Akita University

Studies Toward Total Synthesis of 3-Phenyldibenzofuran Natural Products Based on [2+2+2] Cycloaddition Reaction

([2+2+2]環化付加反応による 3-フェニルジベンゾフラン型天然物の全合成研究)

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Abbreviations

Ac	acetyl
Bn	benzyl
Bu	butyl
^{t}Bu	*tert*-butyl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
H_8-BINAP	[1-(2-diphenylphosphanyl-5,6,7,8-tetrahydronaphthalen-1-yl)-5,6,7,8-tetra-hydronaphthalen-2-yl]-diphenylphosphane
BPPF	1,1'-bis(diphenylphosphino)ferrocene
Bz	benzoyl
cod	1,5-cyclooctadiene
CSA	10-camphorsulfonic acid
DABCO	1,4-diazabicyclo[2,2,2]octane
dba	dibenzylideneacetone
DIPA	diisopropylamine
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N'*-dimethylpropyleneurea
DPPB	1,4-bis(diphenylphosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1'-bis(diphenylphosphino)ferrocene
DPPH	2,2-diphenyl-1-picrylhydrazyl
DPPM	bis(diphenylphosphino)methane
Et	ethyl
eq.	equivalent
JohnPhos	2-(di-*tert*-butylphosphino)biphenyl
*m*CPBA	*m*-chloroperoxybenzoic acid
LHMDS	lithium bis(trimethylsilyl)amide
Me	methyl
MOM	methoxymethyl
Ms	mesyl
NHMDS	sodium bis(trimethylsilyl)amide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide

Ph	phenyl
pin	pinacolato
PMP	4-methoxyphenyl
PTS	4-toluenesulfonic acid
^{i}Pr	isopropyl
quant.	quantitative
Rham	rhamnose
SAR	structure-activity-relationship
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	4-toluenesulfonyl
UHP	urea hydrogen peroxide

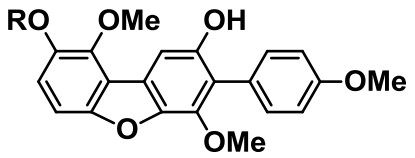
Chapter 1

Introduction

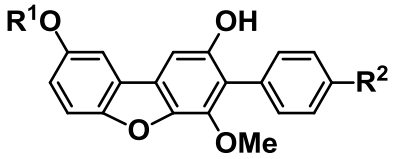
1-1. 3-Phenyldibenzofuran Natural Products

Among polyphenol natural products, a family of compounds characterized by a 2-hydroxy-3-phenyldibenzofuran skeleton, which includes kehokorins (**1-1-5**, Figure 1-1)[1,2], vialinins B-C (**1-6**, **1-7**, Figure 1-1)[3,4], boletopsins (**1-8-10**, Figure 1-1)[5], and candidusins (**1-11-12**, Figure 1-1)[6], recently attracts attention, because remarkable biological activity is seen in many compounds of the family. For example, kehokorins, isolated from the myxomycete, *Trichia favoginea*, show inhibition activity against cancer cell growth. Mushroom-derived vialinins B-C (from the mushroom, *Thelephora vialis*) suppress the production of TNF-α. Boletopsins, originated from the mushroom, *Boletopsis leucomelas*, exhibit lipoxygenase inhibitory activity. Candidusins, produced by the *Aspergillus* and *Penicillium* genera of fungi, are toxic to sea urchin embryos. The particular biological activity of 2-hydroxy-3-phenyldibenzofuran natural polyphenols has thus interested researchers, including synthetic chemists, in the structure activity relationship (SAR).

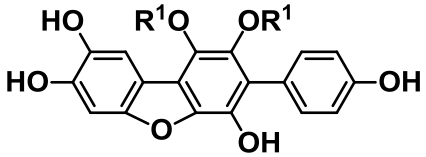
However, the family of compounds is rare in natural environment, and the supply of the compounds from natural resource is difficult. Therefore, several groups of synthetic chemists have recently performed the total synthesis of some 2-hydroxy-3-phenyldibenzofuran natural products for the purpose of supplying the compounds.



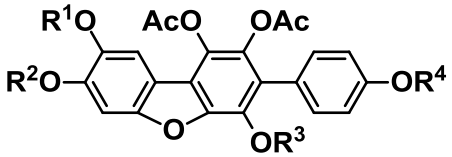
Kehokorin A (1-1): R = L-Rham
Kehokorin B (1-2): R = H



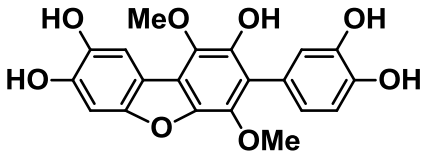
Kehokorin C (1-3): R^1 = H, R_2 = OMe
Kehokorin D (1-4): R^1 = R_2 = H
Kehokorin E (1-5): R^1 = Me, R_2 = H



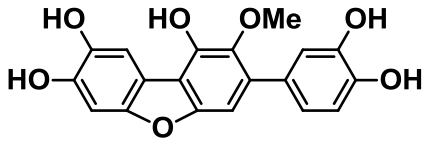
Vaialinin B (1-6): R^1 = $COCH_2Ph$
Vaialinin C (1-7): R^1 = CO*p*-(OH)Ph



Boletopsin 7 (1-8): R^1 = R^2 = R^3 = R^4 = H
Boletopsin 11 (1-9): R^1 = R^2 = R^3 = R^4 = Me
Boletopsin 12 (1-10): R^1 = R^2 = R^3 = Me, R^4 = H



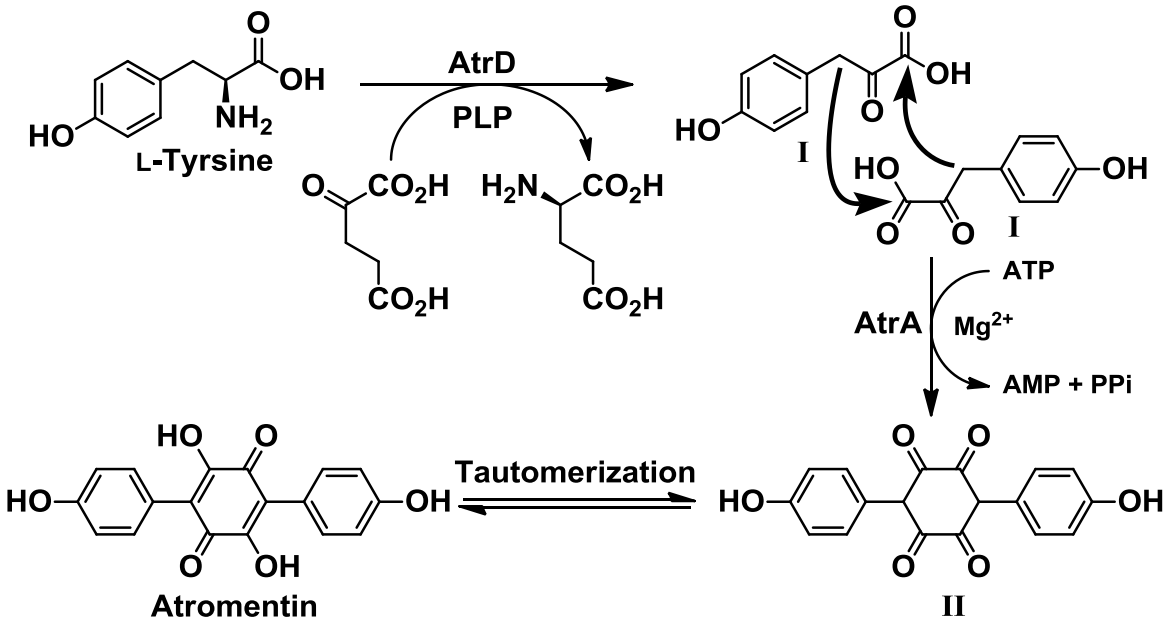
Candidusin B (1-11)



3'-Demethoxy-6'-desmethyl-5'-methoxycandidusin B (1-12)

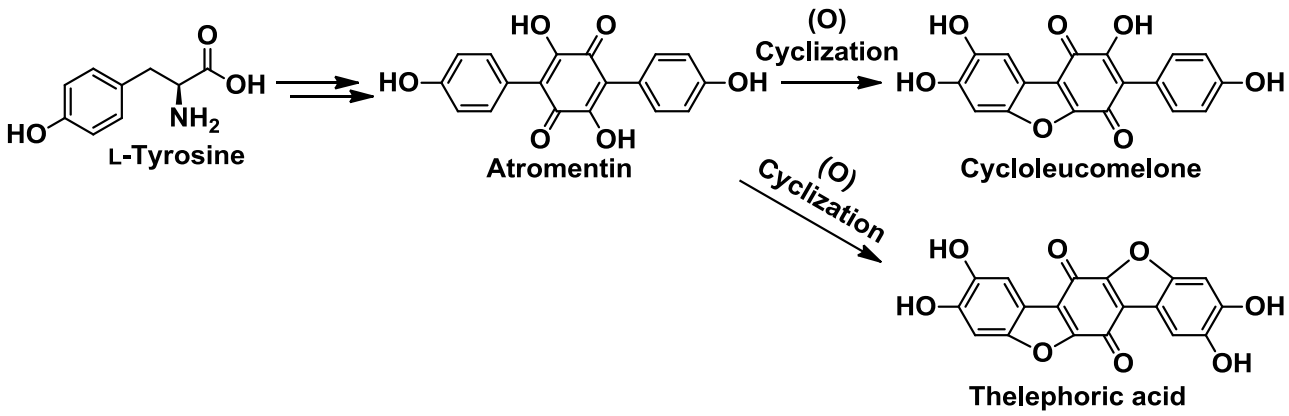
Figure 1-1. 3-Phenyldibenzofuran natural products

The *para*-terphenyl core skeleton of 3-phenyldibenzofuran natural products and related *para*-terphenyl diester natural products has also attracted the interest on biosynthesis. After intensive research, it was clarified that L-tyrosine or L-phenylalanine acts as a building block in the *para*-terphenyl biosynthesis. For example, atromentin, a *para*-terphenylquinone, was demonstrated to be biosynthesized via a route starting from L-tyrosine: deamination of L-tyrosine by pyridoxal 5'-phosphate (PLP) -dependent deaminase AtrD to give 4-hydroxyphenylpyruvic acid (**I**), which was dimerized by tri-domain enzyme atromentin synthetase AtrA to provide artomentin via intermediate **II** (Scheme 1-1)[7].



Scheme 1-1. Biosynthesis of *para*-Terphenylquinone Natural Product Atromentin.

However, the biosynthesis of the dibenzofuran moiety is still unclear, and only several biogenetic pathways are proposed. A plausible biogenetic pathway giving 3-phenyldibenzofuran natural products from atromentin is shown in Scheme 1-2[7,8]. It is believed that the oxidation or dihydroxylation of either or both of the terminal aromatic rings of atromentin followed by cyclization would produce cycloleumelone or thelephoric acid.



Scheme 1-2. Proposed Biosynthetic Pathways of Phenyldibenzofuran Natural Products.

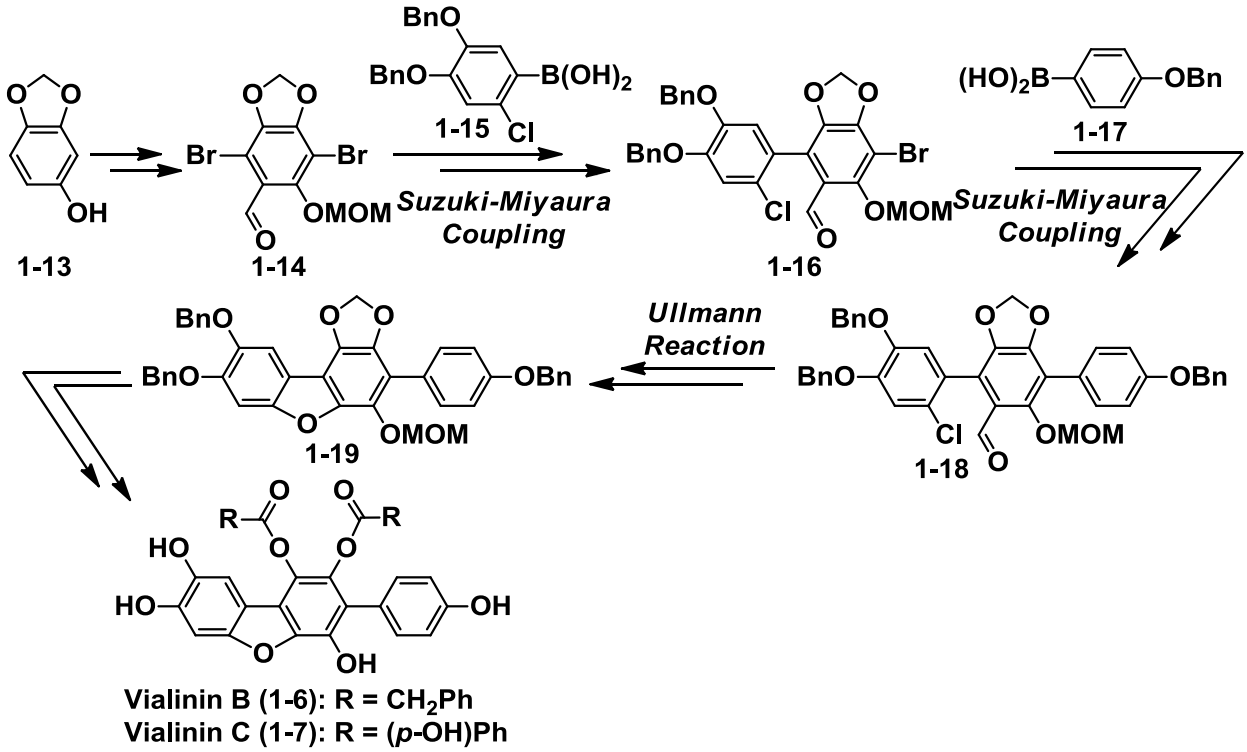
1-2. Reported Total Synthesis of 3-Phenyldibenzofuran Natural Products

Although the isolations of 3-phenyldibenzofuran natural products have been reported since early 1980s, total synthesis of them has been achieved only recently by a few research groups. To date, most of the total syntheses applied only a similar route including Suzuki-Miyaura coupling[9] and Ullmann ether synthesis.[10]

1-2-1. Total Synthesis of Kehokorins A-E and Vialinins B-C by the Takahashi Group

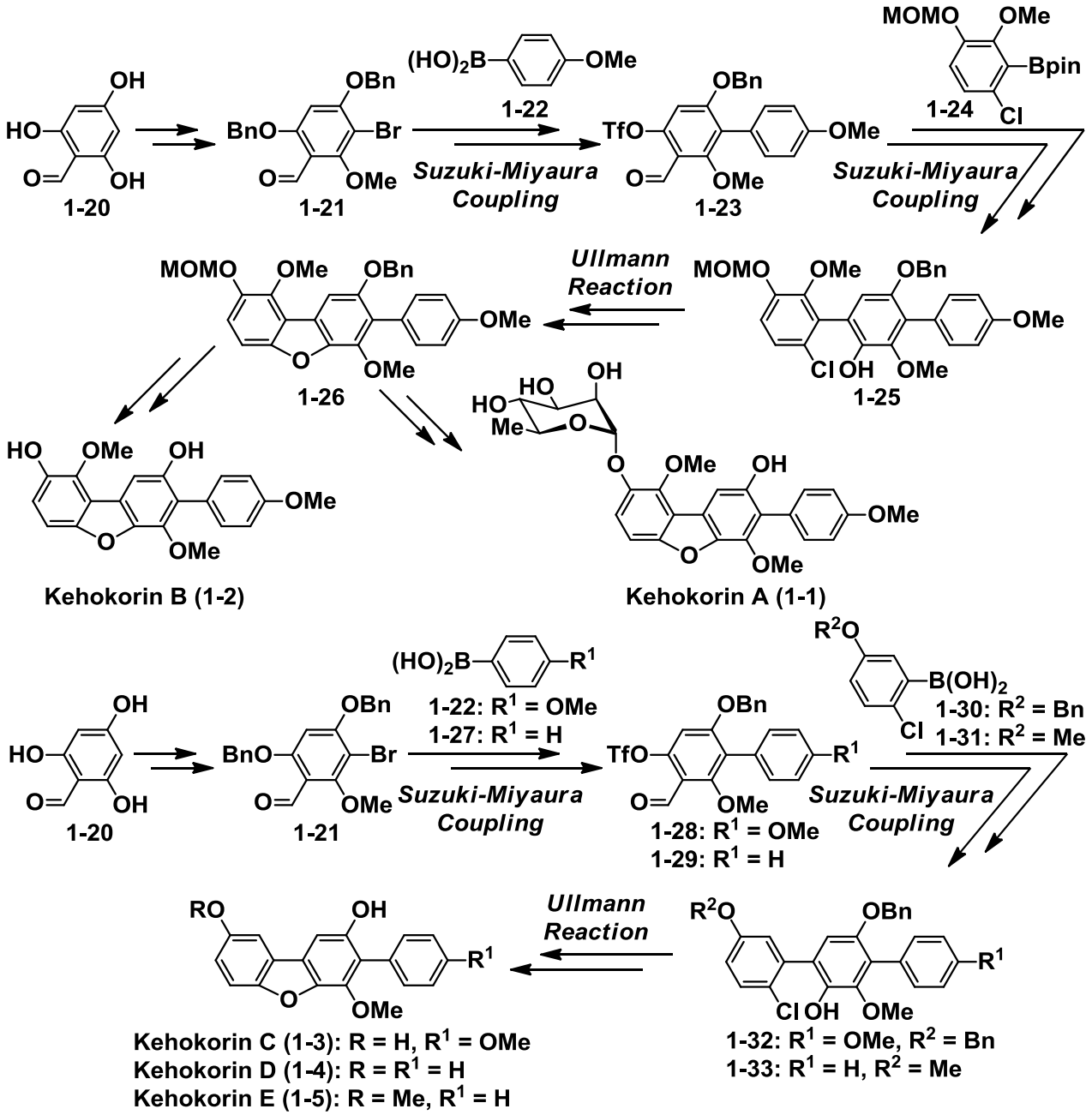
The Takahashi group synthesized vialinin B (**1-6**) in 2009 as a first example of the total synthesis of 3-phenyldibenzofuran natural products (Scheme 1-3).[11] Then, vialinin C (**1-7**) (Scheme 1-3)[4] and kehokorins A–E (**1-1**–**1-5**) (Scheme 1-4)[12] were also synthesized via a common process using Suzuki-Miyaura coupling and Ullmann ether synthesis as key reactions.

In the total synthesis of vialinin B (**1-6**) and C (**1-7**), *p*-terphenyl **1-18** was obtained by stepwise Suzuki-Miyaura coupling reactions of dibromide **1-14**, derived from sesamol (**1-13**), using aryl borans **1-15** as the first coupling partner and **1-17** as the second partner. Then, *p*-terphenyl **1-18** was converted to 3-phenyldibenzofuran **1-19** via Ullmann ether synthesis. After the manipulation of protecting groups and esterification, total synthesis of vialinin B (**1-6**) and vialinin C (**1-7**) was achieved.



Scheme 1-3. Total synthesis of vialinins B and C by the Takahashi group[11]

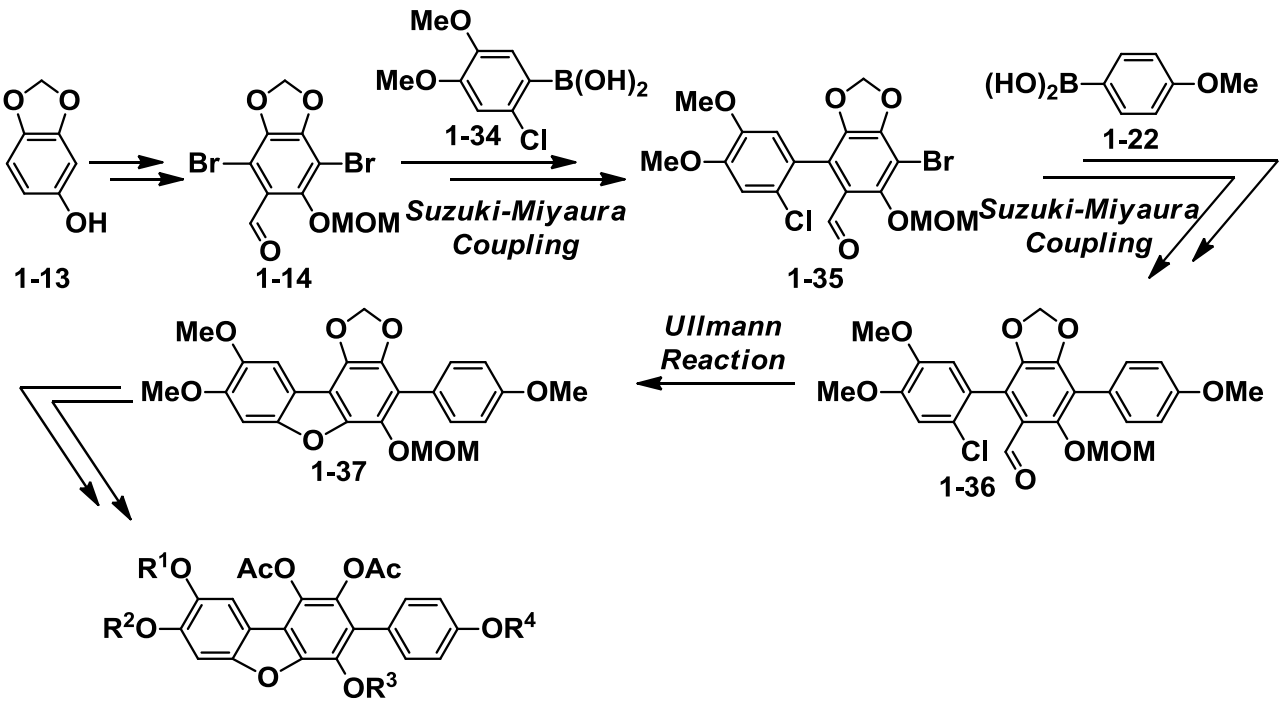
The total synthesis of kehokorins A–E (**1-1**–**1-5**) also accomplished by the similar strategy with modification aiming at efficiency.[12] After 2,4,6-trihydroxybenzaldehyde (**1-20**) was transformed to bromide **1-21**, Suzuki-Miyaura coupling of **1-21** with boronic acid **1-22** followed by functional group interconversion produced biphenyl **1-23**, which was subjected to the second Suzuki-Miyaura coupling with boronic acid **1-24** to give *p*-terphenyl **1-25**. Dibenzofuran formation under Ullmann conditions afforded 3-phenyldibenzofuran **1-26**, which was converted to kehokorins A (**1-1**) and B (**1-2**). Kehokorin C-E (**1-3**–**1-5**) also synthesized the same strategy starting from **1-21** via biphenyls **1-28** and **1-29**. The strategy of the Takahashi group is characterized by the late stage dibenzofuran formation using Ullman ether synthesis.



Scheme 1-4. Total synthesis of kehokorins A-E by the Takahashi group[12]

1-2-2. Total Synthesis of Boletopsins 7, 11 and 12 by the Barrow Group

The total synthesis of boletopsins 7, 11 and 12 (**1-8**–**1-10**) was achieved by Barrow group applying the same strategy as the Takahashi group (Scheme1-5).[12,13] After dibromide **1-14** was prepared from sesamol (**1-13**), a process including the double Suzuki-Miyaura coupling reaction of **1-14** with boromic acids **1-34** and **1-22** produced terphenyl **1-36**, which was transformed to 3-phenyldibenzofuran **1-37** by Ullmann ether synthesis. Finally, the protected dibenzofuran **1-37** was successfully converted to boletopsins 7, 11 and 12 (**1-8**–**1-10**).

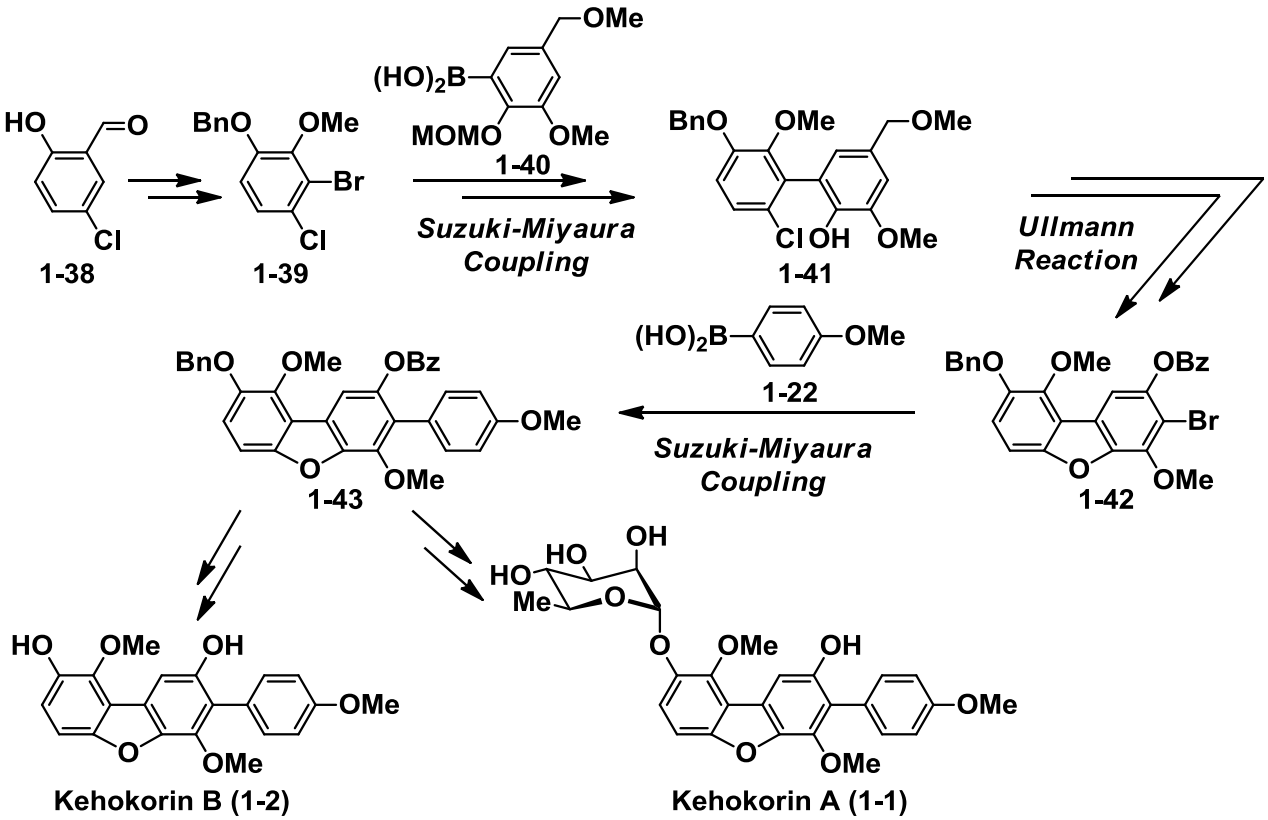


Boletopsin 7 (1-8): $R^1 = R^2 = R^3 = R^4 = H$
Boletopsin 11 (1-9): $R^1 = R^2 = R^3 = R^4 = Me$
Boletopsin 12 (1-10): $R^1 = R^2 = R^3 = Me$, $R^4 = H$

Scheme 1-5. Total synthesis of boletopsins 7, 11 and 12 by the Barrow group[13]

1-2-3. Total Synthesis of Kehokorins A and B by the Fujiwara group

Another total synthesis of Kehokorin A and B was also accomplished by use of Suzuki-Miyaura coupling and Ullmann ether synthesis by the Fujiwara group including the author as a co-worker (Scheme 1-6).[14] The synthesis featured the first formation of the dibenzofuran unit, which was then connected with an aryl group at the 3-position to give a 3-phenyldibenzofuran skeleton. The synthesis was started from 5-chlorosalicylaldehyde **1-38**, which was converted to bromide **1-39**. Suzuki-Miyaura coupling of **1-39** with boronic acid **1-40** provided biphenyl **1-41**, which was transformed to dibenzofuran **1-42** by Ullmann ether synthesis and bromination. Bromide **1-42** was subjected to the second Suzuki-Miyaura coupling with boronic acid **1-22** to give 3-phenyldibenzofuran **1-43**. A process including the manipulation of protecting groups and rhamnosylation converted **1-43** to kehokorin A (**1-1**). The deprotection of **1-43** produced kehokorin B (1-2).



Scheme 1-6. Total synthesis of kehokorins A and B by the Fujiwara group[14]

As shown in this section, the previous syntheses of 3-phenyldibenzofuran natural products employed a common strategy, characterized by the sequential union of three aromatic components by Suzuki-Miyaura coupling and Ullman ether synthesis. In contrast, the author planned to synthesize the 3-phenyldibenzofuran skeleton from two components by [2+2+2] cycloaddition.[15]

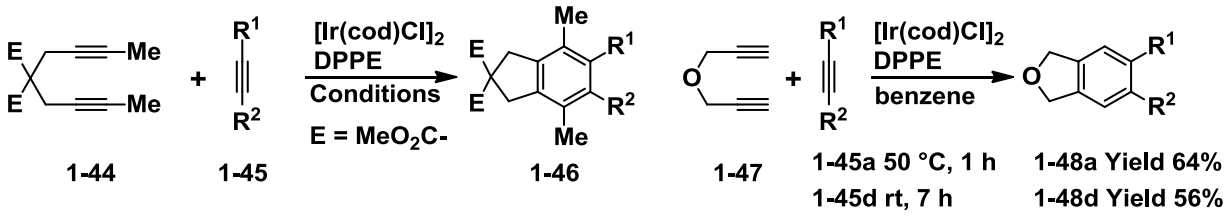
1-3. Reported Examples of Benzene-ring Formation by [2+2+2] Cycloaddition using Transition Metal Catalyst

This section outlines recent examples for the transition-metal-catalyzed [2+2+2] cycloaddition of three alkyne moieties producing a benzene ring, which provides a strategy for constructing a 3-phenyldibenzofurane skeleton.

1-3-1. Iridium Complex-Catalyzed [2+2+2] Cycloaddition Reaction

The Takeuchi group found that an iridium complex, prepared from $[Ir(cod)Cl]_2$ and DPPE, catalyzed the [2+2+2] cycloaddition of α,ω-diynes with monoynes to produce aromatic compounds .[16] This is the first example of iridium-catalyzed [2+2+2] cycloaddition.

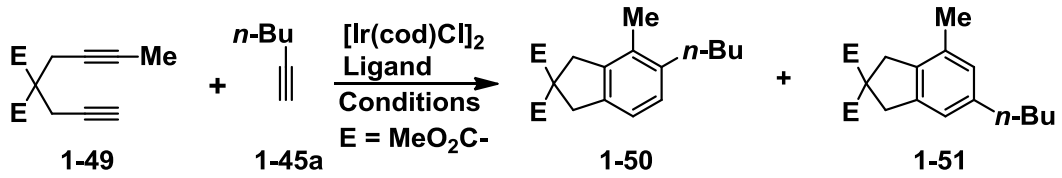
In the [2+2+2] cycloaddition reactions of symmetrical nona-1,6-diyne **1-44** and terminal or internal alkynes **1-45a-e**, $[Ir(cod)Cl]_2$ and DPPE, a bidentate ligand, constructed benzene derivatives in good to high yield (Table 1-1). Dipropargyl ether **1-47** having two terminal alkyne groups also reacted with terminal (**1-45a**) or internal alkyne (**1-45d**) to afford aromatic products. It should be noted that the presence of a terminal alkyne in substrates decreased the yield of aromatic products.



Entry	Monoyne	Conditions	Yield
1	1-45a (R^1 = *n*-Bu, R^2 = H)	toluene, reflux, 7 h	87%
2	1-45b (R^1 = Ph, R^2 = H)	toluene, reflux, 3 h	55%
3	1-45c (R^1 = CH_2OMe, R^2 = H)	toluene, reflux, 5 h	79%
4	1-45d (R^1 = R^2 = Et)	benzene, rt, 2 h	87%
5	1-45e (R^1 = R^2 = CH_2OMe)	benzene, rt, 30 min	94%

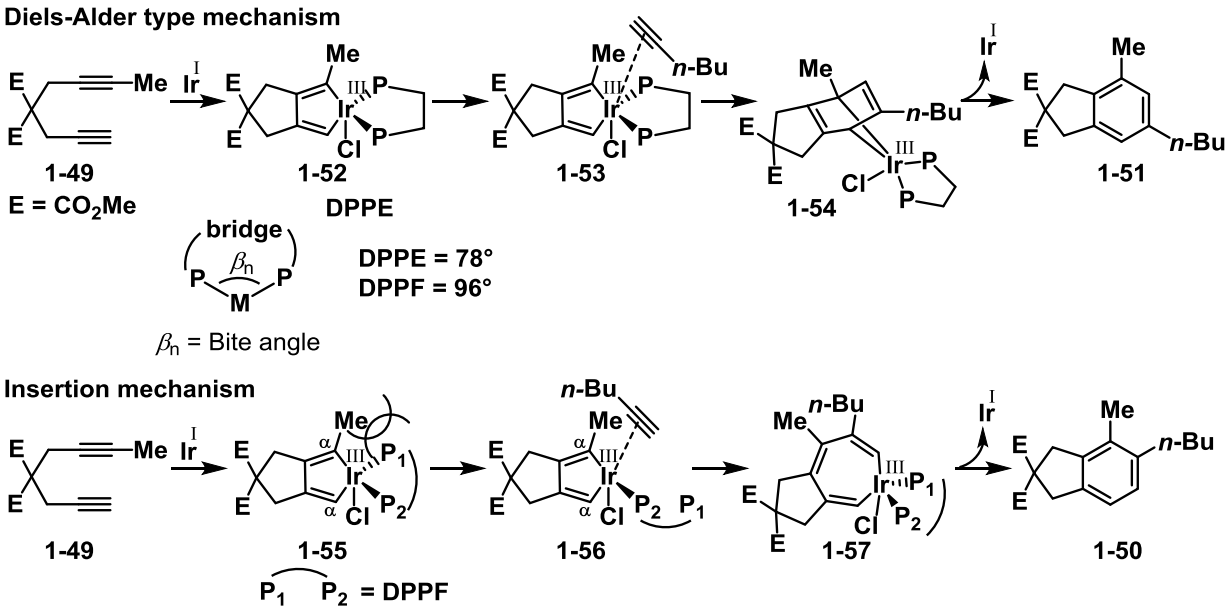
Table 1-1. Iridium-catalyzed cycloaddition of symmetrical α,ω-diyne with 1-alkyne by the Takeuchi group[16]

The Takeuchi group also found that the regioselectivity in the reaction of non-symmetrical diyne **1-49** and 1-hexyne (**1-45a**) was controllable by the selection of the ligand of the iridium catalyst (Table 1-2). Small bite angle ligands[17] such as DPPM and DPPE showed the *meta*-selectivity of the products. The *ortho*-selectivity increased with increasing the distance (the number of methylene carbons) between two phosphorus atoms of the ligand (Entry 3 and 4), though the reactivity decreased with increasing the distance (Entry 5). DPPF having a large bite angle displayed *ortho*-selectivity in good yield (Entry 6).



