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Synthesis of a landomycinone skeleton *via* Masamune–Bergmann cyclization†

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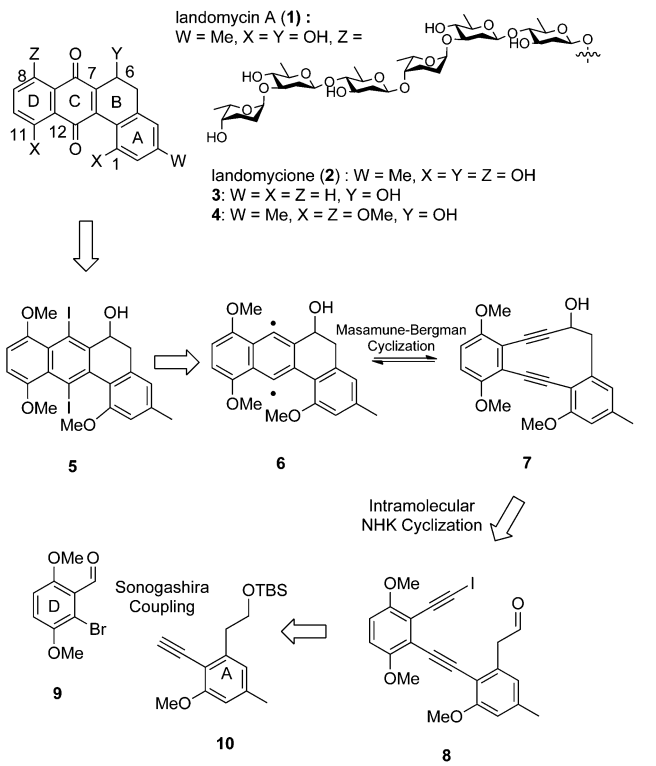
In this report, a synthetic study of landomycinone *via* Masamune–Bergmann cyclization is described. A 10-membered 1,2-dialkynylbenzene derivative was designated as a key intermediate in the formation of an angular tetracyclic core *via* Masamune–Bergmann cyclization. Cyclization was expected to proceed under mild heating conditions based on a DFT transition state analysis of the 10-membered enediyne. The enediyne was successfully prepared by intramolecular NHK cyclization in good yield and underwent Masamune–Bergman cyclization at 70 °C for 2 h. However, an undesired β-elimination of the secondary alcohol was involved in the cyclization. In addition, iodination at the 12 position did not occur due to the steric hindrance of two methyl groups. This methodology should be widely applicable to the synthesis of various types of highly oxy-functionalized anthraquinone derivatives as well as landomycinone, and should be a useful way to clarify structure–activity relationships.

Introduction

Landomycin A (**1**), which was isolated in 1990, is an angucyclic-type antibiotic that exhibits potent antitumor and antibacterial activity, as well as inhibition of G1/S cell-cycle progression resulting in the induction of apoptosis (Scheme 1).[1] It is composed of a highly oxy-functionalized aglycon portion, namely landomycinone (**2**), and a structurally unique, complex deoxyhexasaccharide.[2] Biological evaluation of related natural products varying at the deoxyoligosaccharide revealed the importance of the length of the saccharide chain. However, the structure–activity relationships of the aglycon portion have not been clarified due to the low availability of its derivatives. Therefore, an effective methodology for the synthesis of landomycinone and its related compounds is required.

The aglycon portion of landomycinone involves a highly substituted angular tetracyclic core (Scheme 1, A–D ring). The B ring would be easily aromatized by β-elimination of the hydroxyl group at the 6 position. In addition, the steric repulsion between the oxygen functions at the 1 and 11 positions creates difficulty in the formation of an angucyclic skeleton. Roush *et al.* reported the synthesis of landomycinone based on Dötz annulation and intramolecular Michael addition under basic conditions, which involved the formation of a fully aromatized



Scheme 1 Retrosynthetic plan of synthetic target **4**.

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byproduct.[3] Roulland *et al.* applied a [2 + 2 + 2] transition-metal-catalyzed cycloaddition of alkynes to form a C12 non-substituted C ring.[4] Yu *et al.* have recently accomplished the total synthesis of landomycin A, in which the aglycon was prepared *via* a modified Roush's method.[5] On the other hand, we recently reported on the synthesis of a landomycin skeleton **3** without substituents at the 1,3,8,11 positions *via* Masamune–Bergman cyclization to provide an angucycline tetracyclic skeleton possessing 7,12-diiodide without β-elimination of the C6 hydroxyl group.[6] The diiodide was converted to quione *via* copper-catalyzed etherification followed by oxidation. Hence, in this work, we report the synthesis of a landomycinone skeleton *via* Masamune–Bergmann cyclization.

Results and discussion

Retrosynthetic analysis

As shown in Scheme 1, we planned Masamune–Bergman cyclization of the dialkynylbenzene **6** toward the synthesis of a fully functionalized landomycin skeleton **4**. The dialkynylbenzene **7** would generate the biradical **6** *via* Masamune–Bergman cyclization. The biradical **6** could react with 1,2-diiodoethane to provide aryl dihalide **5**,[7] which can be converted to the naphthoquione derivative **4** *via* copper-catalyzed Ullmann etherification followed by oxidation. Highly reactive radical species could enable oxidation at the sterically hindered 12 position. The 10-membered 1,2-dialkynyl-benzene derivative **7** could be prepared from the intramolecular Nozaki–Hiyama–Kishi (NHK) cyclization precursor **8**, possessing both the iodoacetylene and aldehyde moieties. The palladium-catalyzed Sonogashira coupling with benzaldehyde unit **9** (A ring) and phenylacetylene unit **10** (D ring) could furnish the biaryl alkyne. Benzaldehyde unit **9** and phenylacetylene **10** could be prepared from commercially available 3,5-dimethylphenol **17** and 2,5-dimethoxybenzaldehyde **15** respectively.

