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$InCl_3$-mediated intramolecular Friedel-Crafts-type cyclization and its application to construct the [6-7-5-6] tetracyclic scaffold of liphagal

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A unified strategy toward the construction of the [5.7.6]tricyclic skeleton of liphagal is reported, featuring $InCl_3$–mediated intramolecular Friedel-Crafts-type cyclization.

synthesis, liphagal, $InCl_3$-mediated, intramolecular Friedel-Crafts, annulation

1 Introduction

The tetracyclic meroterpenoid natural product (+)-liphagal (**1**, Figure 1) was isolated in 2006 by Andersen and coworkers from the Caribbean sponge Aka coralliphaga [1], and is one of a number of natural product inhibitors of phosphatidylinositol 3-kinase (PI3K). The other two representative natural product inhibitors include staurosporine and wortmannin (Figure 1) [2].

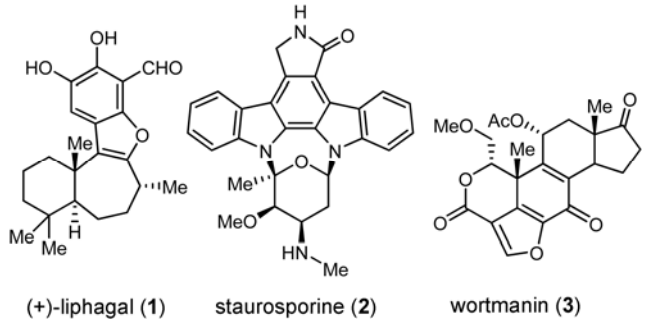

Figure 1 Natural product inhibitors of PI3K.

The hosphatidylinositol 3-kinase (PI3K) family of enzymes participates in the regulation of numerous biological functions and has been directly implicated in the pathogenesis of diabetes and cancer [3]. Liphagal (**1**) inhibited PI3KR with an IC_{50} of 100 nM and showed an approximately 10–fold selectivity for PI3Kα over PI3Kγ [1]. This isoform selectivity and potency of liphagal (**1**) make it an attractive natural product starting point for the development of synthetic PI3K inhibitors that would represent potential drug candidates or cell biology tools.

The unprecedented [6-7-5-6] tetracyclic skeleton of liphagal (**1**), together with its considerable therapeutic potential as an inhibitor against PI3Kα, makes it an attractive target in organic synthesis. Numerous efforts have been devoted to the total syntheses of this novel class of natural products, culminating in the total synthesis of liphagal (**1**) by five laboratories around the world [4].

Our aim is to identify a concise approach to quickly construct its tetracyclic scaffold, which provides a foundation for the total synthesis of liphagal, as well as its library of analogs for further medicinal chemistry studies. Herein we report our effort to develop a concise method by using the $InCl_3$-mediated intramolecular cyclization as a key step for

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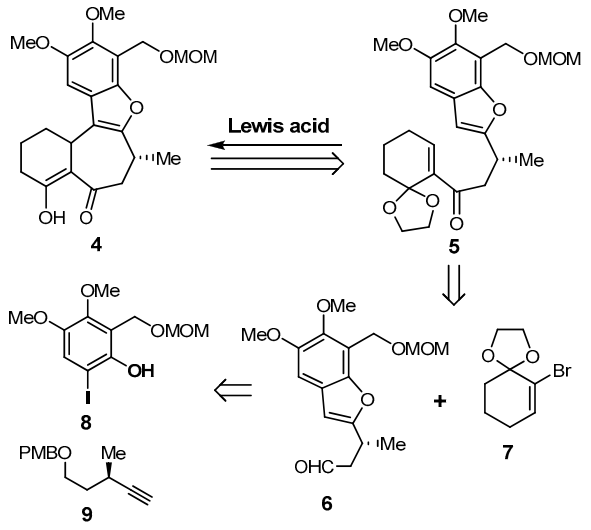


Figure 2 Retrosynthetic analysis.

the synthesis of the core structure of liphagal.