Entry	Ligand	Conditions	Yield	Ratio
1	DPPM	benzene, reflux, 5 h	84%	26:74
2	DPPE	benzene, rt, 30 min	93%	20:80
3	DPPP	benzene, reflux, 1 h	82%	43:57
4	DPPB	benzene, reflux, 1 h	89%	59:41
5	DPPH	benzene, reflux, 24 h	10%	70:30
6	1,2-bis(diphenylphosphino)ethylene	benzene, rt, 3 h	74%	19:81
7	DPPF	benezne, reflux, 1 h	84%	88:12
8	(*R*)-(*S*)-BPPFOAc	toluene, reflux, 3 h	72%	78:22
9	PPh_3	toluene, reflux, 3 h	32%	81:19

Table 1-2. Effect of ligands on regioselectivity in the [2+2+2] cycloaddition of unsymmetrical α,ω-diyne with 1-alkyne[16]



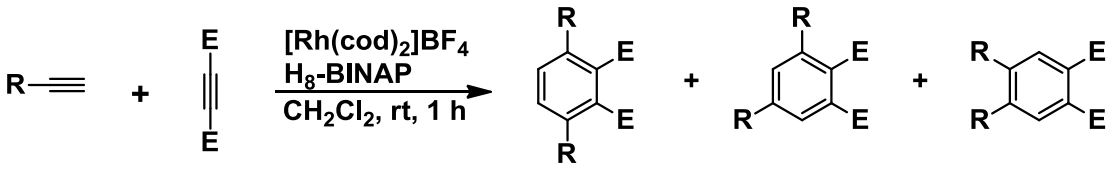
Scheme 1-7. Two plausible reaction mechanisms proposed by Takeuchi

Takeuchi proposed the following two plausible reaction mechanisms for this selectivity (Scheme 1-7). First is a Diels-Alder type mechanism, proposed for the meta-selective reaction with DPPE. The mononuclear species [Ir(cod)Cl](dppe) would be first generated from $[Ir(cod)Cl]_2$ and DPPE. Subsequently, [Ir(cod)Cl](dppe) would oxidatively cyclize **1-49** to give iridacyclopentadiene **1-52**, which would react with monoyne in a way similar to Diels-Alder reaction to give **1-54**. The *meta*-selectivity would be attributable to the alkyne approach avoiding the steric repulsion at this

stage. Reductive elimination from **1-54** would give *meta*-product **1-51**. Second is an insertion mechanism, which accounts for the ortho-selectivity exhibited by large-bite-angle ligands. The steric repulsion between the methyl group and the neighboring phsphanyl group of the iridacycle intermediate **1-55** would induce the dissociation of the phsphanyl group to create a vacant coordination site next to the methyl group. Coordination of a monoyne at this position (**1-56**) followed by insertion would give intermediate **1-57**. Reductive elimination from **1-57** would afford ortho-product **1-50**.

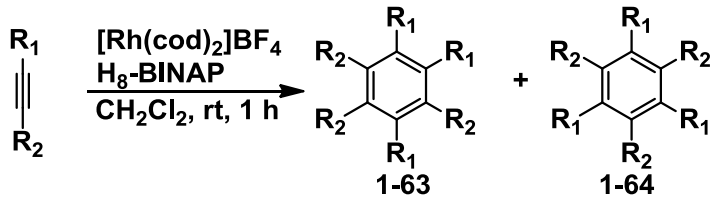
1-3-2. Cationic Rhodium Complex-Catalyzed [2+2+2] Cycloaddition Reaction

Although numerous examples of rhodium-catalyzed [2+2+2] cycloaddition were reported,[15] Tanaka first found that the cationic rhodium complex derived from $[Rh(cod)_2]BF_4$ and H_8-BINAP catalyzed intermolecular [2+2+2] cyclotrimerization of terminal alkynes in a highly regioselective manner with low catalyst loading.[18] It is notable that the complex also realized highly chemo- and regioselective intermolecular cocyclotrimerization of diethyl acetylenedicarboxylate (DEAD) and terminal alkynes, which selectively formed 3,6-disubstituted diethyl phthalates (Table 1-3).



Entry	R	Yield	Ratio
1	1-58a: *n*-$C_{10}H_{21}$	88%	92:6:2
2	1-58b: $Cl(CH_2)_3$	92%	91:8:1
3	1-58c: $MeOCH_2$	61%	86:10:4
4	1-58d: Ph	90%	89:9:2
5	1-58e: *o*-Tol	77%	89:9:2
6	1-58f: 1-cyclohexenyl	90%	91:4:5
7	1-58g: Me_3Si	57%	99:1:0

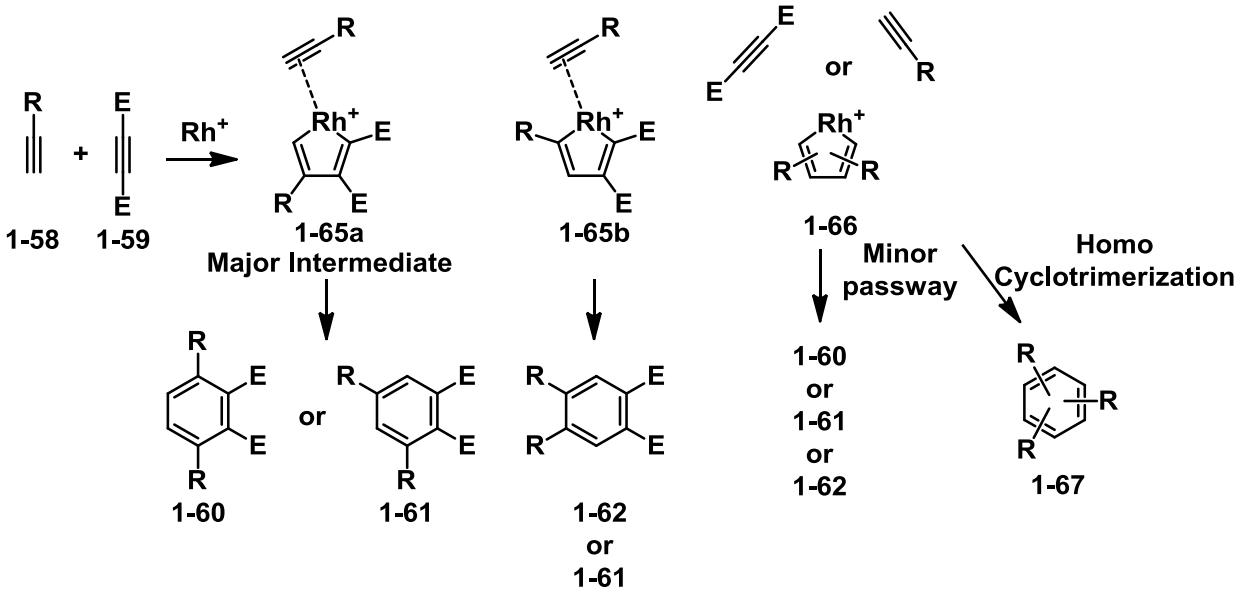
Table 1-3. Cationic Rh (I)/H_8-BINAP complex-catalyzed intermolecular cocyclotrimerization of DEAD and terminal alkynes[18a].



Entry	Substrate	R_1	R_2	Yield 1-63+1-64	Ratio of 1-63:1-64
1	1-58a	*n*-$C_{10}H_{21}$	H	6%	-
2	1-58c	CH_2OMe	H	95%	85:15
3	1-58d	Ph	H	94%	97:3
4	1-58g	Me_3Si	H	36%	83:17
5	1-59a	CO_2Me	CO_2Me	68%	-
6	1-59b	CO_2Et	CO_2Et	78%	-
7	1-59c	$CO_2{}^tBu$	$CO_2{}^tBu$	N.R.	-

Table 1-4. Reactivity of various alkynes in the presence of the cationic rhodium(I)/H_8-BINAP complex[18b].

Tanaka proposed a plausible reaction mechanism (Scheme 1-8). At the first stage, terminal alkyne **1-58** and dialkyl acetylenedicarboxylate **1-59** would produce metallacycle intermediates **1-65a** and **1-65b**. Metallacycles **1-66** may also form from **1-58**. Intermediate **1-65a** would react with **1-58** to give **1-60** and **1-61**, and metallacycle **1-65b** could cyclize with **1-58** to provide **1-61** and **1-62**. Intermediates **1-66** may also produce **1-60**, **1-61** and **1-62** as well as homo-cyclotorimerization products (**1-67**). Since **1-60** was a major cycloadduct, metallacycle **1-65a** or **1-66** should be a main intermediate. However, from the fact that the regioselectivity of intermolecular homo cyclotrimerization of **1-58** deviated from that of crossed-cyclotrimerization of **1-58** and **1-59**, Tanaka concluded that the formation of metallacycles **1-66** would be at least a minor pathway in the crossed-cyclotrimerization of **1-58** and **1-59** and that the main intermediate should be **1-65a**. Tanaka also described that the sterically unfavorable coordination of **1-59** in **1-65a**, which is indispensable for explaining the regioselective formation of **1-60**, would occur under electronic control.

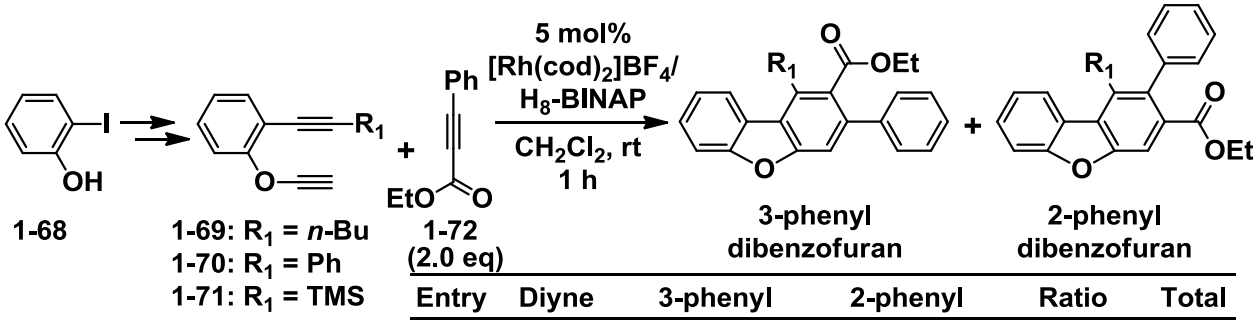


Scheme 1-8. Plausible mechanism for intermolecular crossed-cyclotrimerization of **1-58** and **1-59** catalyzed by the cationic rhodium (I)/H_8-BINAP complex[18].

1-4. Reported Synthesis of 3-Phenyldibenzofurans Based on Two-Component [2+2+2] Cycloaddition

As described above, the author planned to synthesize the 3-phenyldibenzofuran skeleton from two components by [2+2+2] cycloaddition. The synthesis would be achievable from α,ω-diynes with monoynes having a phenyl group. A [2+2+2] cycloaddition providing a 3-phenyldibenzofuran skeleton, close related to the author's purpose, was also reported by Tanaka.

Tanaka's typical two-component [2+2+2] cycloaddition producing 3-phenyldibenzofurans is shown in Table 1-5.[19] Three 1,6-diynes **1-69**, **1-70** and **1-71**, synthesized from 2-iodophenol (**1-68**), were reacted with ethyl phenylpropiolate (**1-72**) in the presence of a cationic rhodium catalyst, prepared from $[Rh(cod)_2]BF_4$ and H_8-BINAP, to produce 3-phenyldibenzofuran along with 2-phenyldibenzofuran in good total yield with modest to low regioselectivity.



Entry	Diyne	3-phenyl	2-phenyl	Ratio	Total
1	1-69	32%	17%	65:35	49%
2	1-70	26%	52%	34:66	78%
3	1-71	36%	36%	50:50	72%

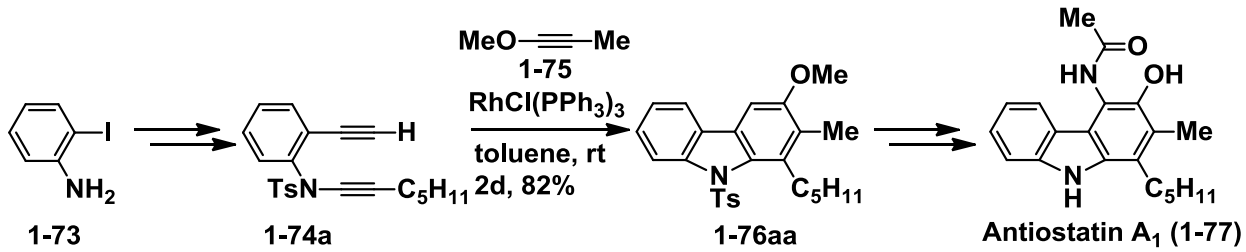
Table 1-5. Substituted dibenzofuran formation by cationic Rh (I)/H_8-BINAP complex-catalyzed [2+2+2] cycloaddition reaction[19]

Tanaka's reaction conditions are attractive to the author. However, for the application of the [2+2+2] cycloaddition reaction to the synthesis of 3-phenyldibenzofuran polyphenol natural products, optimization of the reaction conditions aiming at the improvement of regioselectivity is required. The methods for installing oxygen functional groups to the aromatic skeleton should also be developed.

1-5. Reported Application of [2+2+2] Cycloaddition Reaction to the Total Synthesis of a Carbazole Natural Product, Antiostatin A_1

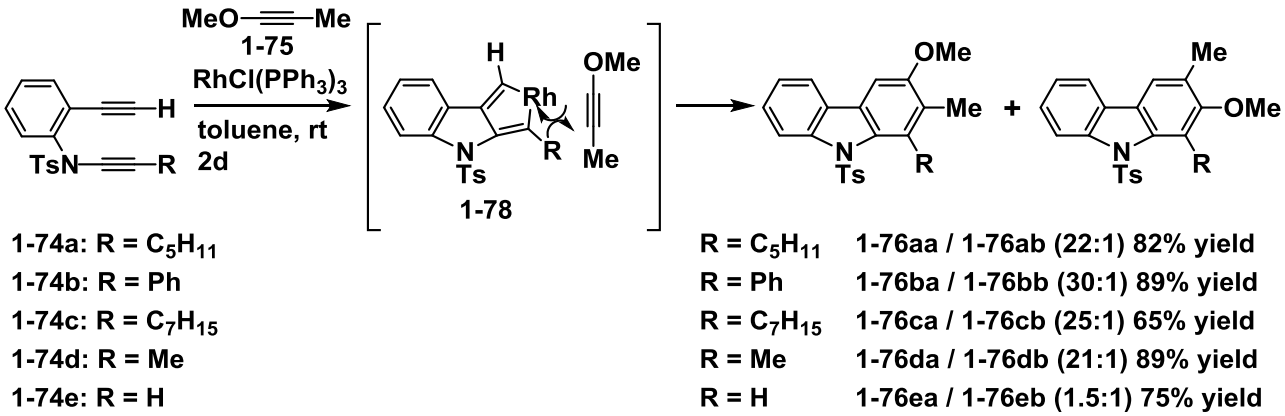
The [2+2+2] cycloaddition reaction was applied to a carbazole-type natural product, antiostatin A_1 (**1-77**),[20] by the Witulski group (Scheme 1-9).[21] This is an only example of the application of two-component [2+2+2] cycloaddition to natural product synthesis.

The synthesis was started from *o*-iodoaniline (**1-73**), which was transformed to diyne **1-74**. The [2+2+2] cycloaddition reaction of **1-74** with 1-methoxypropyne (**1-75**) in the presence of Wilkinson's catalyst, $RhCl(PPh_3)_3$,[22] produced a carbazole skeleton, which led to antiostatin A_1 (**1-77**), in high yield.



Scheme 1-9. Total synthesis of antiostatin A_1 (**1-77**) based on [2+2+2] cycloaddition[21]

The Witulski group also investigated the effect of the substituent of the ynamide of diyne **1-74** on the regioselectivity in the [2+2+2] cycloaddition with 1-methoxypropyne (**1-75**) (Scheme 1-10). The regioselectivity was rationalized by the coordination of the methoxy unit to the rhodium catalyst during the insertion process (**1-78**). Witulski described that further studies are necessary to gain insight into more mechanistic details.



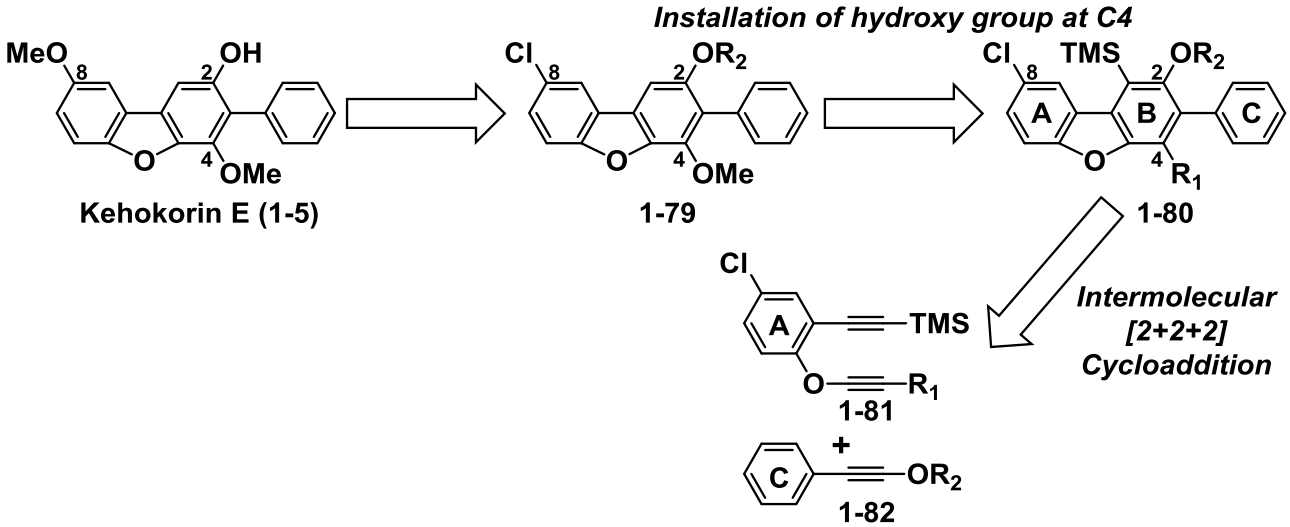
Scheme 1-10. The effect of the substituent of diynes on regioselectivity in Rhodium (I)-catalyzed [2+2+2] cycloaddition of diynes with 1-methoxy-1-propyne[21]

1-6. Plan for the Total Synthesis of Kehokorin E and 3'-Demethoxy-6'-desmethyl-5'-methoxy-candidusin B

The author is interested in the structure of 3-phenyldibenzofuran polyphenol natural products in view of SAR and development of new synthetic methodology. Therefore, total synthesis of 3-phenyldibenzofuran natural products, kehokorin E (**1-5**) and 3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B (**1-12**), via a new route based on a two-component [2+2+2] cycloaddition reaction was planned. The preparation of some synthetic derivatives of the natural products also intended.

First, the author planned the synthesis of kehokorin E (**1-5**) having two methoxy groups at C4 and C8 along with a hydroxy group at C2 (Scheme 1-11). The methoxy group at C8 was planned to be formed from a chloro group at C8 of **1-79** at the final stage of the synthesis. The C4 methoxy group of **1-79** would be constructed from the substituent R_1 of **1-80**. 2-Alkoxy-3-phenylbenzofuran **1-80** was designed to be constructed by a two-component [2+2+2] cycloaddition reaction of alkoxyphenylacetylene **1-82** and 1,6-diyne **1-81** with a substituent R_1, which might control the regioselectivity of cycloaddition.

Optimization of the reaction conditions of [2+2+2] cycloaddition of **1-82** and **1-81** for constructing the 3-phenyldibenzofuran skeleton was a main subject of this synthesis.

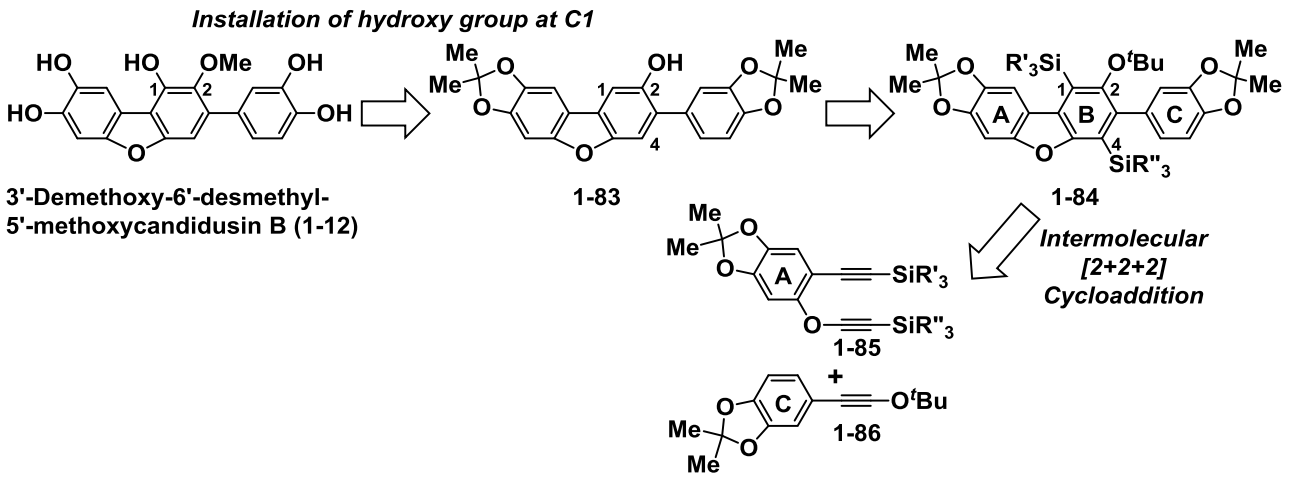


Scheme 1-11. Synthetic plan for kehokorin E (**1-5**)

Next, the synthesis of 3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B (**1-12**) was planned (Scheme 1-12). Polyphenol **1-12** is characterized by three 1,2-dioxy moieties. The 1,2-dihydroxy moieties of both terminal aromatic rings would come from a starting material. The 1,2-dioxy group of the middle benzene ring was intended to construct by introducing a hydroxyl group at C1 of **1-83** at the final stage of the synthesis. 3-Aryldibenzofuran **1-83** would be constructed via **1-84** by two-component [2+2+2] cycloaddition of 1,6-diyne **1-85** with *tert*-butoxy-

phenylacetylene **1-86** under the conditions optimized in the synthetic study of kehokorin E.

In the synthesis, the installation of an oxygen functional group at C1 of the middle benzene ring was an alternative challenge. The solution would be useful for the synthesis of other polyphenol natural products.



Scheme 1-12. Synthetic plan for 3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B (**1-12**)

1-7. The Objectives of the Dissertation Work

In the dissertation work, the author undertook the establishment of a new synthetic methodology for natural 3-phenyldibenzofuran polyphenols based on a two-component [2+2+2] cycloaddition reaction because of the interest in the SAR of the natural products and the development of new synthetic methodology for them.

The objectives of the dissertation work are as follows:

(i) Development of a new methodology based on a two-component [2+2+2] cycloaddition reaction for the construction of the 2-hydroxy-3-phenyldibenzofuran skeleton, seen in polyphenol natural products.

(ii) Application of the methodology to the synthesis of kehokorin E, 2-hydroxy-4,8-dimethoxy-3-phenyldibenzofuran, and the realization of regioselective [2+2+2] cycloaddition in the synthesis.

(iii) Application of the methodology to the synthesis of 3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B and the establishment of 1-hydroxy-2-methoxy substitution at the middle aromatic ring of the 3-phenyldibenzofuran skeleton.

Chapter 2 describes the studies toward objectives (i) and (ii), and Chapter 3 explains the investigation toward objective (iii).

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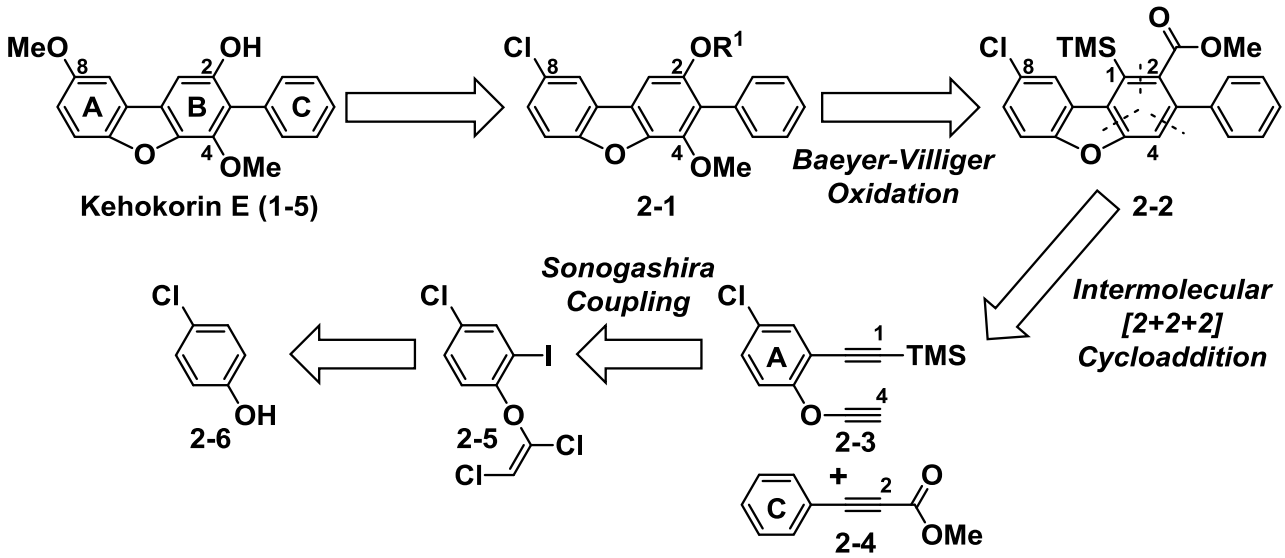
Chapter 2

A Synthetic Approach to Kehokorin E

2-1. Initial Plan for the Synthesis of Kehokorin E

As described in Chapter 1, the author planned to develop synthetic methodologies based on a two-component [2+2+2] cycloaddition reaction during the study toward the total synthesis of kehokorin E (**1-5**).[1]

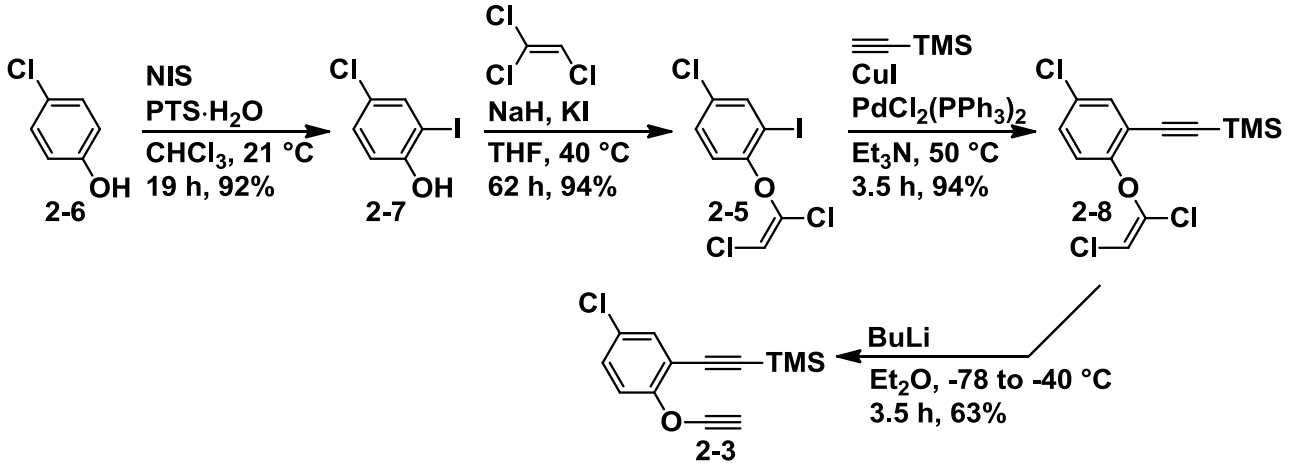
Since the instability of the A-ring of **1-5** was suspected due to the richness of electron, a chloro group was employed as a stable substitute for the methoxy group at C8 during the synthesis. Therefore, 2-alkoxy-8-chloro intermediate **2-1** was envisioned as a precursor of **1-5**. Initially, the [2+2+2] cycloaddition was planned to use Tanaka's conditions,[2] and, therefore, 1,6-diyne **2-3** and methyl phenylpropiolate (**2-4**) were selected as substrates for 3-carbomethoxy-2-trimethylsilyl substituted 3-phenyldibenzofuran **2-2**. The interconversion of functional groups of **2-2**, including Baeyer-Villiger oxidation to install an oxygen functional group at C4, would lead to **2-1**. 1,6-Diyne **2-3** would be derived from commercially available **2-6** according to the procedure reported by Tanaka[2].



Scheme 2-1. Initial synthetic plan for the kehokorin E (**1-5**).

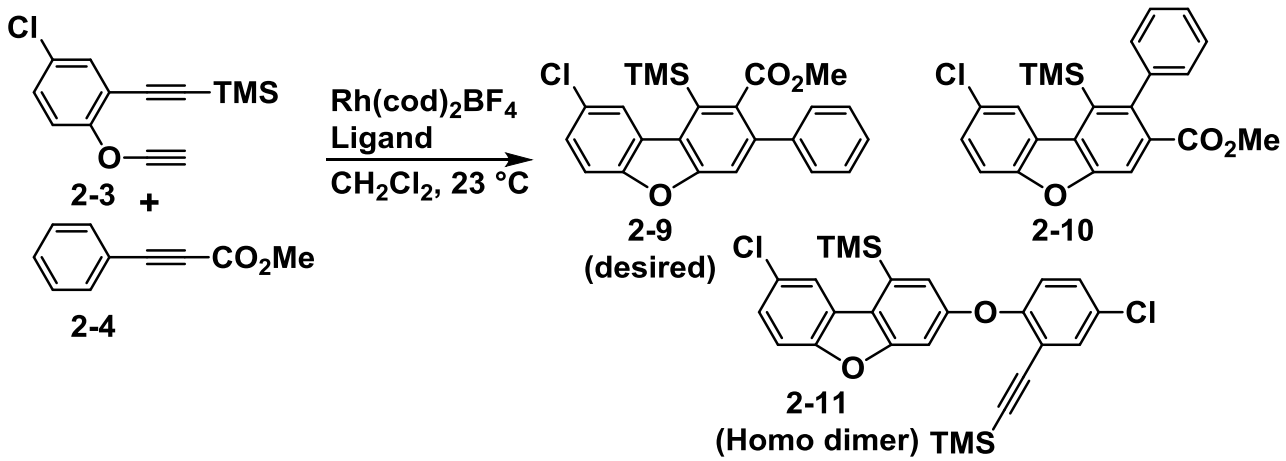
2-2. An Attempt of [2+2+2] Cycloaddition of a 1-Ethynyl-2-(ethynyloxy)benzene and Methyl Phenylpropiolate

Synthesis of 1,6-diyne **2-3** is shown in Scheme 2-2. First, *p*-chlorophenol **2-6** was reacted with NIS in the presence of PTS to give monoiodide **2-7**,[3] which was then transformed to 1,6-diyne **2-3** in good yield over 3 steps [(i) formation of a 1,2-dichlorovinyl ether, (ii) Sonogashira reaction and (iii) formation of an ethynyl ether] according to the procedure reported by Tanaka[2].



Scheme 2-2. Synthesis of 1,6-diyne **2-3**.

Next, [2+2+2] cycloaddition of **2-3** and commercially available **2-4** was examined under the Tanaka conditions[2] (Table 2-1). After the active catalyst was freshly prepared from $[Rh(cod)_2]BF_4$ and H_8-BINAP or BINAP under H_2 atmosphere, the catalyst was treated with **2-3** and **2-4** in CH_2Cl_2 at ambient temperature to produce cyclotrimerization products. However, the desired 3-phenyldibenzofuran **2-9** was obtained as a minor product in 1% yield at most along with regioisomer **2-10**, which was also given in the same yield. The major product was **2-11**, a homo [2+2+2] cycloadduct, of which the structure was determined by NMR analysis. The failure in reproducing Tanaka's result may be due to an initial inexperience, which may cause insufficient complexation of $Rh(cod)_2BF_4$ with H_8-BINAP or BINAP. However, it should be noted that the homo-[2+2+2] reaction of **2-3** was enhanced by such incomplete Rh-catalyst to produce **2-11**. This suggests that alkoxyacetylenes would be highly reactive in Rh-catalyzed [2+2+2] cycloaddition and that the [2+2+2] cycloaddition between a 3-oxahept-1,6-diyne (such as **2-3**) and an alkoxyacetylene (monoyne) would proceed even with a neutral Rh-catalyst such as $Rh(PPh_3)_3Cl$.



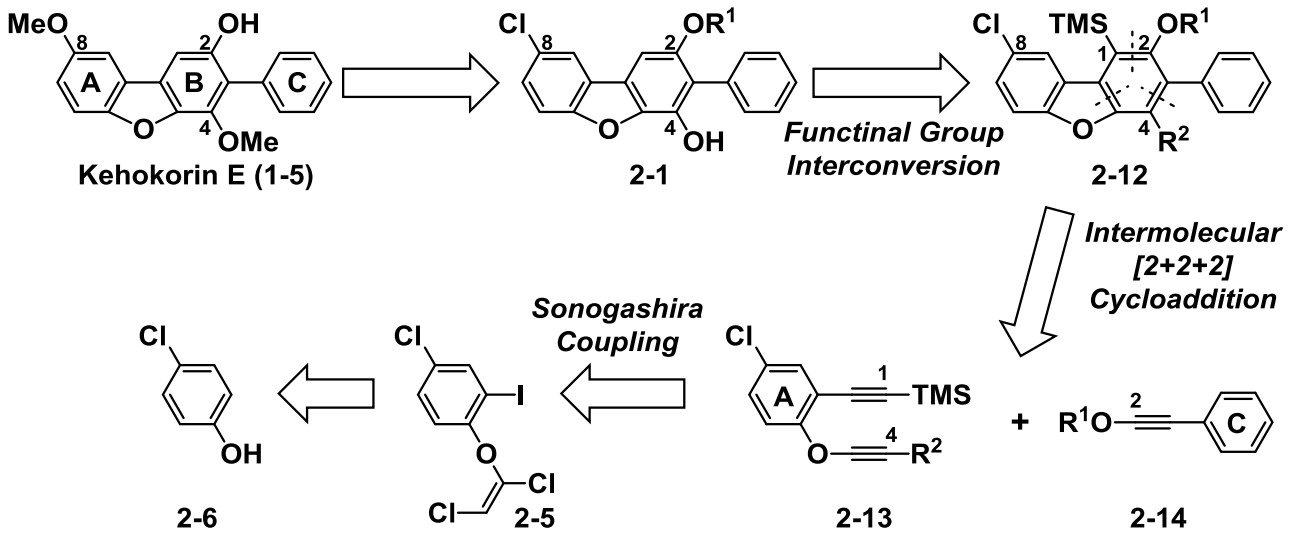
Entry	2-4 (eq)	Catalyst (mol%)	Ligand (mol%)	2-9 (desired)	2-10	2-11 (Homo dimer)
1	2.0	10	BINAP (10)	trace	trace	major
2	2.0	5	H_8-BINAP (5)	>1%	>1%	major

Table 2-1. Attempting two-component [2+2+2] cycloaddition reaction with cationic Rh-catalyst

2-3. The Second Plan for the Synthesis of Kehokorin E

From the above result and consideration, the synthetic route to kehokorin E (**1-5**) was re-designed as shown in Scheme 2-3. The 2-hydroxy-3-phenyldibenzofuran skeleton of **1-5** was conveniently deduced from 1,6-diyne **2-13** and alkoxyacetylene **2-14**. To realize the route, suppression of the dimerization of 1,6-diyne **2-13** was necessary, and, therefore, employment of bulky groups (TMS and R^2) at the both ends of 1,6-diyne **2-13** was planned for inhibiting the dimerization by steric congestion (Figure 2-1). Thus, the intermolecular [2+2+2] cycloaddition of **2-13** and **2-14** was expected to provide **2-12**, which would lead to **2-1** by the removal of TMS and the conversion of R^2 to a hydroxy group. The chloro group at C8 of **2-1** would be transformed to a methoxy group at the final stage to produce **1-5**.