Computational analysis

We performed transition state analysis of the Masamune–Bergman cyclization of the 10-membered 1,2-dialkynyl-benzene derivatives **7** and **12** to biradicals **11** and **13** based on DFT calculation at the B3LYP/6-31G(d) level by Gaussian 03 (Fig. 1).[8] The two types of activation energy for the Masamune–Bergman reactions were approximately equal to each other at 26.1 kJ $mmol^{-1}$ and 26.9 kJ $mmol^{-1}$, respectively. These results indicate that the 10-membered 1,2-dialkynyl-benzene derivatives **7** and **12** both would undergo Masamune–Bergman cyclization under mild heating conditions.

Scheme and discussion

The synthesis of benzaldehyde unit **9** (A ring) is shown in Scheme 2.[9] The aldehyde moiety of 2,5-dimethoxybenzaldehyde **15** was protected as a 6-membered ring acetal with 1,3-propane diol and *p*-toluenesulfonic acid to give the desired substrate in a 72% yield. Then, the bromination with $(BrCF_2)_2$ followed by the deprotection of an acetal afforded the desired A ring unit **9** in 2 steps in a 34% yield.

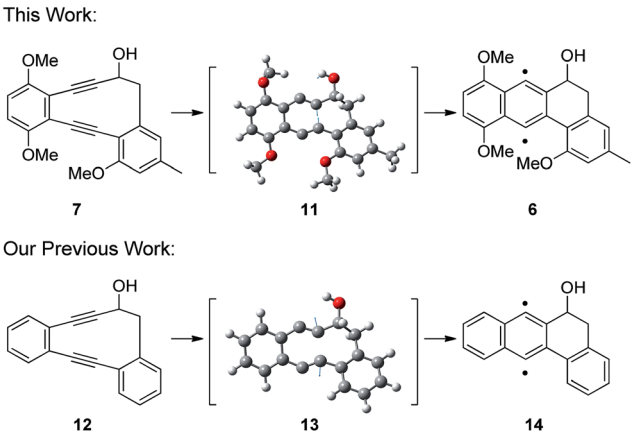
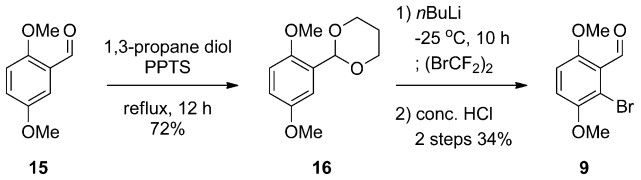
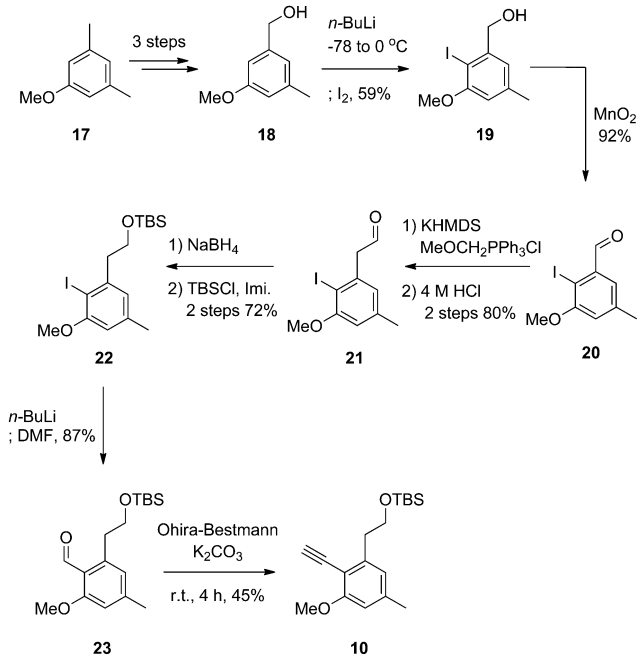


Fig. 1 DFT calculation at the ωB97XD/6-31G* level by Gaussian 09.