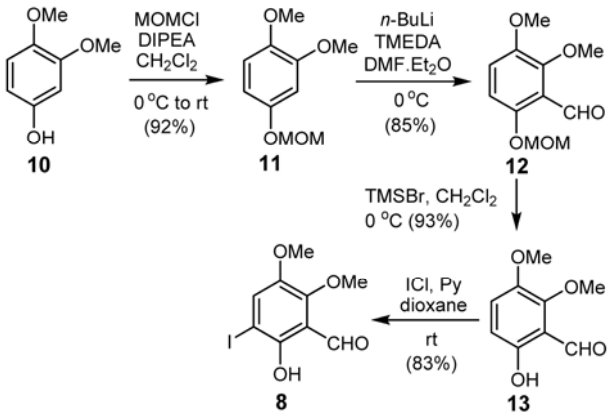
$InCl_3$-mediated cyclization has become a useful method in the construction of functionalized carbocyclic molecules during last decade [5]. In this regard, In(III) catalysts have been widely used in organic synthesis due to their unique π-acidity and alkynophilicity [6], relatively low toxicity, air and water stability, and recyclability.

During the development of effective methods for the synthesis of the core structure of liphagal, we envisaged that the tetracyclic core **4**, endowed with suitable functionalities for further elaboration into the final target liphagal (**1**), could be formed from **5** via intramolecular Friedel-Crafts cyclization (Figure 2) [7]. Intermediate **5** could be generated from **6** and **7** through coupling reaction. Benzofuran **6** in turn could be prepared via the Pd-catalyzed cross-coupling reaction of phenyl iodide **8** and enantiomerically enriched acetylene **9**, followed by base-induced intramolecular *o*-alkynylphenol annulations [8].

2 Results and discussion

Our study began with the synthesis of key intermediate **8** (Scheme 1). In the event, the hydroxyl group in phenol **10** was protected as its MOM ether by reacting with MOMCl with DIPEA as a base. The protected MOM ether **11** was obtained in 92% yield.

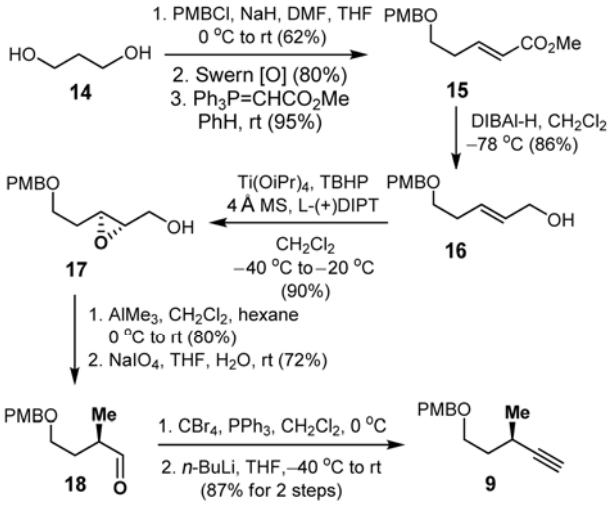
Intermediate **11** was then elaborated to benzoaldehyde **12** by treating **11** with *n*-BuLi in Et_2O, followed by reacting with DMF to regioselectively afford **12** in 85% yield. Subsequent removal of the MOM group with TMSBr in CH_2Cl_2 at 0 °C yielded phenol **13** in 93% yield. Regioselective iodination of **13** was achieved by reacting phenol **13** with ICl in the presence of pyridine to afford the key intermediate **8** in 83% combined yield.



