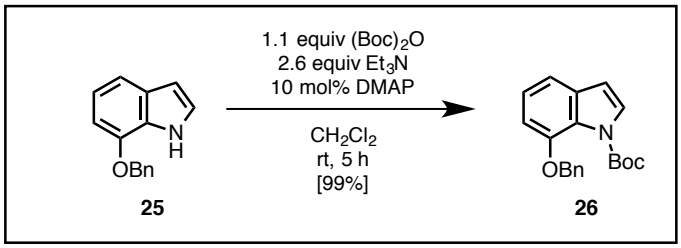
1-(4-Methoxyphenethyl)-3-(4-methoxyphenyl)-1*H*-pyrrole (18)



A 200-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar, was heat-gun-dried under vacuum and filled with nitrogen after cooling to 23 °C. To this vessel were added $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ (150 mg, 126 μmol, 1 mol%), Ag_2CO_3 (2.48 g, 9.0 mmol, 1.0 equiv), 1-[2-(4-methoxyphenyl)ethyl]pyrrole (**9**: 2.70 g, 13.5 mmol, 1.5 equiv), *p*-iodoanisole (**17**: 2.10 g, 9.0 mmol, 1.0 equiv),

1,2-dimethoxyethane (DME; 935 μL, 9.0 mmol, 1.0 equiv) and *m*-xylene (35 mL) under a stream of nitrogen. The vessel was sealed with the O-ring tap, and then heated at 150 °C for 66 h in oil bath with stirring. After cooling the reaction mixture to 23 °C, it was passed through a pad of silica gel (EtOAc) and the filtrate was concentrated *in vacuo*. The residue was purified by silica-gel flash column chromatography (hexane/EtOAc = 30:1) to afford 3-arylpyrrole **18** (1.44 g, 52% yield) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 8.2 Hz, 2H), 6.83–6.81 (m, 3H), 6.57 (dd, *J* = 2.4, 1.8 Hz, 1H), 6.35 (dd, *J* = 2.4, 1.8 Hz, 1H), 4.06 (t, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.01 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.2, 157.4, 130.3, 129.6, 128.8, 125.9, 124.3, 121.3, 116.5, 113.9, 113.8, 105.7, 55.12, 55.06, 51.4, 37.2; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{22}NO_2$ $[M+H]^+$: 308.1645 found: 308.1632.

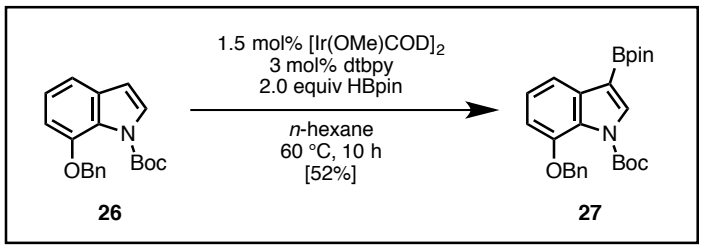
7-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-1*H*-indole (26)



To a solution of 7-benzyloxyindole (**25**: 3.50 g, 11.2 mol, 1.0 equiv) in CH_2Cl_2 (40 mL) were added triethylamine (Et_3N: 4.10 mL, 29.1 mmol, 2.6 equiv), *N*,*N*-dimethyl-4-aminopyridine (DMAP: 136.7 mg, 1.1 mmol, 10 mol%). Then $(Boc)_2O$ (2.70 mL, 12.3 mmol, 1.1 equiv) was added to the reaction mixture dropwise at 23 °C. After stirring for 5 h, the solvent was removed *in vacuo*. The crude mixture was purified by silica-gel flash column chromatography (hexane/EtOAc = 20:1 to 10:1) to afford **26** (3.60 g, 99% yield) as colorless liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53–7.50 (m, 3H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 3.6 Hz, 1H), 5.22 (s, 2H), 1.54 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 149.1, 147.6, 137.3, 133.6, 128.4, 128.3, 127.6, 127.4, 125.0, 123.6, 114.0, 108.6, 106.8, 83.1, 71.0, 27.8; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{21}NO_3Na$ $[M+Na]^+$: 346.1414 found: 346.1397.

7-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-

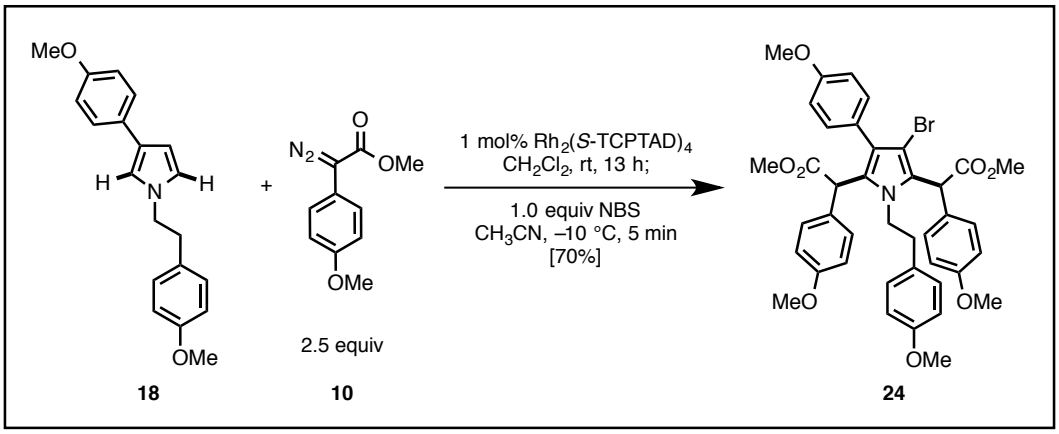
1*H*-indole (27)



A 20-mL Schlenk flask, containing a magnetic stirring bar, was dried and filled with nitrogen after cooling to 23 °C. To this vessel were added $[Ir(OMe)COD]_2$ (19.9 mg, 30.0 μmol, 1.5 mol%), 4,4-di-*tert*-butyl bipyridine (dtbpy; 16.1 mg, 60.0 μmol, 3 mol%) and *n*-hexane (2.0 mL) under a stream of nitrogen. After stirring for 5 min at 23 °C, 0.5 M *n*-hexane solution of indole **26** (647 mg, 2.0 mmol, 1.0 equiv) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (HBpin; 594 μL, 4.0 mmol, 2.0 equiv) were added and the reaction mixture, which was heated at 60 °C for 10 h in an oil bath with stirring. After cooling the reaction mixture to 23 °C, it was passed through a pad of silica gel (EtOAc) and the filtrate was concentrated *in vacuo*. The residue was purified by silica-gel flash column chromatography (hexane/EtOAc = 20:1 to 10:1) to afford boronate **27** (467 mg, 52% yield) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 5.21 (s, 2H), 1.55 (s, 9H), 1.37 (s, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.6, 147.2, 137.5, 137.2, 136.4, 128.1, 127.5, 127.3, 125.7, 123.7, 115.6, 108.5, 106.9, 83.3, 83.1, 70.9, 27.7, 24.8; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{32}BNO_5Na$ $[M+Na]^+$: 472.2266 found: 472.2243.