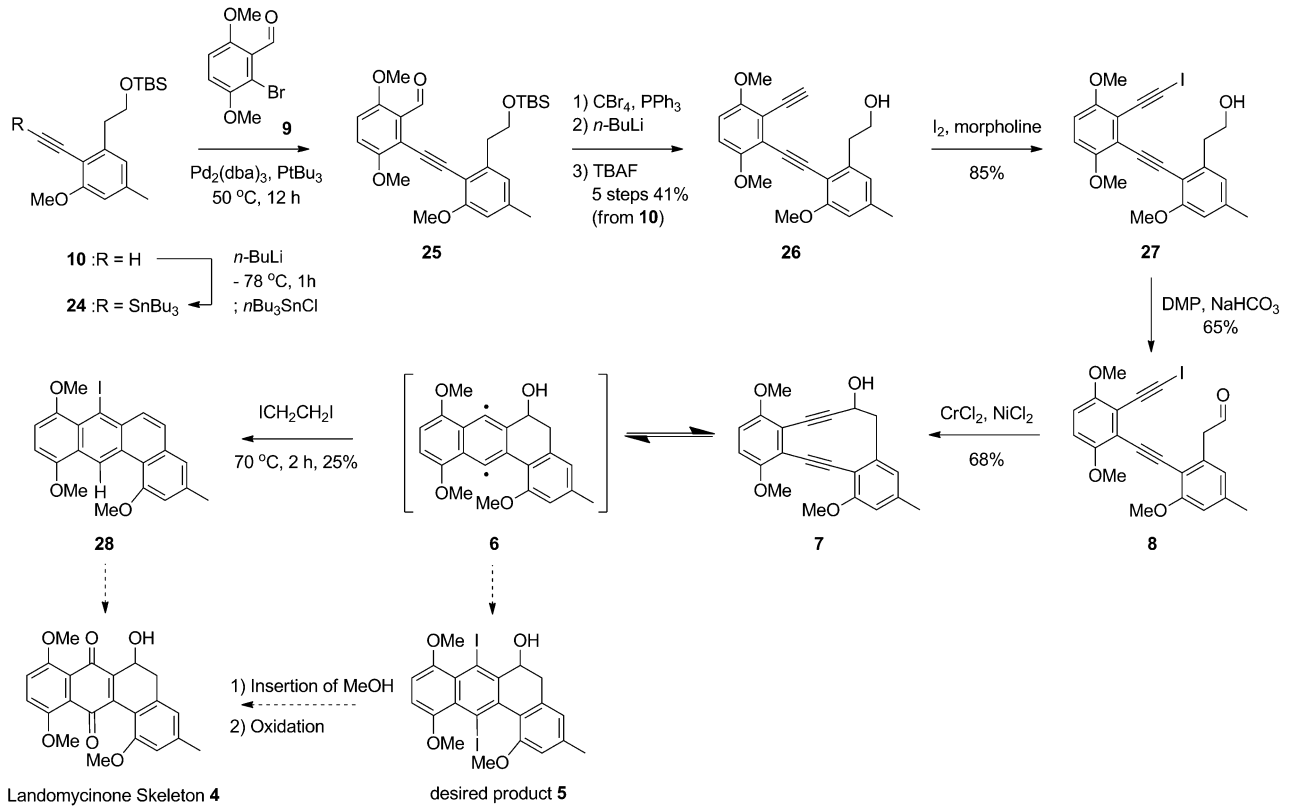


Scheme 2 Synthesis of A ring **9**.

The synthesis of the substrate **10** (D ring), which is a precursor of Sonogashira coupling, was shown in Scheme 3. A benzyl alcohol **18** was prepared from 3,5-dimethylphenol **17** in 3 steps, as noted in a previous report.[10] The iodination with *n*-BuLi and I_2 followed by the oxidation of benzyl alcohol provided the 2-iodobenzaldehyde **20**. Next, hydrolysis under acidic



Scheme 3 Synthesis of D ring **10**.



Scheme 4 Intermolecular NHK cyclization and Masamune–Bergman cyclization.

conditions, following the Wittig reaction with $MeOCH_2PPh_3Cl$, afforded the aldehyde **21** in an 80% yield in 2 steps.[11] Then, the aldehyde moiety was converted to a TBS protected primary alcohol by the reduction of the aldehyde and protection of the primary alcohol in a 72% yield in 2 steps. The treatment of iodobenzene **22** with *n*-BuLi and DMF provided benzaldehyde in an 87% yield. Finally, the conversion of the aldehyde moiety to an acetylene unit was accomplished with the Ohira–Bestmann reagent in a 45% yield.[12]

The synthesis of intramolecular NHK cyclization precursor **8** was examined (Scheme 4).[13] Although we initially attempted the coupling reaction of alkynyl-H **10** and Aryl-Br **9**, only an undesired homo-coupling product[14] was obtained; therefore, a stannylation of alkynyl-H **10** with *n*-BuLi and *n*-Bu_3SnCl was performed to prevent a homo coupling reaction of alkynyl-H **10**. The alkynyl-Sn **24**, however, was unstable during silica gel chromatography, so the residue was used *in situ* for the next reaction without purification. The Sonogashira coupling reaction of alkynyl-Sn **24** and Aryl-Br **9** with $Pd_2(dba)_3$ and $PtBu_3$ resulted in the desired biaryl coupling product **25** in an efficient manner. Then, treatment of the benzaldehyde **25** with CBr_4 and PPh_3 afforded a dibromoalkenyl compound, and conversion of the dibromoalkenyl to an acetylene with *n*-BuLi followed by the deprotection of TBS-groups with TBAF furnished a 41% yield of the desired substrate **26** in 5 steps from **10**. Finally, the iodination of acetylene followed by the oxidation of primary alcohol afforded the intramolecular NHK cyclization precursor **8** in an 85% yield.

The NHK cyclization was examined. Treatment of the precursor **8** with 9.0 equivalents of $CrCl_2$ and 0.64 equiv. of $NiCl_2$ provided the 10-membered 1,2-dialkynylbenzene derivative **7** in a 68% yield. Derivative **7** was stable under ambient conditions and during silica-gel chromatography. Then, Masamune–Bergman cyclization was examined under our optimized reaction conditions.[6] Treatment of the 10-membered 1,2-dialkynylbenzene derivative **7** with 1,2-diiodoethane as a I-source and CH_3CN as a solvent provided the undesired mono-I inserted aromatization compound **28** in a 25% yield.