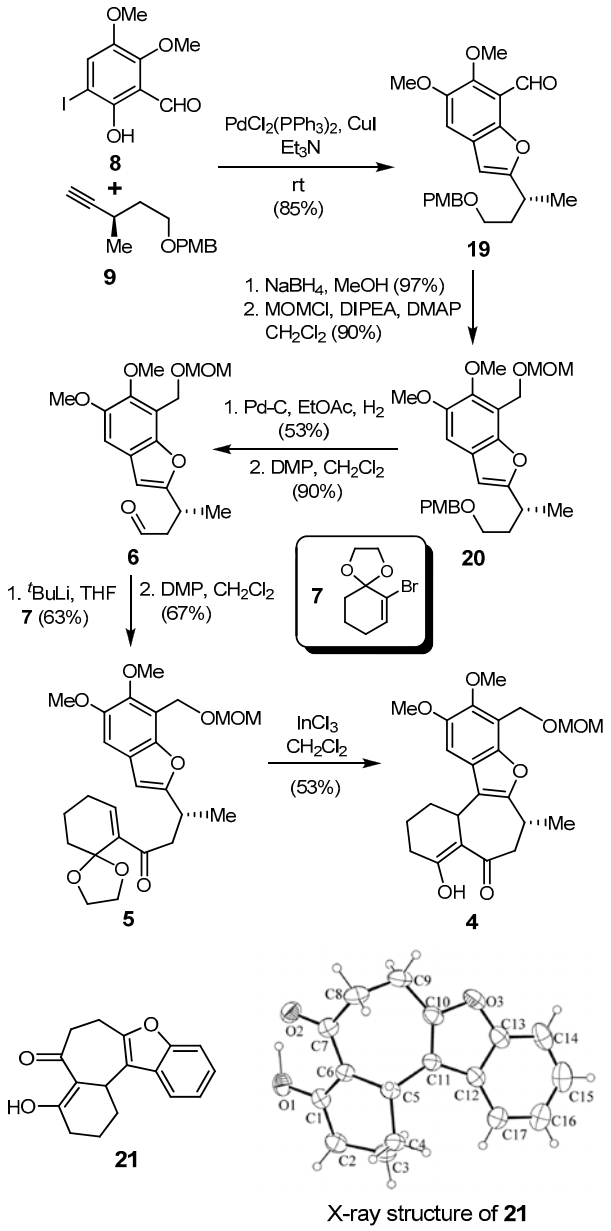
Scheme 1 Synthesis of compound **8**.

Intermediate **9** was synthesized following the literature method [9]. The synthesis commenced with a mono-MPM ether protection of the readily available 1,3-propanediol **14** to afford a mono alcohol (Scheme 2). Exposure of this alcohol to the Swern oxidation conditions resulted in the formation of an aldehyde, which was then reacted with the Wittig reagent $Ph_3P{=}CHCO_2Me$ to exclusively afford *E*-olefin **15**. Reduction of the ester group in **15** with DIBAL afforded the allylic alcohol **16** in 86% yield, which was then subjected to Sharpless epoxidation to give **17** in 90% yield with good enantioselectivity. Further treatment of **17** with Me_3A1 gave the desired methylated diol, which then underwent oxidative cleavage with $NaIO_4$ to afford an aldehyde, which without further purification was treated immediately with CBr_4/Ph_3P (Corey-Fuch's protocol) to give a dibromoolefin, which upon treatment with *n*-BuLi yielded alkyne **9** in 87% yield in two steps.

With compounds **8** and **9** in hand, we then started to prepare our model **4** (Scheme 3). To this end, substrates **8** and **9** were coupled via the Pd-catalyzed Sonogashira reaction to



Scheme 2 Syntheses of compound **9**.



Scheme 3 Completion synthesis of the model **4**.

provide **19** in 85% yield. Subsequent reduction of the aldehyde group in **19** with $NaBH_4$ resulted in a primary alcohol, which was protected as its MOM ether via the reaction with MOMCl/DIPEA in the presence of catalytic amount of DMAP to give **20** in 87% yield for two steps. The forward synthesis commenced with removal of the PMB group of substrate **20** via the palladium-catalyzed hydrogenation, and the resulting primary alcohol was converted to its corresponding aldehyde **6** via DMP oxidation. To accomplish the coupling of aldehyde **6** with vinyl bromide **7**, the vinyl bromide **7** was first treated with *t*-BuLi in THF at −78 °C, and the formed vinyl lithium reacted with aldehyde **6** to result in a formation of a secondary alcohol, which after oxidation with DMP yielded ketone **5** in 42% yield for two steps.

With ketone **5** in hand, we set out to test the key $InCl_3$-mediated annulation reaction. To our delight, we were able to isolate the annulated product **4** in 53% yield using a stoicmetric amount of $InCl_3$ in CH_2Cl_2 at room temperature, with *in situ* removal of its ketal group, followed by ketone enolization. The structure of **4** was determined by its NMR and HRMS studies, and verified by comparison with its analog **21**, whose structure was confirmed by X-ray crystallography.