Dimethyl

2,2'-(3-bromo-1-(4-methoxyphenethyl)-4-(4-methoxyphenyl)-1*H*-pyrrole-2,5-diyl)bis(2-(4-methoxyphenyl)acetate) (24)

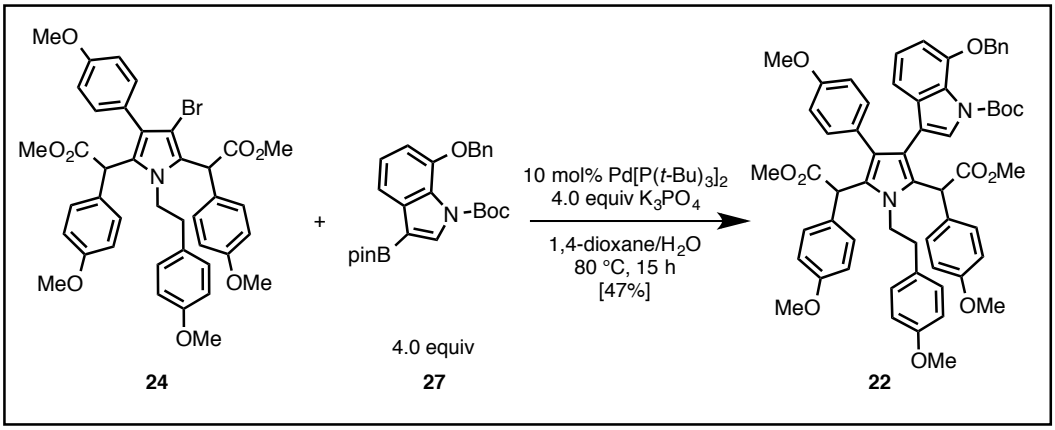


A 100-mL round-bottomed flask, containing a magnetic stirring bar, was dried and filled with nitrogen after cooling to 23 °C. To this vessel were added 3-arylpyrrole **18** (1.00 g, 3.25 mmol, 1.0 equiv), Rh_2(*S*-TCPTAD)$_4$ (34.2 mg, 16.3 μmol, 0.5 mol%) and CH_2Cl_2 (6.5 mL). In a separate vial, diazoester **10** (839 mg, 4.06 mmol, 1.25 equiv) was dissolved in CH_2Cl_2 (13 mL) and then added to the reaction mixture by syringe pump over 3 h. After 5 h of additional stirring, Rh_2(*S*-TCPTAD)$_4$ (34.2 mg, 16.3 μmol, 0.5 mol%) was added to the reaction mixture. Then CH_2Cl_2 solution of diazoester **10** (839 mg, 4.06 mmol, 1.25 equiv) was added by syringe pump over 3 h. After 2 h of additional stirring, dichloromethane was removed *in vacuo* and the residue was dissolved to dry CH_3CN (24 mL). The flask was cooled to –10 °C and *N*-bromosuccinimide (NBS; 579 mg, 3.25 mmol, 1.0 equiv) was added to the reaction mixture. After stirring for 5 min, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$. It was extracted with ethyl acetate (12 mL x 3), dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by silica-gel flash column chromatography (hexane/EtOAc = 3:1 to 2:1) to afford bromopyrrole **24** (mixture of diastereomers, 1.70 g, 70% yield) as an orange solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30–7.23 (m, 4H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 9.0 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 7.8 Hz, 2H), 6.91–6.85 (m, 12H), 6.83–6.73 (m, 8H), 5.27 (s, 2H), 5.20 (s, 1H), 5.17 (s, 1H), 3.86–3.67 (m, 34H), 3.56 (s, 3H), 3.47 (s, 3H), 2.48–2.20 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 171.47, 171.42, 171.35, 158.7, 158.51, 158.48, 158.1, 131.72, 131.67, 129.6, 129.5, 129.4, 129.3, 129.1, 129.0, 128.8, 128.7, 127.99, 127.96, 126.5, 126.4,

126.2, 126.1, 125.4, 125.3, 124.3, 124.0, 113.84, 113.76, 113.74, 113.2, 113.1, 99.1, 99.0, 55.00, 54.96, 54.92, 52.51, 52.48, 52.1, 52.0, 47.6, 47.3, 47.2, 35.9, 35.7; HRMS (ESI) *m*/*z* calcd for $C_{40}H_{39}BrNO_8$ $[M–H]^-$: 740.1854 found: 740.1870.

Dimethyl

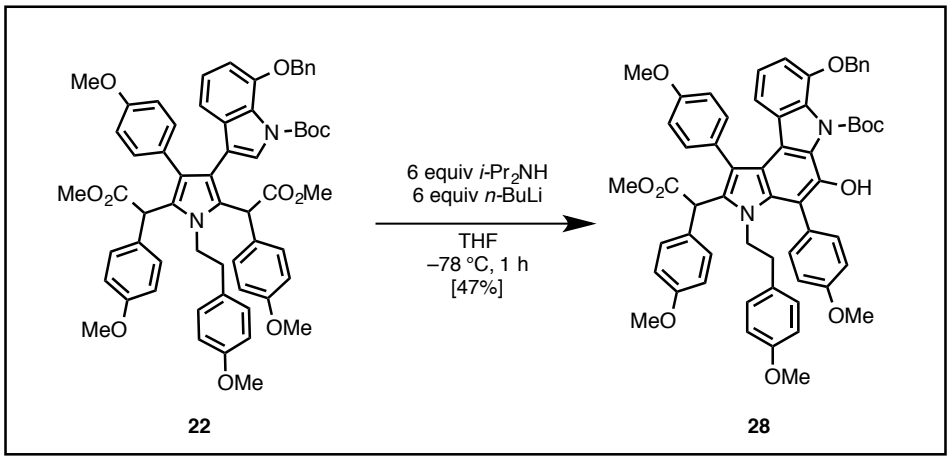
2,2'-(3-(7-(benzyloxy)-1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)-1-(4-methoxyphenethyl)-4-(4-methoxyphenyl)-1*H*-pyrrole-2,5-diyl)bis(2-(4-methoxyphenyl)acetate) (22)



A 20-mL glass vessel equipped with screw cap, containing a magnetic stirring bar, was dried and filled with nitrogen after cooling to 23 °C. To this vessel were added bromopyrrole **24** (74.1 mg, 0.10 mmol, 1.0 equiv), $Pd[P(t\text{-}Bu)_3]_2$ (5.2 mg, 10 μmol, 10 mol%), and K_3PO_4 (85.2 mg, 0.40 mmol, 4.0 equiv) under a stream of nitrogen. Then to the reaction mixture were added the solution of boronate **27** (180 mg, 0.40 mmol, 4.0 equiv) in 1,4-dioxane (1.0 mL) and degassed H_2O (100 μL). After capped, the vessel was heated at 80 °C for 15 h in an oil bath with stirring. After cooling the reaction mixture to 23 °C, it was passed through a pad of silica gel (EtOAc) and the filtrate was concentrated *in vacuo*. The residue was purified by GPC to afford **22** (mixture of diastereomers, 46.3 mg, 47% yield) as an orange solid. ^{1}H NMR (600 MHz, DMSO-d_6, 100 °C) δ 7.50 (d, *J* = 7.8 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.24 (brs, 1H), 7.19 (brs, 1H), 7.12–7.01 (m, 12H), 6.97–6.72 (m, 22H), 6.64 (d, *J* = 9.0 Hz, 2H), 6.62 (d, *J* = 9.0 Hz, 2H), 5.33 (s, 1H), 5.31 (s, 1H), 5.26 (s, 1H), 5.26 (s, 1H), 5.15 (s, 2H), 5.15 (s, 2H), 3.83–3.69 (m, 22H), 3.63 (s, 3H), 3.62 (s, 3H), 3.54 (s, 3H), 3.53 (s, 3H), 2.98 (s, 3H), 2.98 (s, 3H), 2.51–2.41 (m, 4H), 1.48 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (150 MHz, DMSO-d_6, 100 °C) δ 170.92, 170.88, 170.75, 170.68, 157.9, 157.84, 157.78, 157.65, 157.2, 147.8, 146.3, 136.9,

133.7, 133.5, 130.56, 130.48, 129.40, 129.37, 129.10, 129.06, 128.84, 128.79, 127.6, 127.5, 127.3, 127.0, 126.9, 126.8, 125.0, 124.5, 124.4, 124.05, 123.97, 122.39, 122.35, 114.1, 114.0, 113.7, 113.6, 113.5, 113.4, 113.2, 113.1, 112.9, 112.62, 112.57, 108.2, 82.2, 70.1, 54.7, 54.6, 54.4, 51.3, 51.2, 50.94, 50.88, 46.8, 46.7, 46.6, 46.5, 46.0, 45.9, 34.8, 27.1, 26.9; HRMS (ESI) *m*/*z* calcd for $C_{60}H_{60}N_2O_{11}Na$ $[M+Na]^+$: 1007.4089 found: 1007.4055.