In contrast with a DFT transition state analysis, the actual stability of the 10-membered 1,2-dialkynyl-benzene derivative **7** was quite different from **12** in our previous work. The compound **7** was stable under ambient air and on silica gel chromatography, and the cycloaromatization proceeded under harsh conditions. This difference in reactivity seemed to be dependent on the bulky methoxy groups adjacent to the diradical. An unexpected compound **28** might be given as a product of the β-elimination of the hydroxyl group in the C-ring followed by cycloaromatization.

Conclusions

We have described the synthesis of the landomycinone skeleton *via* Masamune–Bergman cyclization. The 10-membered enediyne, which was stable under ambient conditions and during silica-gel chromatography, was prepared *via* intermolecular Sonogashira coupling followed by intramolecular NHK

cyclization. As expected by the DFT transition state analysis, the Masamune–Bergman cyclization proceeded under mild heating conditions and successfully provided an angular tetracyclic core with a foothold for the synthesis of 1,4-benzoquinone. This synthetic method suggests a new approach for the synthesis of natural products containing the anthraquinone skeleton and the synthesis of the more complex oxy-functionalized aromatic derivatives is in progress and will be reported in time.

Experimental

General

NMR spectra were recorded on a JEOL Model EX-270 (270 MHz for ^{1}H, 67.8 MHz for ^{13}C) and a JEOL Model ECP-400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) instrument using the indicated solvent. Chemical shifts are reported in units of parts per million (ppm) relative to the signal for internal tetramethylsilane (0 ppm for ^{1}H) for solutions in $CDCl_3$. NMR spectral data are reported as follows: chloroform (7.26 ppm for ^{1}H) or chloroform-*d* (77.1 ppm for ^{13}C) when the internal standard is not indicated. Multiplicities are reported by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; and, *J*, coupling constants in Hertz. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrophotometer. Only the strongest and/or structurally important absorption is reported as the IR data in cm^{-1}. All reactions were monitored by thin-layer chromatography carried out on 0.2 mm E. Merck silica gel plates (60F-254) with UV light, visualized by *p*-anisaldehyde solution, ceric sulfate or 10% ethanolic phosphomolybdic acid. Merck silica gel 60 (0.063–0.200 mm) was used for column chromatography. ESI TOF Mass spectra were measured with Waters LCT Premier TM XE. HRMS (ESI-TOF) was calibrated with leucine enkephalin (SIGMA) as an internal standard.

2-(2,5-Dimethoxyphenyl)-1,3-dioxane (16)

To a stirred solution of 2,5-dimethoxybenzaldehyde (**15**) (3.00 g, 43.3 mmol) in toluene (30.0 mL), 1,3-propane diol (3.00 mL, 43.3 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. After being stirred at reflux for 12 h, the reaction mixture was poured into aq. $Na_2S_2O_3$. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel with 80 : 20 hexane : ethyl acetate to give 2-(2,5-dimethoxyphenyl)-1,3-dioxane (**16**) (2.92 g, 13.0 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, 1H, J = 2.9 Hz), 6.84–6.77 (m, 2H), 5.83 (s, 1H), 4.21 (m, 2H), 3.97 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 2.20 (m, 1H), 1.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 150.4, 127.5, 115.5, 112.0, 111.7, 96.5, 67.3, 56.1, 55.5, 25.6.

2-Bromo-3,6-dimethoxybenzaldehyde (9)

To a stirred solution of 2-(2,5-dimethoxyphenyl)-1,3-dioxane (**16**) (1.15 g, 5.14 mmol) in hexane (25.0 mL) and benzene (10.0 mL), a 1.63 M solution of *n*-BuLi in hexane (7.00 mL, 11.5 mmol) was added at −25 °C under argon. After being stirred at the same temperature for 10 h, $(BrCF_2)_2$ (1.22 mL, 10.3 mmol) in THF was added. After being stirred at 0 °C for 0.5 h, the reaction mixture was concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a stirred solution of the above residue in THF (10.0 mL), conc. HCl (10.0 mL) was added at room temperature. After being stirred at the same temperature for 10 min, the reaction mixture was poured into diethyl ether. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel with 70 : 30 hexane : ethyl acetate to give 2-bromo-3,6-dimethoxybenzaldehyde (**9**) (627 mg, 0.391 mmol, in 2 steps at 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.4 (s, 1H), 7.01 (s, 1H), 6.93 (s, 1H), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 155.4, 150.4, 124.8, 117.1, 114.7, 111.4, 57.2, 56.6; IR (neat): 1696, 1479, 1264, 1032, 806 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd 244.9815, found 244.9787.