For the required optimization of the [2+2+2] cycloaddition, 1,6-diynes (**2-15**, **2-16** and **2-17**, *vide infra*) having a trimethylsilyl group at the phenyl acetylene moiety and a 2-hydroxypropan-2-yl group or a trialkylsilyl group as R^2 at the terminal of the alkoxy acetylene unit as well as alkynyl ethers (**2-18** and **2-19**, *vide infra*) having a methoxyphenyl or a *tert*-butyl group as R^1 were employed.



Scheme 2-3. The second plan for the synthesis of the kehokorin E (**1-5**)

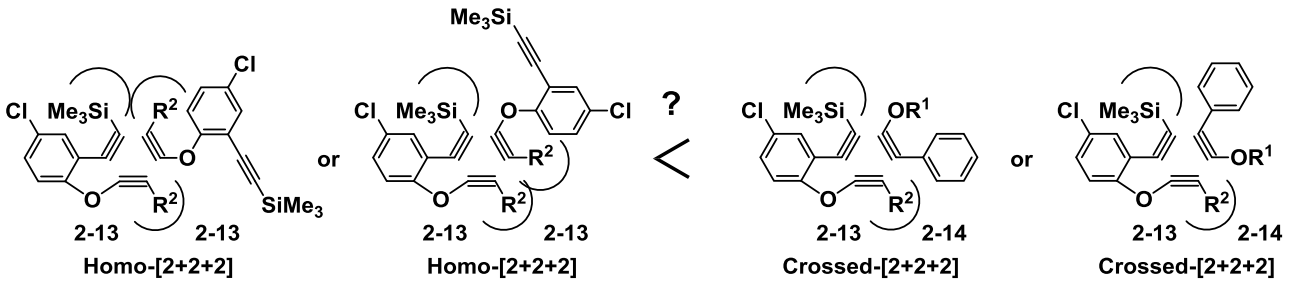
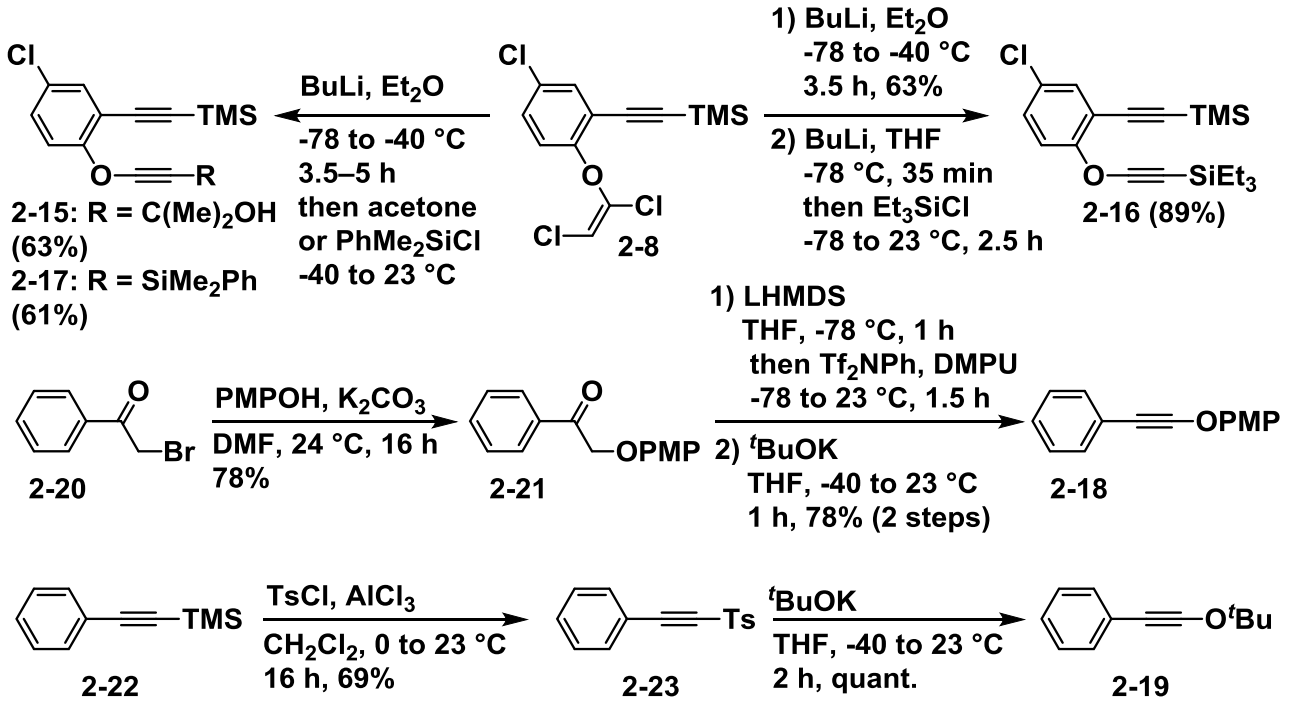


Figure 2-1. Estimation of steric congestion in homo- and crossed-[2+2+2] cycloaddition reactions

2-4. Synthesis of a 3-Phenyldibenzofuran Skeleton Based on [2+2+2] Cycloaddition of a 1-Ethynyl-2-(ethynyloxy)benzene and an Alkynyl Ether

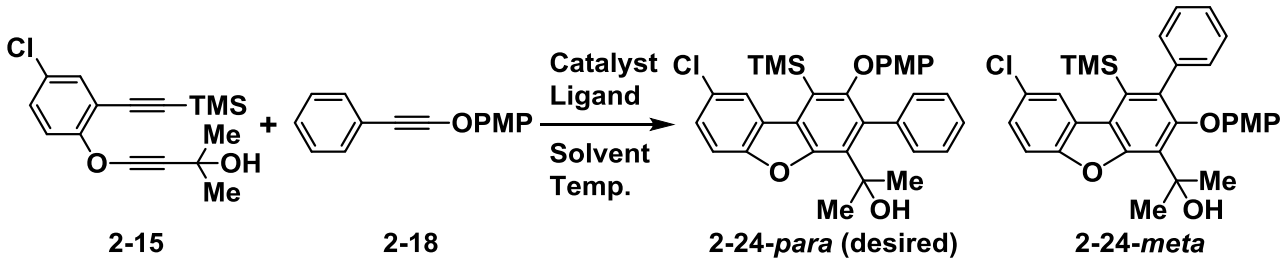
Synthesis of 1,6-diynes **2-15**, **2-16** and **2-17** having bulky groups at the terminal of alkyne groups as well as alkynyl ethers **2-18** and **2-19** is shown in Scheme 2-4. Diyne **2-15** having a 2-hydroxypropan-2-yl group was prepared by lithiation of **2-8** with BuLi followed by reaction with acetone. Bissilyl-1,6-diynes **2-16** and **2-17** were similarly synthesized via a lithiation/silylation sequence from **2-8**. Alkynyl ethers **2-18**[4] and **2-19**[5] were synthesized according to literature procedures. PMP ether **2-18** was unstable and was used immediately in the next reaction. *tert*-Butyl ether **2-19** was fairly stable and storable at low temperature for several days.



Scheme 2-4. Synthesis of 1,6-diynes **2-15**, **2-16** and **2-17** and alkynyl ethers **2-18** and **2-19**

Next, the reaction conditions of the two-component [2+2+2] cycloaddition was optimized using 1,6-diyne **2-15** and alkynyl PMP ether **2-18** (Table 2-2). Initially, the reactions were carried out in a way that all of the substrates and (activated) catalyst were added in one portion to a reaction vessel to start reaction. The reaction of **2-15** and **2-18** was first examined in the presence of $[Ir(cod)Cl]_2$ and BINAP to produce cycloadducts **2-24-*para*** (4%) and **2-24-*meta*** (4%) in modest yields with 1:1 ratio (Entry 1).[6] The Tanaka conditions were also applied to the reaction using BINAP (Entry 2) and H_8-BINAP (Entry 3). The yields of cycloadducts were slightly better than the above results from **2-3** and **2-4**, but were still low. The employment of a neutral catalyst, $Rh(PPh_3)_3Cl$, also result in a small production of **2-24-*para*** and **2-24-*meta*** (Entry 4). At this stage, the author noted that all the reaction shown in Entries 1-4 produced suspected homodimers of **2-15** (not fully assigned), which suggested that a further measure against the homodimerization was

required. Since the dimerization results from the reaction of a rhodacyclopentadiene, initially formed from **2-15** and the catalyst, with another **2-15** molecule, lowering concentration of **2-15** would decrease the dimerization and increase the proper crossed [2+2+2] cycloaddition of **2-15** and **2-18**. Therefore, diyne **2-15** was slowly added dropwise to the mixture of **2-18** and catalyst $Rh(PPh_3)_3Cl$ using a syringe pump (Entry 5). As a result, dimerization of diyne **2-15** was suppressed, and the yields of **2-24-*para*** and **2-24-*meta*** were improved (13% and 7%, respectively) with enhancement of **2-24-*para*** production. Thus, the author found promising reaction conditions for the two-component [2+2+2] cycloaddition.



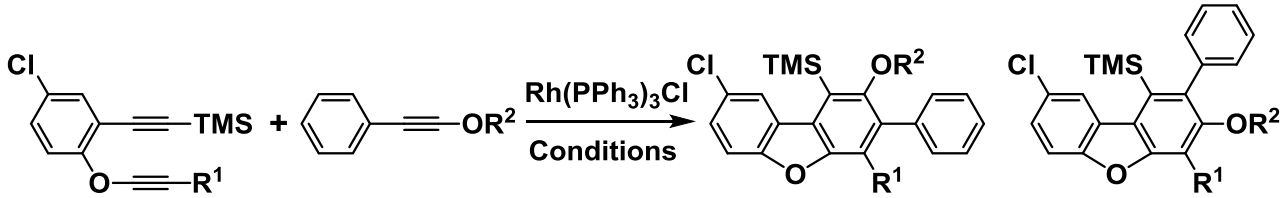
Entry	2-15	Equiv. of 2-18	Catalyst (mol%)	Ligand (mol%)	Solvent	Temp.	Yield *para*	Yield *meta*
1	[b]	2.1 eq	$Ir[(cod)Cl]_2$ (18)	BINAP (45)	benzene	50 °C	4%[a]	4%[a]
2	[b]	1.4 eq	$Rh(cod)_2BF_4$ (15)	BINAP (15)	CH_2Cl_2	22 °C	6%[a]	7%[a]
3	[b]	1.0 eq	$Rh(cod)_2BF_4$ (6)	H_8-BINAP (6)	$(CH_2Cl)_2$	55 °C	6%[a]	5%[a]
4	[b]	1.0 eq	$Rh(PPh_3)_3Cl$ (10)	—	toluene	22 °C	9%[c]	3%[c]
5	Slow Addition	1.0 eq	$Rh(PPh_3)_3Cl$ (14)	—	toluene	22 °C	13%[a]	7%[a]

(a) Isolated yield. (b) Added in one portion. (c) Calculated yield by NMR analysis.

Table 2-2. Optimization of reaction conditions for the [2+2+2] cycloaddition of **2-15** and **2-18**

Then, further optimization of the reaction conditions was undertaken (Table 2-3). The author determined to use $Rh(PPh_3)_3Cl$ as the catalyst of the [2+2+2] cycloaddition because of lower cost and easy availability. The goal of the optimization was to find the conditions giving 2-alkoxy-3-phenyldibenzofuran in high yield with good regioselectivity. In the initial conditions (Entry 1, as a duplicate of Entry 5 of Table **2-2**), a solution **2-15** in toluene was added dropwise to a solution of **2-18** and 14mol% of $Rh(PPh_3)_3Cl$ in toluene at 22 °C over 44 h using a syringe pump, and the mixture was additionally stirred for 49 h. As a result, **2-24-*para*** and **2-24-*meta*** were produced in 13% and 7% yields, respectively. When the amount of catalyst was increased, the yield of cycloadduct **2-24-*para*** and **2-24-*meta*** increased (17% and 12%, respectively) (Entry 2). Rising reaction temperature to 40 °C in the presence of 15 mol% catalyst also increased the yields of **2-24-*para*** and **2-24-*meta*** (20% and 11%, respectively) (Entry 3). When *tert*-butoxyacetylene **2-19** was used instead of 4-methoxyphenyloxyacetylene **2-18**, the reactivity and regioselectivity were improved (**2-25-*para*** and **2-25-*meta*** were obtained in 27% and 8%, respectively) (Entry 4).

Moreover, when the solvent was changed to benzene, cycloadducts **2-25-*para*** and **2-25-*meta*** were obtained with the best yields and selectivity (55% and 14%, respectively) (Entry 5). Interestingly, the cycloaddition of 1,6-diyne **2-16**, having a $SiEt_3$ group instead of the 2-hydroxypropan-2-yl group, with **2-18** showed reverse regioselectivity under the same conditions (**2-26-*para*** and **2-26-*meta*** were obtained in 15% and 36%, respectively) (Entry 6). This reverse reioselectivity was also observed in the reaction of **2-17** possessing a dimethylphenylsilyl group with **2-18** affording **2-27-*para*** and **2-27-*meta*** in 16% and 36%, respectively (Entry 7). Thus, the author found that $Rh(PPh_3)_3Cl$-catalyzed two-component [2+2+2] cycloaddition of diyne **2-15**, having 2-hydroxypropane-2-yl at the terminal of the alkoxy acetylene unit, with *tert*-butoxyacetylene **2-18** under pseudo-high-dilution conditions successfully afforded 2-alkoxy-3-phenyldibenzofuran **2-25-*para*** as a major product without dimerization of **2-15**.



2-15: $R^1 = C(Me)_2OH$ **2-18**: $R^2 = PMP$
2-16: $R^1 = SiEt_3$ **2-19**: $R^2 = {}^tBu$
2-17: $R^1 = SiMe_2Ph$
(Slow Addition)

para* (desired)** ***meta
2-24-*para*: $R^1 = C(Me)_2OH$, $R^2 = PMP$ **2-24-*meta***
2-25-*para*: $R^1 = C(Me)_2OH$, $R^2 = {}^tBu$ **2-25-*meta***
2-26-*para*: $R^1 = SiEt_3$, $R^2 = {}^tBu$ **2-26-*meta***
2-27-*para*: $R^1 = SiMe_2Ph$, $R^2 = {}^tBu$ **2-27-*meta***

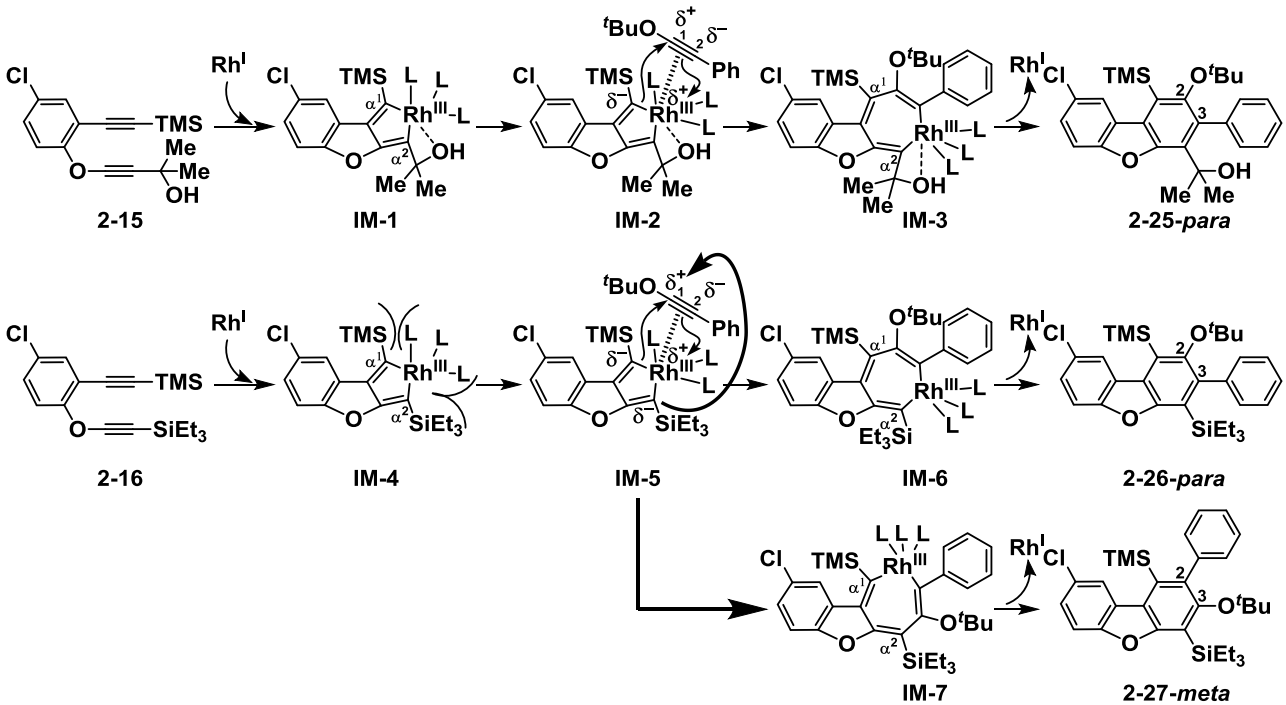
Entry	Diyne	Monoyne (eq)	$Rh(PPh_3)_3Cl$	Solvent	Temp.	Addition Period	Total Time	Prod.	Yield *para*	Yield *meta*
1	**2-15**	**2-18** (1.0)	14 mol%	toluene	22 °C	over 44 h	93 h	**2-24**	13%[a]	7%[a]
2	**2-15**	**2-18** (1.2)	30 mol%	toluene	22 °C	over 17 h	66 h	**2-24**	17%[a]	12%[a]
3	**2-15**	**2-18** (1.4)	15 mol%	toluene	40 °C	over 16 h	42 h	**2-24**	20%[a]	11%[a]
4	**2-15**	**2-19** (1.2)	10 mol%	toluene	40 °C	over 5 h	15 h	**2-25**	27%[b]	8%[b]
5	**2-15**	**2-19** (1.6)	12 mol%	benzene	40 °C	over 5 h	19 h	**2-25**	55%[b]	14%[b]
6	**2-16**	**2-19** (2.0)	15 mol%	benzene	40 °C	over 8 h	16 h	**2-26**	15%[c]	36%[c]
7	**2-17**	**2-19** (3.8)	15 mol%	benzene	40 °C	over 5 h	14 h	**2-27**	16%[c]	35%[c]

(a) Isolated yield. (b) Calculated yield based on the result of the succeeding chemical conversion.
(c) Calculated yield by NMR analysis.

Table 2-3. Optimization of reaction conditions for $Rh(PPh_3)_3Cl$-catalyzed [2+2+2] cycloaddition

At this stage, the reason for the regioselectivity is unknown and only speculated as shown in Scheme 2-5. The rhodium catalyst is first oxidatively added to a 1,6-diyne (**2-15**/**2-16**) to afford a rhodacyclopentadiene (**IM-1**/**IM-4**). The author speculates that the regioselectivity would be accounted by the difference of reactivity between $C\alpha^1$-Rh bond and $C\alpha^2$-Rh bond of the rhodacyclopentadiene intermediate. The difference in intermediate **IM-1**, formed from **2-15**, would

be explained by the hydrogen bonding between the 2-hydroxypropan-2-yl group and Rh, which would inhibit the dissociation of $C\alpha^2$-Rh bond in the next alkyne insertion process. The difference of reactivity between $C\alpha^1$-Rh and $C\alpha^2$-Rh of **IM-4**, generated from **2-16**, would come from the different degrees of steric repulsions between the TMS and the ligand groups and between the Et_3Si and the ligand groups: the bulkier Et_3Si group would have larger degree of steric repulsion against the ligands of Rh, and the resulting weakened $C\alpha^2$-Rh bond would have higher reactivity toward the next alkyne insertion process. In the next insertion step, the nucleophilic β-carbon of the alkoxyacetylene would selectively react with Rh atom, and the reactive (weakened) bond would be cleaved selectively to form a rhodacycloheptatriene intermediate (**IM-3**/**IM-7**). The reductive elimination of the rhodium catalyst from the rhodacycloheptatriene produces a dibenzofuran derivative. The author thus rationalizes the regioselectivity of the $Rh(PPh_3)_3Cl$-catalyzed [2+2+2] cycloaddition.

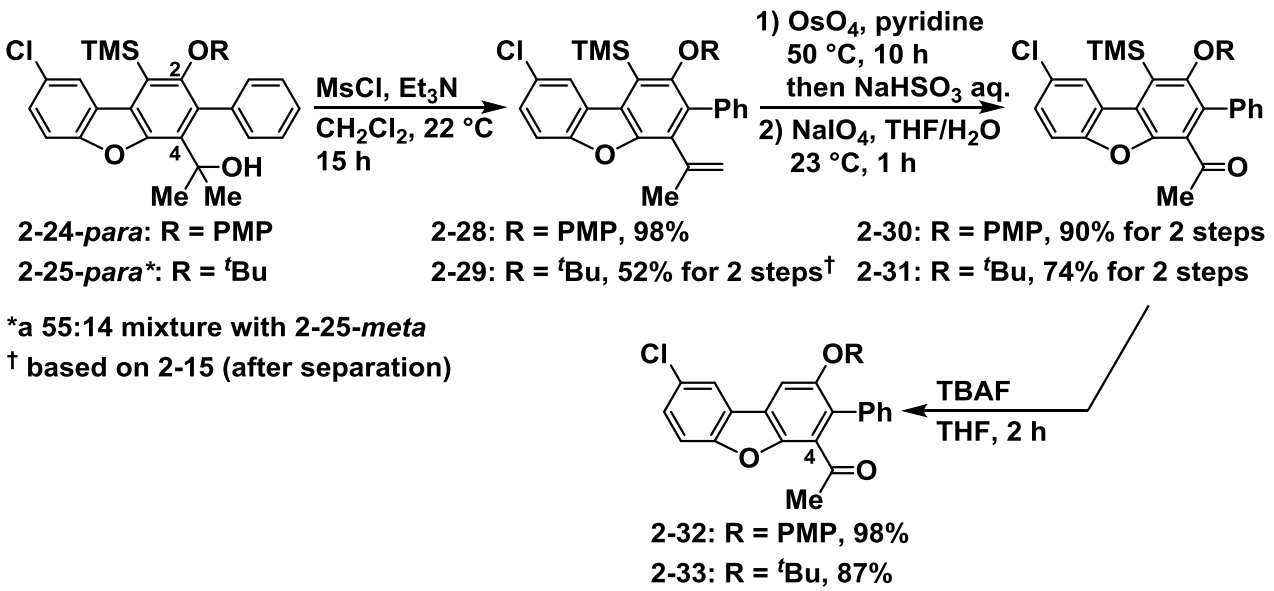


Scheme 2-5. Plausible mechanism of $Rh(PPh_3)_3Cl$-catalyzed [2+2+2] cycloaddition

2-5. Installation of a Hydroxy Group at C4 of the 3-Phenyldibenzofuran Skeleton

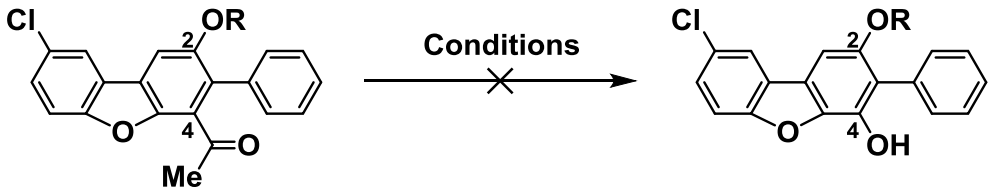
With the desired 2-alkoxy-3-phenyldibenzofurans **2-24-*para*** and **2-25-*para*** in hand, the author next examined the conversion of the 2-hydroxypropan-2-yl group at C4 to a hydroxy group.

Cycloaddition products **2-24-*para*** and **2-25-*para*** were first transformed to methyl ketones **2-32** and **2-33**, respectively (Scheme 2-6). Treatment of **2-24-*para*** with MsCl and Et_3N produced alkene **2-28** (98%), which was subjected to dihydroxylation followed by oxidative cleavage to give methyl ketone **2-30** (90% over 2 steps). The TMS group was removed with TBAF to afford **2-32** (98%). Since cycloadduct **2-25-*para*** and the isomer **2-25-*meta*** were inseparable, the dehydration of **2-25-*para*** was carried out using the mixture (a 55:14 mixture of *para*- and *meta*- isomers) to afford **2-29** (52% from **2-15**) after separation from unreacted **2-25-*meta***. Alkene **2-29** was similarly converted to **2-33** over 3 steps in good yield.



Scheme 2-6. Conversion of the 2-hydroxypropan-2-yl group at C4 to an acetyl group

Next, the author attempted to convert the acetyl group at C4 to an oxygen functional group by Baeyer-Villiger oxidation (Table 2-4). However, no C4-hydroxy compound (**2-35** or **2-36**) was produced under the conditions attempted. The treatment of **2-32** or **2-33** with *m*CPBA under neutral, acidic or basic conditions resulted in decomposition or no reaction (Entries 1, 2, 3 and 7). Dakin oxidation conditions and the modification gave also no desired product (Entries 4 and 8). Furthermore, radical oxidation conditios[7] and Oxone[8] were examined, but no phenol derivative was obtained (Entries 5 and 6). In order to modify the electronic nature of the acetyl group, methanesulfonate **2-34** was then prepared alternatively. However, ketone **2-34** was inert to peroxy acids and produced no oxygenated product (Entries 9, 10 and 11). Therefore, the author undertook an alternative approach.



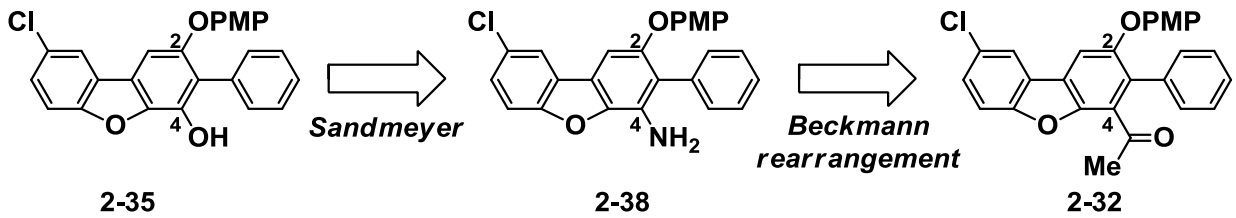
2-32: R = PMP
2-33: R = ^{t}Bu, 2-34: R = Ms

2-35: R = PMP
2-36: R = ^{t}Bu, 2-37: R = Ms

Entry	Substrate	Conditions	Yield
1	2-32	*m*CPBA, CH_2Cl_2, 22 °C	decomp.
2	2-32	*m*CPBA, PTS·H_2O, $(CH_2Cl)_2$, reflux	decomp.
3	2-32	*m*CPBA, KF, $(CH_2Cl)_2$, 50 °C	N.R.
4	2-32	H_2O_2, 2 M aq. NaOH, THF, 40 °C	N.R.
5	2-32	$Cu(OAc)_2$·H_2O, PhCHO, $(CH_2Cl)_2$, O_2 (1 atm), 22 °C	decomp.
6	2-32	Oxone, DMF or MeCN/H_2O (10:1), 22 or 60 °C	N.D.
7	2-33	*m*CPBA, KF, $(CH_2Cl)_2$, 22 °C or reflux	N.R.
8	2-33	H_2O_2, 2 M aq. NaOH, THF, Lewis acid, 22 °C or 50 °C	N.R.
9	2-34	*m*CPBA, CH_2Cl_2, 22 °C	N.R.
10	2-34	*m*CPBA, PTS·H_2O, $(CH_2Cl)_2$, reflux	N.R.
11	2-34	TFAA, Na_2HPO_4, UHP, $(CH_2Cl)_2$, 22 °C	N.R.

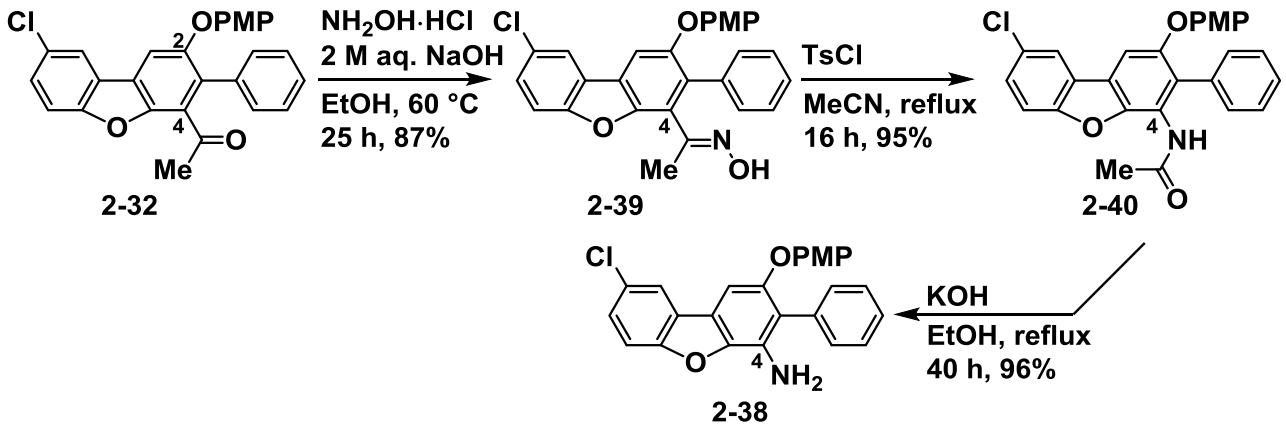
Table 2-4. Attempts to transform the acetyl group at C4 into a hydroxy group

For the formation of the C4 hydroxy group, the Sandmeyer reaction of a C4 amino group was envisioned (Scheme 2-7). Accordingly, a route including Beckmann rearrangement of methyl ketone **2-32** followed by Sandmeyer reaction of the resulting aniline **2-38** was employed. However, the use of **2-33** was excluded due to predicted instability of the *tert*-butoxy group under the acidic conditions of Beckmann rearrangement.



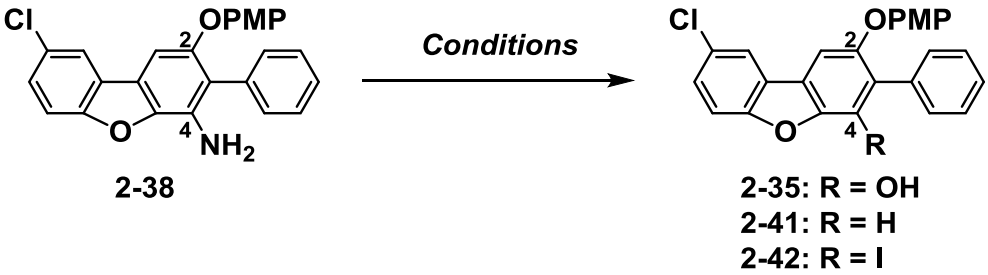
Scheme 2-7. An alternative plan for the installation of a hydroxy group at C4

The conversion of methyl ketone **2-32** to aniline **2-38** is shown in Scheme 2-8. Upon treatment with hydroxylamine hydrochloride, methyl ketone **2-32** gave oxime **2-39** (87%), which was reacted with TsCl to produce acetamide **2-40** (95%). The Beckmann rearrangement product was then hydrolyzed to afford aniline **2-38** (96%) successfully.



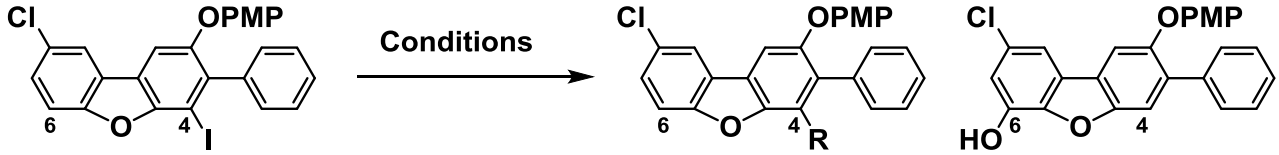
Scheme 2-8. Preparation of aniline **2-38**.

The next Sandmeyer reaction of aniline **2-38** to phenol **2-35** was, however, problematic. Although standard conditions (HCl and $NaNO_2$) converted **2-38** to a diazonium salt without problem, the diazonium salt was inert to hydroxylation under several conditions (simple worming and copper catalyzed conditions) (Table 2-5, Entries 1-4). The reactions only produced a mixture of byproducts including hydrogen substituted **2-41**. On the other hand, the reaction of the diazonium salt with potassium iodide facilely produced iodide **2-42** in 80%. Hence, the author subsequently examined the transformation of iodide **2-42** into **2-35**.



Entry	Conditions	Yield
1	3 M HCl, $NaNO_2$, MeOH, 0 °C, then $Cu(NO_3)_2{\cdot}3H_2O$, Cu_2O	**2-41 + mixture**
2	3 M HCl, $NaNO_2$, MeCN, -2 °C, then $Cu(NO_3)_2{\cdot}3H_2O$, Cu_2O	**2-41 + mixture**
3	10 M H_2SO_4, $NaNO_2$, MeCN, 0 to 21 °C	**2-41 + mixture**
4	^{t}BuNO$_2$, TFA, 0 to 21 °C, then MeOH, K_2CO_3	**2-41 + mixture**
5	3 M HCl, $NaNO_2$, MeOH, 0 °C, then KI	**2-42** (80%)

Table 2-5. Sandmeyer reaction of aniline **2-38**



2-42 **2-35: R = OH** **2-41: R = H** **2-43**

Entry	Conditions	Yield
1	KOH, CuI, 1,10-phenanthroline, DMSO/H_2O (1:1), 100 °C	**2-41**
2	CuI, Bu_4NOH in MeOH, 60 °C	**2-41**
3	BuLi, THF, -78 °C then $B(OMe)_3$, 0 °C then H_2O_2, NaOH aq, 22 °C	**2-41 + 2-43**
4	MeLi, O_2 (baloon), THF, -78 to 0 °C	**2-41**
5	$Pd_2(dba)_3{\cdot}CHCl_3$, JohnPhos, KOH, dioxane/H_2O (1:1), 100 °C	**2-35** (63%)

Table 2-6. Attempts to transform iodine **2-42** to phenol **2-35**

The conversion of **2-42** to **2-35** was also difficult (Table 2-5). First, Ullmann-type reaction using copper (II) iodide was attempted, but only hydrogenated product **2-41** was obtained (Entries 1[9] and 2[10]). Then, A stepwise hydroxylation process including lithiation, boronation and oxidative rearrangement was examined (Entry 3). However, no desired **2-35** was produced, while protonated **2-41** and C6-hydroxy substituted **2-43** were produced. This result suggested that the severe steric hinderance around C4 inhibited the carbanion at C4 from reacting with a large electrophile, such as $B(OMe)_3$, but permitted the carbanion to react with proton, a small electrophile. Therefore, the carbanion was attempted to react with O_2, but only protonation occurred to give **2-41** (Entry 4). Then, Buchwald's phenol synthesis was examined (Entry 5).[11] When **2-42** was treated with $Pd_2(dba)_3{\bullet}CHCl_3$, JohnPhos and potassium hydroxide in a 1:1 blend of dioxane-H_2O at 100 °C, phenol **2-35** was produced in 63% yield. However, even though the reaction was repeated several times, phenol **2-35** was given only once. The reproducibility of the reaction is a problem to be solved in the future.