In summary, we developed a concise approach for the construction of the core structure of liphagal via the $InCl_3$-mediated annulations as the key step, which paves the way for the total synthesis of liphagal.

3 Experimental

3.1 Materials and methods

All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. All the chemicals were purchased commercially, and used without further purification. Yields refer to chromatographically pure compounds, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm Tsingdao silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heated as developing agents. Tsingdao silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. NMR spectra were recorded on either a Brüker Advance 300 (^{1}H: 300 MHz, ^{13}C: 75 MHz), or Brüker Advance 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz). Mass spectrometric data were obtained using a Quadrupole time-of-flight (QqTOF) mass spectrometer. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad.

3.2 Experimental procedures

*Synthesis of 1,2-dimethoxy-4-(methoxymethoxy)-benzene (**11**)*

To a solution of phenol **10** (1.54 g, 10 mmol) in CH_2Cl_2 (100 mL) were added DIPEA (15 mmol), DMAP (147 mg, 1.2 mmol) and MOMCl (12 mmol) at 0 °C, and the resulting mixture was stirred at room temperature overnight. The reaction was worked up by addition of water (20 mL), and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine (2 × 20 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to give

product **11** (1.82 g) in 92% yield as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.8 Hz, 1H), 6.64 (d, J = 2.7 Hz, 1H), 6.59 (dd, J_1 = 8.8 Hz, J_2 = 2.7 Hz, 1H), 5.12 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 149.7, 144.3, 111.9, 106.9, 102.1, 95.2, 56.4, 55.8; HRMS (ESI) calcd for $C_{10}H_{14}NaO_4$ $[M+Na]^+$ 221.0790; found: 221.0782.

*Synthesis of 2,3-dimethoxy-6-(methoxymethoxy) benzaldehyde (**12**)*

To a solution of **11** (9.9 g, 50 mmol) in Et_2O (500 mL) was added TMEDA (55 mmol), and the resulting mixture was cooled to 0 °C. To this solution was added *n*-BuLi (22 mL, 2.5 N in hexane), and the formed mixture was stirred at the same temperature for 5 h. To this solution was added DMF (7.7 mL, 100 mmol), and the formed mixture was stirred overnight. The reaction was worked up by addition of a saturated NH_4Cl solution (200 mL), and the formed mixture was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to give product **12** (9.6 g) in 85% yield as a colorless oil (9.6 g, 85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.43 (s, 1H), 7.03 (d, J = 9.1 Hz, 1H), 6.86 (d, J = 9.1 Hz, 1H), 5.15 (s, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.5, 152.1, 151.5, 147.9, 121.0, 118.8, 111.2, 95.6, 61.9, 56.6, 56.3; HRMS (ESI) calcd for $C_{11}H_{14}NaO_5$ $[M+Na]^+$ 249.0739; found: 249.0732.

*Synthesis of 6-hydroxy-2,3-dimethoxybenzaldehyde (**13**)*

To a solution of **12** (1.13 g, 5 mmol) in CH_2Cl_2 (50 mL) was added TMSBr (12.5 mmol) at 0 °C, and the formed mixture was stirred at the same temperature for 30 min. The reaction was worked up by addition of a saturated solution of $NaHCO_3$, and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (2 × 20 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to give product **13** (840 mg) in 93% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.16 (s, 1H), 10.30 (s, 1H), 7.16 (d, J = 9.0 Hz, 1H), 6.61 (d, J = 9.0 Hz, 1H), 3.99 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0, 156.3, 152.0, 144.3, 124.4, 114.7, 111.7, 62.2, 57.3; HRMS (ESI) calcd for $C_9H_{11}O_4$ $[M+H]^+$ 183.0657; found: 183.0652.