(3-Methoxy-5-methylphenyl)methanol (18)

To a stirred solution of 3,5-dimethoxyanisole (**17**) (707 μL, 5.00 mmol, 1.00 eq.) in CCl_4 (10.0 mL), NBS (890 mg, 5.00 mmol, 1.00 eq.) and a catalytic amount of $(PhCOO)_2$ were added at room temperature under argon. After being stirred at reflux for 4 h, the reaction mixture was poured into diethyl ether and H_2O. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a stirred solution of the above residue in dioxane (10.0 mL) and H_2O (10.0 mL), $CaCO_3$ (1.00 g, 10.0 mmol, 2.00 eq.) were added at room temperature under argon. After being stirred at reflux for 12 h, the reaction mixture was poured into diethyl ether and 1 N HCl. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel with 70 : 30 hexane : ethyl acetate to give (3-methoxy-5-methylphenyl)methanol (**18**) (320 mg, 2.10 mmol, 2 steps 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (s, 1H), 6.72 (s, 1H), 6.65 (s, 1H), 4.61 (s, 2H), 3.79 (s, 3H), 2.32 (s, 3H), 1.90 (br-s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 142.3, 139.7, 120.0, 114.0, 109.2, 69.2, 55.2, 21.4; IR (neat): 3377, 2940, 1613, 1463, 1297, 1166, 1042, 838, 756 cm^{-1}.

(2-Iodo-3-methoxy-5-methylphenyl)methanol (19)

To a stirred solution of (3-methoxy-5-methylphenyl)methanol (**18**) (793 mg, 5.21 mmol) in Et_2O (26.0 mL), a 1.63 M solution of *n*-BuLi in hexane (7.00 mL, 11.5 mmol) was added at −78 °C under argon. After being stirred at room temperature for 4 h, the solution was cooled to 0 °C. THF (13.0 mL) was then added to the solution and the reaction mixture was stirred for 1 h, followed by the slow addition of I_2 (1.59 g, 6.25 mmol) dissolved in THF (6.50 mL). After being stirred at 0 °C for 30 min, the reaction mixture was poured into aq. $Na_2S_2O_3$. The combined extract was washed with brine, dried over $MgSO_4$, and

concentrated *in vacuo*. The residue was chromatographed on silica gel with 70 : 30 hexane : ethyl acetate to give (2-iodo-3-methoxy-5-methylphenyl)methanol (**19**) (855 mg, 3.07 mmol, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.58 (s, 1H), 4.65 (d, 2H, J = 5.9 Hz), 3.87 (s, 3H), 2.34 (s, 3H), 1.90 (t, 1H, J = 5.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 157.8, 143.9, 139.7, 121.9, 111.2, 69.5, 56.5, 21.3; IR (neat): 3274, 2912, 1576, 1457, 1309, 1169, 1041, 838 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd 556.9698, found 556.9683.

2-Iodo-3-methoxy-5-methylbenzaldehyde (20)

To a stirred solution of (2-iodo-3-methoxy-5-methylphenyl)-methanol (**19**) (730 mg, 2.63 mmol) in CH_2Cl_2 (10.0 mL), a large amount of MnO_2 was added at room temperature under argon. After being stirred at room temperature for 24 h, the solution was filtered through a pad of Celite and concentrated *in vacuo*. The residue was chromatographed on silica gel with 80 : 20 hexane : ethyl acetate to give 2-iodo-3-methoxy-5-methyl-benzaldehyde (**20**) (668 mg, 2.42 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.2 (s, 1H), 7.30 (s, 1H), 6.87 (s, 1H), 3.92 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 158.1, 139.9, 136.1, 132.8, 122.8, 117.1, 56.7, 21.1; IR (neat): 3274, 2912, 1576, 1457, 1309, 1169, 1041, 838 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd 276.9726, found 276.9729.

2-(2-Iodo-3-methoxy-5-methylphenyl)acetaldehyde (21)

To a suspension of (methoxymethyl)triphenylphosphonium chloride (2.41 g, 5.86 mmol) in anhydrous THF (10.0 mL), a 0.5 M solution of KHMDS in toluene (12.9 mL, 6.45 mmol) was added at −78 °C. The mixture was stirred at −78 °C for 1 h, and then a solution of 2-iodo-3-methoxy-5-methylbenzaldehyde (**20**) (1.62 g, 5.86 mmol) in anhydrous THF (10.0 mL) was added. The reaction was allowed to warm to 0 °C over 3 h, and then hexane was added (50.0 mL). The resultant mixture was filtered through Celite and thoroughly washed with hexane. The filtrate was concentrated *in vacuo* and the residue was diluted with hexane (50.0 mL). The resultant mixture was filtered through Celite again to remove the remaining triphenylphosphine oxide. After evaporation, the residue was used for the next reaction without further purification.

The residue was taken up in THF (5.00 mL)–H_2O (5.00 mL) and 3 M HCl (5.00 mL) was added. The mixture was refluxed for 2 h, and then quenched with saturated aqueous Na_2CO_3. The aqueous layer was extracted with two portions of EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel with 5–6% EtOAc–hexane to give 2-(2-iodo-3-methoxy-5-methylphenyl) acetaldehyde (**21**) (1.36 mg, 4.69 mmol, 2 steps 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, 1H, J = 1.9 Hz), 6.69 (s, 1H), 6.58 (s, 1H), 3.89–3.87 (m, 5H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 158.5, 139.7, 137.5, 124.2, 110.9, 89.2, 56.4, 54.7, 21.2; IR (neat): 3274, 2912, 1723, 1457, 1309, 1169, 1041, 838 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd 290.9882, found 290.9885.

tert-Butyl(2-iodo-3-methoxy-5-methylphenethoxy)dimethyl silane (22)