Through the investigation toward the installation of C4 hydroxy group described in this section, it is clarified that the steric hinderance around C4 of a 3-phenyldibenzofuran is severe and inhibits C4 from reacting with external reagents. The Baeyer-Villiger reaction of C4-acetyl group using an external peroxide was inhibited, while Beckmann rearrangement of C4-1-(hydroxyimino)-ethyl group was permitted. These interesting difference of reactivity between intermolecular and intramolecular reactions may give an information to solve the problem of oxygen-installation at C4. The difference of nucleophilicity between iodide and hydroxide ions in Sandmeyer reaction, which may be explained by the polarizability of the center atom, would also provide important information.

2-6. Conclusion

The author examined a two-compornent [2+2+2] cycloaddition reaction to construct 3-phenyldibenzofuran polyphenol skeleton of kehokorin E (**1-5**). From the initial study of the [2+2+2] cycloaddition reaction of 1,6-diyne **2-3** with methyl phenylpropiolate (**2-4**), in which homodimer **2-11** was given mainly, it was suggested that alkoxyacetylenes shows high reactivity in [2+2+2] cycloaddition, that a neutral rhodium catalyst would have sufficient reactivity and that inhibition of homodimerization would be effective to install steric congestion at the terminals of alkynes of 1,6-diyneis. After extensive investigation according to the suggestions, the author found that the $RhCl(PPh_3)_3$-catalyzed [2+2+2] cycloaddition reaction of 1,6-diyne **2-15** having a 2-hydroxypropane-2-yl group with *tert*-butoxyacetylene **2-18** in benzene under pseudo-high-dilution conditions using a sylinge pump produced 2-alkoxy-3-phenyldibenzofuran **2-25-*para*** selectively (*para*:*meta* = 3.7:1) in 55% yield without formation of homodimers of **2-15**.

Next, in order to synthesize kehokorin E (**1-5**), the installation of the required C4 hydroxy group was examined using **2-24-*para*** having a PMP ether at C2 and a 2-hydroxypropane-2-yl group at C4. The 2-hydroxypropane-2-yl group was first converted to an acetyl group (**2-32**). Since the direct conversion of the acetyl group to an oxygen functional group was problematic, the acetyl group was transformed to an amino group (**2-38**) by a process including Beckmann rearrangement. Initial attempts to introduce C4 hydroxy group by Sandmeyer reaction of aniline **2-38** was also difficult. However, it was found that the introduction of an iodo group at C4 was possible under Sandmeyer conditions to afford **2-42**. Then, after intensive efforts to convert the iodo group to a hydroxy group, Buchwald's conditions were found to produce the desired phenol **2-35** from **2-42**. However, even though the reaction was repeated several times, phenol **2-35** was given only once. The reproducibility of the reaction is a problem to be solved in the future.

Thus, the author found that the optimized conditions of $RhCl(PPh_3)_3$-catalyzed [2+2+2] cycloaddition reaction of 1,6-diynes and alkoxyacetylenes. The application of the cycloaddition to the synthesis of kehokorin E is ongoing. The cycloaddition was also applied to another 3-phenyldibenzofuran natural product having different substitution pattern of oxygen functional groups. The details of the second application is described in Chapter 2.

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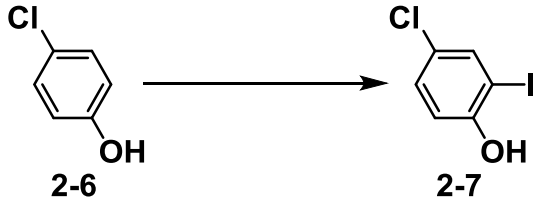
Experimental Sections

General Experimental Methods

All air sensitive reactions were carried out under nitrogen atmosphere in oven-dried glassware using standard syringe, cannula and septa techniques. Anhydrous solvents were purchased from commercial sources. The solvents used for column chromatography and extraction were reagent-grade and were used as supplied. All reactions were monitored by thin-layer chromatography (TLC) with precoated silica gel plates (Merck, silica gel 60 F254, 0.25 mm in thickness or Wako, silica gel 70 F254, 0.25 mm in thickness). Plates were visualized by ultraviolet light and by treatment with acidic ceric ammonium molybdate solution stain followed by heating. Column chromatography was performed on YMC Silica Gel 60 (63-40 µm or 230-63 µm) as a stationary phase. High-performance liquid chromatography (HPLC) was performed on a JASCO 880-PU HPLC pump equipped with a pre-packed column (YMC-Pack SIL-06, 5 µm, 300 mm × 10 mm ID or 250 mm × 20 mm ID or 500 mm × 20 mm ID [for normal-phase chromatography]) and a JASCO UV-975 UV detector (UV 254 nm detection). Melting points were measured on an ASONE ATM-02 without calibration. Infrared spectra (IR) were measured on a JASCO FT/IR-4700 infrared spectrometer in noted states and are reported in wave numbers (cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 300 (^{1}H at 300 MHz, ^{13}C at 75 MHz) or a JEOL JNM-ECA 500 (^{1}H at 500 MHz, ^{13}C at 125 MHz) magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm based on the resonance of tetramethylsilane (0 ppm for ^{1}H NMR in $CDCl_3$) or the respective solvent (^{1}H NMR: 7.26 ppm in $CDCl_3$, 3.34 ppm in CD_3OD; ^{13}C NMR: 77.0 ppm in $CDCl_3$) as the internal standard. The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, dd = double doublets, t = triplet, q = quartet, m = multiplet, and br = broad. Coupling sonstants (J) are reported in Hz. High resolution mass spectra (HRMS) were measured using a Shimadzu LCMS-IT-TOF time-of-flight mass spectrometer under electronspray ionization (ESI) conditions or using a Thermo Scientific Exactive Fourier transform ion cyclotron resonance mass spectrometer under electronspray ionization (ESI) or atmospheric pressure chemical ionization (APCI) conditions.

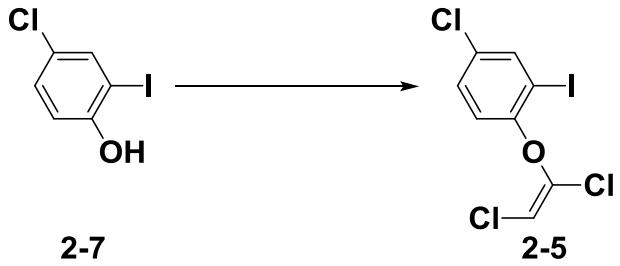
Compound **2-7**



To a solution of *p*-chlorophenol (**2-6**) (300 µL, 3.05 mmol) in $CHCl_3$ (30 mL) was added PTS·H_2O (588.5 mg, 3.09 mmol) at 21 °C. After 10 min, NIS (685.8 mg, 3.05 mmol) was added to the mixture, and the mixture was stirred for 19 h. The reaction was quenched with saturated aq. $Na_2S_2O_3$, and the mixture was extracted with $CHCl_3$ several times. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5) to give **2-7** (714.9 mg, 2.81 mmol, 92%) as a colorless solid.

2-7: The spectral data were reported in literature (ref. 3). The NMR data of **2-7** obtained by the author were identical with those of ref. 3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (1H, s), 6.92 (1H, d, *J* = 8.7 Hz), 7.22 (1H, dd, *J* = 2.5, 8.7 Hz), 7.63 (1H, d, *J* = 2.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.4, 115.7, 126.1, 130.1, 137.2, 153.8; ESI-HRMS (neg.) *m/z* calcd for $C_6H_3O^{35}Cl^{127}I$ $[M - H]^-$: 252.8923, found: 252.8924.

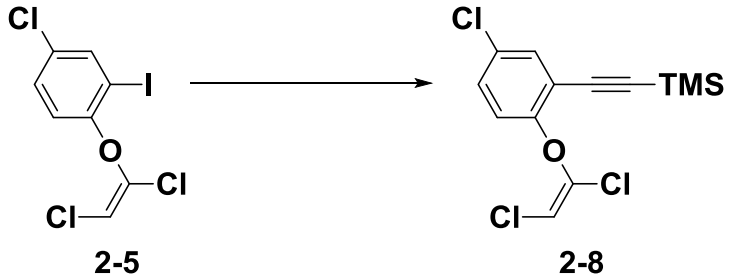
Compound **2-5**



To a solution of **2-7** (1.041 g, 4.09 mmol) in THF (14.0 mL) were added NaH (55% in mineral oil, 381.7 mg, 8.75 mmol) and KI (1.412 g, 8.51 mmol) at 0 °C. The mixture was warmed to 19 °C and stirred for 1 h. Then, trichloroethylene (1.9 mL, 21.11 mmol) was added dropwise to the mixture. Then, the mixture was heated to 40 °C and stirred for 62 h. After the mixture was cooled to 20 °C, the reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 40 → 10) to give **2-5** (1.348 g, 3.86 mmol, 94%) as a colorless solid.

2-5: IR (film) *ν* 3101, 3077, 2360, 2342, 1624, 1569, 1462, 1267, 1252, 1211, 1140, 1102, 1065, 1034, 874, 829, 794, 715, 683, 580, 543 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (1H, s), 6.91 (1H, d, *J* = 8.7 Hz), 7.32 (1H, dd, *J* = 2.5, 8.8 Hz), 7.82 (1H, d, *J* = 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.3 (C), 104.1 (CH), 116.6 (CH), 129.1 (CH), 130.1 (C), 138.8 (CH), 139.2 (C), 151.6 (C).

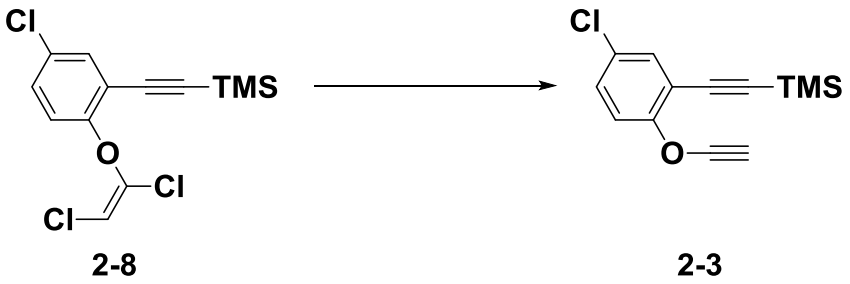
Compound **2-8**



To a solution of **2-5** (653.5 mg, 1.87 mmol) in Et_3N (3.8 mL) were added CuI (48.5 mg, 0.25 mmol), $Pd(PPh_3)_2Cl_2$ (65.7 mg, 0.094 mmol) and TMS acetylene (400 µL, 2.89 mmol) at 20 °C. Then, the mixture was heated to 50 °C and stirred for 3.5 h. The mixture was cooled to ambient temperature, diluted with H_2O and extracted with Et_2O several times. The combined organic layers were washed with saturated aq. NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 100) to give **2-8** (562.0 mg, 1.76 mmol, 94%) as a yellow oil.

2-8: IR (neat) *ν* 3102, 2960, 2899, 2166, 1631, 1480, 1390, 1272, 1252, 1234, 1186, 1127, 1093, 1066, 906, 843, 760, 646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.25 (9H, s), 5.87 (1H, s), 6.96 (1H, d, *J* = 8.8 Hz), 7.26 (1H, dd, *J* = 2.6, 8.8 Hz), 7.46 (1H, d, *J* = 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.0 (CH_3×3), 97.7 (C), 102.4 (C), 102.8 (CH), 117.1 (C), 119.1 (CH), 129.9 (CH), 130.1 (C), 133.9 (CH), 140.0 (C), 153.0 (C).

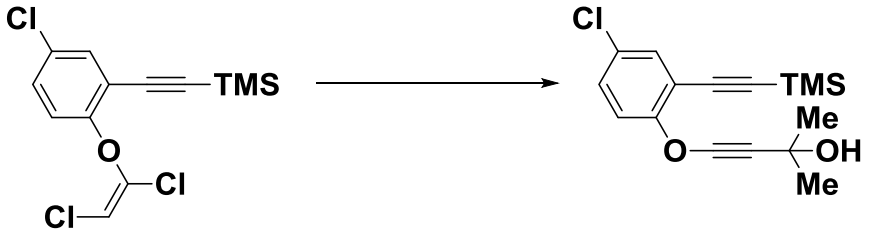
Compound **2-3**



To a solution of **2-8** (273.8 mg, 0.86 mmol) in Et_2O (6.4 mL) was added BuLi (1.64 mol/L in hexane, 2.1 mL, 3.44 mmol) at –78 °C, and the mixture was stirred for 30 min. Then, the mixture was gradually warmed to –40 °C over 2 h and stirred for an additional 1 h. The reaction was quenched with H_2O, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 100) to give **2-3** (134.0 mg, 0.54 mmol, 63%) as a pale yellow oil.

2-3: ^1H NMR (300 MHz, $CDCl_3$) δ 0.27 (9H, s), 2.19 (1H, s), 7.31 (1H, dd, *J* = 2.5, 8.9 Hz), 7.43 (1H, d, *J* = 2.6 Hz), 7.48 (1H, d, *J* = 8.9 Hz).

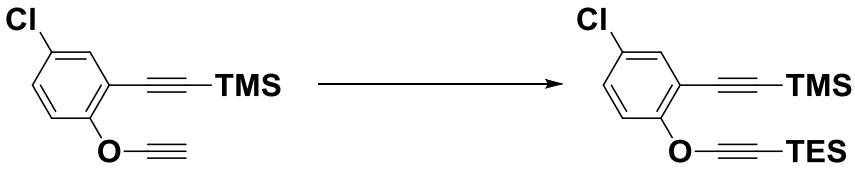
Compound **2-15**



2-8 **2-15**

To a solution of **2-8** (409.4 mg, 1.28 mmol) in Et_2O (6.4 mL) was added BuLi (1.64 mol/L in hexane, 3.5 mL, 5.43 mmol) at –78 °C, and the mixture was stirred for 30 min. Then, the mixture was gradually warmed to –40 °C over 2 h and stirred for an additional 1 h. Then, acetone (0.7 mL, 9.50 mmol) was added to the mixture, and the mixture was warmed to 22 °C and stirred for 2 h. The reaction was quenched with H_2O, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **2-15** (247.6 mg, 0.81 mmol, 63%) as a pale yellow solid. **2-15**: IR (film) *v* 3388, 2980, 2934, 2900, 2277, 2165, 1651, 1480, 1251, 1178, 1131, 954, 903, 846, 814, 761, 644, 580, 411 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ; ^{13}C NMR (125 MHz, $CDCl_3$) δ -0.2 (CH_3 ×3), 32.1 (CH_3×2), 51.4 (C), 65.3 (C), 84.5 (C), 97.1 (C), 102.2 (C), 113.8 (C), 114.9 (CH), 129.1 (C), 129.6 (CH), 133.4 (CH), 154.8 (C); ESI-HRMS (neg.) *m/z* calcd for $C_{16}H_{18}O_2Si^{35}Cl$ $[M - H]^-$: 305.0770, found: 305.0762.

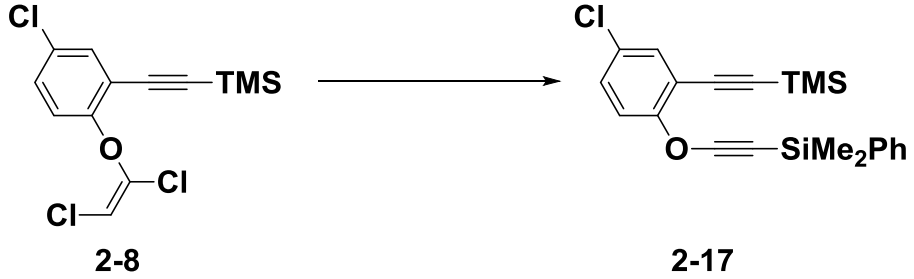
Compound **2-16**



2-3 **2-16**

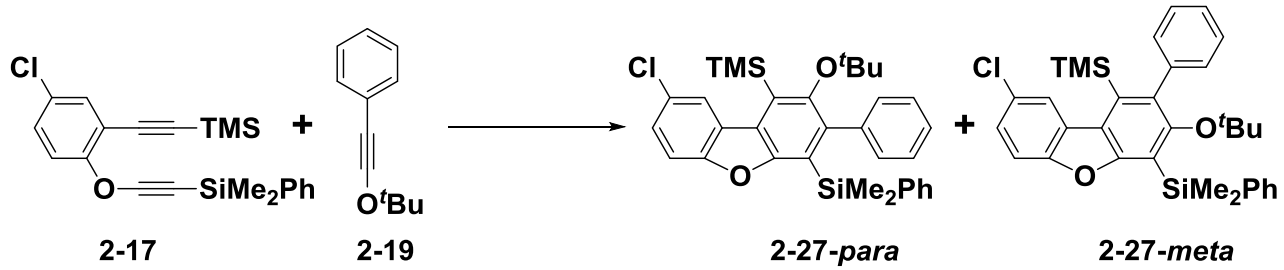
To a solution of **2-3** (57.9 mg, 0.23 mmol) in THF (1.0 mL) was added BuLi (1.57 mol/L in hexane, 0.18 mL, 0.28 mmol) at –40 °C, and the mixture was stirred for 30 min. Then, chlorotriethylsilane (70 µL, 0.42 mmol) was added to the mixture, and the mixture was warmed to 22 °C and stirred for 3.5 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane) to give **2-16** (73.5 mg, 0.20 mmol, 89%) as a yellow oil. **2-16**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.26 (9H, s), 0.65 (6H, q, *J* = 7.9 Hz), 1.03 (9H, t, *J* = 15.7 Hz), 7.31 (1H, dd, *J* = 2.5, 8.9 Hz), 7.43 (1H, d, *J* = 2.6 Hz), 7.46 (1H, d, *J* = 8.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ -0.2 (CH_3×3), 4.7 (CH_2×3), 7.5 (CH_3×3), 43.8 (C), 97.1 (C), 102.1 (C), 102.2 (C), 113.7 (C), 115.0 (CH), 129.1 (C), 129.7 (CH), 133.4 (CH), 154.6 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{19}H_{27}OSi_2{}^{35}Cl$ $Na[M + Na]^+$: 385.1181, found: 385.1153.

Compound **2-17**



To a solution of **2-8** (152.3 mg, 0.48 mmol) in Et_2O (6.4 mL) was added BuLi (1.64 mol/L in hexane, 1.3 mL, 2.04 mmol) at –78 °C, and the mixture was stirred for 30 min. Then, the mixture was gradually warmed to –40 °C over 2 h and stirred for an additional 2 h. Then, chlorodimethylphenylsilane (120 μL, 0.72 mmol) was added to the mixture, and the mixture was warmed to 22 °C and stirred for overnight. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane) to give **2-17** (111.6 mg, 0.29 mmol, 61%) as a yellow oil. **2-17**: IR (neat) *ν* 3069, 2960, 2899, 2189, 1479, 1428, 1390, 1250, 1207, 1116, 1103, 901, 843, 815, 780, 760, 731, 702, 671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.26 (9H, s), 0.47 (6H, s), 7.29 (1H, dd, *J* = 2.6, 8.8 Hz), 7.37-7.45 (5H, m), 7.65-7.68 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ –0.5 (CH_3×2), –0.2 (CH_3×3), 44.8 (C), 96.9 (C), 102.3 (C), 102.8 (C), 113.8 (C), 115.1 (CH), 127.9 (CH×2), 129.3 (C), 129.4 (CH), 129.7 (CH), 133.4 (CH), 133.6 (CH×2), 137.3 (CH), 154.4 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{21}H_{23}OSi_2{}^{35}ClNa$ $[M + Na]^+$: 405.0868, found: 405.0857.

Compound **2-27**

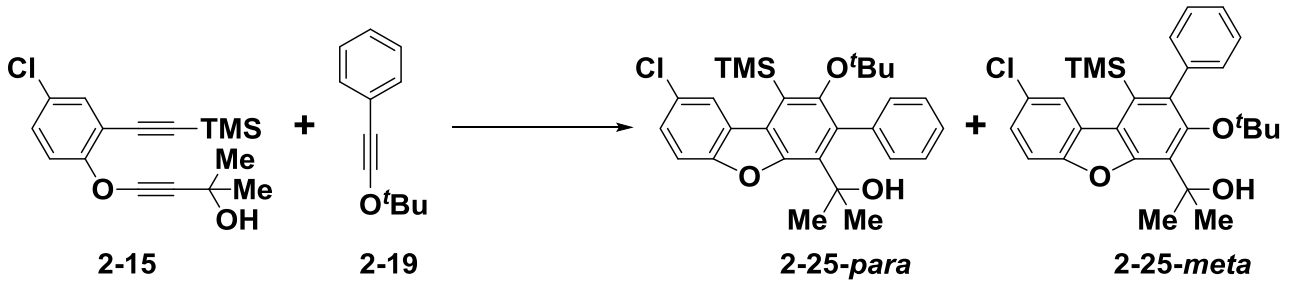


To a solution of **2-19** (40.9 mg, 0.235 mmol) and $RhCl(PPh_3)_3$ (8.3 mg, 0.00897 mmol) in benzene (0.25 mL) was added a solution of **2-17** (35.7 mg, 0.098 mmol) in benzene (0.50 mL) dropwise via a syringe pump over 5 h, and then the mixture was stirred for 8.5 h. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 100) to give a mixture of 3-phenyldibenzofuran (**2-27-*para***) and 2-phenyldibenzofuran (**2-27-*meta***). Futher purification by HPLC (hexane/EtOAc = 100) gave **2-27-*para*** (mg, mmol, %) as an amorphous solid and **2-27-*meta*** (mg, mmol, %) as an amorphous solid.

2-27-*para*: ^{1}H NMR (500 MHz, $CDCl_3$) δ -0.19 (3H, br-s), 0.54 (3H, br-s), 0.58 (9H, s), 0.81 (9H, s), 7.25-7.28 (4H, br), 7.31-7.35 (4H, m), 7.37 (1H, dd, *J* = 2.1, 8.7 Hz), 7.44 (1H, d, *J* = 8.6 Hz), 7.57-7.59 (2H, m), 7.97 (1H, d, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ -2.1 (CH_3), 2.2 (CH_3), 2.5 (CH_3×3), 29.0 (CH_3×3), 80.9 (C), 112.4 (CH), 122.3 (C), 123.8 (CH), 126.1 (CH), 126.66 (C), 126.68 (C), 127.12 (CH), 127.16 (CH), 127.23 (CH×2), 127.7 (CH×2), 128.7 (CH), 132.6 (C), 133.9 (CH×2), 140.5 (C), 141.5 (C), 145.4 (C), 154.5 (C), 155.0 (C), 158.5 (C).

2-27-*meta*: IR (film) *ν* 3067, 3053, 3024, 2975, 2932, 2901, 1513, 1453, 1429, 1390, 1365, 1334, 1265, 1252, 1213, 1152, 1115, 1074, 1037, 1025, 1013, 889, 838, 819, 770, 739, 703, 659 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (9H, s), 0.58 (9H, s), 0.77 (6H, s), 7.30-7.39 (6H, m), 7.40-7.44 (3H, m), 7.67-7.69 (2H, m), 7.97 (1H, d, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.9 (CH_3×2), 1.5 (CH_3×3), 29.1 (CH_3×3), 82.6 (C), 112.2 (CH), 117.5 (C), 123.3 (C), 124.1 (CH), 125.6 (CH), 126.5 (C), 127.1 (C), 127.2 (CH), 127.57 (CH×2), 127.62 (CH×2), 128.8 (CH), 133.4 (CH×2), 134.2 (CH×2), 138.0 (C), 139.7 (C), 142.0 (C), 142.3 (C), 154.5 (C), 159.4 (C), 162.0 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{33}H_{37}O_2Si_2{}^{35}ClNa$ $[M + Na]^+$: 579.1913, found: 579.1954.

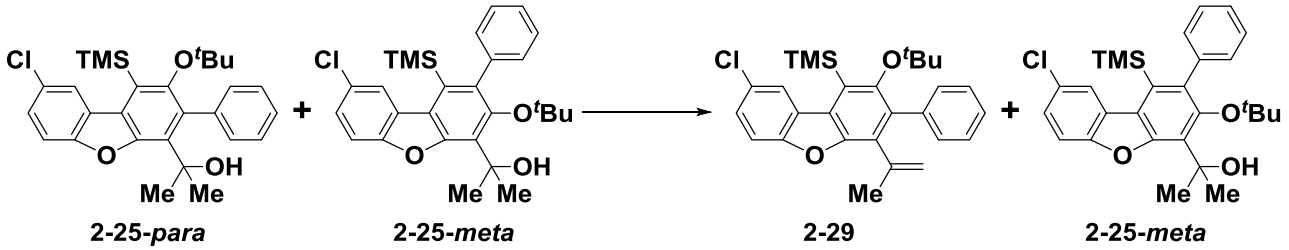
Compound **2-25**



To a solution of **2-19** (83.0 mg, 0.476 mmol) and $RhCl(PPh_3)_3$ (33.2 mg, 0.0359 mmol) in benzene (0.9 mL) was added a solution of **2-15** (89.9 mg, 0.293 mmol) in benzene (1.0 mL) dropwise via a syringe pump over 5 h, and then the mixture was stirred for 8 h. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 50) to give a mixture of 3-phenyldibenzofuran (**2-25-*para***) and 2-phenyldibenzofuran (**2-25-*meta***) (97.0 mg).

2-25-*meta*: IR (film) *ν* 3451, 2977, 2932, 1736, 1667, 1454, 1392, 1368, 1338, 1266, 1253, 1220, 1146, 1074, 1037, 1015, 838, 807, 720, 704, 691 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (9H, s), 0.88 (9H, s), 1.90 (6H, s), 6.89 (1H, s), 7.37-7.45 (5H, br-m), 7.38 (1H, dd, *J* = 2.1, 8.5 Hz), 7.50 (1H, d, *J* = 8.7 Hz), 7.96 (1H, d, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 1.5 (CH_3×3), 29.1 (CH_3×5), 73.6 (C), 85.6 (C), 112.3 (CH), 124.3 (CH), 125.1 (C), 126.1 (CH), 126.3 (C), 127.3 (C), 127.9 (CH), 128.0 (CH×2), 128.2 (C), 133.3 (CH×2), 133.7 (C), 141.6 (C), 142.3 (C), 150.0 (C), 153.2 (C), 154.4 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{28}H_{33}O_3Si^{35}ClNa$ $[M + Na]^+$: 503.1780, found: 503.1764.

Compound **2-29**

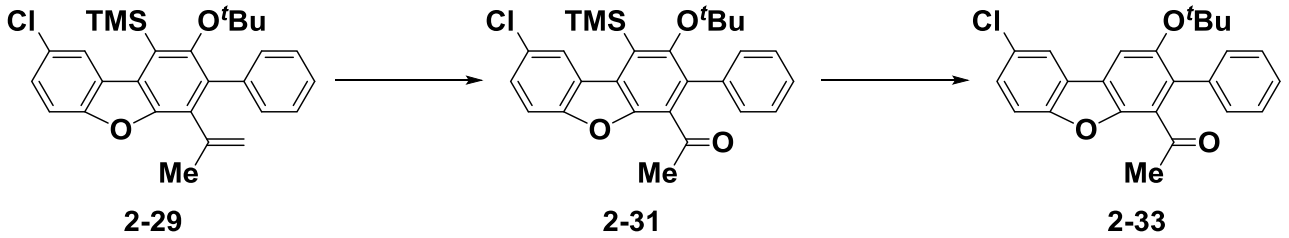


To a solution of the above mixture of 3-phenyldibenzofuran (**2-25-*para***) and 2-phenyldibenzofuran (**2-25-*meta***) (97.0 mg) in CH_2Cl_2 (7.0 mL) were added triethylamine (0.85 mL, 6.10 mmol) and methanesulfonyl chloride (0.24 mL, 3.10 mmol) at 0 °C. Then, the mixture was warmed to 22 °C and stirred for 14 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **2-29** (70.4 mg, 0.152 mmol, 52% for 2 steps) as an amorphous solid and **2-25-*meta*** (19.1 mg, 0.0397 mmol, 14%) as an amorphous solid.

2-29: IR (film) *ν* 2975, 2357, 1643, 1494, 1464, 1389, 1364, 1337, 1290, 1254, 1224, 1150, 1093, 930, 861, 840, 806, 756, 729, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.57 (9H, s), 0.91 (9H, s), 1.76 (3H, s), 5.07 (1H, br-s), 5.37 (1H, t, *J* = 3.2 Hz), 7.27-7.33 (3H, m), 7.37 (1H, dd, *J* = 2.1, 8.6

Hz), 7.45-7.48 (2H, m), 7.50 (1H, d, J = 8.6 Hz), 8.00 (1H, d, J = 2.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 2.6 (CH_3×3), 23.5 (CH_3), 28.9 (CH_3×3), 81.1 (C), 112.7 (CH), 119.0 (CH_2), 123.9 (CH), 126.3 (CH), 126.6 (CH), 126.96 (C), 126.99 (C), 127.14 (CH×3), 127.17 (C), 128.6 (C), 129.5 (C), 132.4 (CH), 136.2 (C), 139.0 (C), 139.6 (C), 150.7 (C), 154.6 (C), 154.9 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{28}H_{31}O_2Si^{35}ClNa$ $[M + Na]^+$: 485.1674, found: 485.1682.

Compound **2-33**



To a solution of **2-29** (66.3 mg, 0.143 mmol) in pyridine (5.0 mL) was added OsO_4 (0.0197 mol/L in ^{t}BuOH, 8.8 mL, 0.173 mmol) at 22 °C. Then, the mixture was heated to 50 °C and stirred for 10 h. Then, saturated aq. $NaHSO_3$ was added to the mixture, and the mixture was stirred for 19 h. The mixture was cooled to ambient temperature, diluted with saturated aq. $Na_2S_2O_3$ and extracted with EtOAc several times. The combined organic layers were washed with 1 mol/L aq. HCl and then with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude diol, which was used in the next reaction without purification.

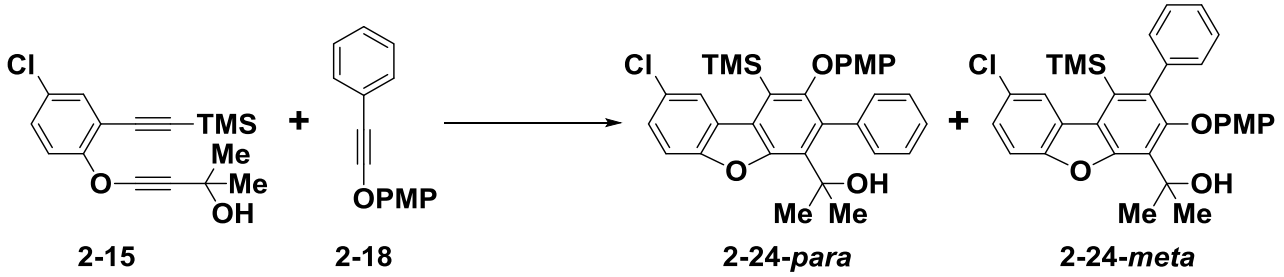
To a solution of the above crude diol in a blend of THF (2.0 mL) and H_2O (1.0 mL) was added $NaIO_4$ (224.6 mg, 1.050 mmol) at 22 °C, and the mixture was stirred for 45 min. The reaction was quenched with saturated aq. $Na_2S_2O_3$, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **2-31** (49.1 mg, 0.106 mmol, 74%, 95% based on recovered **2-29**) as a pale yellow solid, along with recovered **2-29** (15.0 mg, 0.0323 mmol, 23%) as an amorphous solid.

2-31: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.59 (9H, s), 0.90 (9H, s), 2.03 (3H, s), 7.35-7.43 (6H, m), 7.51 (1H, d, J = 8.8 Hz), 8.00 (1H, d, J = 2.0 Hz);

To a solution of **2-31** (49.1 mg, 0.106 mmol) in THF (2.0 mL) was added TBAF (1.0 mol/L in THF, 0.2 mL, 0.200 mmol) at 22 °C, and the mixture was stirred for 1.5 h. Then, an extra amount of TBAF (1.0 mol/L in THF, 0.1 mL, 0.100 mmol) was added to the mixture, and the mixture was stirred for 1 h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **2-33** (36.3 mg, 0.0924 mmol, 87%) as a colorless solid.

2-33: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (9H, s), 2.08 (3H, s), 7.37-7.42 (5H, m), 7.43 (1H, dd, J = 2.1, 8.8 Hz), 7.52 (1H, d, J = 8.6 Hz), 7.68 (1H, s), 7.92 (1H, d, J = 1.8 Hz); ESI-HRMS (pos.) *m/z* calcd for $C_{27}H_{29}O_3Si^{35}ClNa$ $[M + Na]^+$: 487.1467, found: 487.1453.

Compound **2-24**



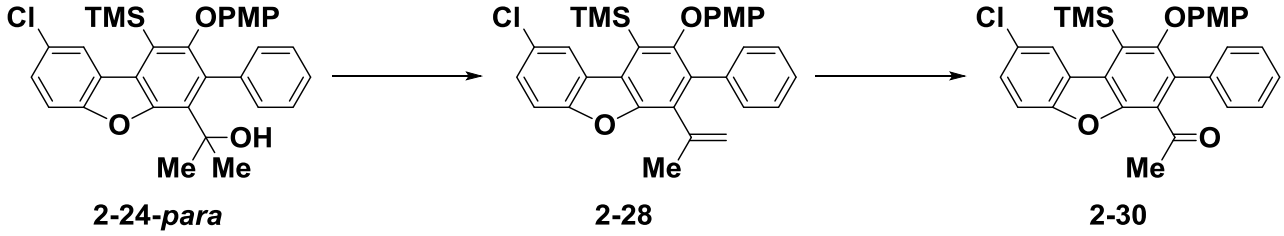
2-15 **2-18** **2-24-*para*** **2-24-*meta***

To a solution of **2-18** (40.7 mg, 0.181 mmol) and $RhCl(PPh_3)_3$ (17.8 mg, 0.0192 mmol) in toluene (0.4 mL) was added a solution of **2-15** (40.6 mg, 0.132 mmol) in toluene (1.0 mL) dropwise at 40 °C via a syringe pump over 16 h, and the mixture was stirred for an additional 21.5 h. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 30) to give a mixture of 3-phenyldibenzofuran (**2-24-*para***) and 2-phenyldibenzofuran (**2-24-*meta***) (26.3 mg). Futher purification by HPLC (hexane/EtOAc = 25) gave **2-24-*para*** (14.3 mg, 0.0269 mmol, 20%) as a colorless solid and **2-24-*meta*** (8.0 mg, 0.0151 mmol, 11%) as a colorless solid.