*Synthesis of 2–hydroxyl-3-iodo-5,6-dimethoxybenzaldehyde (**8**)*

To a solution of **13** (2.93 g, 16 mmol) in dioxane (50 mL) were added ICl (19.4 mmol) and pyridine (9.2 mL, 113 mmol) at 0 °C, and the formed mixture was stirred for 80 h. The reaction was quenched by addition of saturated NH_4Cl solution (50 mL), and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to give product **8** (4.46 g mg) in 90% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.96 (s, 1H), 10.20 (s, 1H), 7.58 (s, 1H), 4.02 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.4, 155.2, 152.7, 145.3, 132.4, 124.4, 111.3, 111.7, 76.1, 62.3, 57.4; HRMS (ESI) calcd for $C_9H_{10}IO_4$ $[M+H]^+$ 308.9624; found: 308.9624.

*Synthesis of (E)-methyl 5-(4-methoxybenzyloxy)pent-2-enoate (**15**)*

To a solution of NaH (8.4 g) in THF (300 mL) and DMF (210 mL) was added PMBCl (200 mmol) at 0 °C. To this solution was added diol **14** (200 mmol), and the formed mixture was stirred overnight at room temperature. The reaction was quenched by addition of a saturated solution of NH_4Cl (100 mL), and the formed mixture was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine (2 × 30 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 2/1) to give the mono-protected alcohol (26.3 g) in 62% yield.

To a solution of DMSO (2.8 mL, 40 mmol) in CH_2Cl_2 (50 mL) was added oxyl chloride (1.9 mL, 20 mmol) at 78 °C, and the mixture was stirred at the same temperature for 1 h. To this solution was added Et_3N (100 mmol), and the mixture was stirred at room temperature for 2 h. The reaction was worked up by addition of saturated solution of NH_4Cl (100 mL), and the mixture was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to give the aldehyde (1.55 g) in 80% yield.

To a solution of $BrCH_2COOEt$ (0.5 mol) in EtOAc (1000 mL) was added PPh_3 (165.3 g, 0.63 mol), and the mixture was stirred at room temperature for 1 h. The formed solid was filtered off, and the solid was dissolved in CH_2Cl_2 (1000 mL). To this solution was added NaOH (1000 mL, 1 N), and the formed mixture was stirred for 20 min at room temperature. The organic layer was separated, and water phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine (2 × 15 mL), and dried over Na_2SO_4. The solvent was removed under vacuum to give the Wittig reagent Ph_3P=CHCOOEt.

To a solution of the aldehyde prepared above (14.8 g, 76.3 mmol) in toluene (600 mL) was added the Wittig reagent (40 g) at room temperature, and the formed mixture was stirred at the same temperature overnight. The reaction was worked up by addition of NH_4Cl (100 mL), and the

formed mixture was extracted with EtOAc (3 × 300 mL). The combined extracts were washed with brine, and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to give product **15** (19.18 g) in 95% yield.

*Synthesis of (E)-5-(4-methoxybenzyloxy)pent-2-en-1-ol (**16**)*

To a solution of ester **15** (10.2 g, 75.5 mmol) in CH_2Cl_2 (500 mL) was added DIBAL-H (1 N in toluene, 190 mL, 0.19 mol) at −78 °C, and the mixture was stirred at the same temperature for 1.5 h. The reaction was quenched by slow addition of MeOH (50 mL) at −78 °C, and the formed mixture was then warmed up to room temperature, and stirred for 30 min. To this solution was added a saturated solution of sodium potassium tartrate (100 mL), and the formed mixture was stirred at room temperature until a clear solution was obtained. The mixture was extracted with EtOAc (3 × 300 mL), and the combined organic phases were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to give product **16** (14.4 g) in 86% yield.

*Synthesis of ((2S,3S)-3-(2-(4-methoxybenzyloxy)ethyl) oxiran-2-yl)methanol (**17**)*

To a mixture of molecular sieves (17.5 g), $Ti(O^iPr)_4$ (5.5 mL, 18.2 mmol), and CH_2Cl_2 (500 mL) was added L-(+)DIPT (4.5 mL, 21.5 mL), and the mixture was stirred at −40 °C for 2 h. To this solution was added a solution of TBHP (28 mL, 153.5 mmol) by thringer pump, and the formed mixture was stirred at −20 °C for 2 h.