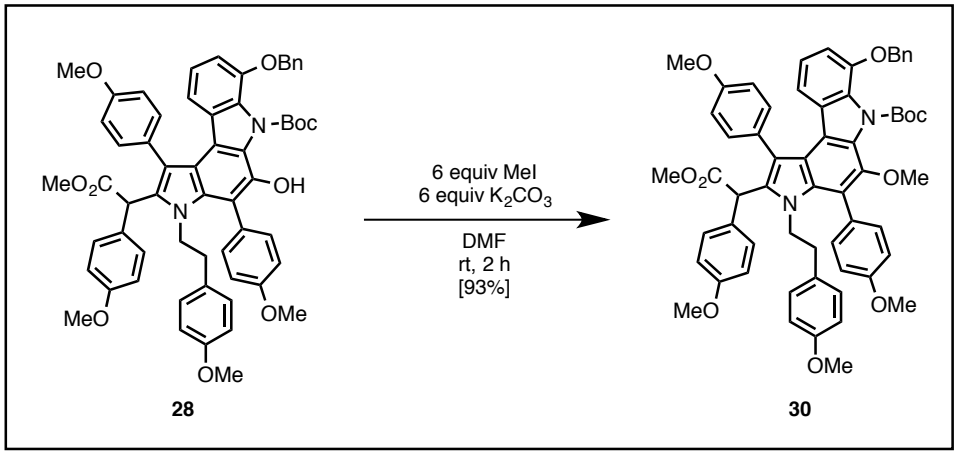
Methyl 2-(7-(benzyloxy)-6-(*tert*-butoxycarbonyl)-5-hydroxy-3-(4-methoxyphenethyl)-1,4-bis(4-methoxyphenyl)-3,6-dihydropyrrolo[2,3-*c*]carbazol-2-yl)-2-(4-methoxyphenyl)acetate (28)



A 20-mL Schlenk flask, containing a magnetic stirring bar, was dried and filled with nitrogen after cooling to 23 °C. To this vessel were added diisopropylamine (75.0 μL, 530 μmol, 6.0 equiv) and THF (0.70 mL). After cooled to 0 °C, 1.6 M *n*-hexane solution of *n*-butyllithium (330 μL, 530 μmol, 6.0 equiv) was added and the reaction mixture was stirred for 30 min at 0 °C. After the reaction mixture was cooled to –78 °C, the solution of pyrrole **22** (87.1 mg, 88.0 μmol, 1.0 equiv) in THF (1.2 mL) was added dropwise. After stirring for 1 h at –78 °C, the reaction mixture was quenched by saturated aqueous NH_4Cl (2.0 mL) and extracted with EtOAc (5.0 mL x 3). The combined organic layer was dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The crude residue was purified by preparative HPLC to afford pyrrolocarbazole **28** (39.4 mg, 47% yield) as a brown solid. ^1H NMR (600 MHz, $CDCl_3$) δ 10.83 (s, 1H), 7.55–7.53 (m, 3H), 7.41 (d, *J* = 7.2 Hz, 2H), 7.38 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 9.0 Hz, 2H), 7.06–7.01 (m, 3H), 6.97 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.82–6.77 (m, 4H), 6.60 (t, *J* = 7.8 Hz, 2H), 6.33 (d, *J* = 9.0 Hz, 2H), 5.79

(d, J = 8.4 Hz, 1H), 5.35 (s, 1H), 5.12 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.80–3.72 (m, 2H) 3.76 (s, 3H), 3.71 (s, 3H), 3.63 (s, 3H), 2.34–2.22 (m, 2H) 1.32 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 159.2, 159.0, 158.5, 157.9, 156.1, 148.6, 141.2, 136.7, 133.4, 133.3, 133.0, 132.92, 132.87, 130.5, 130.3, 130.1, 129.7, 129.5, 129.3, 128.8, 128.5, 128.1, 127.9, 127.6, 124.5, 120.5, 117.9, 117.1, 116.6, 113.9, 113.80, 113.75, 113.70, 113.68, 113.3, 112.9, 110.1, 85.4, 71.2, 55.4, 55.3, 55.24, 55.15, 52.2, 47.0, 46.9, 35.1, 27.4; HRMS (ESI) m/z calcd for $C_{59}H_{55}N_2O_{10}$ $[M–H]^-$: 951.3851 found: 951.3869.

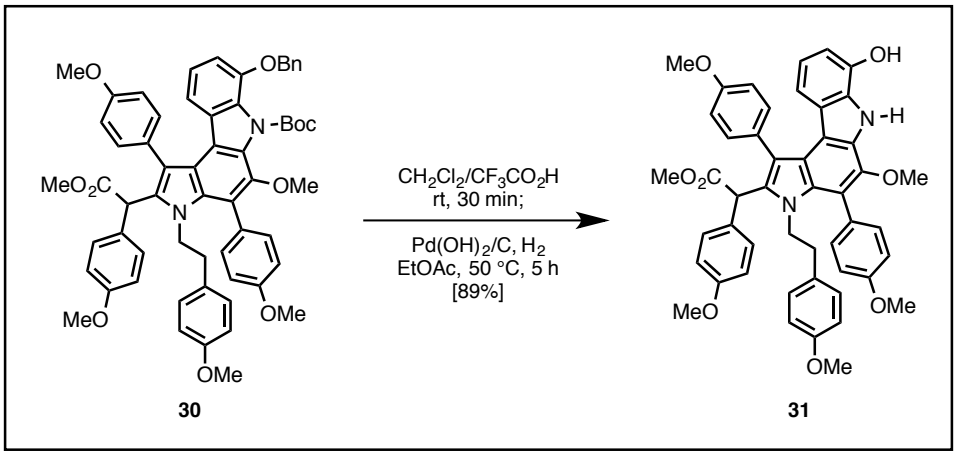
Methyl 2-(7-(benzyloxy)-6-(*tert*-butoxycarbonyl)-5-methoxy-3-(4-methoxyphenethyl)-1,4-bis(4-methoxyphenyl)-3,6-dihydropyrrolo[2,3-*c*]carbazol-2-yl)-2-(4-methoxyphenyl)acetate (30)



To a solution of pyrrolocarbazole **28** (11.3 mg, 11.8 μmol, 1.0 equiv) in DMF (1.0 mL) were added K_2CO_3 (9.8 mg, 71 μmol, 6.0 equiv) and methyl iodide (4.4 μL, 71 μmol, 6.0 equiv). After stirring for 2 h at 23 °C, the reaction mixture was quenched by saturated aqueous NH_4Cl (1.0 mL). It was extracted by EtOAc (1.5 mL x 3), washed with brine (3.0 mL), and dried over Na_2SO_4. The solvent was removed *in vacuo*. The crude residue was purified by preparative HPLC to afford pyrrolocarbazole **30** (10.7 mg, 93% yield) as a brown solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.53 (dd, J = 9.0, 2.4 Hz, 1H), 7.47 (d, J = 6.6 Hz, 1H), 7.38 (dd, J = 8.4, 2.4 Hz, 1H), 7.34 (t, J = 7.2 Hz, 2H), 7.27 (t, J = 7.8 Hz, 1H), 7.15 (d, J = 9.0 Hz, 2H), 7.06 (dd, J = 7.8, 2.4 Hz, 1H), 7.03–7.01 (m, 2H), 6.97 (dd, J = 8.4, 3.0 Hz, 1H), 6.81 (d, J = 9.0 Hz, 2H), 6.72 (d, J = 8.4 Hz, 1H), 6.63–6.58 (m, 3H), 6.25 (d, J = 8.4 Hz, 2H), 5.71 (d, J = 7.8 Hz, 2H), 5.34 (s, 1H), 5.27 (s, 2H), 3.90–3.83 (m, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.77 (s, 3H),