2-24-*para*: IR (film) *v* 3583, 2970, 1601, 1502, 1464, 1442, 1341, 1254, 1206, 1180, 1089, 1038, 986, 845, 756, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.43 (9H, s), 1.63 (6H, s), 2.66 (1H, br-s), 3.70 (3H, s), 6.19 (2H, d, *J* = 9.2 Hz), 6.55 (2H, d, *J* = 9.1 Hz), 6.95-6.98 (2H, br-m), 7.10-7.19 (3H, br-m), 7.46 (1H, dd, *J* = 2.1, 8.8 Hz), 7.58 (1H, d, *J* = 8.6 Hz), 8.07 (1H, d, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 1.2 (CH_3×3), 31.4 (CH_3×2), 55.6 (CH_3), 74.5 (C), 112.6 (CH), 114.0 (CH×2), 115.8 (CH), 124.3 (CH), 125.6 (C), 126.9 (CH), 127.0 (CH), 127.2 (CH×2), 127.5 (C×2), 127.8 (C), 129.9 (CH×3), 133.7 (C), 134.7 (C), 137.5 (C), 151.2 (C), 153.5 (C), 153.7 (C), 154.1 (C), 154.3 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{31}H_{31}O_4Si^{35}ClNa$ $[M + Na]^+$: 553.1572, found: 553.1547.

2-24-*meta*: IR (film) *v* 3548, 3058, 2945, 2851, 1733, 1503, 1464, 1388, 1361, 1335, 1269, 1240, 1221, 1199, 1076, 1033, 836, 807, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (9H, s), 1.82 (6H, s), 3.66 (3H, s), 4.67 (1H, br-s), 6.23 (2H, d, *J* = 9.0 Hz), 6.49 (2H, d, *J* = 9.0 Hz), 7.01-7.04 (2H, br-m), 7.09-7.13 (3H, br-m), 7.43 (1H, dd, *J* = 2.1, 8.7 Hz), 7.56 (1H, d, *J* = 8.7 Hz), 8.03 (1H, d, *J* = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 1.1 (CH_3×3), 29.7 (CH_3), 30.9 (CH_3), 55.6 (CH_3), 73.6 (C), 112.5 (CH), 114.0 (CH×2), 116.6 (CH×2), 124.5 (CH), 125.8 (C), 126.4 (CH), 127.15 (CH×2), 127.18 (CH), 127.3 (C), 127.7 (C), 131.5 (CH×2), 135.5 (C), 138.8 (C), 149.0 (C), 152.0 (C×2), 153.3 (C), 154.2 (C), 154.5 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{31}H_{31}O_4Si^{35}ClNa$ $[M + Na]^+$: 553.1572, found: 553.1532.

Compound **2-30**



To a solution of **2-24-*para*** (47.8 mg, 0.0900 mmol) in CH_2Cl_2 (3.0 mL) were added triethylamine (0.65 mL, 4.664 mmol) and methanesulfonyl chloride (0.20 mL, 2.584 mmol) at 0 °C. Then, the mixture was warmed to 22 °C and stirred for 19 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **2-28** (45.1 mg, 0.0879 mmol, 98%) as a pale brawn solid.

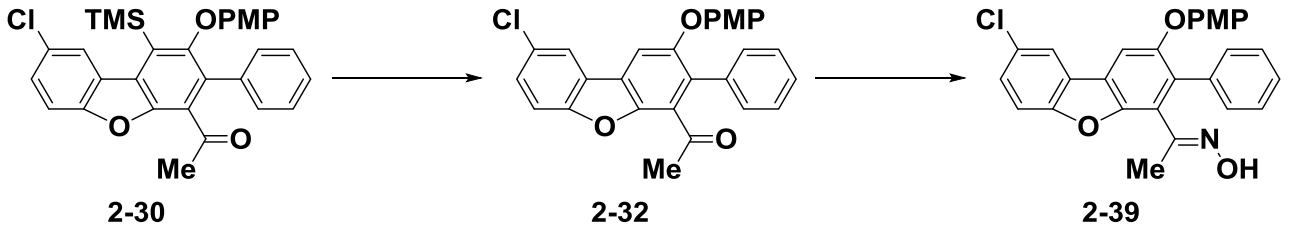
2-28: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.47 (9H, s), 1.85 (3H, br-s), 3.68 (3H, s), 4.95 (1H, br-s), 5.26 (1H, t, *J* = 3.3 Hz), 6.29 (2H, d, *J* = 9.2 Hz), 6.55 (2H, d, *J* = 9.2 Hz), 7.01-7.05 (2H, m), 7.12-7.14 (3H, m), 7.43 (1H, dd, *J* = 2.2, 8.7 Hz), 7.56 (1H, d, *J* = 8.5 Hz), 8.07 (1H, d, *J* = 2.2 Hz)

To a solution of **2-28** (24.1 mg, 0.0470 mmol) in pyridine (1.6 mL) was added OsO_4 (0.0197 mol/L in ^{t}BuOH, 2.9 mL, 0.0571 mmol) at 22 °C. Then, the mixture was heated to 50 °C and stirred for 21 h. Then, saturated aq. $NaHSO_3$ was added to the mixture, and the mixture was stirred for 23 h. The mixture was cooled to ambient temperature, diluted with saturated aq. $Na_2S_2O_3$ and extracted with EtOAc several times. The combined organic layers were washed with 1 mol/L aq. HCl and then with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude diol, which was used in the next reaction without purification.

To a solution of the above crude diol in a blend of THF (1.6 mL) and H_2O (0.8 mL) was added $NaIO_4$ (110.1 mg, 0.515 mmol) at 22 °C, and the mixture was stirred for 5.5 h. The reaction was quenched with saturated aq. $Na_2S_2O_3$, and the mixture extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **2-30** (21.8 mg, 0.0423 mmol, 90% for 2 steps) as a pale yellow solid.

2-30: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.48 (9H, s), 2.13 (3H, s), 3.66 (3H, s), 6.28 (2H, d, *J* = 8.9 Hz), 6.53 (2H, d, *J* = 9.0 Hz), 7.12-7.16 (2H, m), 7.19-7.21 (3H, m), 7.47 (1H, dd, *J* = 2.1, 8.7 Hz), 7.57 (1H, d, *J* = 8.8 Hz), 8.06 (1H, d, *J* = 2.1 Hz)

Compound **2-39**



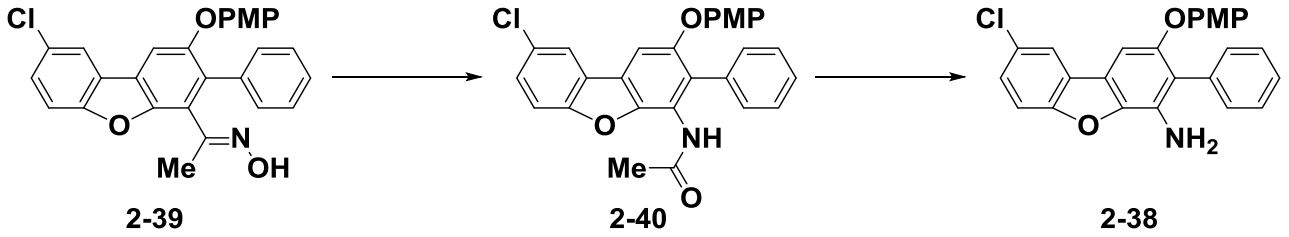
To a solution of **2-30** (41.7 mg, 0.0810 mmol) in THF (1.0 mL) was added TBAF (1.0 mol/L in THF, 0.1 mL, 0.100 mmol) at 22 °C, and the mixture was stirred for 13.5 h. The mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **2-32** (35.0 mg, 0.0790 mmol, 98%) as a colorless solid.

2-32: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (3H, s), 3.79 (3H, s), 6.81-6.88 (4H, m), 7.36-7.41 (5H, m), 7.43 (1H, dd, *J* = 2.2, 8.8 Hz), 7.48 (1H, s), 7.52 (1H, d, *J* = 8.7 Hz), 7.81 (1H, d, *J* = 2.4 Hz)

To a solution of **2-32** (23.1 mg, 0.0522 mmol) in EtOH (0.5 mL) were added $NH_2OH \cdot HCl$ (19.3 mg, 0.278 mmol) and 2 mol/L aq. NaOH (0.1 mL, 0.200 mmol) at 22 °C, and the mixture was heated to 60 °C and stirred for 25 h. The mixture was cooled to ambient temperature and diluted with H_2O, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5) to give **2-39** (20.8 mg, 0.0454 mmol, 87%) as a colorless solid.

2-39: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (3H, s), 3.78 (3H, s), 3.79 (1H, br-s), 6.80-6.88 (4H, m), 7.31-7.40 (5H, m), 7.41 (1H, dd, *J* = 2.4, 9.0 Hz), 7.45 (1H, s), 7.51 (1H, d, *J* = 8.6 Hz), 7.80 (1H, d, *J* = 1.8 Hz)

Compound **2-38**



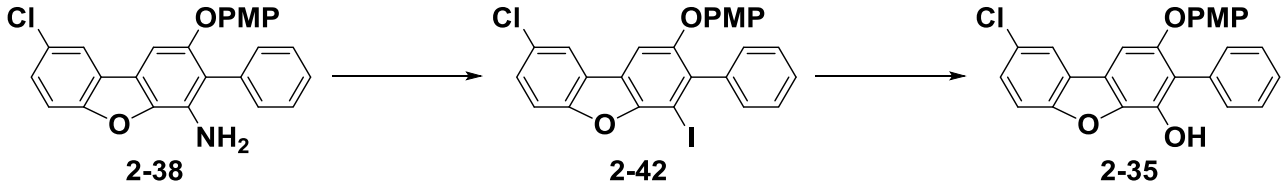
To a solution of **2-39** (20.8 mg, 0.0454 mmol) in MeCN (3.0 mL) was added TsCl (54.3 mg, 0.285 mmol) at 22 °C, and the mixture was refluxed and stirred for 15 h. The mixture was cooled to ambient temperature, diluted with saturated aq. $NaHCO_3$ and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5 → $CHCl_3$/MeOH = 5) to give **2-40** (19.8 mg, 0.0432 mmol, 95%) as a colorless solid.

2-40: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (3H, br-s), 3.78 (3H, s), 6.69 (1H, br-s), 6.79-6.87 (4H,

m), 7.33-7.44 (7H, m), 7.51 (1H, d, J = 8.4 Hz), 7.79 (1H, d, J = 2.0 Hz)

To a solution of **2-40** (15.2 mg, 0.0332 mmol) in EtOH (2.5 mL) was added KOH (53.1 mg, 0.946 mmol) at 22 °C, and the mixture was refluxed and stirred for 40 h. The mixture was cooled to ambient temperature, diluted with H_2O and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5 → $CHCl_3$/MeOH = 5) to give **2-38** (13.2 mg, 0.0317 mmol, 96%) as a colorless solid.
2-38: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (3H, s), 4.08 (2H, br-s), 6.78 (2H, d, J = 9.3 Hz), 6.838 (1H, s), 6.843 (2H, d, J = 9.3 Hz), 7.32-7.44 (5H, m), 7.47 (1H, d, J = 8.8 Hz), 7.76 (1H, d, J = 2.1 Hz).

Compound **2-35**



To a solution of **2-38** (13.2 mg, 0.0317 mmol) in a blend of MeOH (2.0 mL) and 3 mol/L aq. HCl (0.18 mL, 0.540 mmol) was added a solution of $NaNO_2$ (excess) in H_2O (0.12 mL) at 0 °C, and the mixture was stirred for 25 min. Then, to the mixture was added a solution of KI (36.1 mg, 0.217 mmol) in H_2O (0.10 mL), and the mixture was warmed to 23 °C and stirred for 1.5 h. The reaction was quenched with saturated aq. $Na_2S_2O_3$, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5) to give **2-42** (13.4 mg, 0.0254 mmol, 80%) as a colorless solid.
2-42: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (3H, s), 6.80 (4H, s), 7.26-7.29 (2H, m), 7.38-7.47 (5H, m), 7.58 (1H, d, J = 8.8 Hz), 7.79 (1H, d, J = 2.2 Hz).

To a solution of **2-42** (1.2 mg, 0.00228 mmol) in a blend of 1,4-dioxane (0.3 mL) and H_2O (0.3 mL) were added $Pd_2(dba)_3 \cdot CHCl_3$ (cat.), JohnPhos (cat.) and KOH (excess) at 22 °C, and the mixture was heated to 100 °C and stirred for 17 h. The mixture was cooled to ambient temperature, diluted with H_2O and extracted with $CHCl_3$ several times. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 5) to give **2-35** (0.6 mg, 0.00144 mmol, 63%) as a colorless oil.
2-35: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (3H, s), 6.02 (1H, br-s), 6.82 (2H, d, J = 9.2 Hz), 6.91 (2H, d, J = 9.1 Hz), 6.99-7.04 (2H, m), 7.28-7.34 (3H, m), 7.42 (1H, dd, J = 2.0, 8.8 Hz), 7.48 (1H, d, J = 6.4 Hz), 7.60 (1H, s), 7.82 (1H, d, J = 2.1 Hz).

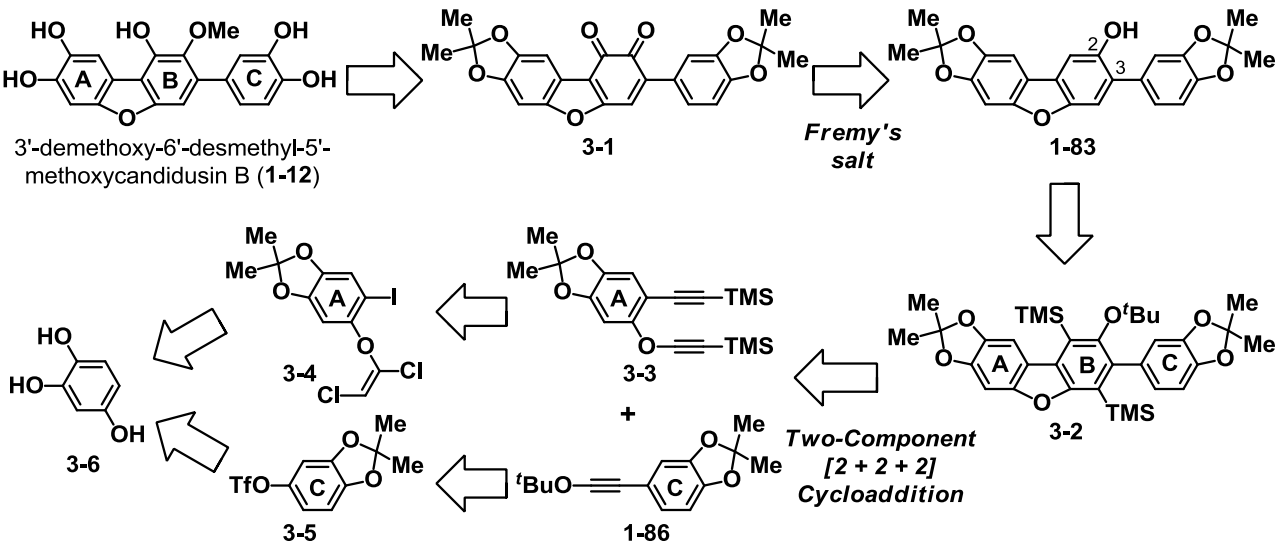
Chapter 3

Total Synthesis of 3'-Demethoxy-6'-desmethyl-5'-methoxycandidusin B

3-1. Plan for the Synthesis of 3'-Demethoxy-6'-desmethyl-5'-methoxycandidusin B

As described in Chapter 2, the author developed a $RhCl(PPh_3)_3$-catalyzed two-component [2+2+2] cycloaddition reaction for the construction of a 2-alkoxy-3-phenyldibenzofuran skeleton. Herein, the application of the cycloaddition reaction to the total synthesis of naturally occurring 3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B (**1-12**).[1]

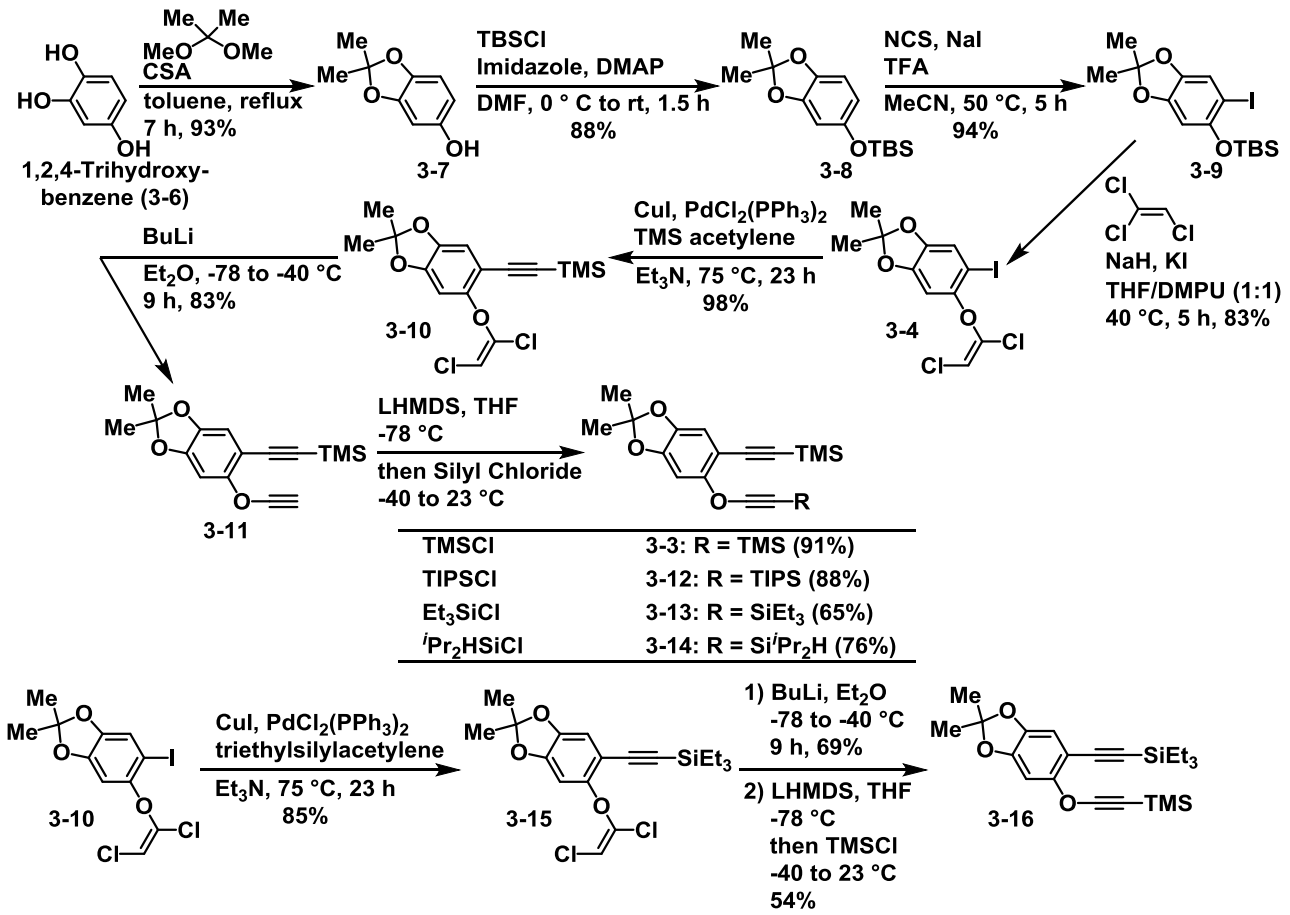
A plan for the synthesis of 3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B (**1-12**) is shown in Scheme 3-1. The 1,2-dihydroxy moieties of both terminal aromatic rings (A- and C-rings) of **1-12** would be derived from a starting material. The 1,2-dioxy group of the middle benzene ring (B-ring) would be constructed by introducing a hydroxyl group at C1 of **1-83** at the final stage of the synthesis. From these considerations, acetonide-protected *o*-quinone **3-1** was designed to be a precursor of **1-12**. *o*-Quinone **3-1** would be derived from **1-83** by *ortho*-oxidation using Fremy's salt. 2-Hydroxy-3-aryldibenzofuran **1-83** was planned to be synthesized by a sequence including $RhCl(PPh_3)_3$-catalyzed [2+2+2] cycloaddition giving **3-2** from 1,6-diyne **3-3** (A-ring segment) and *tert*-butoxyacetylene **1-86** (C-ring segment) followed by deprotection. Both alkyne segments **3-3** and **3-4** could be derived from commercially available 1,2,4-trihydroxybenzene (**3-6**).



Scheme 3-1. Synthetic Plan for 3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B

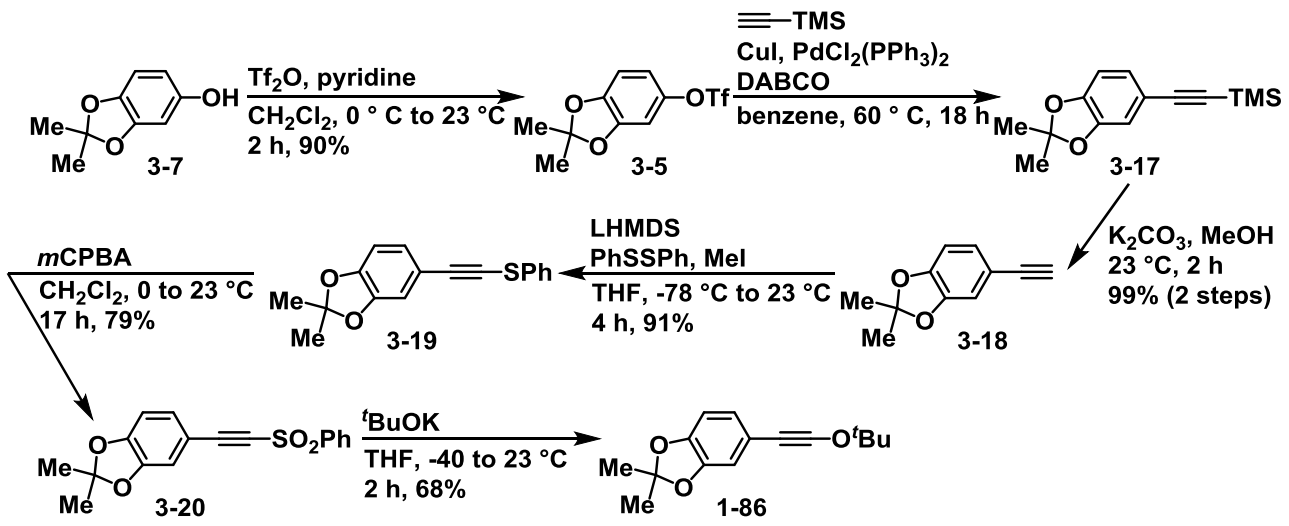
3-2. Synthesis of the 1-Ethynyl-2-(ethynyloxy)benzene and the Alkynyl Ether Segments

First, 1,6-diynes **3-3**, **3-12**, **3-13**, **3-14** and **3-16** were prepared from commercially available 1,2,4-trihysroxybenzene (**3-6**) in order to examine the effect of the silyl groups on the regioselectivity in the [2+2+2] cycloaddition reaction. Upon treatment with 1,2-dimethoxypropane and CSA under refluxed conditions, 1,2,4-trihydroxybenzene (**3-6**) was first converted to **3-7**.[2] Since monoiodination of **3-7** resulted in decomposition, a sequence involving the protection as a TBS ether followed by iodination was employed for the preparation of **3-9** according to the procedure reported by Ferreira[3a] and Poli.[3b] TBS ether **3-9** was then converted to **3-4** in one pot using a 1:1 blend of THF and DMPU as a solvent. The transformation of **3-4** into bissilylated 1,6-diynes **3-3**, **3-12**, **3-13** and **3-14** was according to the procedure described in Chapter 2. 1,6-Diyne **3-16** was alternatively prepared from **3-4** via a three-step process (Sonogashira reaction with triethylsilylacetylene, conversion of the 1,2-dichlorovinyl ether to an ethynyl ether, and protection of the ethynyl group with TMSCl). Thus, required 1,6-diynes **3-3**, **3-12**, **3-13**, **3-14** and **3-16** were prepared.



Scheme 3-2. Preparation of 1,6-diynes **3-3**, **3-12**, **3-13**, **3-14** and **3-16**

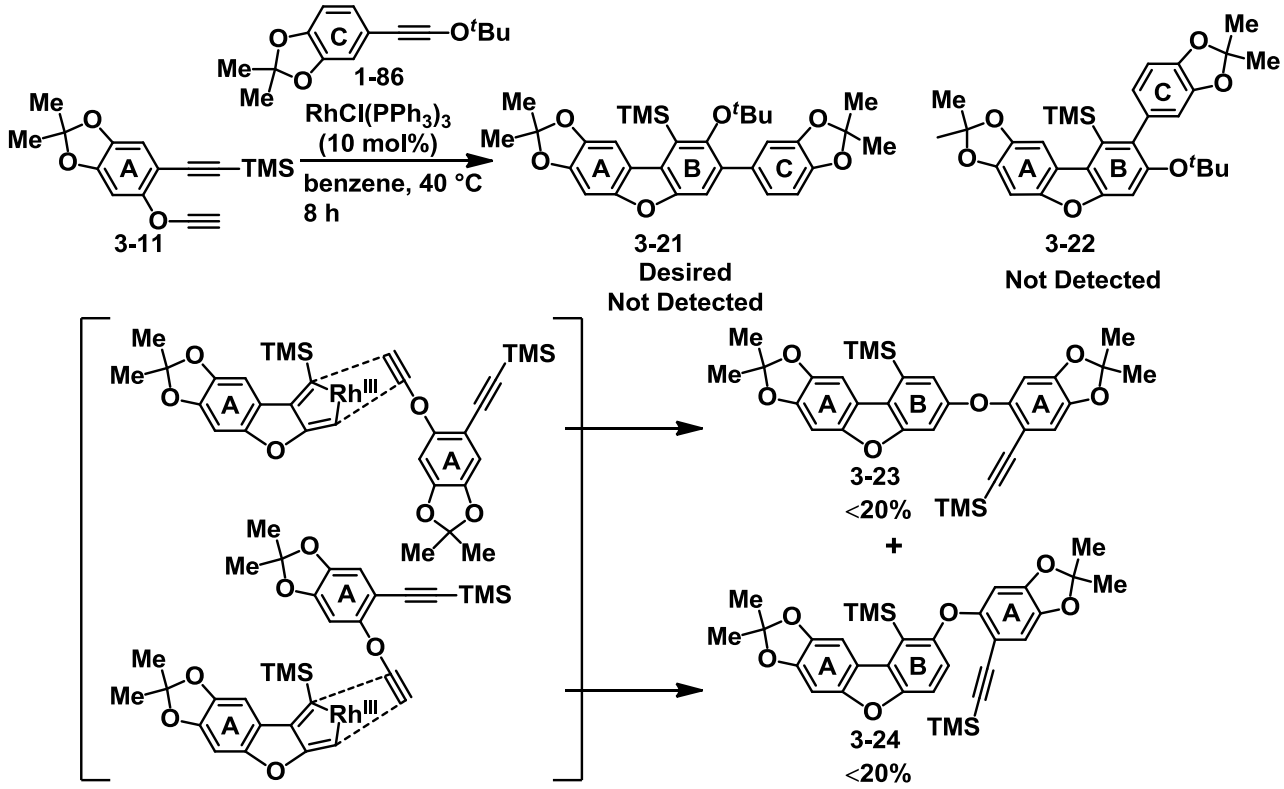
Next, alkynyl ether **1-86** was synthesized as shown in Scheme 3-3. First, above described **3-7** was reacted with Tf_2O in the presence of pyridine to give **3-5**, which was subjected to Sonogashira coupling with ethynyltrimethylsilane using DABCO as base[4] followed by removal of the TMS group to give **3-18** in high yield. Next, according to the report by Zhang[5], alkyne **3-18** was converted to *tert*-butoxyacetylene **1-86** via sulfonylalkyne **3-20**. Thus, preparation of **1-86** was achieved from **3-7** over 6 steps in 44% overall yield.



Scheme 3-3. Preparation of alkynylether **1-86**

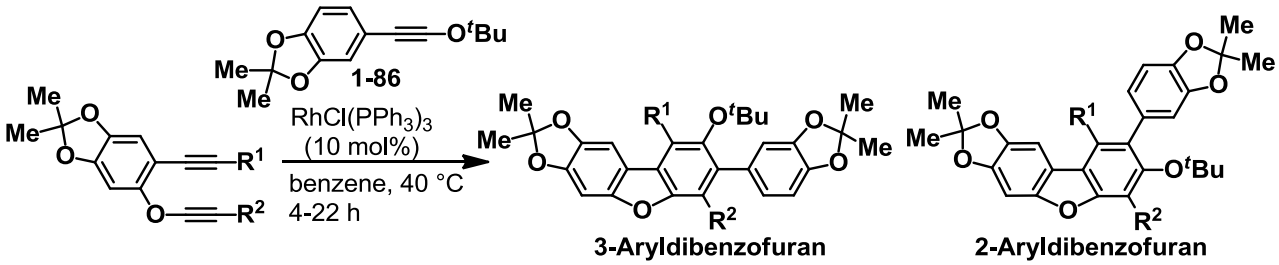
3-3. Optimization of [2+2+2] Cycloaddition to form the 3-Phenyldibenzofuran Skeleton

First, the author examined the two-component [2+2+2] cycloaddition reaction between 1,6-diyne **3-11**, having a non-protected ethynyl ether, and *tert*-butoxyacetylene **1-86** (Scheme 3-4). 1,6-Diyne **3-11** was added dropwise over 8 h to a solution of C-ring segment **1-86** and Wilkinson's catalyst ($RhCl(PPh_3)_3$) in benzene at 40 °C to afford only dibenzofuran-3-yl aryl ethers (**3-23** and **3-24**) as homodimers without production of any detectable amounts of crossed [2+2+2] cycloadducts **3-21** and **3-22**. Apparently, the ethynyl ether group of **3-11** reacted as a monoyne with a 1,6-diyne unit of another **3-11** molecule to give a homodimer. Therefore, in order to suppress homodimerization, the terminal of the ethynyl ether group was then protected with a bulky trialkyl silyl group, which would inhibit the approach of the ethynyl ether group to the 1,6-diyne unit by steric repulsion as described in Chapter 2.



Scheme 3-4. Attempt of the [2+2+2] cycloaddition of diyne **3-11** and alkynyl ether **1-86**.

The result of the $RhCl(PPh_3)_3$ catalyzed [2+2+2] cycloaddition of bissilyl-protected 1,6-diynes **3-3**, **3-12**, **3-13**, **3-14** and **3-16** with *tert*-butoxyacetylene **1-86** is shown in Table 3-1. Most of the 1,6-diynes, except **3-12**, produced cycloadducts under the same conditions as those optimized in the synthesis of kehokorin E skeleton (Chapter 2). It should be noted that the bissilyl-protection of the 1,6-diynes was sufficient to suppress the homodimerization, and no pseudo-high-dilution conditions were required in the [2+2+2] cycloaddition of the diynes with **1-86**. On the other hand, the yield and selectivity of the cycloaddition were influenced by the kind of the silyl groups of 1,6-diynes. The cycloaddition of **3-12** having a TIPS group as R^2 with **1-86** produced only trace amounts of cycloproducts **3-26** and **3-27** (Entry 1). It was found that the decreasing size of R^2 was likely to increase the total yield of cycloadducts and the ratio of the 3-aryldibenzofuran to 2-aryldibenzofuran (Entries 2, 3 and 4). However, the combination of TES as R^1 and TMS as R^2 (**3-16**) decreased both 3-aryl selectivity and the total yield (Entry 5). Thus, the $RhCl(PPh_3)_3$ catalyzed [2+2+2] cycloaddition of **3-3** with **1-86** was found to show the best production of the desired 3-aryldibenzofuran **3-2** (33% isolated yield), although the production ratio of **3-2** to **3-25** was low (45:55) (Entry 4).



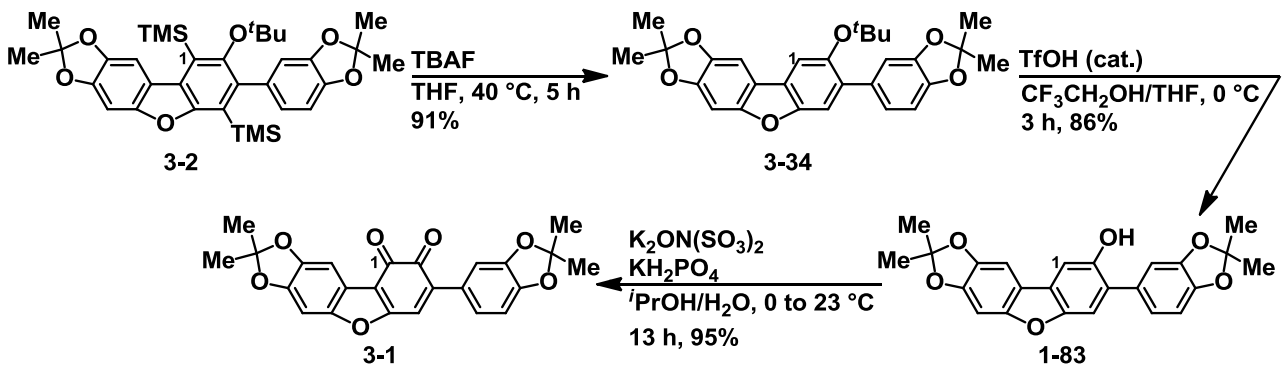
3-3: R^1= TMS, R^2 = TMS — **3-2 : R^1= TMS, R^2 = TMS** — **3-25**
3-12: R^1= TMS, R^2 = TIPS — **3-26: R^1= TMS, R^2 = TIPS** — **3-27**
3-13: R^1= TMS, R^2 = TES — **3-28: R^1= TMS, R^2 = TES** — **3-29**
3-14: R^1= TMS, R^2 = $Si(^iPr)_2H$ — **3-30: R^1= TMS, R^2 = $Si(^iPr)_2H$** — **3-31**
3-16: R^1= TES, R^2 = TMS — **3-31: R^1= TES, R^2 = TMS** — **3-33**

Entry	Substrate	R^1	R^2	Dibenzofurans 3-Aryl-	Dibenzofurans 2-Aryl-	Ratio	Total	Homodimers
1	**3-12**	TMS	TIPS	trace	trace	—	trace	trace
2	**3-13**	TMS	TES	23%	52%	31:69	75%	trace
3	**3-14**	TMS	$Si(^iPr)_2H$	16%	25%	39:61	41%	trace
4	**3-3**	TMS	TMS	33%	41%	45:55	74%	trace
5	**3-16**	TES	TMS	18%	28%	39:61	46%	trace

Table 3-1. $RhCl(PPh_3)_3$ catalyzed [2+2+2] cycloaddition of bissilyl-protected 1,6-diynes with **1-86**.

3-4. Total Synthesis of 3'-Demethoxy-6'-desmethyl-5'-methoxycandidusin B and the Isomers

With the desired 3-aryldibenzofuran **3-2** in hand, the author next examined the introduction of a hydroxyl group at the C1 position toward the total synthesis of 3'-demethoxy-6'-des-methyl-5'-methoxycandidusin B (Scheme 3-5). First, the two trimethylsilyl groups of **3-2** were removed with TBAF to afford **3-34** (91%). The *tert*-butyl group of **3-34** was removed using trifluoromethanesulfonic acid in a 5:1 blend of CF_3CH_2OH and THF to give **1-83**, which was transformed to *o*-quinone **3-1** using potassium nitrosodisulfonate[2]. Thus, an oxygen functional group was installed at C1.