To a stirred solution of $NaBH_4$ (167 mg, 4.38 mmol) in EtOH (5.00 mL), 2-(2-iodo-3-methoxy-5-methylphenyl) acetaldehyde (**21**) (635 mg, 2.19 mmol) in EtOH (5.00 mL) was added at 0 °C under argon. After being stirred at the same temperature for 1 h, the reaction mixture was poured into saturated aq. NH_4Cl. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a stirred solution of the above residue in DMF (10.0 mL), TBSCl (396 mg, 2.63 mmol) and imidazole (224 mg, 3.29 mmol) were added at 0 °C under argon. After being stirred at the same temperature for 1 h, the reaction mixture was poured into 1 N HCl. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with saturated aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo.* The residue was chromatographed on silica gel with 90 : 10 hexane : ethyl acetate to give *tert*-butyl(2-iodo-3-methoxy-5-methylphenethoxy)dimethylsilane (**22**) (641 mg, 1.58 mmol, 2 steps 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, 1H, J = 1.9 Hz), 6.69 (s, 1H), 6.58 (s, 1H), 3.89–3.87 (m, 5H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 158.5, 139.7, 137.5, 124.2, 110.9, 89.2, 56.4, 54.7, 21.2; IR (neat): 3274, 2912, 1723, 1457, 1309, 1169, 1041, 838 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd 407.0903, found 407.0901.

2-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-6-methoxy-4-methyl-benzaldehyde (23)

To a stirred solution of *tert*-butyl(2-iodo-3-methoxy-5-methyl-phenethoxy)dimethylsilane (**22**) (504 mg, 1.24 mmol) in Et_2O (3.00 mL), a 1.63 M solution of *n*-BuLi in hexane (836 μL, 1.36 mmol) was added at −78 °C under argon. The mixture was stirred at the same temperature for 30 min, then dimethylformamide (192 μL, 2.48 mmol) was added. After being stirred at same temperature for 1 h, the reaction mixture was poured into saturated aq. NH_4Cl. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with saturated aq. $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was chromatographed on silica gel with 90 : 10 hexane : ethyl acetate to give 2-(2-(*tert*-butyldimethylsilyloxy)ethyl)-6-methoxy-4-methylbenzaldehyde (**23**) (333 mg, 1.08 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.5 (s, 1H), 6.68 (s, 1H), 6.65 (s, 1H), 3.86 (s, 3H), 3.80 (t, 2H, J = 6.3 Hz), 3.24 (t, 2H, J = 6.3 Hz), 2.34 (s, 3H), 0.84 (s, 9H), −0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 163.4, 145.3, 142.7, 125.9, 120.9, 110.2, 63.7, 55.7, 37.3, 25.9, 22.1, 18.2, −5.50; IR (neat): 2956, 1721, 1608, 1460, 1257, 1091, 837, 709 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd 309.1886, found 309.1884.

tert-Butyl(2-ethynyl-3-methoxy-5-methylphenethoxy)dimethyl silane (10)

To a stirred solution of 2-(2-(*tert*-butyldimethyl silyloxy)ethyl)-6-methoxy-4-methylbenzaldehyde (**23**) (437 mg, 1.42 mmol) in

MeOH (7.10 mL), Ohira–Bestmann Reagent (300 mg, 1.56 mmol) in MeOH (7.10 mL) and K_2CO_3 (236 mg, 1.70 mmol) were added at 0 °C under argon. After being stirred at room temperature for 3 h, the reaction mixture was poured into 1 N HCl. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel with 85 : 15 hexane : ethyl acetate to give *tert*-butyl(2-ethynyl-3-methoxy-5-methylphenethoxy)dimethyl silane (**10**) (195 mg, 0.639 mmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.57 (s, 1H), 3.87 (s, 3H), 3.83 (t, 2H, $J = 7.3$ Hz), 3.46 (s, 1H), 2.99 (t, 2H, $J = 7.3$ Hz), 2.32 (s, 3H), 0.88 (s, 9H), 0.00 (s, 6H); IR (neat): 3312, 2958, 2102, 1609, 1463, 1217, 1091, 837, 771, 668 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd 305.1937, found 305.1935.

2-((2-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-6-methoxy-4-methylphenyl) ethynyl)-3,6-dimethoxybenzaldehyde (26)