3.71 (s, 3H), 3.63 (s, 3H), 3.31 (s, 3H), 2.22–2.17 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 159.3, 159.2, 158.5, 157.8, 153.5, 144.9, 141.4, 137.1, 133.6, 133.3, 133.1, 133.0, 130.1, 129.8, 129.59, 129.57, 129.51, 129.3, 129.1, 128.9, 128.4, 127.7, 127.4, 127.1, 125.6, 120.00, 119.95, 118.6, 118.2, 116.9, 115.7, 113.8, 113.7, 113.6, 113.4, 113.3, 107.6, 83.9, 70.4, 60.9, 55.5, 55.4, 55.3, 55.2, 52.3, 47.3, 47.2, 35.3, 27.3; HRMS (ESI) *m*/*z* calcd for $C_{60}H_{58}N_2O_{10}Na$ $[M+Na]^+$: 989.3984 found: 989.4011.

Methyl
2-(7-hydroxy-5-methoxy-3-(4-methoxyphenethyl)-1,4-bis(4-methoxyphenyl)-3,6-dihydropyrrolo[2,3-*c*]carbazol-2-yl)-2-(4-methoxyphenyl)acetate (31)

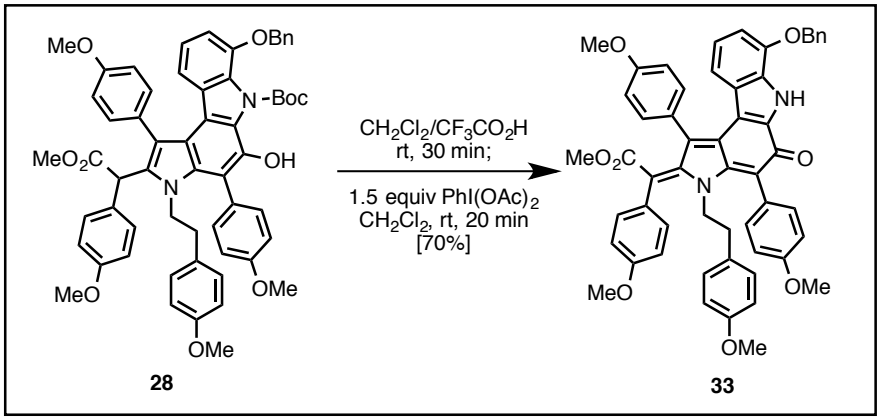


To a solution of pyrrolocarbazole **30** (8.4 mg, 8.7 μmol, 1.0 equiv) in CH_2Cl_2 (1.5 mL) was added CF_3CO_2H (250 μL) and the reaction mixture was stirred for 30 min at 23 °C. Then toluene (2.0 mL) was added and the reaction mixture was evaporated *in vacuo*. The residue was dissolved in EtOAc (1.5 mL) and 40 wt% $Pd(OH)_2/C$ (1.7 mg, 20wt%) was added. The vessel was filled with hydrogen and the reaction mixture was stirred for 5 h at 50 °C. The reaction mixture was passed through a pad of Celite® (EtOAc) and evaporated *in vacuo*. The crude residue was purified by preparative HPLC to afford pyrrolocarbazole **31** (6.0 mg, 89% yield) as a pale brown solid. The NMR spectra of **31** were identical to those of synthesized **31** reported by Tokuyama *et al*.[3f,g] ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (brs, 1H), 7.61–7.54 (m, 3H), 7.41 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.14 (d, *J* = 7.8 Hz, 2H), 7.07–6.99 (m, 4H), 6.80 (d, *J* = 7.8 Hz, 2H), 6.67 (d, *J* = 7.8 Hz, 1H), 6.61–6.59 (m, 3H), 6.28 (d, *J* = 8.4 Hz, 2H), 5.70 (d, *J* = 8.4 Hz, 1H), 5.35 (s, 1H), 5,11 (brs, 1H), 3.92 (s, 3H), 3.92–3.84 (m, 2H), 3.90 (s, 3H), 3.77 (s, 3H), 3.72 (s, 3H), 3.61 (s, 3H), 3.55 (s, 3H), 2.28–2.25 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.0, 159.3, 159.2, 158.5, 157.8,

140.8, 140.7, 133.7, 133.4, 133.0, 132.7, 132.6, 130.1, 129.6, 129.5, 129.4, 129.0, 128.9, 128.6, 127.4, 125.5, 120.4, 118.7, 118.0, 117.9, 117.0, 115.2, 113.8, 113.6, 113.5, 113.3, 109.0, 60.9, 55.5, 55.4, 55.3, 55.2, 52.3, 47.4, 47.1, 35.4; HRMS (ESI) *m*/*z* calcd for $C_{48}H_{43}N_2O_8$ $[M–H]^-$: 775.3014 found: 775.3024.

Methyl

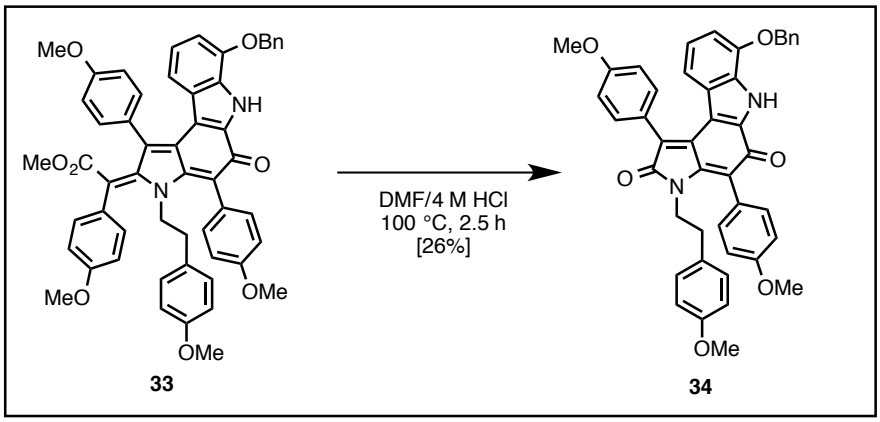
(*E*)-2-(7-(benzyloxy)-3-(4-methoxyphenethyl)-1,4-bis(4-methoxyphenyl)-5-oxo-5,6-dihydropyrrolo[2,3-*c*]carbazol-2(3*H*)-ylidene)-2-(4-methoxyphenyl)acetate (33)