Scheme 3-5. Preparation of the *o*-quinone **3-1.**

Then, reduction of *o*-quinone **3-1** to catechol **3-35** followed by the regioselective protection was examined (Table 3-2). The hydrogenation of **3-1** in the presence of Adams' catalyst (PtO_2) facilely produced catechol **3-35**. However, due to instability under the conditions, catechol **3-35** was difficult to isolate (Entry 1). Therefore, tandem hydrogenation/mono-methylation reactions were examined in one pot (Entries 2 and 3). Although the hydrogenation of **3-1** with PtO_2 followed by the addition of NaHMDS and MeI to the solution of generated **3-35** resulted in decomposition, the hydrogenation of **3-1** in a blend of MeOH-toluene followed by the reaction with $TMSCHN_2$ produced a 1:10 mixture of the desired **3-36** and **3-37** in total 30% yield (Entry 3). To overcome the disappointing regioselectivity of the methylation, the author envisioned a hydrogenation/protection/methylation/deprotection sequence. Therefore, regioselective protection of **3-35** was then examined. After hydrogenation of **3-1**, the resulting **3-35** was reacted in situ with benzoyl chloride to give the desired monobenzoate **3-38** (~30%) and dibenzoate **3-39** (~8%) (Entry 4). Similar in situ reaction of **3-35** with MOMCl in the presence of DIPEA produced only the desired MOM ether **3-40** (Entry 5). Interestingly, when the hydrogenation and the MOM protection were carried out in the dark, the yield of **3-40** was improved, and catechol **3-35** was isolated. It was found that, in the presence of Pt catalyst, catechol **3-35** is easily decomposed by light. Thus, protected catechols **3-38** and **3-40** were prepared.

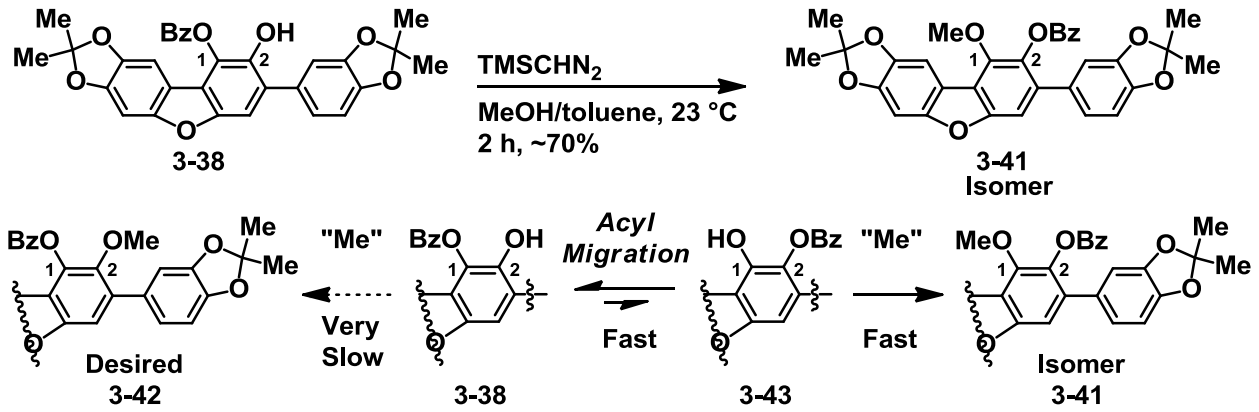
3-1

3-35: R^1 = H, R^2 = H, 3-36: R^1 = H, R^2 = Me
3-37: R^1 = Me, R^2 = H, 3-38: R^1 = Bz, R^2 = H
3-39: R^1 = Bz, R^2 = Bz, 3-40: R^1 = MOM, R^2 = H

Entry	Conditions	Yields
1	PtO_2 (cat.), H_2 (1 atm), THF, 23 °C, 1.5 h	**3-35:** not isolated, not determined
2	PtO_2 (cat.), H_2 (1 atm), THF, 23 °C, 0.5 h then -78 °C, NaHMDS, MeI, 2 h	**decomp.**
3	PtO_2 (cat.), H_2 (1 atm), MeOH/toluene, 23 °C, 1 h then $TMSCHN_2$, 40 °C, 1 d	**3-36**+**3-37**: 30% (1 : 10)
4	PtO_2 (cat.), H_2 (1 atm), DMF, 23 °C, 0.5 h then 0 °C, Et_3N, BzCl, 1 h	**3-38:** ~30% (NMR yield) **3-39**: ~8% (NMR yield)
5	PtO_2 (cat.), H_2 (1 atm), DMF, 23 °C, 0.5 h then 0 °C, DIPEA, MOMCl, 2 h	**3-40**: 26%
6	PtO_2 (cat.), H_2 (1 atm), DMF, 23 °C, 0.5 h (**in the dark**) then 0 °C, DIPEA, MOMCl, 2 h (**in the dark**)	**3-35**: 50%, **3-40**: 46%

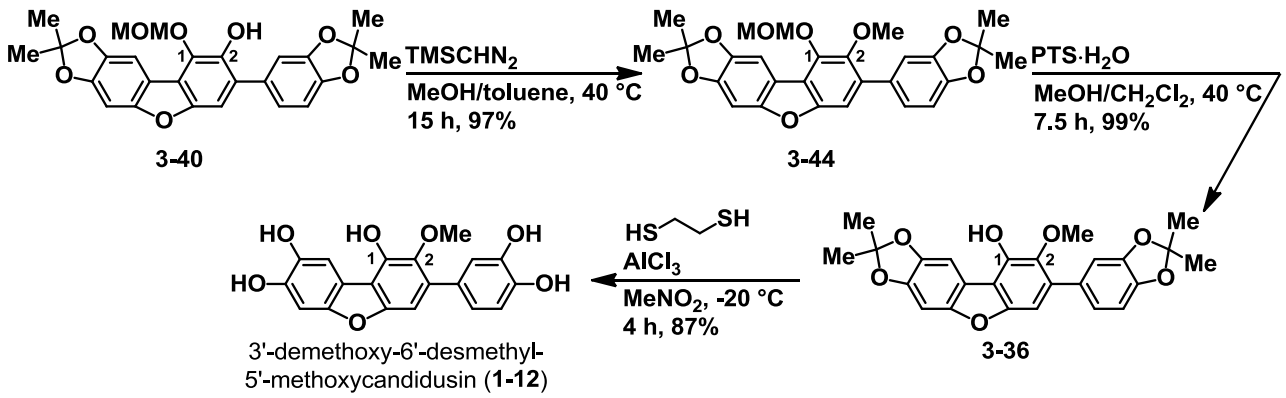
Table 3-2. Transformation of *o*-quinone **3-1** into regioselectively protected catechol derivatives

Next, the methylation of monobenzoate **3-38** was examined using $TMSCHN_2$ expecting the formation of **3-42** (Scheme 3-6). However, an acyl migration occurred before methylation, and undesired **3-41** was produced exclusively (~70%). This is explained as follows: The methylation of the hydroxy group at C2 of **3-38** is very slow due to steric hindrance. There is a rapid acyl migration equilibrium between **3-38** and **3-43**. The hydroxy group at C1 of **3-43** is reactive because of less steric hindrance, and, therefore, methylation of **3-43** is faster than that of **3-38**. Thus, methylation of phenol **3-38** produced undesired **3-41** via an acyl migration.



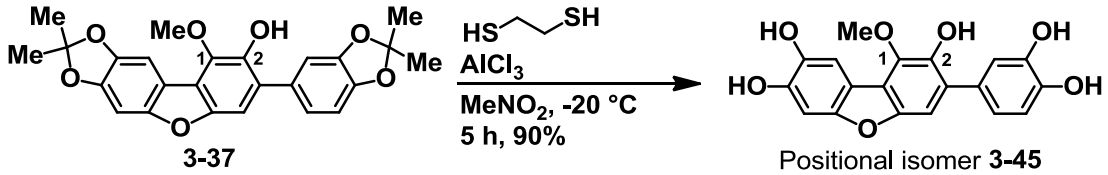
Scheme 3-6. A benzoate shift in methylation of **3-38** with $TMSCHN_2$

Next, the author examined the final stage of the total synthesis of 3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B (**1-12**) from **3-40**, protected with non-migrating MOM group (Scheme 3-7). The methylation of **3-40** with $TMSCHN_2$ gave **3-44** (97%), of which the MOM group was removed under acidic conditions to afford **3-36** (99%). The acetonide groups of **3-45** were removed on treatment with 1,2-ethanedithiol and aluminum chloride to furnish **1-12** (87%). The spectral data of **1-12** were identical with those reported in literature, thereby completing the total synthesis of 3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B (over 15 steps from 1,2,4-trihydroxybenzene in 4.5% overall yield).



Scheme 3-7. Synthesis of 3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B (**1-12**) from **3-40**

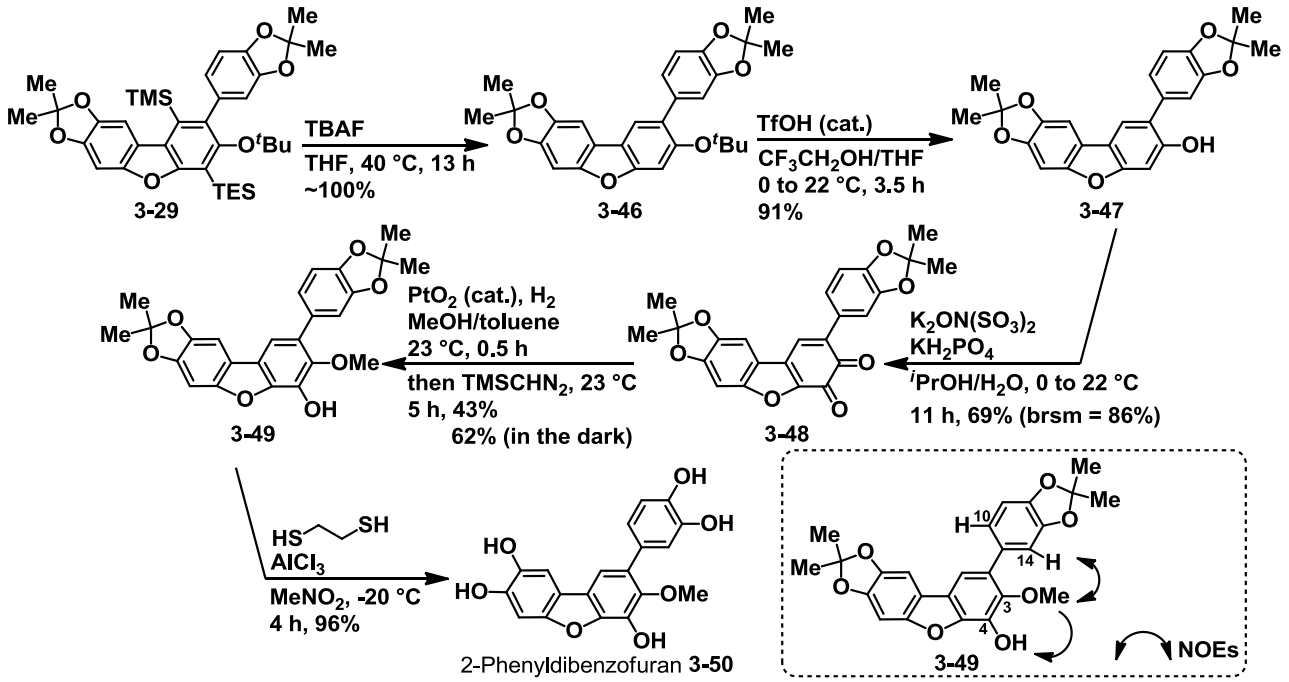
In addition, positional isomer **3-45** was also synthesized by the removal of the acetonide groups of **3-37**. (over 13 steps from 1,2,4-trihydroxybenzene in 4.2% overall yield) (Scheme 3-8).



Scheme 3-8. Synthesis of positional isomer **3-45**

The 2-aryl isomer of **1-12** was also synthesized from 2-phenyldibenzofuran **3-29** obtained from the [2+2+2] cycloaddition (Scheme 3-9). 2-Aryldibenzofuran **3-29** was desilylated with TBAF to give **3-46** (100%), of which the *tert*-butyl group was removed under acidic conditions to afford **3-47** (91%). Upon treatment with potassium nitrosodisulfonate, phenol **3-47** was oxidized to *ortho*-quinone **3-48** (69%, 86% brsm). When tandem hydrogenation/methylation process was applied to **3-48**, methyl ether **3-49** was selectively produced (43%, 62% in the dark). The position of the methyl ether of **3-49** was confirmed by NMR analysis. Since the NOE correlation between the protons of methoxy group and H14 was observed, the position of the methyl ether was assigned

to be C3. The acetonide groups of **3-49** was removed with 1,2-ethanedithiol and $AlCl_3$ to furnish **3-50** (96%) as a 2-aryl isomer of **1-12** (over 13 steps from 1,2,4-trihydroxybenzene in 9.2% overall yield).



Scheme 3-9. Synthesis of 2-phenyldibenzofuran **3-50** and positional assignment of the methyl group of **3-49**

3-5. Conclusion

The author planned the total synthesis of a 3-phenyldibenzofuran natural product, 3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B (**1-12**), based on the two-component [2+2+2] cycloaddition of a 1,6-diyne and a alkoxyacetylene for the construction of the natural product's 3-phenyldibenzofuran skeleton.

The [2+2+2] cycloaddition of 1,6-diyne **3-11** with *tert*-butoxyacetylene **1-86** was carried out in the presence of $RhCl(PPh_3)_3$ under pseudo-high-dilution conditions. However, homodimerization of 1,6-diyne **3-11** predominated. Therefore, in order to suppress the homodimerization of 1,6-diynes, the terminal of the ethynyl ether group was protected with a bulky trialkyl silyl group. Thus, 1,6-diyne **3-11** was reacted with trialkyl silyl chloride to give 1,6-diynes **3-3**, **3-12**, **3-13** and **3-14**. Alternatively, bissilylated 1,6-diyne **3-16** was prepared as a positional isomer of **3-13**. Most of the 1,6-diynes, except **3-12**, produced cycloadducts under the same conditions as above, except pseudo-high-dilution. It should be noted that the bissilyl-protection of the 1,6-diynes was sufficient to suppress the homodimerization, and no pseudo-high-dilution conditions were required in the [2+2+2] cycloaddition of the diynes with **1-86**. On the other hand, the yield and selectivity of the cycloaddition were influenced by the kind of the silyl groups of 1,6-diynes. Thus, the $RhCl(PPh_3)_3$ catalyzed [2+2+2] cycloaddition of **3-3** with **1-86** was found to show the best production of the desired 3-aryldibenzofuran **3-2**.

The next introduction of a hydroxy group at C1 and a methoxy group at C2 was achieved by a process including the ortho-oxidation of the phenol group with Fremy's salt (potassium nitrosodisulfonate), tandem hydrogenation/MOM-protection, methylation with $TMSCHN_2$, and deptotection. Remarkably, catechol **3-35**, produced from **3-1** by Adams' hydrogenation, was unstable to light in the presence of Pt catalyst, and, therefore, the tandem reaction and the work up had to be carried out in the dark. Thus, the author achieved the total synthesis of 3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B (**1-12**). The regioisomers of **1-12** were also synthesized (**3-45**, **3-50**).

References

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[2] K. Fujiwara, T. Sato, Y. Sano, T. Norikura, R. Katoono, T. Suzuki, and H. Matsue, *J. Org. Chem.* **2012**, *77*, 5161.

[3] a) K. Q. Huynh, C. A. Seizert, T. J. Ozumerzifon, P. A. Allegretti, and E. M. Ferreira, *Org. Lett.* **2017**, *19*, 294.; b) F. Liron, F. Fontana, J. -O. Zirimwabagabo, G. Prestat, J. Rajabi, C. L. Rosa, and G. Poli, *Org. Lett.* **2009**, *11*, 4378.

[4] M. J. Mio, L. C. Kopel, J. B. Braun, T. L. Gadzikwa, K. L. Hull, R. G. Brisbois, C. J. Markworth, and P. A. Grieco, *Org. Lett.* **2002**, *4*, 3199.

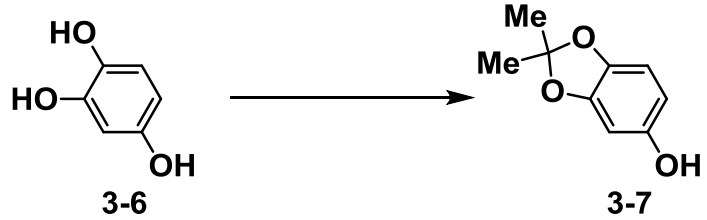
[5] H. Chen and L. Zhang, *Angew. Chem. Int. Ed.* **2015**, *54*, 11775.

Experimental Sections

General Experimental Methods

All air sensitive reactions were carried out under nitrogen atmosphere in oven-dried glassware using standard syringe, cannula and septa techniques. Anhydrous solvents were purchased from commercial sources. The solvents used for column chromatography and extraction were reagent-grade and were used as supplied. All reactions were monitored by thin-layer chromatography (TLC) with precoated silica gel plates (Merck, silica gel 60 F254, 0.25 mm in thickness or Wako, silica gel 70 F254, 0.25 mm in thickness). Plates were visualized by ultraviolet light and by treatment with acidic ceric ammonium molybdate solution stain followed by heating. Column chromatography was performed on YMC Silica Gel 60 (63-40 µm or 230-63 µm) as a stationary phase. High-performance liquid chromatography (HPLC) was performed on a JASCO 880-PU HPLC pump equipped with a pre-packed column (YMC-Pack SIL-06, 5 µm, 300 mm × 10 mm ID or 250 mm × 20 mm ID or 500 mm × 20 mm ID [for normal-phase chromatography]) and a JASCO UV-975 UV detector (UV 254 nm detection). Melting points were measured on an ASONE ATM-02 without calibration. Infrared spectra (IR) were measured on a JASCO FT/IR-4700 infrared spectrometer in noted states and are reported in wave numbers (cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 300 (^{1}H at 300 MHz, ^{13}C at 75 MHz) or a JEOL JNM-ECA 500 (^{1}H at 500 MHz, ^{13}C at 125 MHz) magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm based on the resonance of tetramethylsilane (0 ppm for ^{1}H NMR in $CDCl_3$) or the respective solvent (^{1}H NMR: 7.26 ppm in $CDCl_3$, 3.34 ppm in CD_3OD; ^{13}C NMR: 77.0 ppm in $CDCl_3$, 49.90 ppm in CD_3OD) as the internal standard. The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, dd = double doublets, t = triplet, q = quartet, m = multiplet, and br = broad. Coupling sonstants (J) are reported in Hz. High resolution mass spectra (HRMS) were measured using a Shimadzu LCMS-IT-TOF time-of-flight mass spectrometer under electronspray ionization (ESI) conditions or using a Thermo Scientific Exactive Fourier transform ion cyclotron resonance mass spectrometer under electronspray ionization (ESI) or atmospheric pressure chemical ionization (APCI) or atmospheric pressure photoionization (APPI) conditions.

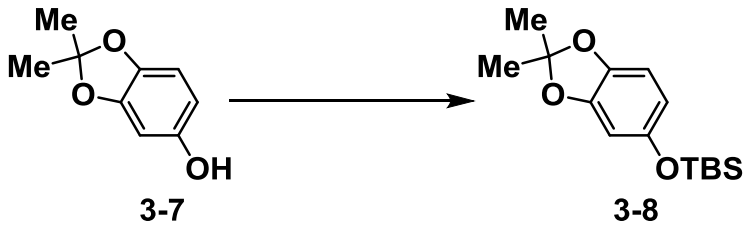
Compound **3-7**



To a refluxed, stirred suspention of 1,2,4-trihydroxybenzene (**3-6**) (not purified by silica gel column chromatography, 1.277 g, 10.13 mmol) in toluene (100 mL) was added 2,2-dimethoxypropane (1.85 mL, 15.10 mmol) dropwise via a syringe pump over 5 h, and the mixture was stirred for an additional 2 h. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20 → 10) to give **3-7** (1.57 g, 9.45 mmol, 93%) as a colorless oil.

3-7: The spectral data were reported in literature (ref. 2). The NMR data of **3-7** obtained by the author were identical with those of ref. 2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (6H, s), 4.85 (1H, br-s), 6.21 (1H, dd, *J* = 2.6, 8.3 Hz), 6.34 (1H, d, *J* = 2.6 Hz), 6.55 (1H, d, *J* = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7 (CH_3×2), 98.1 (CH), 105.9 (CH), 107.9 (CH), 118.1 (C), 141.4 (C), 148.0 (C), 150.2 (C); ESI-HRMS (neg.) *m/z* calcd for $C_9H_9O_3$ $[M - H]^-$: 165.0557, found: 165.0555.

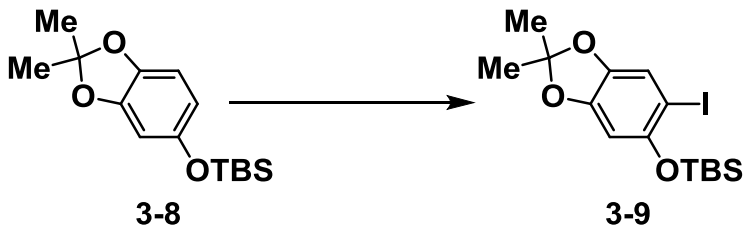
Compound **3-8**



To a solution of **3-7** (332.7 mg, 2.00 mmol) and DMAP (30.5 mg, 0.250 mmol) in DMF (4.0 mL) were added imidazole (450.4 mg, 6.62 mmol) and TBSCl (597.6 mg, 3.96 mmol) at 0 °C, and the mixture was stirred for 1.5 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with hexane/EtOAc = 3 several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **3-8** (495.6 mg, 1.77 mmol, 88%) as a colorless oil.

3-8: IR (neat) *ν* 2991, 2956, 2931, 2895, 2859, 1630, 1611, 1493, 1472, 1443, 1408, 1385, 1376, 1362, 1349, 1279, 1255, 1227, 1168, 1112, 1075, 981, 959, 876, 842, 781, 707, 622 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.16 (6H, s), 0.96 (9H, s), 1.65 (6H, s), 6.22 (1H, dd, *J* = 2.4, 8.3 Hz), 6.30 (1H, d, *J* = 2.4 Hz), 6.55 (1H, d, *J* = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.5 (CH_3×2), 18.1 (CH), 25.69 (CH_3×3), 25.73 (CH_3×2), 102.2 (CH), 107.6 (CH), 110.9 (CH), 117.9 (C), 141.8 (C), 147.7 (C), 150.0 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{15}H_{25}O_3Si$ $[M + H]^+$: 281.1567, found: 281.1572.

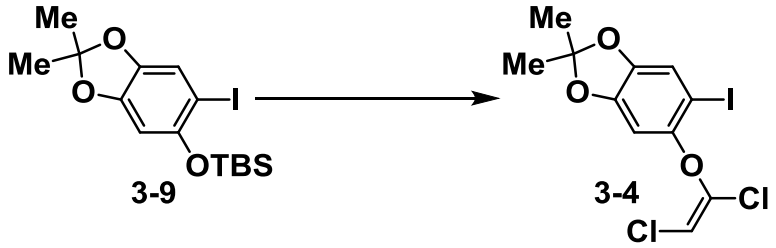
Compound **3-9**



To a solution of *N*-chlorosuccinimide (612.8 mg, 4.59 mmol) in CH_3CN (8.50 mL) was added NaI (729.1 mg, 4.86 mmol) at 22 °C under N_2. The mixture was stirred for 30 min. Then, a solution of **3-8** (1.02 g, 3.64 mmol) in CH_3CN (7.50 mL) and TFA (20 µL, 0.26 mmol) were added to the mixture in the order. The mixture was heated to 50 ºC and stirred for 5 h. The mixture was cooled to ambient temperature and diluted with EtOAc. The solution was washed with sat. aq. $Na_2S_2O_3$ and then with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **3-9** (1.38 g, 3.40 mmol, 94%) as a yellow oil.

3-9: IR (neat) *ν* 2991, 2956, 2930, 2895, 2858, 1619, 1604, 1486, 1403, 1377, 1362, 1346, 1257, 1174, 1083, 990, 959, 939, 877, 841, 781, 718, 676, 611 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.25 (6H, s), 1.04 (9H, s), 1.65 (6H, s), 6.36 (1H, s), 7.03 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.0 (CH_3×2), 18.3 (C), 25.7 (CH_3×2), 25.9 (CH_3×3), 100.6 (CH), 117.1 (CH), 119.0 (C×2), 142.7 (C), 148.4 (C), 149.5 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{15}H_{23}O_3Si^{127}INa$ $[M + Na]^+$: 429.0353, found: 407.0357.

Compound **3-4**

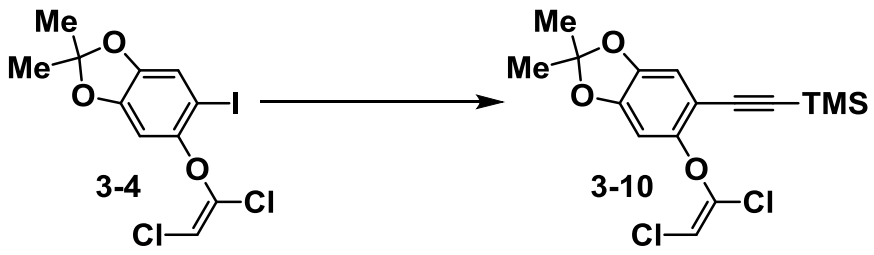


To a solution of **3-9** (821.4 mg, 2.02 mmol), KI (682.6 mg, 4.11 mmol) and trichloroethylene (1.1 mL, 12.22 mmol) in a blend of THF (10 mL) and DMPU (10 mL) was added NaH (60% in oil, 361.6 mg, 9.04 mmol) at 22 °C under N_2. The mixture was heated to 40 °C and stirred for 5 h. Then, to the mixture was added an additional amount of NaH (520.1 mg, 13.01 mmol) at 40 °C, and the mixture was stirred for overnight. The mixture was cooled to ambient temperature, diluted with saturated aq. NH_4Cl and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 50) to give **3-4** (648.8 mg, 1.68 mmol, 83%) as a pale brown oil.

3-4: IR (neat) *ν* 3101, 3051, 2991, 2935, 2857, 2691, 2611, 2341, 2132, 1669, 1632, 1615, 1564, 1486, 1386, 1361, 1255, 1149, 1065, 984, 859, 783, 747, 659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.67 (6H, s), 5.88 (1H, s), 6.51 (1H, s), 7.08 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8 (CH_3×2),

73.9 (C), 99.6 (CH), 102.7 (CH), 117.3 (CH), 120.1 (C), 140.5 (C), 145.7 (C), 147.5 (C), 148.9 (C); APCI-HRMS (pos.) *m/z* calcd for $C_{11}H_9O_3Cl_2I$ $[M]^+$: 385.8968, found: 385.8968.

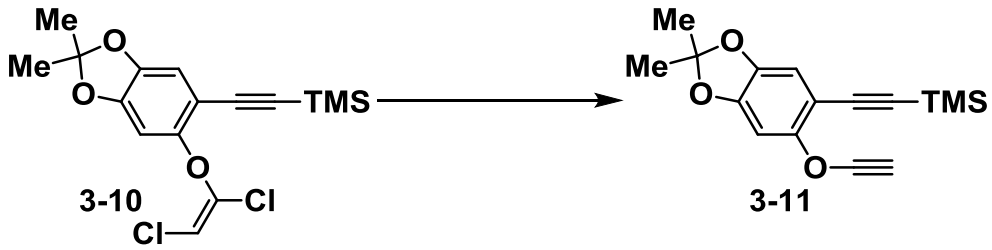
Compound **3-10**



To a solution of **3-4** (398.5 mg, 1.03 mmol) and CuI (22.1 mg, 0.12 mmol) and $PdCl_2(PPh_3)_2$ (142.6 mg, 0.20 mmol) in Et_3N (4.1 mL) was added ethynyltrimethylsilane (190 µL, 1.37 mmol) at 22 °C under N_2, and the mixture was heated to 75 °C and stirred for 24 h. The mixture was cooled to ambient temperature, diluted with saturated aq. NH_4Cl and extracted with Et_2O several times. The combined organic layers were washed with 1 mol/L aq. HCl and then with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 100) to give **3-10** (361.2 mg, 1.01 mmol, 98%) as a yellow oil.

3-10: IR (neat) *ν* 3107, 2992, 2960, 2156, 1621, 1490, 1377, 1251, 1219, 1162, 1140, 1080, 1046, 981, 892, 842, 784, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.23 (9H, s), 1.67 (6H, s), 5.76 (1H, s), 6.48 (1H, s), 6.76 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 0.0 (CH_3×3), 25.9 (CH_3×2), 98.6 (C), 99.3 (C), 100.6 (CH), 100.8 (CH), 107.6 (C), 111.7 (CH), 119.9 (C), 140.7 (C), 144.5 (C), 148.6 (C), 149.8 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{16}H_{18}O_3Si_2{}^{35}Cl_2Na$ $[M + Na]^+$: 379.0294, found: 379.0281.

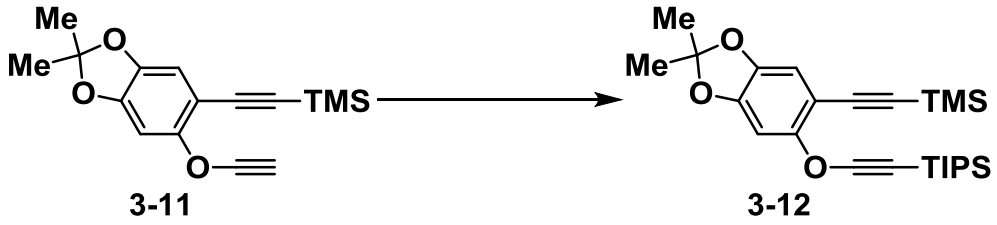
Compound **3-11**



To a solution of **3-10** (363.7 mg, 1.02 mmol) in Et_2O (7.0 mL) was added BuLi (1.57 mol/L in hexane, 4.6 mL, 7.22 mmol) at –78 °C, and the mixture was stirred for 30 min. Then, the mixture was gradually warmed to –40 °C over 2 h and stirred at –40 °C for an additional 9 h. The reaction was quenched with H_2O, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 100) to give **3-11** (241.9 mg, 0.84 mmol, 83%) as a red oil.

3-11: IR (neat) *ν* 2992, 2958, 2898, 2859, 2182, 2152, 1626, 1488, 1425, 1377, 1251, 1218, 1163, 1079, 981, 959, 908, 885, 842, 781, 760, 699, 651, 626 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.24 (9H, s), 1.67 (6H, s), 2.09 (1H, s), 6.75 (1H, s), 7.00 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.1 (CH_3×3), 25.7 (CH_3×2), 33.4 (C), 84.6 (CH), 96.6 (C), 98.7 (CH), 103.5 (CH), 111.6 (C), 119.9 (C), 143.6 (C), 148.6 (C), 151.7 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{16}H_{18}O_3SiNa$ $[M + Na]^+$: 309.0917, found: 309.0915.

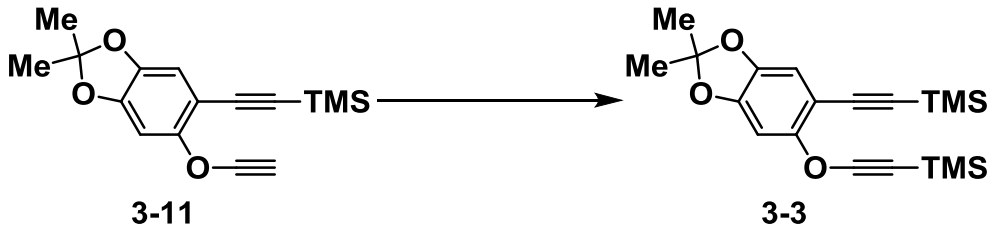
Compound **3-12**



To a solution of **3-11** (36.3 mg, 0.127 mmol) in THF (1.3 mL) was added LHMDS (1.30 mol/L in THF, 0.14 mL, 0.182 mmol) at –78 °C, and the mixture was stirred for 30 min. Then, to the mixture was added TIPSCl (42 µL, 0.196 mmol), and the mixture was warmed to 22 °C and stirred for 19 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 100) to give **3-12** (49.2 mg, 0.111 mmol, 88%) as a yellow oil.

3-12: IR (neat) *ν* 2943, 2893, 2865, 2180, 2156, 1488, 1377, 1250, 1219, 1192, 1162, 981, 885, 843, 760, 678 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.25 (9H, s), 1.10-1.11 (21H, m), 1.67 (6H, s), 6.75 (1H, s), 7.01 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ -0.0 (CH_3×3), 11.5 (CH×3), 18.7 (CH_3×6), 25.8 (CH_3×2), 41.3 (C), 96.2 (CH), 98.5 (C), 98.9 (C), 103.19 (C), 103.25 (C), 111.7 (CH), 119.8 (C), 143.5 (C), 148.6 (C), 152.0 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{25}H_{38}O_3Si_2Na$ $[M + Na]^+$: 465.2252, found: 465.2277.

Compound **3-3**

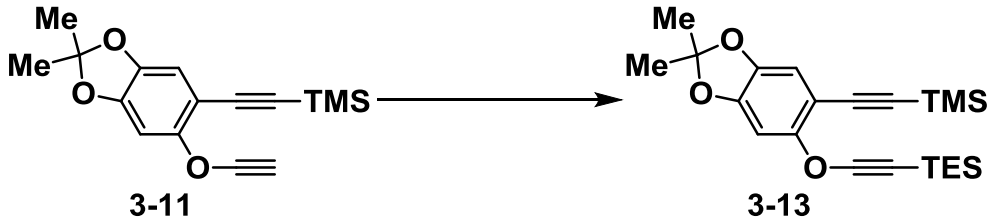


To a solution of **3-11** (261.3 mg, 0.91 mmol) in THF (4.6 mL) was added LHMDS (1.30 mol/L in THF, 0.92 mL, 1.12 mmol) at –40 °C, and the mixture was stirred for 30 min. Then, to the mixture was added TMSCl (220 µL, 1.79 mmol) at –40 °C, and the mixture was warmed to 22 °C and stirred for 3.5 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by

column chromatography (silica gel, hexane/EtOAc = 100) to give **3-3** (297.7 mg, 0.83 mmol, 91%) as a yellow oil.

3-3: IR (neat) *ν* 2992, 2959, 2898, 2859, 2224, 2184, 2156, 1626, 1613, 1487, 1424, 1376, 1251, 1221, 1164, 1100, 1040, 981, 886, 840, 781, 760, 699, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.21 (9H, s), 0.24 (9H, s), 1.67 (6H, s), 6.74 (1H, s), 6.98 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.0 (CH_3×3), 0.4 (CH_3×3), 25.7 (CH_3×2), 45.1 (C), 96.4 (CH), 98.6 (C), 98.8 (C), 102.4 (C), 103.5 (C), 111.7 (CH), 119.8 (C), 143.7 (C), 148.5 (C), 151.8 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{19}H_{27}O_3Si_2$ $[M + H]^+$: 359.15, found: 359.15.