To the above solution was added a solution of **16** (14.5 g, 65 mmol) in CH_2Cl_2 (200 mL) at −20 °C, and the mixture was stirred at the same temperature for 16 h. The reaction was quenched by slow addition of a saturated solution of $Na_2S_2O_3$ (20 mL), and the formed mixture was filtrated through a silica gel pad, and the filtrate was extracted with EtOAc (3 × 300 mL). The combined extracts were washed with brine, and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to give product **17** (13.86 g) in 90% yield.

*Synthesis of (R)-4-(4-methoxybenzyloxy)-2-methy-butanal (**18**)*

To a solution of epoxide **17** (13.8 g, 58.2 mmol) in a mixed solvent of CH_2Cl_2 (100 mL) and hexane (200 mL) was added $AlMe_3$ (1.0 N in hexane, 175 mL, 0.175 mol) at 0 °C, and the mixture was stirred at room temperature for 2 d. The reaction was quenched by slow addition of water (20 mL), followed by addition of a NaOH solution (10% in water) until a clear solution was obtained. The mixture was extracted with EtOA (3 × 300 mL), and the combined organic phases were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to give a diol (11.8 g) in 80% yield.

To a solution of the diol made above (6.23 g, 24.5 mmol) in a mixed solvent of THF (125 mL) and water (125 mL) was added $NaIO_4$ (6.29 g) at room temperature, and the mixture was stirred at room temperature for 10 min. The reaction was first quenched by addition of EtOAc (200 mL), and then the mixture was washed with brine (2 x 15 ml), and finally dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was filtered through a pad of silica gel to give the crude aldehyde **18** in 72% yield without further purification.

*Synthesis of (R)-1-methoxy-4-((3-methylpent-4-ynyloxy)methyl)benzene (**9**)*

To a solution of CBr_4 (16.9 g, 51 mmol) and PPh_3 (26.7, 102 mmol) in CH_2Cl_2 (100 mL was added a solution of the crude aldehyde **18** made above (3.77 g, 16.9 mmol) and 2,6-dimethyl pyridine (9.9 mL, 68 mmol) in CH_2Cl_2 (70 mL) at 0 °C, and the mixture was stirred at the same temperature for 90 min. The reaction was worked up by filtration of the reaction mixture through a pad of silica gel, and washed with CH_2Cl_2 (3 × 50 mL). The filtrate was concentrated under vacuum, and the resulting crude dibromide was utilized in the next step without further purification.

To a solution of the crude dibromide in THF (150 mL) was added *n* − BuLi (2.5 N in THF, 17 mL, 42.5 mmol) at −40 °C, and the mixture was stirred at the same temperature under N_2 for 40 min. The reaction was quenched by addition of saturated NH_4Cl solution, and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with brine, and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 30/1) to give acetylene **9** (3.22 g) in 87% yield over three steps.

*Synthesis of (R)-2-(4-(benzyloxymethoy)butan-2-yl)-5,6-dimethoxybenzofuran-7-carbaldehyde (**19**)*

To a mixture of $PdCl_2(PPh_3)_2$ (210 mg, 0.3 mmol) and CuI (57 mg, 0.3 mmol) were added iodide **8** (616 mg, 2 mmol), acetylene **9** (651 mg, 3 mmol) and Et_3N (20 mL), and the mixture was stirred at 80 °C for 8 h. After cooling back to room temperature, the reaction was worked up by filtration of the reaction mixture through a pad of celite, and washed with EtOAc (3 × 50 mL). The filtrate was concentrated under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to give product **19** (677 mg) in 85% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.6 (s, 1H), 7.25–7.23 (m, 3H), 6.86 (d, J = 8.6 Hz, 2H), 6.28 (s, 1H), 4.42 (s, 2H), 3.99 (s, 3H), 3.92 (s, 3H), 3.80 (s, 3H), 3.51 (m, 2H), 3.21 (m, 1H), 2.11 (m, 1H), 1.90 (m, 1H), 1.35 (d, J = 7.0 Hz, 3H), 2.89 (t, J = 7.5 Hz, 2H), 2.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.2, 165.5, 159.2, 150.0, 149.4, 146.4,

130.7, 129.2, 125.3, 115.7, 113.8, 109.8, 100.2, 72.6, 67.7, 62.9, 56.8, 55.3, 35.4, 30.6, 19.1.