To a solution of pyrrolocarbazole **28** (43.3 mg, 45.4 μmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added CF_3CO_2H (330 μL) and the reaction mixture was stirred for 30 min at 23 °C. Then toluene (2.0 mL) was added and the reaction mixture was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (2.0 mL) and cooled to 0 °C. To the solution was added $PhI(OAc)_2$ (22.0 mg, 68.1 μmol, 1.5 equiv) and the reaction mixture was allowed to warm to 23 °C and stirred for 20 min. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (1.0 mL) and saturated aqueous $NaHCO_3$ (1.0 mL). It was extracted with EtOAc (4.0 mL x 3), washed with brine (4.0 mL), and dried over Na_2SO_4. The solvent was removed *in vacuo*. The crude residue was purified by silica-gel flash column chromatography (hexane/EtOAc = 2:1 to 1:1) to afford **33** (27.1 mg, 70% yield) as a reddish brown solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.48 (d, *J* = 9.0 Hz, 2H), 7.45 (d, *J* = 6.6 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.36–7.33 (m, 3H), 7.28 (d, *J* = 9.0 Hz, 2H), 7.04 (d, *J* = 9.0 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H) 6,90 (d, *J* = 9.0 Hz, 2H), 6.67–6.65 (m, 3H), 6.62–6.59 (m, 3H), 5.18 (s, 2H), 5.04 (d, *J* = 9.0 Hz, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.66 (s, 3H), 3.10 (s, 3H), 3.00 (t, *J* = 7.8 Hz, 2H), 2.35 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.4, 169.0, 160.1, 159.8, 158.9, 158.0, 154.9, 150.6, 145.6, 138.9, 136.6, 133.6, 132.6, 132.0, 131.7, 131.6, 130.0, 129.8, 128.9, 128.6, 128.5, 128.2, 127.6,

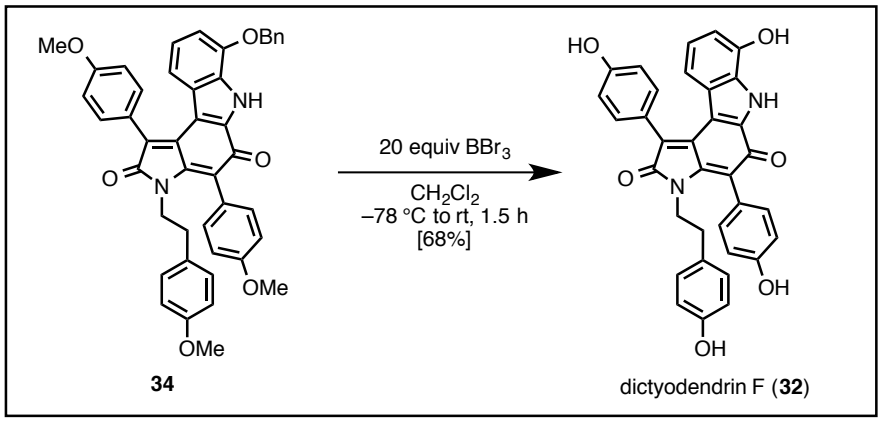
126.4, 126.1, 125.0, 121.1, 119.6, 116.1, 114.3, 113.78, 113.75, 113.6, 113.5, 111.9, 105.4, 70.3, 55.6, 55.33, 55.26, 55.15, 52.07, 48.9, 33.0; HRMS (ESI) *m*/*z* calcd for $C_{54}H_{46}N_2O_8Na$ $[M+Na]^+$: 873.3146 found: 873.3162.

7-(Benzyloxy)-3-(4-methoxyphenethyl)-1,4-bis(4-methoxyphenyl)pyrrolo[2,3-*c*]carbazole-2,5(3*H*,6*H*)-dione (34)



Pyrrolocarbazole **33** (10.7 mg, 15.5 μmol, 1.0 equiv) was dissolved in DMF (1.3 mL) and 4 M HCl (1.3 mL). The reaction mixture was stirred for 2.5 h at 100 °C. Upon completion of the reaction, the reaction mixture was quenched with water (2.0 mL). It was extracted with EtOAc (4.0 mL x 3), washed with brine (3.0 mL x 3), and dried over Na_2SO_4. The solvent was removed *in vacuo*. The crude residue was purified by GPC to afford **34** (2.3 mg, 26% yield) as a greenish brown solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.34 (brs, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 6.6 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.78–6.69 (m, 6H), 6.03 (d, *J* = 7.8 Hz, 1H), 5.19 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.73 (s, 3H), 3.46 (t, *J* = 7.8 Hz, 2H), 2.46 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 178.9, 171.3, 160.1, 159.9, 158.1, 149.3, 146.0, 136.3, 133.7, 132.4, 132.3, 131.6, 129.9, 129.7, 129.1, 129.0, 128.7, 128.4, 127.8, 124.7, 124.0, 123.5, 122.1, 117.1 116.9 113.9, 113.8, 113.6, 113.1, 106.1, 70.4, 55.44, 55.38, 55.2, 43.0, 34.0; HRMS (ESI) *m*/*z* calcd for $C_{44}H_{35}N_2O_6$ $[M–H]^–$: 687.2490 found: 687.2500.

Dictyodendrin F (32)



Compound **34** (5.3 mg, 7.7 μmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2.0 mL) and the solution was cooled to –78 °C. Then BBr_3 (154 μL, 1 M in CH_2Cl_2, 154 μmol, 20 equiv) was added dropwise and the reaction mixture was allowed to warm to 23 °C. After stirring for 1.5 h, the reaction mixture was cooled to 0 °C then quenched with water (2.0 mL). It was extracted with EtOAc (4.0 mL x 3), washed with brine (4.0 mL), and dried over Na_2SO_4. The solvent was removed *in vacuo*. The crude residue was purified by preparative HPLC to afford **32** (2.9 mg, 68% yield) as a greenish brown solid. The ^{1}H NMR spectrum of **32** were identical to that of isolated dictyodendrin F (**32**) reported by Capon *et al*.[2] ^{1}H NMR (600 MHz, CD_3OD) δ 7.31 (d, *J* = 9.0 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 9.0 Hz, 2H), 6.60–6.56 (m, 4H), 5.83 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.42 (t, *J* = 7.8 Hz, 2H), 2.41 (t, *J* = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, CD_3OD) δ 180.9, 173.4, 160.2, 159.2, 156.9, 150.5, 146.0, 135.6, 133.8, 133.5, 133.2, 130.9, 130.7, 130.1, 130.0, 126.4, 124.2, 123.9, 123.1, 119.3, 116.4, 116.3, 116.1, 116.0, 114.0, 110.0, 44.2, 34.9; HRMS (ESI) *m*/*z* calcd for $C_{34}H_{23}N_2O_6$ $[M–H]^-$: 555.1551 found: 555.1544.