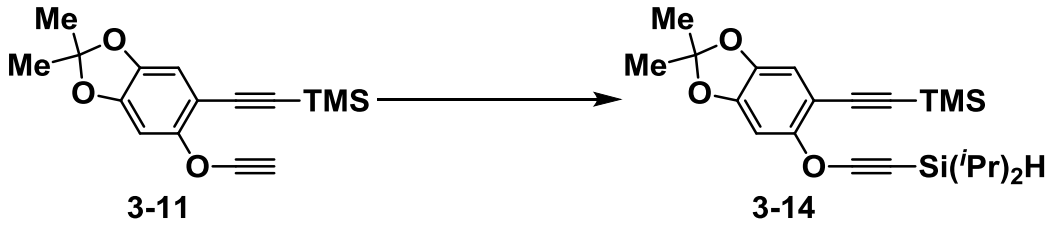
Compound **3-13**



To a solution of **3-11** (129.0 mg, 0.45 mmol) in THF (2.3 mL) was added LHMDS (1.30 mol/L in THF, 0.45 mL, 0.59 mmol) at –40 °C, and the mixture was stirred for 30 min. Then, to the mixture was added TESCl (140 µL, 0.84 mmol) at –40 °C, and the mixture was warmed to 22 °C and stirred for 2.5 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 100) to give **3-13** (155.5 mg, 0.39mmol, 86%) as a yellow oil.

3-13: IR (neat) *ν* 2991, 2956, 2912, 2875, 2181, 2156, 1625, 1487, 1423, 1377, 1250, 1219, 1163, 1100, 1040, 1016, 981, 885, 842, 760, 726 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.24 (9H, s), 0.64 (6H, q, *J* = 7.9 Hz), 1.03 (9H, t, *J* = 15.8 Hz), 1.67 (6H, s), 6.74 (1H, s), 7.00 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ -0.0 (CH_3×3), 4.8 (CH_2×3), 7.5 (CH_3×3), 25.68 (CH_3), 25.75 (CH_3), 42.5 (C), 96.3 (CH), 98.5 (C), 98.9 (C), 102.9 (C), 103.3 (C), 111.7 (CH), 119.8 (C), 143.6 (C), 148.5 (C), 151.9 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{22}H_{32}O_3Si_2Na$ $[M + Na]^+$: 423.1782, found: 423.1804.

Compound **3-14**

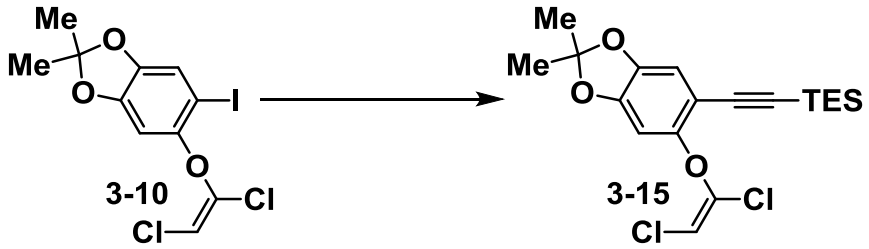


To a solution of **3-11** (106.4 mg, 0.37 mmol) in THF (1.9 mL) was added LHMDS (1.30 mol/L in THF, 0.38 mL, 0.49 mmol) at –40 °C, and the mixture was stirred for 30 min. Then, the mixture was added chlorodiisopropylsilane (110 µL, 0.64 mmol) at –40 °C, and the mixture was warmed to 22 °C and stirred for 5.5 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture

was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 100) to give **3-14** (113.3 mg, 0.28 mmol, 76%) as a pale yellow oil.

3-14: IR (neat) *ν* 2992, 2955, 2895, 2865, 2184, 2155, 2117, 1626, 1613, 1487, 1424, 1377, 1250, 1164, 1100, 1040, 1001, 981, 909, 885, 842, 798, 760, 672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.01-1.07 (2H, m), 1.09 (6H, d, *J* = 9.8 Hz), 1.10 (6H, d, *J* = 9.9 Hz), 1.68 (6H, s), 3.79 (1H, t, *J* = 4.7 Hz), 6.75 (1H, s), 7.00 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ -0.0 (CH_3×3), 11.0 (CH_3×2), 18.3 (CH_3×2), 18.5 (CH_3×2), 25.7 (CH_3×2), 39.1 (C), 96.3 (CH), 98.67 (C), 98.72 (C), 103.4 (C), 103.9 (C), 111.7 (CH), 119.9 (C), 143.7 (C), 148.6 (C), 151.7 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{22}H_{33}O_3Si_2$ $[M + H]^+$: 401.1963, found: 401.1968.

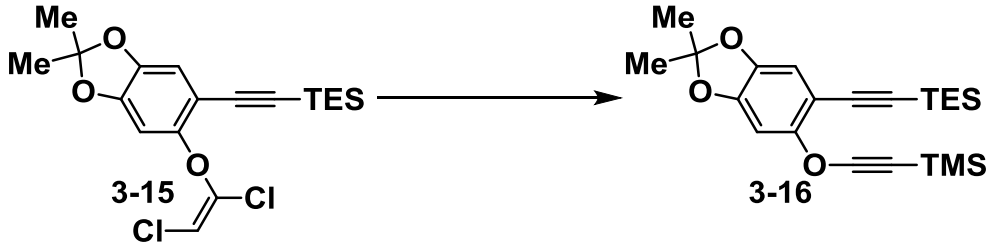
Compound **3-15**



To a solution of **3-10** (80.6 mg, 0.21 mmol), CuI (4.8 mg, 0.025 mmol) and $PdCl_2(PPh_3)_2$ (16.6 mg, 0.024 mmol) in Et_3N (1.0 mL) was added ethynyltriethylsilane (48 µL, 0.27 mmol) at 23 °C under N_2, and the mixture was heated to 75 °C and stirred for 16 h. The mixture was cooled to ambient temperature, diluted with saturated aq. NH_4Cl and extracted with Et_2O several times. The combined organic layers were washed with 1 mol/L aq. HCl and then with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 100) to give **3-15** (70.5 mg, 0.18 mmol, 85%) as a yellow oil.

3-15: IR (neat) *ν* 3105, 2992, 2955, 2912, 2875, 2152, 1621, 1488, 1420, 1378, 1251, 1162, 1080, 1046, 1016, 981, 890, 863, 837, 789, 726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.65 (6H, q, *J* = 7.9 Hz), 1.03 (9H, t, *J* = 15.9 Hz), 1.67 (6H, s), 5.76 (1H, s), 6.47 (1H, s), 6.78 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.4 (CH_2×3), 7.4 (CH_3×3), 25.8 (CH_3×2), 96.0 (C), 100.38 (CH), 100.42 (C), 100.7 (CH), 107.6 (C), 111.7 (CH), 119.8 (C), 140.6 (C), 144.3 (C), 148.4 (C), 149.8 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{19}H_{25}O_3Si^{35}Cl_2$ $[M + H]^+$: 399.0945, found: 399.0947.

Compound **3-16**



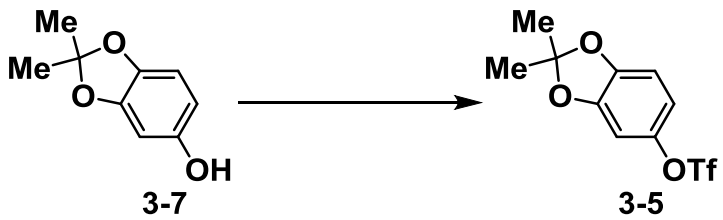
To a solution of **3-15** (146.1 mg, 0.37 mmol) in Et_2O (3.7 mL) was added BuLi (1.57 mol/L in hexane, 1.65 mL, 2.59 mmol) at –78 °C, and the mixture was stirred for 30 min. Then, the mixture was gradually warmed to –40 °C over 2 h and stirred for an additional 16 h. The reaction was quenched with H_2O, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 100) to give a diyne (82.3 mg, 0.25 mmol, 69%) as a yellow oil.

The obtained diyne shows the following spectral data: IR (neat) *ν* 2992, 2955, 2912, 2875, 2183, 2151, 1681, 1626, 1487, 1425, 1377, 1263, 1162, 1079, 1016, 980, 883, 863, 840, 792, 727, 622 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.67 (6H, q, *J* = 7.9 Hz), 1.16 (9H, t, *J* = 15.6 Hz), 1.67 (6H, s), 2.08 (1H, s), 6.76 (1H, s), 7.01 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 4.4 (CH_2×3), 7.5 (CH_3×3), 25.7 (CH_3×2), 33.4 (C), 84.6 (CH), 96.3 (C), 96.6 (CH), 99.9 (C), 103.8 (C), 111.6 (CH), 119.8 (C), 143.7 (C), 148.5 (C), 151.8 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{19}H_{25}O_3SiNa$ $[M + Na]^+$: 329.1567, found: 329.1569.

To a solution of the above diyne (46.0 mg, 0.140 mmol) in THF (0.7 mL) was added LHMDS (1.30 mol/L in THF, 0.14 mL, 0.182 mmol) at –40 °C, and the mixture was stirred for 30 min. Then, to the mixture was added TMSCl (26 µL, 0.211 mmol) at –40 °C, and the mixture was warmed to 22 °C and stirred for 3 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 100) to give **3-16** (30.1 mg, 0.0751 mmol, 54%) as a yellow oil.

3-16: IR (neat) *ν* 2992, 2956, 2912, 2875, 2183, 2153, 1626, 1487, 1424, 1377, 1250, 1219, 1162, 1099, 1040, 1016, 980, 883, 843, 792, 160, 726, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.21 (9H, s), 0.66 (6H, q, *J* = 7.9 Hz), 1.04 (9H, t, *J* = 15.8 Hz), 1.67 (6H, s), 6.75 (1H, s), 6.98 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.4 (CH_3×3), 4.4 (CH_2×3), 7.5 (CH_3×3), 25.7 (CH_3×2), 44.8 (C), 96.1 (C), 96.5 (CH), 100.0 (C), 102.5 (C), 103.7 (C), 111.7 (CH), 119.8 (C), 143.6 (C), 148.4 (C), 151.2 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{22}H_{32}O_3Si_2Na$ $[M + Na]^+$: 423.1782, found: 423.1765.

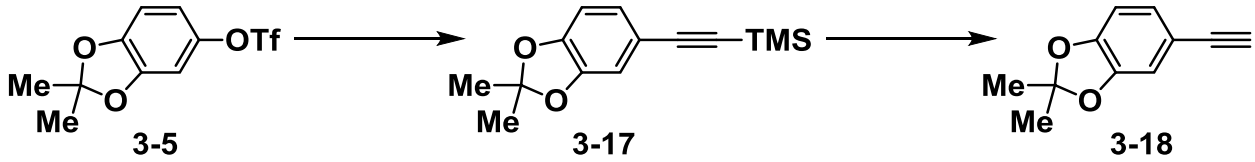
Compound **3-5**



To a solution of **3-7** (509.0 mg, 3.06 mmol) in CH_2Cl_2 10.0 mL) was added pyridine (0.5 mL, 6.21 mmol) at 0 °C, and the mixture was stirred for 5 min. Then, Tf_2O (0.64 mL, 3.90 mmol) was added dropwise to the mixture, and the mixture was warmed to 22 °C and stirred for 2 h. The reaction was quenched with H_2O, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were washed with 1 mol/L aq. HCl, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 20) to give **3-5** (791.1 mg, 2.65 mmol, 87%) as a pale yellow oil.

3-5: IR (neat) *v* 2996, 2942, 1635, 1609, 1495, 1424, 1381, 1211, 1143, 1120, 1104, 1076, 981, 944, 871, 841, 803, 729, 660, 608 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.70 (6H, s), 6.66-6.69 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8 (CH_3×2), 103.0 (CH), 107.9 (CH), 113.6 (CH), 117.4 (C), 120.2 (C), 143.1 (C), 147.3 (C), 148.2 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{10}H_{10}O_5F_3S$ $[M + H]^+$: 299.0196, found: 299.0175.

Compound **3-18**



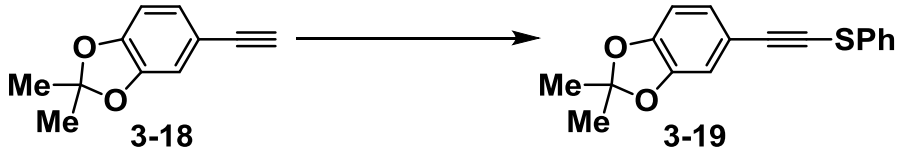
To a solution of **3-5** (2.09 g, 7.02 mmol), CuI (141.6 mg, 0.74 mmol), $PdCl_2(PPh_3)_2$ (474.1 mg, 0.68 mmol) and DABCO (2.48 g, 22.12 mmol) in benzene (36.0 mL) was added ethynyltrimethylsilane (1.25 mL, 9.04 mmol) at 22 °C under N_2, and the mixture was heated to 60 °C and stirred for 18 h. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with 1 mol/L aq. HCl, then brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **3-17**, which was used in the next reaction without purification.

To a solution of the above crude **3-17** in MeOH (24.0 mL) was added K_2CO_3 (974.8 mg, 7.05 mmol) at 22 °C, and the mixture was stirred for 2 h. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with Et_2O several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 100) to give **3-18** (1.21 g, 6.95 mmol, 99% for 2 steps) as a pale brown solid.

3-18: IR (film) *v* 2992, 2937, 2107, 1604, 1494, 1439, 1378, 1340, 1250, 1144, 1119, 981, 935, 863, 838, 811, 660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.67 (6H, s), 2.95 (1H, s), 6.66 (1H, d, *J* = 8.0 Hz), 6.84 (1H, d, *J* = 1.5 Hz), 6.98 (1H, dd, *J* = 1.6, 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8

(CH_3×2), 75.2 (CH), 83.8 (C), 108.2 (CH), 111.8 (CH), 114.6 (C), 118.6 (C), 126.4 (CH), 147.2 (C), 148.2 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{11}H_{11}O_2$ $[M + H]^+$: 175.0760, found: 175.0754.

Compound **3-19**



To a solution of **3-18** (1.25 g, 7.18 mmol) in THF (18 mL) was added LHMDS (1.30 mol/L in THF, 7.2 mL, 9.36 mmol) at –78 °C, and the mixture was stirred for 1 h. Then, to the mixture was added a solution prepared in advance with diphenyl disulfide (1.74 g, 7.97 mmol) and MeI (490 µL, 7.87 mmol) in THF (14 mL) at –78 °C, and the mixture was warmed to 22 °C and stirred for 2 h. The reaction was quenched with saturated aq. NH_4Cl, and the mixture was extracted with hexane several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 100) to give **3-19** (1.92 g, 6.80 mmol, 94%) as an orange solid.

3-19: IR (film) *ν* 3074, 2991, 2935, 1583, 1494, 1441, 1377, 1277, 1252, 1217, 1171, 981, 840, 809, 738, 687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (6H, s), 6.69 (1H, d, *J* = 8.0 Hz), 6.88 (1H, d, *J* = 1.5 Hz), 7.03 (1H, dd, *J* = 1.6, 8.1 Hz), 7.19-7.24 (1H, m), 7.31-7.36 (2H, m), 7.45-7.48 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8 (CH_3×2), 73.0 (C), 98.2 (C), 108.3 (CH), 111.9 (CH), 115.4 (C), 118.8 (C), 126.0 (CH×2), 126.3 (CH), 126.7 (CH), 129.2 (CH×2), 133.4 (C), 147.3 (C), 148.4 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{17}H_{15}O_2S$ $[M + H]^+$: 283.0787, found: 283.0752.

Compound **3-20**

To a solution of **3-19** (1.60 g, 5.65 mmol) in CH_2Cl_2 (30 mL) was added *m*CPBA (3.01 g, 13.09 mmol) at 0 °C, and the mixture was stirred for 1 h. Then, the mixture was warmed to 23 °C and stirred for 16 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 several times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 5) to give **3-20** (1.41 g, 4.49 mmol, 79%) as a pale yellow solid.

3-20: IR (film) *ν* 3071, 2992, 2937, 2170, 1727, 1495, 1446, 1380, 1330, 1310, 1258, 1220, 1159, 1125, 1087, 982, 948, 842, 805, 755, 725, 687, 664, 588, 569 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.67 (6H, s), 6.70 (1H, d, *J* = 8.1 Hz), 6.84 (1H, d, *J* = 1.4 Hz), 7.06 (1H, dd, *J* = 1.6, 8.0 Hz), 7.58-7.61 (2H, m), 7.66-7.69 (1H, m), 8.06-8.08 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8

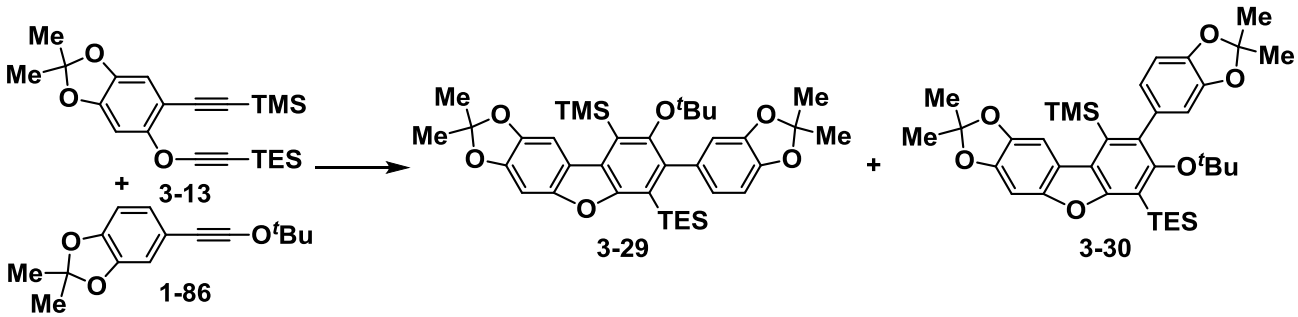
(CH_3×2), 83.8 (C), 94.8 (C), 108.7 (CH), 109.9 (C), 111.8 (CH), 119.7 (C), 127.2 (CH×2), 128.4 (CH), 129.3 (CH×2), 134.0 (C), 142.0 (C), 147.5 (C), 150.6 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{17}H_{15}O_4S$ $[M + H]^+$: 315.0697, found: 315.0691.

Compound **1-86**

To a cooled (–40 °C) solution of potassium *tert*-butoxide (1.0 mol/L in THF, 10.0 mL, 10.0 mmol) was added a solution of **3-20** (466.1 mg, 1.48 mmol) in THF (5.0 mL), and the mixture was stirred for 10 min. Then, the mixture was warmed to 22 °C and stirred for 4 h. The mixture was filtered through a short pad of florisil using a 20:1 blend of hexane and EtOAc as eluent. The eluate was concentrated under reduced pressure. The residue was purified by column chromatography (fluorisil, hexane) to give **1-86** (247.2 mg, 1.00 mmol, 68%) as a colorless oil.

1-86: IR (neat) *ν* 2981, 2936, 2251, 1602, 1497, 1445, 1372, 1341, 1312, 1236, 1156, 1123, 1081, 1042, 1027, 979, 912, 831, 817, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (9H, s), 1.65 (6H, s), 6.61 (1H, d, *J* = 8.0 Hz), 6.73 (1H, d, *J* = 1.6 Hz), 6.81 (1H, dd, *J* = 1.7, 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8 (CH_3×2), 27.1 (CH_3×3), 42.5 (C), 86.5 (C), 93.5 (C), 108.1 (CH), 111.6 (CH), 117.1 (C), 117.9 (C), 124.9 (CH), 146.3 (C), 147.1 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{15}H_{18}O_3K$ $[M + K]^+$: 285.0888, found: 285.0913.

Compound **3-29-30**



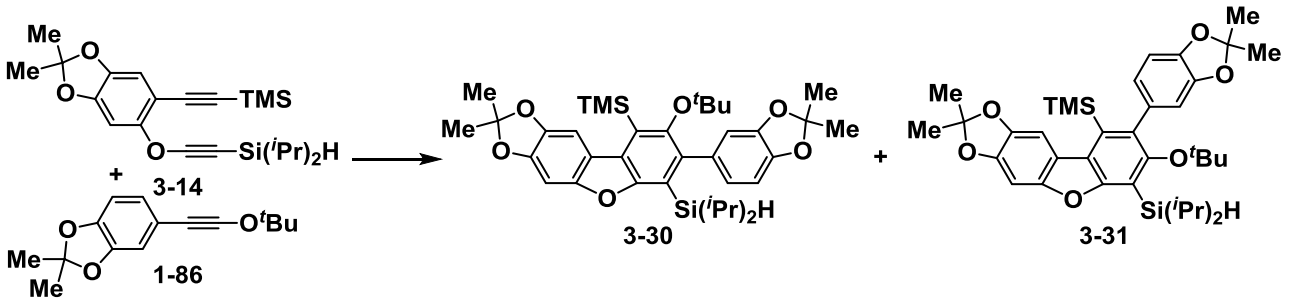
To a mixture of **3-13** (47.8 mg, 0.12 mmol), **1-86** (29.2 mg, 0.12 mmol) and $RhCl(PPh_3)_3$ (15.0 mg, 0.016 mmol) was added benzene (1.2 mL) at 22 °C under N_2. Then, the mixture was heated to 40 °C and stirred for 22 h. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 100) to give a mixture of **3-28** and **3-29**. Futher purification by HPLC (hexane/EtOAc = 100) gave **3-28** (17.8 mg, 0.0275 mmol, 23%) as an amorphous solid and **3-29** (39.8 mg, 0.0615 mmol, 52%) as an amorphous solid.

3-28: IR (film) *ν* 2954, 2873, 1628, 1496, 1475, 1386, 1376, 1326, 1253, 1233, 1147, 980, 873, 842, 730, 687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.52 (9H, s), 0.58-0.66 (6H, br-m), 0.80 (9H, t, *J* = 15.5 Hz), 0.89 (9H, s), 1.71-1.77 (12H, br-m), 6.69-6.90 (3H, br-m), 6.94 (1H, s), 7.32 (1H, s); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 2.6 (CH_3×3), 5.0 (CH_2×3), 7.9 (CH_3×3), 25.4 (CH_3), 25.5 (CH_3), 25.8 (CH_3), 25.9 (CH_3), 29.2 (CH_3×3), 80.4 (C), 93.2 (CH×2), 102.5 (CH×2), 106.6 (C), 113.3 (C), 117.3 (C), 117.4 (C), 118.5 (C×2), 121.2 (C), 125.8 (CH), 127.7 (C), 142.6 (C), 143.4 (C), 146.6 (C), 146.7 (C), 146.9 (C), 151.4 (C), 158.2 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{37}H_{50}O_6Si_2Na$ [M + Na]$^+$: 669.3038, found: 669.3005.

3-29: IR (film) *v* 2954, 2874, 1627, 1495, 1476, 1386, 1376, 1350, 1330, 1254, 1233, 1146, 1014, 979, 843, 739, 725, 698, 683 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (9H, s), 0.86 (9H, s), 1.00 (9H, t, *J* = 15.0 Hz), 1.06 (6H, m), 1.71-1.74 (12H, br-m), 6.72-6.85 (3H, br-m), 6.94 (1H, s), 7.29 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 1.8 (CH_3×3), 5.3 (CH_2×3), 7.9 (CH_3×3), 25.5 (CH_3×2), 25.78 (CH_3), 25.83 (CH_3), 29.4 (CH_3×3), 81.3 (C), 93.2 (CH), 103.0 (CH), 107.3 (CH), 113.8 (CH), 116.7 (C), 117.2 (C), 117.5 (C), 118.4 (C), 124.6 (C), 126.3 (CH), 135.2 (C), 136.5 (C), 140.6 (C), 143.3 (C), 146.5 (C), 146.7 (C), 146.9 (C), 151.3 (C), 157.2 (C), 161.6 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{37}H_{50}O_6Si_2Na$ [M + Na]$^+$: 669.3038, found: 669.3005.

Compound **3-30-31**



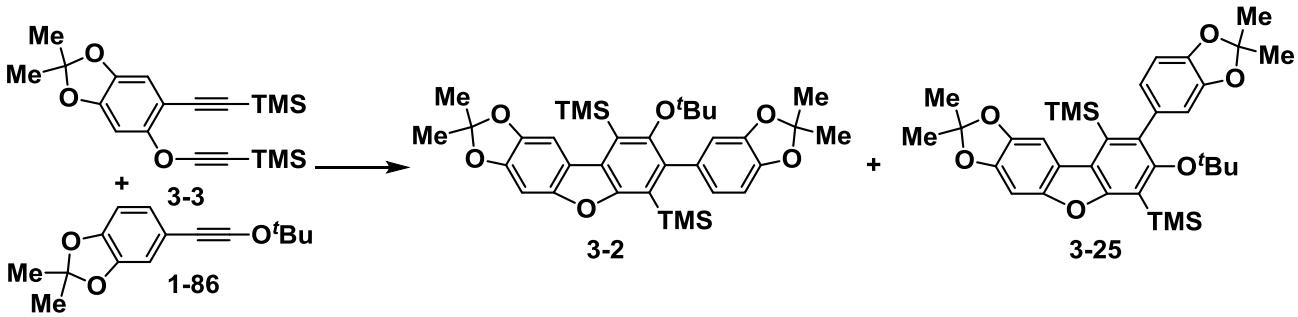
To a mixture of **3-14** (40.3 mg, 0.10 mmol), **1-86** (24.7 mg, 0.10 mmol) and $RhCl(PPh_3)_3$ (12.6 mg, 0.014 mmol) was added benzene (1.0 mL) at 22 °C under N_2. Then, the mixture was heated to 40 °C and stirred for 22 h. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 100) to give a mixture of **3-30** and **3-31**. Futher purification by HPLC (hexane/EtOAc = 100) gave **3-30** (10.7 mg, 0.0165 mmol, 16%) as an amorphous solid and **3-31** (16.6 mg, 0.0257 mmol, 25%) as an amorphous solid.

3-30: IR (film) *v* 2938, 2862, 2142, 1627, 1496, 1465, 1386, 1376, 1327, 1253, 1233, 1146, 980, 841 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.52 (9H, s), 0.92 (9H, s), 0.95-1.34 (14H, brm), 1.72 (6H, s), 1.74 (6H, brs), 3.66 (1H, t, *J* = 8.4 Hz), 6.71-6.79 (3H, brm), 6.94 (1H, s), 7.33 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 2.6 (CH_3×3), 11.9 (CH×2), 19.6 (CH_3×4), 25.6 (CH_3×2), 25.8 (CH_3×2), 29.1 (CH_3×3), 80.4 (C), 93.3 (CH×2), 102.6 (CH×2), 117.4 (C×2), 117.5 (C), 118.5 (C×2), 119.8 (C), 126.0 (CH), 127.3 (C), 130.5 (C), 134.9 (C), 142.9 (C), 143.5 (C), 146.9 (C), 151.8 (C), 154.3 (C), 157.4 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{37}H_{50}O_6Si_2Na$ [M + Na]$^+$: 669.3038, found: 669.3008.

3-31: IR (film) *v* 2940, 2863, 2156, 1627, 1495, 1477, 1386, 1376, 1350, 1332, 1254, 1232, 1015, 979, 841 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10 (9H, s), 0.88 (5H, t, *J* = 13.6 Hz), 0.92 (9H, s), 1.04 (3H, d, *J* = 7.0 Hz), 1.14 (3H, d, *J* = 6.8 Hz), 1.21 (3H, d, *J* = 7.3 Hz), 1.68-1.74 (12H, br-t, *J* =

29.0 Hz), 4.44 (1H, t, J = 7.7 Hz), 6.73 (2H, brs), 6.80 (1H, s), 6.93 (1H, s), 7.31 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 1.7 (CH_3×3), 12.0 (CH×2), 19.5 (CH_3×4), 25.5 (CH_3), 25.6 (CH_3), 25.8 (CH_3×2), 29.6 (CH_3×3), 81.5 (C), 93.2 (CH), 103.3 (CH), 107.4 (CH), 113.7 (CH), 115.2 (C), 117.1 (C), 117.5 (C), 118.5 (C), 124.0 (C), 125.9 (CH), 135.6 (C), 136.3 (C), 140.2 (C), 143.3 (C), 146.5 (C), 146.8 (C), 147.0 (C), 151.6 (C), 157.6 (C), 160.5 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{37}H_{50}O_6Si_2Na$ $[M + Na]^+$: 669.3038, found: 669.3036.

Compound **3-2, 3-25**

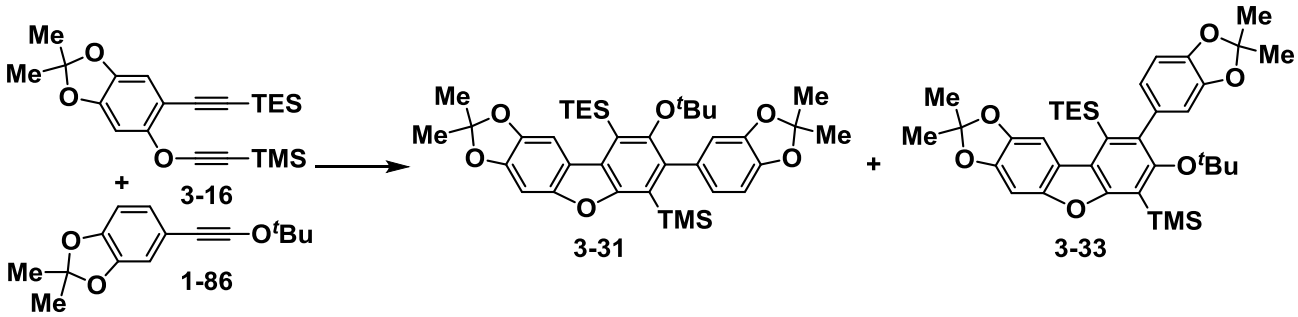


To a mixture of **3-3** (42.7 mg, 0.12 mmol), **1-86** (28.9 mg, 0.12 mmol) and $RhCl(PPh_3)_3$ (13.0 mg, 0.014 mmol) was added benzene (1.2 mL) at 22 °C under N_2. Then, the mixture was heated to 40 °C and stirred for 4 h. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 100) to give a mixture of **3-2** and **3-25**. Futher purification by HPLC (hexane/EtOAc = 100) gave **3-2** (23.0 mg, 0.0380 mmol, 33%) as an amorphous solid and **3-25** (28.7 mg, 0.0474 mmol, 41%) as an amorphous solid.

3-2: IR (film) *v* 2987, 2899, 1626, 1497, 1475, 1465, 1386, 1376, 1362, 1348, 1327, 1252, 1233, 1147, 1119, 980, 878, 842, 765, 685 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.12 (9H, s), 0.52 (9H, s), 0.89 (9H, s), 1.71 (9H, br-s), 1.76 (3H, br-s), 6.69-6.71 (2H, br-m), 6.91 (1H, br), 6.94 (1H, s), 7.31 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 1.4 (CH_3×3), 2.6 (CH_3×3), 25.5 (CH_3×2), 25.8 (CH_3×2), 29.3 (CH_3×3), 80.5 (C), 93.3 (CH), 102.5 (CH), 106.8 (CH), 113.1 (CH), 117.4 (C), 117.5 (C), 118.5 (C), 123.8 (C), 125.9 (CH), 128.0 (C), 135.9 (C), 141.9 (C), 143.4 (C), 146.7 (C), 147.0 (C), 151.6 (C), 154.8 (C), 157.9 (C); APPI-HRMS (pos.) *m/z* calcd for $C_{34}H_{45}O_6Si_2$ $[M + H]^+$: 605.2749, found: 605.2750.

3-25: IR (film) *v* 32988, 2899, 1627, 1495, 1477, 1386, 1376, 1365, 1350, 1330, 1251, 1233, 1146, 1119, 1014, 979, 842, 765, 741, 683, 631 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10 (9H, s), 0.51 (9H, s), 0.87 (9H, s), 1.70 (3H, br-s), 1.72 (6H, br-s), 1.74 (3H, br-s), 6.72-6.79 (2H, br-m), 6.87 (1H, br-s), 6.95 (1H, s), 7.29 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 1.6 (CH_3×3) 1.8 (CH_3×3), 25.51 (CH_3), 25.57 (CH_3), 25.78 (CH_3), 25.82 (CH_3), 29.3 (CH_3×3), 81.4 (C), 93.2 (CH), 103.0 (CH), 107.3 (CH), 113.8 (CH), 117.2 (C), 117.5 (C), 118.4 (C), 119.2 (C), 124.7 (C), 126.4 (CH), 135.2 (C), 136.4 (C), 140.6 (C), 143.3 (C), 146.5 (C), 146.7 (C), 146.9 (C), 151.5 (C), 156.6 (C), 161.1 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{34}H_{44}O_6Si_2Na$ $[M + Na]^+$: 627.2569, found: 627.2539.

Compound **3-31, 3-33**

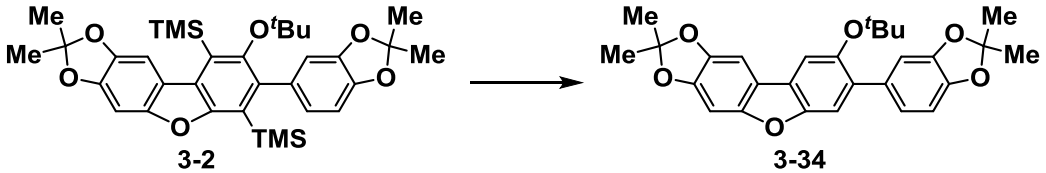


To a mixture of **3-16** (30.2 mg, 0.0754 mmol), **1-86** (33.5 mg, 0.136 mmol) and $RhCl(PPh_3)_3$ (9.1 mg, 0.00984 mmol) was added benzene (0.75 mL) at 22 °C under N_2. Then, the mixture was heated to 40 °C and stirred for 12 h. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane → hexane/EtOAc = 100) to give a mixture of **3-31** and **3-33**. Futher purification by HPLC (hexane/EtOAc = 100) gave **3-31** (8.9 mg, 0.0138 mmol, 18%) as an amorphous solid and **3-33** (13.7 mg, 0.0212 mmol, 28%) as an amorphous solid.

3-31: IR (film) *ν* 2955, 2875, 2184, 2152, 1626, 1496, 1488, 1472, 1386, 1376, 1326, 1251, 1233, 1146, 980, 877, 843, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.11 (9H, s), 0.89 (9H, s), 0.97 (9H, t, *J* = 15.5 Hz), 1.06-1.20 (6H, m), 1.71 (9H, br-s), 1.78 (3H, br-s), 6.71 (2H, br), 6.86 (1H, br), 6.93 (1H, s), 7.29 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 1.3 (CH_3×3), 5.8 (CH_2×3), 8.2 (CH_3×3), 25.5 (CH_3×2), 25.8 (CH_3), 25.9 (CH_3), 29.2 (CH_3×3), 80.4 (C), 93.2 (CH×2), 102.1 (CH×2), 111.7 (CH), 117.5 (C×2), 117.6 (C), 118.5 (C×2), 123.6 (C), 128.2 (C), 141.7 (C), 143.4 (C×2), 146.9 (C×2), 151.5 (C×2), 158.0 (C×2); APPI-HRMS (pos.) *m/z* calcd for $C_{37}H_{51}O_6Si_2$ $[M + H]^+$: 647.3219, found: 647.3216.