*Synthesis of (R)-2-(4-(benzyloxymethoxy)butan-2-yl)-5,6-dimethoxy-7-((methoxymethoxy)methyl)benzofuran (**20**)*

To a solution of **19** (350 mg, 0.89 mmol) in MeOH (20 mL) was added $NaBH_4$ (50 mg, 1.33 mmol) at 0 °C, and the formed reaction mixture was stirred at the same temperature for 2 h. The reaction was quenched by addition of a saturated solution of NH_4Cl (5 mL). Methanol was removed under vacuum, and the residue was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to give an alcohol **20** (340 mg) as a colorless oil in 97% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, J = 8.7 Hz, 2H), 6.92 (s, 1H), 6.86 (dd, J = 6.7, 1.9 Hz, 2H), 6.27 (s, 1H), 4.98 (s, 2H), 4.41 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.80 (s, 3H), 3.48 (m, 2H), 3.13 (q, J = 7.0 Hz, 1H), 2.07 (m, 1H), 1.89 (m, 1H), 1.32 (d, J = 7.0 Hz, 3H), 2.89 (t, J = 7.5 Hz, 2H), 2.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.8, 159.2, 149.6, 147.1, 144.9, 130.7, 129.2, 124.0, 117.9, 113.8, 102.8, 101.0, 72.6, 67.7, 61.7, 56.5, 56.0, 55.3, 35.4, 30.6, 19.1.

To a solution of the alcohol synthesized above (340 mg, 0.85 mmol) were added DIPEA (0.71 mL), DMAP (30 mg, 0.26 mmol) and MOMCl (0.2 mL, 2.6 mmol), and the formed mixture was stirred at room temperature for 8 h. The reaction was quenched by addition of water (5 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 5/1) to give product **20** (345 mg) in 90% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, J = 8.6 Hz, 2H), 6.97 (s, 1H), 6.87 (dd, J = 6.7, 1.9 Hz, 2H), 6.27 (s, 1H), 4.89 (s, 2H), 4.78 (s, 2H), 4.41 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.80 (s, 3H), 3.49 (m, 2H), 3.42 (s, 3H), 3.15 (q, J = 7.0 Hz, 1H), 2.07 (m, 1H), 1.88 (m, 1H), 1.32 (d, J = 7.0 Hz, 3H), 2.89 (t, J = 7.5 Hz, 2H), 2.02 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.6, 159.2, 149.8, 148.2, 145.7, 130.7, 129.2, 123.9, 115.2, 113.8, 103.3, 101.0, 96.2, 72.6, 67.8, 62.0, 59.0, 56.5, 55.3, 55.2, 35.4, 30.6,19.1.

*Synthesis of (R)-3-(5,6-dimethoxy-7-((methoxymethoxy)methyl)benzofuran-2-yl)butanal (**6**)*

To a solution of **20** (160 mg, 0.36 mmol) in EtOAc (30 mL) was added Pd/C (50 mg, 10% on charcoal), and the resulting mixture was stirred under H_2 (1 atm) for 2 h. The reaction was worked up by filtration of the mixture through a pad of celite, and washed with EtOAc (3 × 10 mL). The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 4/1) to give an alcohol (60 mg) in 53% yield (90% based on recovery of the starting material).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (s, 1H), 6.31 (d, J = 0.4 Hz, 1H), 4.89 (s, 2H), 4.76 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.71 (m, 2H), 3.46 (s, 3H), 3.14 (q, J = 7.0 Hz, 1H), 1.99 (m, 1H), 1.84 (m, 1H), 1.34 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.5, 149.7, 147.9, 145.5, 123.7, 114.9, 103.0, 100.9, 95.8, 62.0, 60.6, 58.7, 56.4, 55.2, 38.5, 30.2, 19.1.