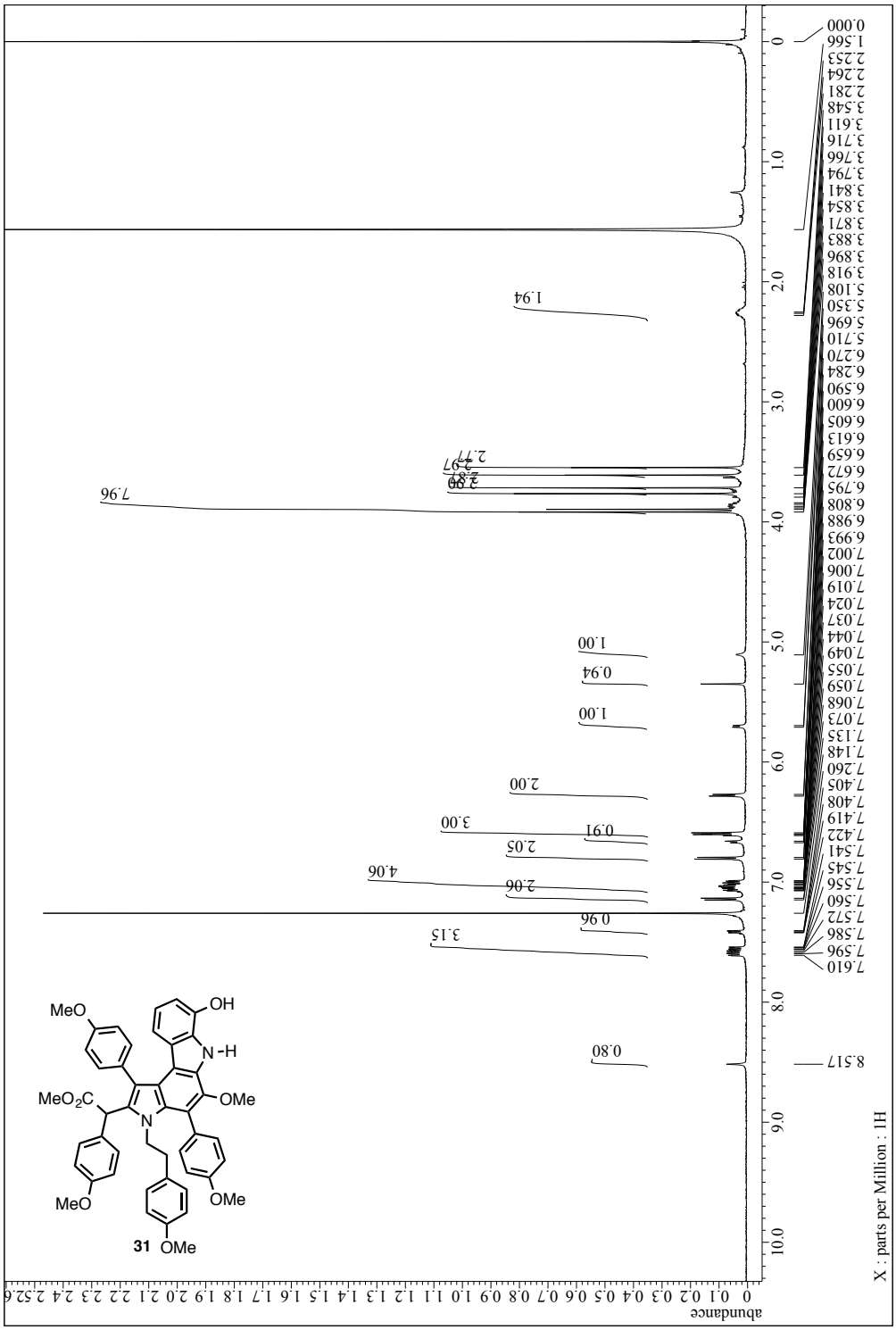


Figure 1. ^{1}H-NMR (600 MHz, $CDCl_3$) of **31**.

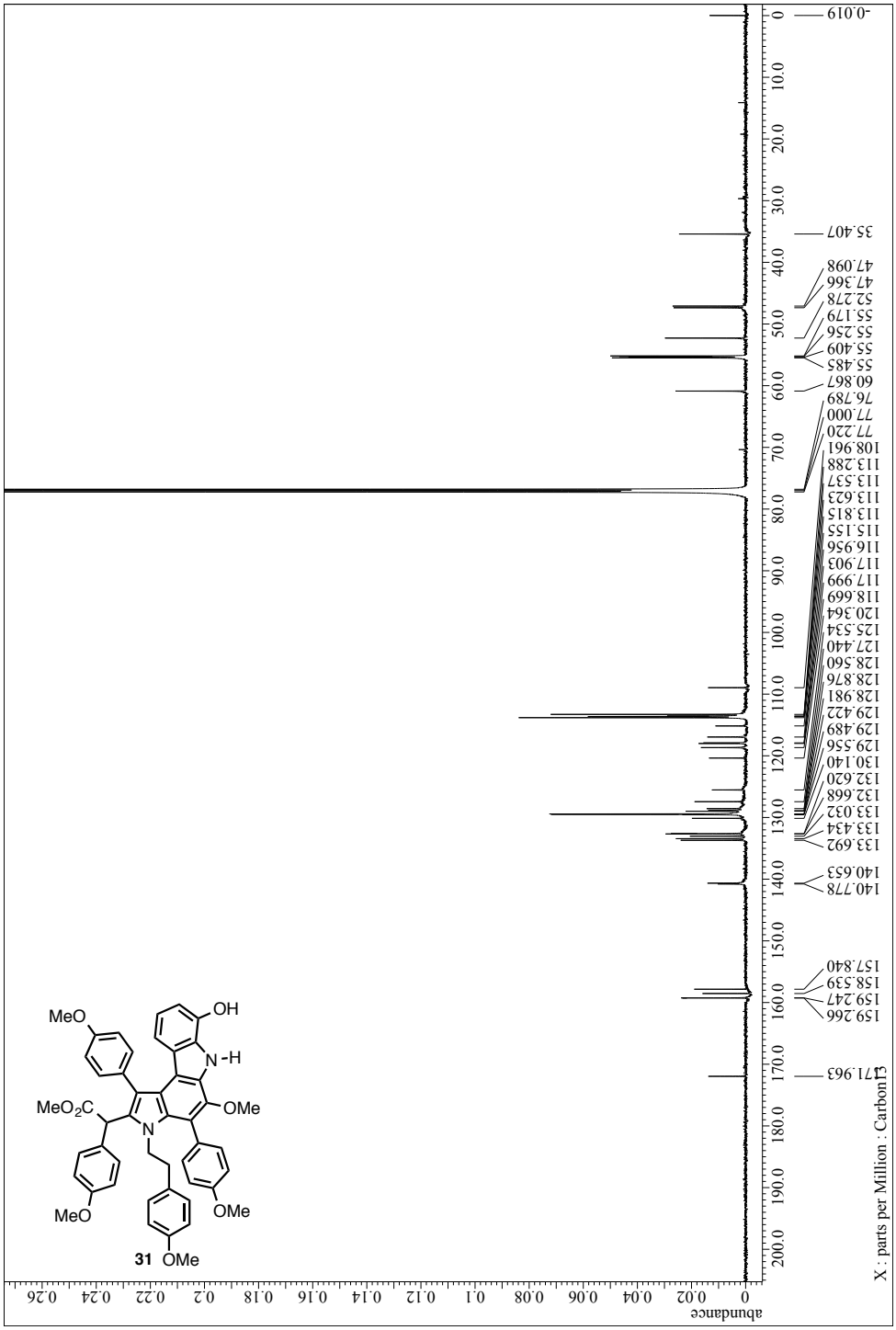


Figure 2. ^{13}C-NMR (150 MHz, $CDCl_3$) of **31**.