3-33: IR (film) *ν* 2955, 2874, 1494, 1476, 1442, 1386, 1376, 1350, 1329, 1250, 1232, 1146, 1119, 1015, 979, 871, 841, 727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.49 (9H, s), 0.61-0.66 (6H, m), 0.78 (9H, t, *J* = 15.7 Hz), 0.85 (9H, s), 1.06-1.20 (6H, m), 1.72 (9H, br-s), 1.75 (3H, br-s), 6.71-6.79 (2H, br-m), 6.88 (1H, br), 6.94 (1H, s), 7.28 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 1.6 (CH_3×3), 4.9 (CH_2×3), 8.3 (CH_3×3), 25.43 (CH_3), 25.51 (CH_3), 25.79 (CH_3), 25.84 (CH_3), 29.3 (CH_3×3), 81.3 (C), 93.2 (CH), 102.8 (CH), 107.0 (CH), 114.1 (CH), 117.44 (C), 117.47 (C), 118.4 (C), 119.1 (C), 125.1 (C), 126.8 (CH), 133.7 (C), 136.4 (C), 141.4 (C), 143.2 (C), 144.4 (C), 146.6 (C), 146.7 (C), 151.4 (C), 156.4 (C), 161.2 (C); APCI-HRMS (pos.) *m/z* calcd for $C_{37}H_{51}O_6Si_2$ $[M + H]^+$: 647.3219, found: 647.3217.

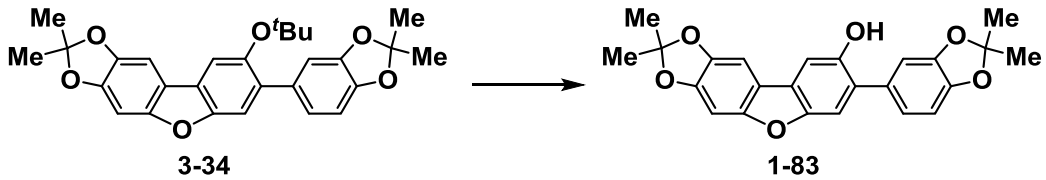
Compound **3-34**



To a solution of **3-2** (42.8 mg, 0.0708 mmol) in THF (1.5 mL) was added TBAF (1.0 mol/L in THF, 0.58 mL, 0.58 mmol) at 22 °C. Then, the mixture was heated to 40 °C and stirred for 4 h. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 50 → 20) to give **3-34** (34.3 mg, <0.0708 mmol, <100%) as an amorphous solid.

3-34: IR (film) *ν* 2982, 2359, 1633, 1505, 1469, 1376, 1364, 1285, 1258, 1236, 1132, 979, 842 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (9H, s), 1.72 (6H, s), 1.73 (6H, s), 6.78 (1H, d, *J* = 7.9 Hz), 6.96 (1H, s), 7.03 (1H, dd, *J* = 1.7, 8.0 Hz), 7.06 (1H, d, *J* = 1.7 Hz), 7.16 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.75 (CH_3×2), 25.78 (CH_3×2), 28.7 (CH_3×3), 80.0 (C), 93.8 (CH), 99.0 (CH), 107.7 (CH), 110.7 (CH), 112.3 (CH), 114.8 (CH), 116.4 (C), 117.7 (C), 118.7 (C), 123.7 (C), 133.6 (C), 135.0 (C), 144.2 (C), 146.3 (C), 147.0 (C), 147.7 (C), 148.4 (C), 152.2 (C), 152.9 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{28}H_{29}O_6$ $[M + H]^+$: 461.1959, found: 461.1964.

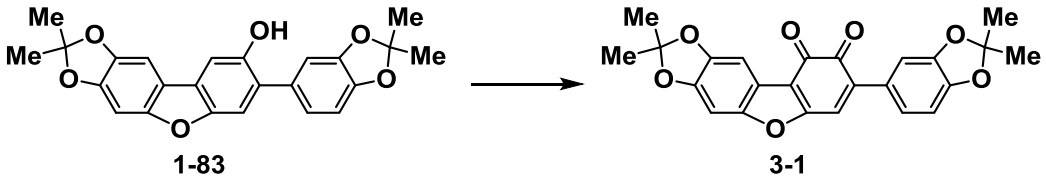
Compound **1-83**



To a solution of **3-34** (56.2 mg, 0.122 mmol) in a blend of CF_3CH_2OH (1.0 mL) and THF (0.2 mL) was added CF_3SO_3H (1.2 μL, 0.0136 mmol) at 0 °C. Then, the mixture was warmed to 22 °C and stirred for 3.5 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 5) to give **1-83** (42.6 mg, 0.105 mmol, 86%, 91% based on recovered **3-34**) as a colorless oil, along with recovered **3-34** (2.7 mg, 0.00586 mmol, 4.8%) as an amorphous solid.

1-83: IR (film) *ν* 3520, 2990, 1638, 1493, 1471, 1377, 1315, 1286, 1239, 1136, 979, 887, 841, 815, 790, 738, 703, 676 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.73 (6H, s), 1.74 (6H, s), 5.2 (1H, s), 6.85 (1H, d, *J* = 7.9 Hz), 6.88 (1H, d, *J* = 1.5 Hz), 6.92 (1H, dd, *J* = 1.7, 8.9 Hz), 6.93 (1H, s), 7.15 (1H, s), 7.31 (1H, s), 7.32 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8 (CH_3×2), 26.0 (CH_3×2), 93.7 (CH), 99.1 (CH), 105.1 (CH), 108.8 (CH), 109.6 (CH), 111.9 (CH), 116.3 (C), 118.6 (C), 118.7 (C), 121.9 (CH), 125.0 (C), 125.9 (C), 130.2 (C), 144.1 (C), 147.3 (C), 147.9 (C), 148.3 (C), 148.4 (C), 151.0 (C), 152.4 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{24}H_{21}O_6$ $[M + H]^+$: 405.1333, found: 405.1337.

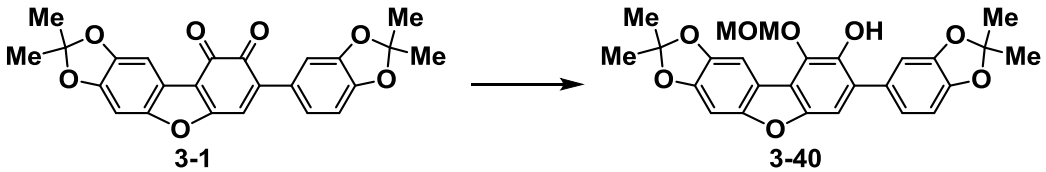
Compound **3-1**



To an ice-cooled, vigorously stirred suspension of KH_2PO_4 (42.0 mg, 0.309 mmol) and potassium nitrosodisulfonate (198.0 mg, 0.517 mmol) in H_2O (1.0 mL) was added dropwise a solution of **1-83** (12.4 mg, 0.0307 mmol) in ^{i}PrOH (0.4 mL), and the mixture was warmed to 22 °C and stirred for 12.5 h. The reaction was quenched with brine, and the mixture was extracted with EtOAc several times. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5 → 2) to give **3-1** (12.2 mg, 0.0292 mmol, 95%) as a dark blue solid.

3-1: IR (film) *v* 2991, 2924, 2852, 1666, 1496, 1470, 1378, 1361, 1278, 1257, 1136, 981, 839, 807, 736, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71 (6H, s), 1.72 (6H, s), 6.78 (1H, d, *J* = 8.0 Hz), 6.907 (1H, s), 6.914 (1H, d, *J* = 1.8 Hz), 6.99 (1H, dd, *J* = 1.9, 8.1 Hz), 7.28 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8 (CH_3×2), 25.9 (CH_3×2), 93.6 (CH), 99.9 (CH), 108.3 (CH), 108.7 (CH), 116.8 (C), 117.3 (C), 118.8 (C), 119.7 (C), 122.5 (CH), 125.7 (CH), 127.3 (C), 137.4 (C), 147.2 (C), 147.7 (C), 148.2 (C), 148.7 (C), 151.9 (C), 161.9 (C), 173.3 (C), 181.3 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{24}H_{18}O_7Na$ $[M + Na]^+$: 441.0945, found: 441.0977.

Compound **3-40**

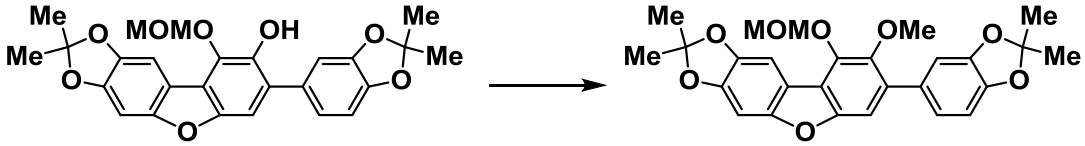


To a suspension of **3-1** (19.0 mg, 0.0454 mmol) in DMF (0.5 mL) was added PtO_2 (cat.), and the mixture was stirred in the dark under H_2 atmosphere at 22 °C. After being stirred for 30 min, to the mixture was added DIPEA (11 µL, 0.0631 mmol) and MOMCl (4.5 µL, 0.0592 mmol), and the mixture was stirred for 9 h. The reaction was quenched with saturated aq. $NaHCO_3$, and the mixture was extracted with a 1:1 blend of hexane and EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **3-40** (9.6 mg, 0.0207 mmol, 46%) as a colorless oil and catechol **3-35** (9.6 mg, 0.0229 mmol, 50%) as a colorless oil.

3-40: IR (neat) *v* 3333, 2990, 2936, 1619, 1509, 1493, 1472, 1440, 1386, 1377, 1357, 1298, 1238, 1138, 1033, 980, 960, 928, 890, 840, 814, 738, 694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72 (6H, s), 1.73 (6H, s), 3.67 (3H, s), 5.29 (2H, s), 6.81 (1H, d, *J* = 7.8 Hz), 6.94 (1H, s), 7.05-7.08 (3H, m), 7.20 (1H, s), 7.29 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8 (CH_3×2), 26.0 (CH_3×2), 57.6 (CH_3), 93.7 (CH), 99.7 (CH_2), 100.4 (CH), 108.0 (CH), 108.6 (CH), 109.9 (CH), 115.0 (C), 117.2 (C), 118.0 (C), 118.8 (C), 122.3 (CH), 127.6 (C), 131.4 (C), 138.5 (C), 141.5 (C), 144.1 (C), 146.8 (C),

147.4 (C), 147.6 (C), 150.7 (C), 151.9 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{26}H_{24}O_8Na$ $[M + Na]^+$: 487.1363, found: 487.1357.

Compound **3-44**

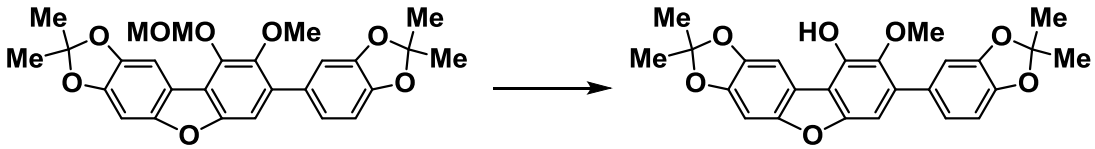


3-40 **3-44**

To a solution of **3-40** (11.0 mg, 0.0237 mmol) in a blend of toluene (0.3 mL) and MeOH (0.2 mL) was added TMS diazomethane (2.0 M in Et_2O, 250 µL, 0.500 mmol) at 22°C under N_2, the mixture was warmed to 40 °C and stirred for 15 h. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **3-44** (11.0 mg, 0.0230 mmol, 97%) as a colorless oil.

3-44: IR (neat) *v* 2990, 2933, 2853, 1506, 1490, 1469, 1415, 1400, 1385, 1377, 1356, 1287, 1241, 1221, 1149, 1137, 1042, 980, 954, 928, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.72 (6H, s), 1.74 (6H, s), 3.60 (3H, s), 3.63 (3H, s), 5.43 (2H, s), 6.80 (1H, d, *J* = 8.5 Hz), 6.94 (1H, s), 7.01 (1H, d, *J* = 1.7, 6.7 Hz), 7.02 (1H, s), 7.18 (1H, s), 7.44 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.84 (CH_3×2), 25.92 (CH_3×2), 57.9 (CH_3), 60.9 (CH_3), 93.5 (CH), 99.1 (CH_2), 101.0 (CH), 107.96 (CH), 108.00 (CH), 109.8 (CH), 115.4 (C), 118.0 (C×2), 118.7 (C), 122.3 (CH), 131.6 (C), 133.7 (C), 143.9 (C), 144.2 (C), 145.2 (C), 146.8 (C), 147.3 (C), 147.6 (C), 151.8 (C), 153.2 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{27}H_{26}O_8Na$ $[M + Na]^+$: 501.1520, found: 501.1485.

Compound **3-36**



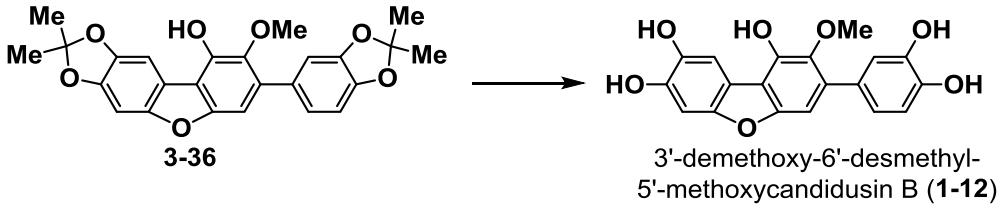
3-44 **3-36**

To a solution of **3-44** (3.0 mg, 0.00627 mmol) in a blend of CH_2Cl_2 (0.2 mL) and MeOH (0.2 mL) was added PTS·H_2O (1.8 mg, 0.00946 mmol) at 22°C, and the mixture was warmed to 40 °C and stirred for 7.5 h. The mixture was cooled to ambient temperature, diluted with saturated aq. $NaHCO_3$ and extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **3-36** (2.6 mg, 0.00598 mmol, 99 %) as an amorphous solid.

3-36: IR (neat) *v* 3443, 2990, 1621, 1507, 1468, 1421, 1376, 1327, 1309, 1239, 1217, 1135, 1034, 979, 876, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.731 (6H, s), 1.732 (6H, s), 3.49 (3H, s), 6.28 (1H, s), 6.81 (1H, d, *J* = 8.5 Hz), 6.94 (1H, s), 6.97 (1H, s), 7.06-7.08 (2H, m), 7.41 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.81 (CH_3×2), 25.88 (CH_3×2), 61.0 (CH_3), 93.4 (CH), 101.2 (CH), 103.8 (CH), 108.2 (CH), 109.2 (CH), 112.2 (C), 115.7 (C), 118.1 (C), 118.5 (C), 121.9 (CH), 131.4

(C×2), 139.2 (C), 143.1 (C), 144.1 (C), 146.9 (C), 147.1 (C), 147.5 (C), 151.4 (C), 153.6 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{25}H_{23}O_7$ $[M + H]^+$: 435.1438, found: 435.1443.

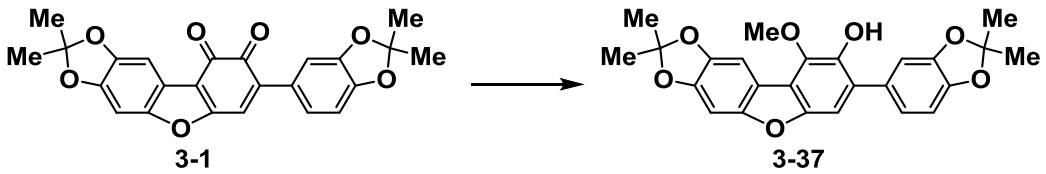
3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B **(1-12)**



To a solution of **3-36** (6.5 mg, 0.0150 mmol) and 1,2-ethanedithiol (14 µL, 0.166 mmol) in $MeNO_2$ (0.5 mL) was added $AlCl_3$ (20.6 mg, 0.155 mmol) at –20 °C, and the mixture was stirred for 4 h. The reaction was quenched with saturated aq. potassium sodium tartrate, H_2O, and EtOAc. The mixture was stirred at 23 °C for 1 h. Then, the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH = 15 → 5) to give 3'-Demethoxy-6'-desmethyl-5'-methoxycandidusin B (**1-12**) (5.0 mg, 0.0141 mmol, 94%) as an amorphous gum.

3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B (**1-12**): IR (neat) *ν* 3347, 2931, 2852, 1620, 1526, 1469, 1451, 1419, 1332, 1277, 1223, 1150, 1126, 1038, 987, 876, 813, 795 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 3.42 (3H, s), 6.83 (1H, d, *J* = 8.2 Hz), 6.85 (1H, s), 6.93 (1H, s), 6.96 (1H, dd, *J* = 2.1, 8.1 Hz), 7.11 (1H, d, *J* = 2.1 Hz), 7.47 (1H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 61.0 (CH_3), 98.8 (CH), 103.7 (CH), 108.6 (CH), 113.8 (C), 116.2 (CH), 116.6 (C), 117.4 (CH), 121.8 (CH), 131.9 (C), 133.9 (C), 141.2 (C), 142.9 (C), 145.7 (C), 145.9 (C), 146.1 (C), 146.4 (C), 152.0 (C), 154.9 (C); ESI-HRMS (neg.) *m/z* calcd for $C_{19}H_{13}O_7$ $[M - H]^-$: 353.0667, found: 353.0667.

Compound **3-37**

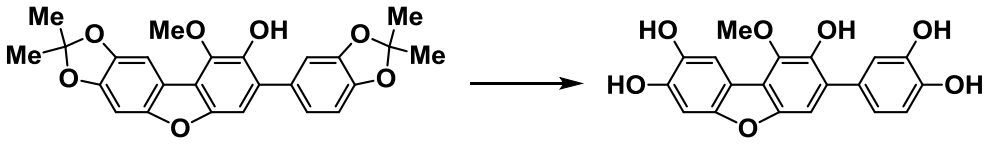


To a suspension of **3-1** (16.5 mg, 0.0394 mmol) in a blend of toluene (0.6 mL) and MeOH (0.4 mL) was added PtO_2 (cat.), and the mixture was stirred in the dark under H_2 atmosphere at 22 °C. After being stirred for 50 min, to the mixture was added TMS diazomethane (2.0 M in Et_2O, 30 µL, 0.0600 mmol), and the mixture was stirred for 5 h. The mixture was filtered through a Celite pad, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10 → 5) to give **3-37** (7.0 mg, 0.0161 mmol, 41%) as an amorphous solid and catechol **3-35** (3.9 mg, 0.00928 mmol, 24%) as a colorless oil.

3-37: IR (neat) *ν* 3502, 2990, 2936, 2853, 1664, 1621, 1508, 1494, 1471, 1422, 1377, 1358, 1303, 1239, 1137, 980, 891, 840, 813, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.72 (6H, s), 1.74 (6H, s), 4.05 (3H, s), 5.67 (1H, s), 6.82 (1H, d, *J* = 8.4 Hz), 6.95 (1H, s), 7.04-7.05 (2H, m), 7.19 (1H, s),

7.31 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8 (CH_3×2), 26.0 (CH_3×2), 61.0 (CH_3), 93.7 (CH), 100.7 (CH), 107.9 (CH), 108.2 (CH), 109.7 (CH), 114.6 (C), 116.9 (C), 118.1 (C), 118.8 (C), 122.2 (CH), 126.4 (C), 130.8 (C), 139.8 (C), 141.4 (C), 144.2 (C), 146.9 (C), 147.6 (C), 147.7 (C), 151.0 (C), 151.9 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{25}H_{23}O_7$ $[M + H]^+$: 435.1438, found: 435.1456

Compound **3-45**

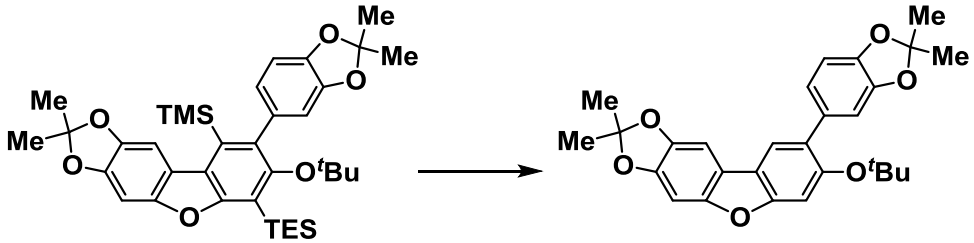


3-37 **3-45**

To a solution of **3-37** (7.0 mg, 0.0161 mmol) and 1,2-ethanedithiol (6.0 μL, 0.0713 mmol) in $MeNO_2$ (1.0 mL) was added $AlCl_3$ (12.0 mg, 0.0900 mmol) at –20 °C, and the mixture was stirred for 1 h. The reaction was quenched with saturated aq. potassium sodium tartrate, H_2O, and EtOAc. The mixture was stirred at 23 °C for 1 h. Then, the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH = 15 → 5) to give **3-45** (4.5 mg, 0.0127 mmol, 79%) as an amorphous gum.

3-45: IR (neat) *ν* 3347, 2931, 2851, 1607, 1525, 1482, 1446, 1422, 1310, 1274, 1232, 1156, 1124, 1047, 981, 856, 813, 691 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 3.99 (3H, s), 6.82 (1H, d, *J* = 8.2 Hz), 6.94 (1H, s), 6.95 (1H, dd, *J* = 2.0, 8.2 Hz), 7.09 (1H, s), 7.11 (1H, d, *J* = 1.9 Hz), 7.40 (1H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 61.1 (CH_3), 99.1 (CH), 108.1 (CH), 108.4 (CH), 115.3 (C), 116.1 (CH), 117.9 (CH), 118.0 (C), 122.2 (CH), 129.3 (C), 131.9 (C), 142.4 (C), 143.2 (C), 143.3 (C), 145.6 (C), 145.8 (C), 147.2 (C), 152.1 (C), 152.5 (C); APCI-HRMS (neg.) *m/z* calcd for $C_{19}H_{13}O_7$ $[M - H]^-$: 353.0667, found: 353.0662.

Compound **3-46**



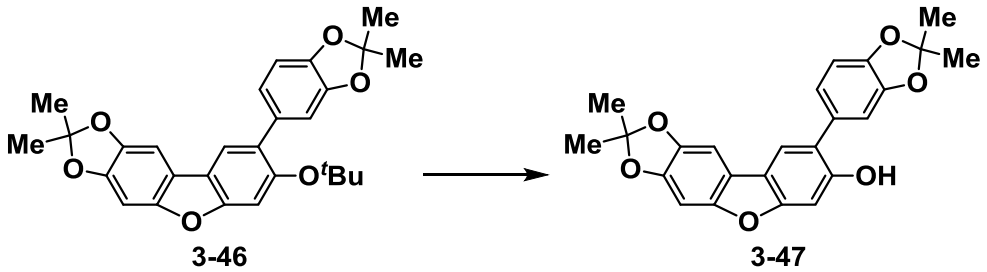
3-29 **3-46**

To a solution of **3-29** (42.1 mg, 0.0651 mmol) in THF (0.7 mL) was added TBAF (1.0 mol/L in THF, 0.55 mL, 0.55 mmol) at 22 °C. Then, the mixture was heated to 40 °C and stirred for 13 h. The mixture was cooled to ambient temperature and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 50 → 20) to give **3-46** (31.2 mg, 0.0651 mmol, ~100%) as an amorphous solid.

3-46: IR (film) *ν* 2983, 2935, 1635, 1499, 1469, 1386, 1376, 1365, 1287, 1258, 1236, 1171, 1127, 978, 842, 763, ,739 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (9H, s), 1.722 (6H, s), 1.727 (6H, s), 6.78 (1H, d, *J* = 7.5 Hz), 6.96 (1H, s), 6.98-7.03 (2H, m), 7.14 (1H, s), 7.24 (1H, s), 7.68 (1H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 25.8 (CH_3×4), 28.8 (CH_3×3), 80.6 (C), 93.8 (CH), 98.8 (CH), 107.2 (CH), 107.7 (CH), 110.8 (CH), 116.5 (C), 117.6 (C), 118.6 (C), 120.3 (CH), 120.6 (C), 122.9 (CH), 132.6 (C), 133.6 (C), 144.2 (C), 146.1 (C), 146.9 (C), 147.1 (C), 151.2 (C), 151.8 (C), 155.6 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{28}H_{28}O_6Na$ $[M + Na]^+$: 483.1778, found: 483.1755.

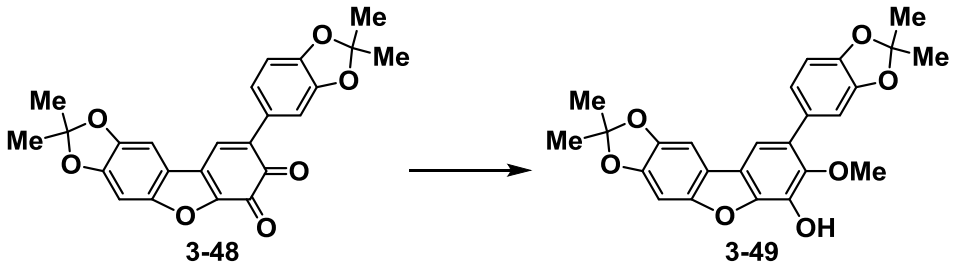
Compound **3-47**


Me
O
Me
O
Me
Me
O
O
O

The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 5 → 2) to give **3-48** (16.9 mg, 0.0404 mmol, 69%, 86% based on recovered **3-47**) as a dark red solid, along with recovered **3-47** (4.7 mg, 0.0116 mmol, 20%) as an amorphous solid.

3-48: IR (film) *v* 2992, 2919, 1659, 1623, 1556, 1494, 1475, 1378, 1361, 1276, 1258, 1221, 1141, 981, 841, 807 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.71 (6H, s), 1.75 (6H, s), 6.78 (1H, d, *J* = 8.0 Hz), 6.89 (1H, d, *J* = 1.5 Hz), 6.929 (1H, s), 6.933 (1H, s), 6.96 (1H, dd, *J* = 1.9, 8.0 Hz), 7.34 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.89 (CH_3×2), 25.93 (CH_3×2), 94.1 (CH), 97.8 (CH), 108.2 (CH), 108.9 (CH), 117.5 (C), 118.6 (C), 120.8 (C), 122.3 (CH), 127.0 (CH), 127.7 (C), 130.5 (C), 138.3 (C), 145.7 (C), 147.4 (C), 147.5 (C), 148.4 (C), 152.5 (C), 155.2 (C), 165.6 (C), 181.6 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{24}H_{18}O_7Na$ $[M + Na]^+$: 441.0945, found: 441.0928.

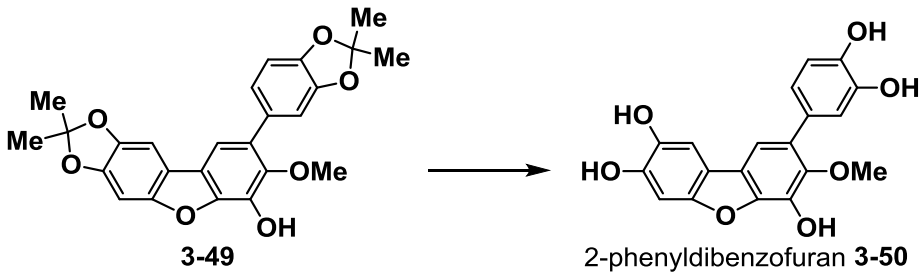
Compound **3-49**



To a suspension of **3-48** (24.0 mg, 0.0574 mmol) in a blend of toluene (0.6 mL) and MeOH (0.4 mL) was added PtO_2 (cat.), and the mixture was stirred in the dark under H_2 atmosphere at 22 °C. After being stirred for 30 min, to the mixture was added TMS diazomethane (2.0 mol/L in Et_2O, 50 µL, 0.100 mmol), and the mixture was stirred for 2.5 h. The mixture was filtered through a Celite pad, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc = 10) to give **3-49** (17.9 mg, 0.0299 mmol, 72%) as an amorphous solid and a catechol (5.7 mg, 0.0136 mmol, 23%) as a colorless oil.

3-49: IR (film) *v* 3500, 2990, 2938, 1616, 1503, 1473, 1425, 1377, 1358, 1289, ,1234, 1132, 1024, 979, 840, 737, 687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.72 (6H, s), 1.73 (6H, s), 4.29 (3H, s), 5.91 (1H, s), 6.82 (1H, d, *J* = 8.5 Hz), 6.96 (1H, s), 7.026 (1H, dd, *J* = 1.8, 7.5 Hz), 7.036 (1H, s), 7.10 (1H, s), 7.34 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8 (CH_3×2), 26.0 (CH_3×2), 60.9 (CH_3), 93.8 (CH), 98.6 (CH), 108.1 (CH), 109.8 (CH), 113.1 (CH), 116.6 (C), 118.0 (C), 118.7 (C), 119.2 (C), 122.1 (CH), 124.4 (C), 131.2 (C), 131.7 (C), 143.0 (C), 144.4 (C), 146.0 (C), 146.6 (C), 146.9 (C), 147.4 (C), 151.4 (C); ESI-HRMS (pos.) *m/z* calcd for $C_{25}H_{23}O_7$ $[M + H]^+$: 435.1438, found: 435.1446.

2-phenyldibenzofuran **3-50**



To a solution of **3-49** (14.6 mg, 0.0336 mmol) and 1,2-ethanedithiol (12 μL, 0.143 mmol) in $MeNO_2$ (1.0 mL) was added $AlCl_3$ (22.3 mg, 0.167 mmol) at –20 °C, and the mixture was stirred for 50 min. The reaction was quenched with saturated aq. potassium sodium tartrate, H_2O, and EtOAc. The mixture was stirred at 23 °C for 1 h. Then, the mixture was extracted with EtOAc several times. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, $CHCl_3$/MeOH = 15 → 5) to give **3-50** (10.0 mg, 0.0282 mmol, 84%) as an amorphous gum.

3-50: IR (neat) *v* 3354, 2925, 2854, 2359, 1711, 1611, 1526, 1466, 1426, 1357, 1303, 1248, 1145, 1111, 1026, 854, 813 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 4.15 (3H, s), 6.82 (1H, d, *J* = 8.1 Hz), 6.92 (1H, dd, *J* = 2.2, 8.3 Hz), 6.99 (1H, s), 7.09 (1H, d, *J* = 2.1 Hz), 7.22 (1H, s), 7.30 (1H, s); ^{13}C NMR (125 MHz, CD_3OD) δ 61.3 (CH_3), 99.3 (CH), 105.9 (CH), 115.1 (CH), 116.0 (CH), 117.2 (C), 118.0 (CH), 119.9 (C), 122.2 (CH), 126.8 (C), 132.2 (C), 134.0 (C), 143.4 (C), 145.3 (C), 145.5 (C), 145.7 (C), 146.3 (C), 148.0 (C), 152.0 (C); ESI-HRMS (neg.) *m/z* calcd for $C_{19}H_{13}O_7$ $[M - H]^+$: 353.0667, found: 353.0668.

Chapter 4

Conclusion

4-1. Conclusion

In the dissertation work, the author undertook the establishment of a new synthetic methodology for natural 3-phenyldibenzofuran polyphenols based on a two-component [2+2+2] cycloaddition reaction because of the interest in the SAR of the natural products and the development of new synthetic methodology for them.

The achievements of the dissertation work are as follows:

(i) Establishment of a new methodology based on a $RhCl(PPh_3)_3$-catalyzed two-component [2+2+2] cycloaddition reaction between a 1,6-diyne and an alkoxyacetylene for the construction of the 2-hydroxy-3-phenyldibenzofuran skeleton, seen in polyphenol natural products, without formation of homodimers of the 1,6-diyne.

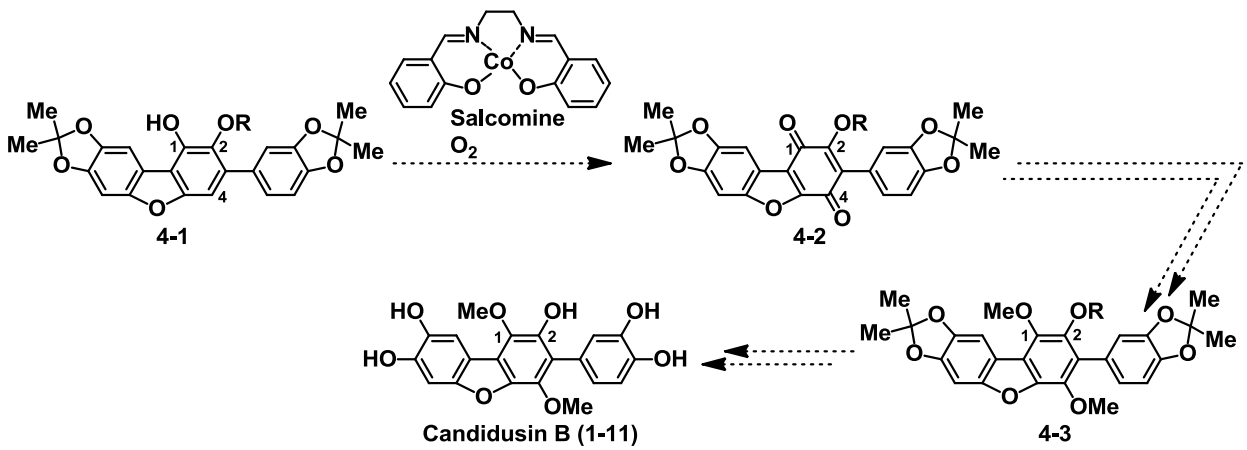
(ii) Application of the methodology to the skeletal synthesis of kehokorin E,[1] 2-hydroxy-4,8-dimethoxy-3-phenyldibenzofuran, and the realization of regioselective [2+2+2] cycloaddition in the synthesis.

(iii) Successful application of the methodology to the total synthesis of 3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B[2] and the establishment of 1-hydroxy-2-methoxy substitution at the middle aromatic ring of the 3-phenyldibenzofuran skeleton.

4-2. Scope for Future Work

The author successfully achieved the total synthesis of 3'-demethoxy-6'-desmethyl-5'-methoxycandidusin B (**1-12**), a natural product of 3-phenyldibenzofuran polyphenol, using [2+2+2] cycloaddition reaction. However, in the field of the synthesis of 3-phenyldibenzofuran polyphenol natural products, there remain problems to be solved. For example, one of the challenges is the introduction of a hydroxyl group at C4 of the 3-phenyldibenzofuran skeleton, which is a remaining problem in the synthesis of kehokorin E (**1-5**) as described in Chapter 2. If a method for the introduction of the hydroxy group at C4 is developed, the scope of the synthetic application of the [2+2+2] cycloaddition will be extended to more difficult natural products, such as kehokorins,[1] candidusin B,[2] and vialinins.[3] For a solution, the author suggests a scheme that introduces an oxygen functional groups at C4 of a 1-hydroxy-2-methoxy-3-aryldibenzofran skeleton, seen in candidusin B (**1-11**) (Scheme 4-1). The oxidation of 1-hydroxy-2-alkoxy-3-aryldibenzofran **4-1** with salcomine, a salen-cobalt complex, and molecular oxygen is a candidate reaction for introducing an oxygen functional group at C4.[4] The resulting *p*-quinone **4-2** would be reduced to a hydroquinone, of which the methylation (leads to **4-3**) followed by deprotection would afford candidusin B (**1-11**). This scheme may be further available for vialinins (**1-6** and **1-7**)[3] and boletopsins (**1-8**, **1-9** and **1-10**).[5]

The development of a methodology for changing the oxidation state of the middle benzene ring of the 3-phenyldibenzofuran skeleton, which is often seen in natural products, would be a key for widening the scope of synthetic application of the $RhCl(PPh_3)_3$-catalyzed two-component [2+2+2] cycloaddition to 3-phenyldibenzofuran natural products.



Scheme 4-1. A future plan for the total synthesis of candidusin B

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