To a stirred solution of *tert*-butyl(2-ethynyl-3-methoxy-5-methylphenethoxy)dimethylsilane (**10**) (27.6 mg, 0.0905 mmol) in THF (1.00 mL), a 1.63 M solution of *n*-BuLi in hexane (66.6 μL, 0.109 mmol) was added at −78 °C under argon. The mixture was stirred at the same temperature for 1 h, then *n*-Bu_3SnCl (29.6 μL, 0.109 mmol) was added. After being stirred at the same temperature for 1 h, the reaction mixture was poured into saturated aq. NH_4Cl. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with saturated aq. $NaHCO_3$, brine, dried over $MgSO_4$, and was then filtered and concentrated *in vacuo*. The residue was filtered through a pad of alumina and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a stirred solution of the residue and 2-bromo-3,6-dimethoxybenzaldehyde (**9**) (22.2 mg, 0.0905 mmol) in toluene (1.50 mL), $Pd_2(dba)_3$ (0.470 mg, 0.453 μmol, 0.00500 eq.) and $PtBu_3$ (0.240 mg, 0.996 μmol, 0.0110 eq.) were added at room temperature under argon. The mixture was stirred at the same temperature for 12 h, then the residue was filtered through a pad of Celite and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a stirred solution of the above residue in CH_2Cl_2 (1.00 mL), CBr_4 (67.6 mg, 0.181 mmol) and PPh_3 (94.7 mg, 0.362 mmol) were added at room temperature under argon. After being stirred at the same temperature for 30 min, the reaction mixture was poured into saturated aq. $NaHCO_3$. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a stirred solution of the above residue in THF (2.00 mL), a 1.63 M solution of *n*-BuLi in hexane (138 μL, 0.226 mmol) was added at −78 °C under argon. After being stirred at the same temperature for 30 min, the reaction mixture was poured into saturated aq. NH_4Cl. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a stirred solution of the above residue in THF (1.00 mL), TBAF (46.8 mg, 0.181 mmol) was added at 0 °C under argon. After being stirred at the same temperature for 1 h, the reaction mixture was poured into saturated aq. NH_4Cl. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel with 85 : 15 toluene : ethyl acetate to give 2-(2-((2-ethynyl-3,6-dimethoxyphenyl)ethynyl)-3-methoxy-5-methylphenyl)ethanol (**26**) (13.0 mg, 37.1 μmol, 5 steps 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, 1H, $J = 9.2$ Hz), 6.78 (d, 1H, $J = 9.2$ Hz), 6.70 (s, 1H), 6.60 (s, 1H), 3.94 (t, 2H, $J = 6.8$ Hz), 3.91 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.64 (s, 1H), 3.18 (t, 2H, $J = 6.8$ Hz), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 155.1, 154.1, 142.5, 140.0, 129.0, 128.2, 125.3, 122.8, 118.2, 114.1, 112.3, 110.9, 109.8, 93.7, 91.5, 85.3, 79.0, 63.4, 56.7, 56.4, 56.0, 38.2, 29.7, 22.0; IR (neat): 3446, 3020, 1651, 1217, 771, 669 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd 351.1596, found 351.1593.

2-(2-((2-(Iodoethynyl)-3,6-dimethoxyphenyl)ethynyl)-3-methoxy-5-methylphenyl)ethanol (27)

To a stirred solution of 2-(2-((2-ethynyl-3,6-dimethoxyphenyl)-ethynyl)-3-methoxy-5-methylphenyl)ethanol (**26**) (10.2 mg, 0.0291 mmol) in toluene (1.00 mL), morpholine (38.0 μL, 0.437 mmol) and I_2 (37.0 mg, 0.146 mmol) were added at room temperature under argon. After being stirred at 50 °C for 1 h, the reaction mixture was poured into 10% aq. $Na_2S_2O_3$. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel with 80 : 20 hexane : ethyl acetate to give 2-(2-((2-(iodoethynyl)-3,6-dimethoxyphenyl)ethynyl)-3-methoxy-5-methylphenyl)ethanol (**27**) (11.7 mg, 0.0247 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, 1H, $J = 9.2$ Hz), 6.75 (d, 1H, $J = 9.2$ Hz), 6.72 (s, 1H), 6.61 (s, 1H), 3.97 (t, 2H, $J = 6.3$ Hz), 3.96 (s, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.18 (t, 2H, $J = 6.3$ Hz), 2.35 (s, 3H); ^{13}C NMR (68.7 MHz, $CDCl_3$) δ 160.6, 155.7, 154.0, 142.7, 140.0, 122.8, 118.3, 115.3, 112.1, 110.8, 109.8, 93.7, 91.4, 89.2, 63.5, 56.7, 56.5, 56.3, 38.2, 22.0, 14.1; IR (neat): 3446, 3020, 1638, 1218, 772, 661 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd 477.0563, found 477.0564.

2-(2-((2-(Iodoethynyl)-3,6-dimethoxyphenyl)ethynyl)-3-methoxy-5-methylphenyl)acetaldehyde (8)

To a stirred solution of 2-(2-((2-(iodoethynyl)-3,6-dimethoxyphenyl)ethynyl)-3-methoxy-5-methyl phenyl)ethanol (**27**) (11.7 mg, 0.0245 mmol) in CH_2Cl_2 (0.500 mL), $NaHCO_3$ (10.3 mg, 0.123 mmol) and Dess–Martin periodinane (21.0 mg, 0.0490 mmol) were added at 0 °C under argon. After being stirred at room temperature for 1 h, the reaction mixture was poured into saturated aq. $NaHCO_3$. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel with 80 : 20 hexane : ethyl acetate to give 2-(2-((2-(iodoethynyl)-3,6-dimethoxyphenyl)ethynyl)-3-methoxy-5-methylphenyl)acetaldehyde

(**8**) (7.60 mg, 0.0160 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (t, 1H, $J = 1.9$ Hz), 6.79 (d, 1H, $J = 9.2$ Hz), 6.76 (d, 1H, $J = 9.2$ Hz), 6.67 (d, 2H, $J = 8.2$ Hz), 4.02 (d, 2H, $J = 1.9$ Hz), 3.99 (s, 3H), 3.84 (s, 6H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 160.6, 155.5, 154.1, 140.4, 136.1, 123.1, 117.7, 115.2, 111.8, 111.1, 110.6, 110.4, 93.1, 92.5, 89.1, 56.4, 56.3, 49.2, 21.9, 14.2; IR (neat): 3453, 1722, 1607, 1463, 1255, 1065, 736 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd 475.0406, found 475.0401.