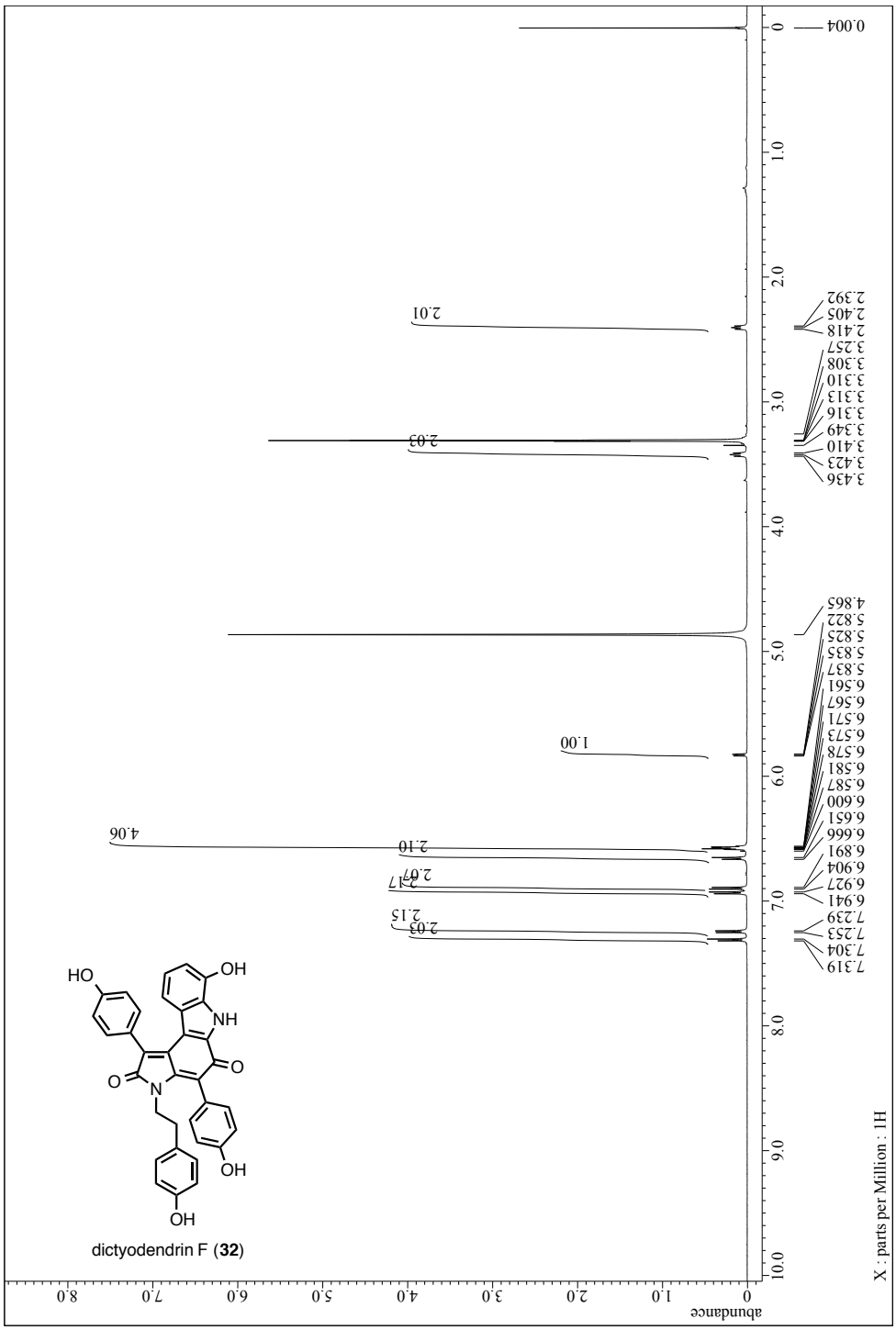


Figure 3. ^{1}H-NMR (600 MHz, CD_3OD) of **32**.

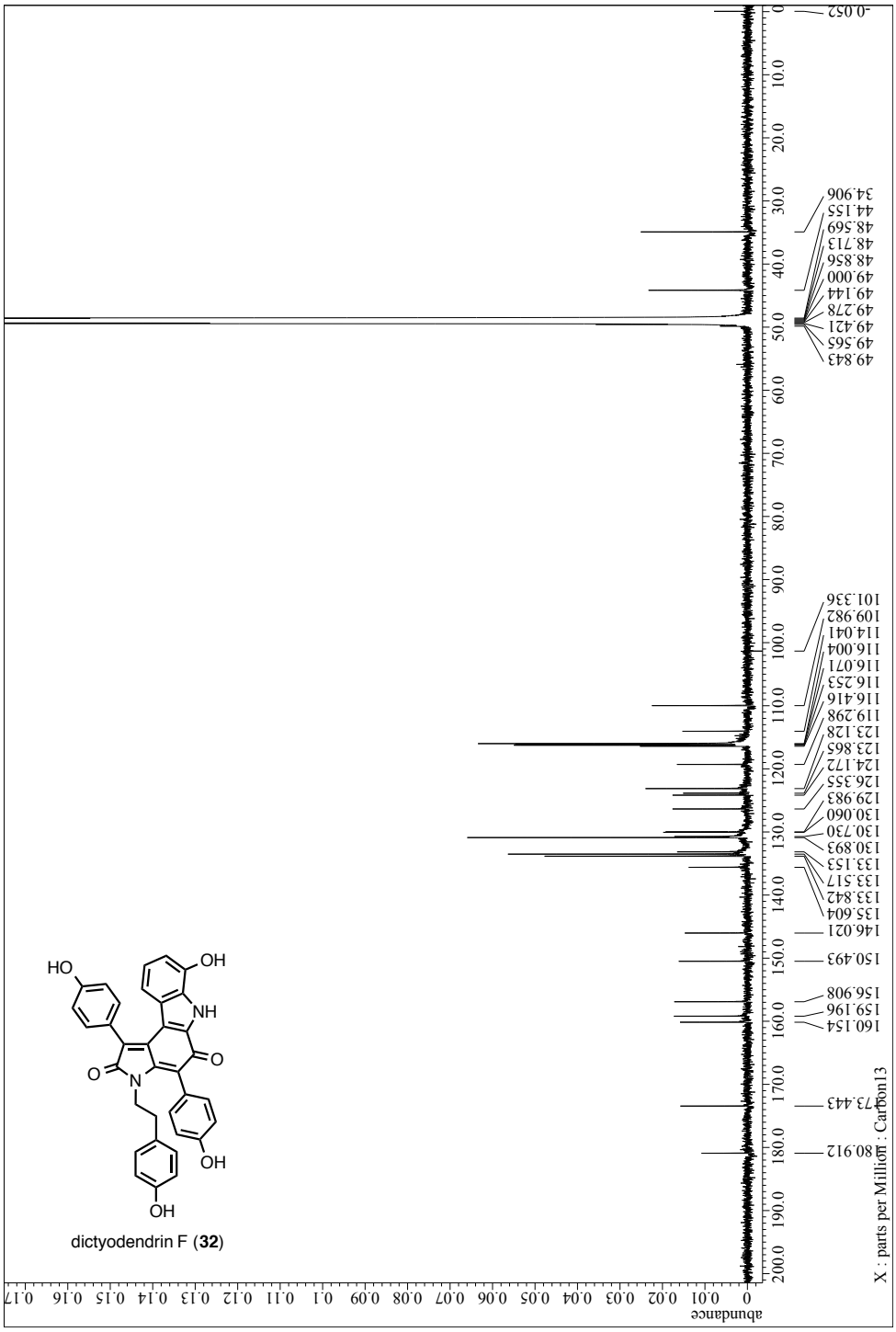
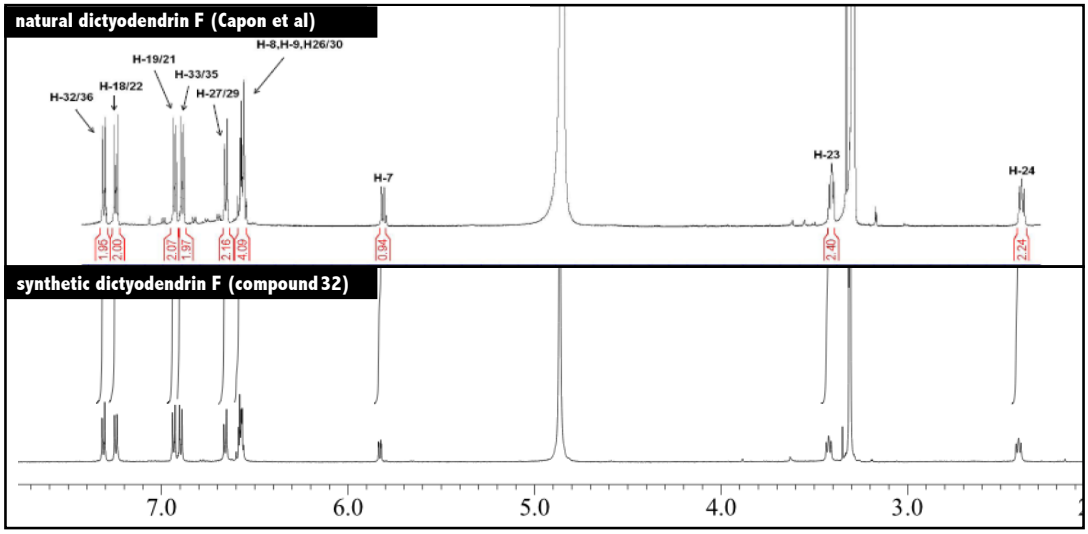


Figure 4. ^{13}C-NMR (150 MHz, CD_3OD) of **32**.