To a solution of the alcohol made above (60 mg, 0.18 mmol) in CH_2Cl_2 (5 mL) was added DMP (110 mg, 0.27 mmol) under N_2, the formed mixture was stirred at room temperature for 1 h. The reaction was quenched by addition of saturated solutions of $Na_2S_2O_3$ (1 mL) and $NaHCO_3$ (1 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (5 mL), and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 3/1) to give aldehyde **6** (50 mg) in 90% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.80 (t, J = 1.7 Hz, 1H), 6.97 (s, 1H), 6.33 (d, J = 0.4 Hz, 1H), 4.88 (s, 2H), 4.77 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.55 (q, J = 7.0 Hz, 1H), 2.90 (ddd, J = 17.0, 6.4, 1.8 Hz, 1H), 2.66 (ddd, J = 17.0, 6.4, 1.8 Hz, 1H), 1.39 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.9, 161.5, 149.8, 148.1, 145.8, 123.5, 115.1, 103.1, 101.5, 96.1, 62.0, 58.7, 56.3, 55.2, 48.8, 28.2, 18.8.

*Synthesis of (R)-3-(5,6-dimethoxy-7-((methoxymethoxy)methyl)benzofuran-2-yl)-1-(1,4-dioxaspiro[4.5]dec-6-en-6-yl)butan-1-one (**5**)*

To a solution of 6-bromo-1,4-dioxaspiro[4.5]dec-6-ene (480 mg, 2.2 mmol) (**7**) in THF (25 mL) was added *t*-BuLi (0.85 mL, 5.5 mmol, 1.6 N in hexane) at −78 °C, and the mixture was stirred at the same temperature for 3 h. To this solution was added a solution of aldehyde **6** (310 mg, 1.1 mmol) in THF (10 mL) at −78 °C, and the mixture was stirred at the same temperature for additional 2 h. The reaction was worked up by addition of a saturated solution of NH_4Cl (5 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1) to give the coupling product as a secondary alcohol (317 mg) in 63% yield.

To a solution of the alcohol (290 mg, 0.63mmol) made above in CH_2Cl_2 (25 mL) was added DMP (320 mg, .075 mmol) at room temperature, and the mixture was stirred under N_2 for 1 h. The reaction was quenched by addition of the saturated solutions of $Ns_2S_2O_3$ (5 mL) and $NaHCO_3$ (5 mL), and the mixture was extracted with Et_2OAc (3 × 20

mL). The combined organic extracts were dried over Na_2SO_4. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 8/1) to give ketone **5** (200 mg) in 70% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (s, 1H), 6.85 (t, J = 3.8 Hz, 1H), 6.29 (s, 1H), 4.87 (s, 2H), 4.77 (s, 2H), 4.19 (dd, J = 5.7, 2.2 Hz, 2H), 4.01 (dd, J = 5.7, 3.0 Hz, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.57 (q, J = 7.4 Hz, 1H), 3.42 (s, 3H), 3.13 (dd, J = 16.8, 5.1 Hz, 1H), 2.81 (dd, J = 16.8, 5.1 Hz, 1H), 2.20 (m, 2H), 1.74 (m, 4H), 1.37 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.0, 163.1, 149.6, 148.0, 145.5, 143.5, 139.4, 123.8, 114.9, 106.3, 103.1, 100.9, 96.1, 77.2, 65.0, 64.9, 62.0, 58.8, 56.4, 55.2, 45.5, 34.0, 29.3, 25.7, 19.6, 18.6.

*Synthesis of model compound (**4**)*

To a solution of ketone **5** (33 mg, 0.073 mmol) in CH_2Cl_2 (5 mL) was added $InCl_3$ (16 mg, 0.073 mmol), and the mixture was stirred at 40 °C under N_2 for 8 h. The reaction mixture was filtrate through a pad of celite, and washed with EtOAc (3 × 5 mL). The filtrate was concentrated under vacuum, and the residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 30/1) to give the annulated product **4** (18 mg) in 53% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (s, 2H), 4.87 (m, 4H), 4.77 (m, 4H), 4.32 (s, 1H), 4.22 (s, 1H), 3.90 (s, 6H), 3.89 (s, 6H), 3.50 (m, 1H), 3.24 3.19 (m, 6H), 2.75 (m, 1H), 2.55 2.33 (m, 8H), 1.45 (d, J = 7.0 Hz, 3H), 1.32 (d, J = 7.0 Hz, 3H). HRMS (ESI) calcd for $C_{23}H_{29}O_7$ $[M+H]^+$ 417.1908; found: 417.1870.

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