1,2-Dialkynylbenzene derivative (7)

To a stirred solution of 2-(2-((2-(iodoethynyl)-3,6-dimethoxyphenyl)ethynyl)-3-methoxy-5-methyl phenyl)acetaldehyde (**8**) (5.40 mg, 0.0114 mmol) in THF (2.80 mL), $CrCl_2$ (12.7 mg, 0.103 mmol) and $NiCl_2$ (0.940 mg, 0.00730 mmol) were added at room temperature under argon. After being stirred at the same temperature for 10 min, the reaction mixture was poured into H_2O. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel with 50 : 50 hexane : ethyl acetate to give 1,2-dialkynylbenzene derivative (**7**) (2.70 mg, 0.00776 mmol, 68%, rotamer 55 : 45). The ratio of rotamers was determined by ^{1}H NMR analysis. Major: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81–6.62 (m, 4H), 4.87 (br-s, 1H), 3.97 (m, 1H), 3.89–3.84 (m, 9H), 3.29 (dd, 1H, $J = 8.8$ Hz, $J = 13.7$ Hz), 2.37 (s, 3H). Minor: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81–6.62 (m, 4H), 4.65 (d, 1H, $J = 10.2$ Hz), 4.08 (m, 1H), 3.89–3.84 (m, 9H), 3.01 (d, 1H, $J = 13.2$ Hz), 2.37 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 160.3, 159.9, 152.8, 152.6, 152.3, 146.9, 146.8, 140.8, 140.0, 139.7, 138.0, 127.2, 124.7, 120.7, 118.3, 112.4, 112.0, 111.6, 110.7, 110.3, 105.8, 105.3, 98.5, 98.2, 95.6, 95.1, 85.0, 84.0, 83.0, 65.2, 60.4, 59.4, 56.4, 55.9, 48.8, 44.1, 29.7, 21.9, 14.2; IR (neat): 3393, 2929, 1493, 1260, 1101, 771 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd 349.1440, found 349.1447.

7-Iodo-1,8,11-trimethoxy-3-methyltetraphene (28)

To a stirred solution of 2-(2-((2-(iodoethynyl)-3,6-dimethoxyphenyl)ethynyl)-3-methoxy-5-methyl phenyl)acetaldehyde (**7**) (7.60 mg, 0.0160 mmol) in THF (3.20 mL), $CrCl_2$ (17.7 mg, 0.144 mmol) and $NiCl_2$ (1.33 mg, 0.0102 mmol) were added at room temperature under argon. After being stirred at the same temperature for 10 min, the reaction mixture was poured into H_2O. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a stirred solution of the residue in CH_3CN (3.20 mL), a large amount of 1,2-diiodoethane was added at room temperature under argon. After being stirred at 70 °C for 2 h, the reaction mixture was poured into H_2O. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel with 80 : 20 hexane : ethyl acetate to give 7-iodo-1,8,11-trimethoxy-3-methyltetraphene (**28**) (1.64 mg, 0.00272 mmol, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.7 (s, 1H), 8.68 (d, 1H, $J = 9.7$ Hz), 7.61 (d, 1H, $J = 9.7$ Hz), 7.30 (s, 1H), 7.05 (s, 1H), 6.95 (d, 1H, $J = 8.2$ Hz), 6.77 (d, 1H, $J = 8.2$ Hz), 4.19 (s, 3H), 4.08 (s, 3H), 3.99 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 158.6, 148.6, 137.7, 134.4, 134.2, 134.1, 132.2, 130.3, 129.7, 123.3, 121.4, 111.4, 107.6, 102.5, 77.6, 56.2, 56.0, 29.7, 21.6; IR (neat): 3734, 2923, 2851, 1731, 1615, 1560, 1452, 1265, 1099, 801 cm^{-1}; HRMS (ESI-TOF) [2 × M] calcd 917.0836, found 917.0835.

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14 Data of homo-coupling product: to a stirred solution of $PdCl_2(PPh_3)_2$ (4.60 mg, 0.00649 mmol, 0.0100 eq.) and CuI (3.70 mg, 0.0195 mmol, 0.0300 eq.) was added DMF (1.50 mL), Et_2NH (134 μL, 1.30 mmol, 2.00 eq.), 2-bromo-3,6-dimethoxy benzaldehyde (**9**) (159 mg, 0.649 mmol, 1.00 eq.) and *tert*-butyl(2-ethynyl-3-methoxy-5-methylphenethoxy)-dimethyl silane (**10**) (129 mg, 0.423 mmol, 0.652 eq.) at room temperature under argon. After being stirred at 80 °C for 6 h, the reaction mixture was poured into 1 N HCl. The aqueous layer was extracted with two portions of diethyl ether. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel with 85 : 15 hexane : ethyl acetate to give homocoupling product (90.8 mg, 0.149 mmol, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (s, 2H), 6.55 (s, 2H), 3.86 (s, 6H), 3.84 (t, 4H, J = 6.8 Hz), 2.99 (t, 4H, J = 6.8 Hz), 2.32 (s, 6H), 0.87 (s, 18H), 0.01 (s, 12H); IR (neat): 3688, 2857, 1607, 1463, 1255, 1090, 775 cm^{-1}; HRMS (ESI-TOF) $[M + H]^+$ calcd 624.3904, found 624.3921.