Reported (Isolated by Capon et al)	Observed (Synthetic)
7.32 (d, *J* = 8.6 Hz, 2H)	7.31 (d, *J* = 9.0 Hz, 2H)
7.25 (d, *J* = 8.6 Hz, 2H)	7.25 (d, *J* = 8.4 Hz, 2H)
6.94 (d, *J* = 8.6 Hz, 2H)	6.93 (d, *J* = 8.4 Hz, 2H)
6.90 (d, *J* = 8.6 Hz, 2H)	6.90 (d, *J* = 8.4 Hz, 2H)
6.66 (d, *J* = 8.5 Hz, 2H)	6.66 (d, *J* = 9.0 Hz, 2H)
6.60-6.55 (m, 4H)	6.60–6.56 (m, 4H)
5.83 (dd, J= 7.8, 1,2 Hz, 1H)	5.83 (dd, *J* = 7.2, 1.8 Hz, 1H)
3.43 (t like, *J* = 7.8 Hz, 2H)	3.42 (t, *J* = 7.8 Hz, 2H)
2.41 (t like, *J* = 7.8 Hz, 2H)	2.41 (t, *J* = 7.8 Hz, 2H)

Figure 5. Comparison of ^{1}H-NMR Data.[2]

References and Notes

1. Warabi, K.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *J. Org. Chem.* **2003**, *68*, 2765.
2. Zhang, H.; Conte, M. M.; Khalil, Z.; Huang, X.-C.; Capon, R. J. *RSC Adv.* **2012**, *2*, 4209.
3. Fürstner's synthesis: (a) Fürstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2005**, *127*, 11620. (b) Fürstner, A.; Domostoj, M. M.; Scheiper, B. *J. Am. Chem. Soc.* **2006**, *128*, 8087. (c) Buchgraber, P.; Domostoj, M. M.; Scheiper, B.; Wirtz, C.; Mynott, R.; Rust, J.; Fürstner, A. *Tetrahedron* **2009**, *65*, 6519. Ishibashi's synthesis: (d) Hirao, S.; Yoshinaga, Y.; Iwao, M.; Ishibashi, F. *Tetrahedron Lett.* **2010**, *51*, 533. (e) Hirao, S.; Sugiyama, Y.; Iwao, M.; Ishibashi, F. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 1764. Tokuyama's synthesis: (f) Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5925. (g) Tokuyama, H.; Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T. *Chem. Asian J.* **2011**, *6*, 560. Jia's synthesis: (h) Liang, J.; Hu, W.; Tao, P.; Jia, Y. *J. Org. Chem.* **2013**, *78*, 5810. (i) Tao, P.; Liang, J.; Jia, Y. *Eur. J. Org. Chem.* **2014**, 5735.
4. Yamaguchi, A. D.; Chepiga, K. M.; Yamaguchi, J.; Itami, K.; Davies, H. M. L. *J. Am. Chem. Soc.* **2015**, *137*, 644.
5. For selected example of direct α-arylation of pyrroles, see: (a) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. (b) Rogera, J.; Doucet, H. *Adv. Synth. Catal.* **2009**, *351*, 1977. (c) Gryko, D. T.; Vakuliuk, O.; Gryko, D.; Koszarna, B. *J. Org. Chem.* **2009**, *74*, 9517. (d) Rene, O.; Fagnou, K. *Adv. Synth. Catal.* **2010**, *352*, 2116. (e) Jafarpour, F.; Rahiminejadan, S.; Hazrati, H. *J. Org. Chem.* **2010**, *75*, 3109. (f) Nadres, E. T.; Lazareva, A.; Daugulis, O. *J. Org. Chem.* **2011**, *76*, 471.
6. (a) Maryanoff, B. E. *J. Org. Chem.* **1979**, *44*, 4410. (b) Maryanoff, B. E. *J. Org. Chem.* **1982**, *47*, 3000. (c) Davies, H. M. L.; Hedley, S. J. *Chem. Soc. Rev.* **2007**, *36*, 1109. (d) Lian, Y.; Davies, H. M. L. *Org. Lett.* **2010**, *12*, 924.
7. (a) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *J. Am. Chem. Soc.* **2006**, *128*, 11748. (b) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *Tetrahedron* **2008**, *64*, 6073.
8. Ueda, K.; Yanagisawa, S.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2010**, *49*,

8946.

9. (a) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K.; *J. Am. Chem. Soc.* **2009**, *131*, 14622.
10. Kirchberg, S.; Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2387.
11. Wagner, A. M.; Sanford, M. S. *Org. Lett.* **2011**, *13*, 288.
12. Ueda, K.; Amaike, K.; Maceiczyk, R. M.; Itami, K.; Yamaguchi, J. *J. Am. Chem. Soc.* **2014**, *136*, 13226.
13. (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (b) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360.
14. Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, R. E., Jr.; Smith, M. R. III. *J. Org . Chem.* **2009**, *74*, 9199.
15. Wynne, J. H.; Stalick, W. M. *J. Org . Chem.* **2003**, *68*, 4845.
16. (a) Bernardo, P. H.; Chai, C. L. L. *J. Org. Chem.* **2003**, *68*, 8906. (b) Fernandez, M.; Barcia, C.; Estévez, J. C.; Estévez, R. J.; Castedo, L. *Synlett* **2004**, 267. (c) Bernardo, P. H.; Chai, C. L.; Heath, G. A.; Mahon, P. J.; Smith, G. D.; Waring, P.; Wilkes, B. A. *J. Med. Chem.* **2004**, *47*, 4958.
17. Zhu, M.; Jalalian, N.; Olofsson, B. *Synlett* **2008**, 592.
18. van Leeuwen, P. W. N. M.; Roobeek, C. F. *Tetrahedron* **1981**, *37*, 1973.
19. Reddy, R. P.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 5013.
20. Qin, C.; Boyarskikh, V.; Hansen, J. H.; Hardcastle, K. I.; Musaev, D. G.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011**, *133*, 19198.
21. Watanabe, N.; Ogawa, T.; Ohtake, Y.; Ikegami, S.; Hashimoto, S. *Synlett* **1996**, *1*, 85.
22. Yamawaki, M.; Tanaka, M.; Abe, T.; Anada, M.; Hashimoto, S. *Heterocycles* **2007**, *72*, 709.
23. Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063.

List of Publications

(副論文)

1. Oxidative C–H/C–H Coupling of Azine and Indole/Pyrrole Nuclei: Palladium Catalysis and Synthesis of Eudistomin U
   Atsushi D. Yamaguchi, Debashis Mandal, Junichiro Yamaguchi, Kenichiro Itami
   Chem. Lett. **2011**, *40*, 555–557.

2. Concise Syntheses of Dictyodendrins A and F by a Sequential C–H Functionalization Strategy
   Atsushi D. Yamaguchi, Kathryn M. Chepiga, Junichiro Yamaguchi, Kenichiro Itami, Huw M. L. Davies
   J. Am. Chem. Soc. **2015**, *137*, 644–647.

(参考論文)

1. Synthesis of Dragmacidin D via Direct C–H Couplings
   Debashis Mandal, Atsushi D. Yamaguchi, Junichiro Yamaguchi, and Kenichiro Itami
   J. Am. Chem. Soc. **2011**, *133*, 19660–19663.

2. C–H Bond Functionalization: Emerging Synthetic Tools for Natural Products and Pharmaceuticals
   Junichiro Yamaguchi, Atsushi D. Yamaguchi, and Kenichiro Itami
   Angew. Chem., Int. Ed. **2012**, *51*, 8960–9009.