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ARTICLE

Asymmetric Synthesis of *ent*-Fragransin C_1

Santikorn Chaimanee, Manat Pohmakotr, Chutima Kuhakarn, Vichai Reutrakul, and Darunee Soorukram*

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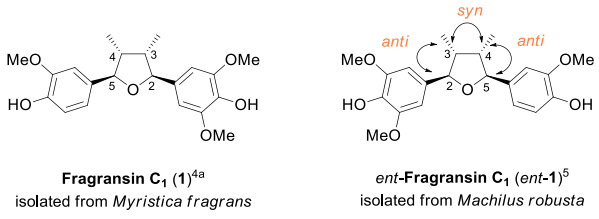
The first asymmetric synthesis of *ent*-fragransin C_1 was reported. The key step involves an intramolecular C–O bond formation (furan ring formation) *via* chemoselective generation of the benzylic carbocation leading to the 2,3-*anti*-3,4-*syn*-4,5-*anti*-tetrahydrofuran moiety as a single diastereomer in good yield. Our synthesis confirms that *ent*-fragransin C_1 possesses 2*R*,3*R*,4*S*,5*S* configurations.

Introduction

Lignans are a large group of natural products formed by the dimerization of two phenylpropanoid (C6–C3) units with a broad structural diversity.[1] These secondary plant metabolites have been found to possess a wide range of important biological activities including antioxidant, anti-inflammatory, antitumor, antifungal, and antiviral properties.[2] In recent years, new lignans and neolignans bearing unprecedented carbon skeletons and stereochemistries have been actively isolated and identified.[3]

Fragransin C_1 (**1**) and its enantiomer, *ent*-**1**, are naturally occurring 2,5-diaryl-3,4-dimethyltetrahydrofuran lignans (Figure 1). The chemical structure of **1** was first reported in 1987 by Namba and co-workers[4a] and was proposed to possess 2*S*,3*S*,4*R*,5*R* configurations. In 2011, *ent*-**1** was isolated by Zhu and Shi and was reported to contain a similar relative configuration of 2,3-*anti*-3,4-*syn*-4,5-*anti* as observed in **1**. It was assigned to have 2*R*,3*R*,4*S*,5*S* configurations according to the CD spectral data.[5] Having focused on asymmetric synthesis of lignans[6] and taken the significance of the structure–activity relationship (SAR) observed for 2,5-diaryltetrahydrofurans[7] into account, we aim to develop an asymmetric synthesis of *ent*-**1**. Our study will benefit the confirmation of its absolute configuration prior to further evaluation of its biological activity. Notably, despite numerous reports on asymmetric synthesis of 2,5-diaryl-3,4-dimethyltetrahydrofurans,[8] stereoselective synthesis of **1** or *ent*-**1** has never been reported.

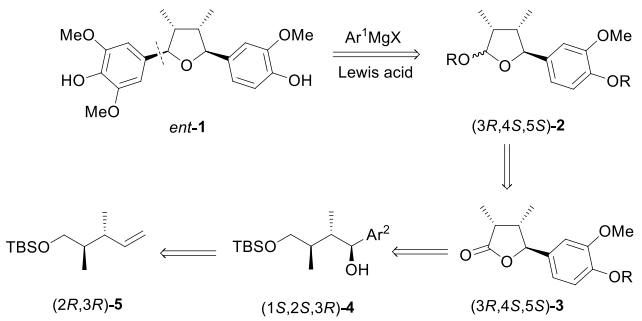
On the basis of our recent report on the formal synthesis of (+)-3-*epi*-eupomatilone-6 and its 3,5-bis-epimer, primary synthetic plan to *ent*-**1** will utilize stereoselective construction of chiral trisubstituted γ-butyrolactone cores bearing the *syn*-dimethyl stereocenters as a key step.[6c] As depicted in Scheme 1, it was envisioned that *ent*-**1** should be obtained through the nucleophilic addition[8h] of arylmagnesium halide (Ar^1MgX) to a trisubstituted γ-lactol **2**, which in turn would be readily prepared from (3*R*,4*S*,5*S*)-γ-butyrolactone **3** possessing the 3,4-*syn*-4,5-*anti* stereochemistries. The (3*R*,4*S*,5*S*)-γ-butyrolactone **3** should be obtained with high stereoselectivity from (1*S*,2*S*,3*R*)-alcohol **4** *via* oxidative lactonization reaction. Finally, using our previous synthetic strategy, (1*S*,2*S*,3*R*)-**4** should be stereoselectively synthesized from the substrate-controlled addition of aryllithium (Ar^2Li) to an aldehyde derived from (2*R*,3*R*)-alkene **5**.



Fragransin C_1 (1)[4a] isolated from *Myristica fragrans*

***ent*-Fragransin C_1 (*ent*-1)**[5] isolated from *Machilus robusta*

Figure 1. Structures of naturally occurring fragransin C_1 (**1**) and its enantiomer, *ent*-**1**.



Scheme 1. Primary synthetic plan to *ent*-**1** *via* chiral γ-butyrolactone **3**.

Department of Chemistry and Center of Excellence for Innovation in Chemistry (PERCH-CIC), Faculty of Science, Mahidol University, Rama VI Road, Bangkok 10400, Thailand. E-mail: darunee.soo@mahidol.ac.th; Fax: +662 354 7151; Tel: +662 201 5148.

† Footnotes relating to the title and/or authors should appear here.
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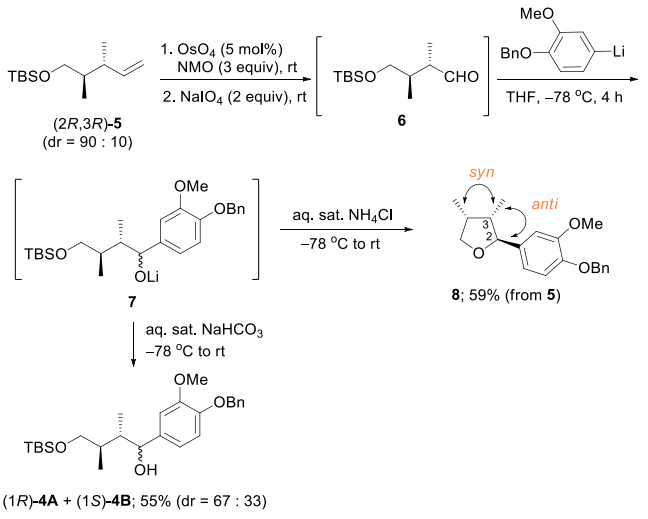
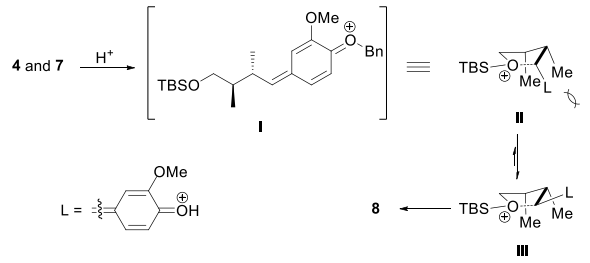
Results and discussion

As outlined in Scheme 2, the (2*R*,3*R*)-alkene **5** [diastereomeric ratio (dr) = 9 : 1, ^{1}H NMR analysis] was subjected to oxidative cleavage using OsO_4, *N*-methylmorpholine-*N*-oxide (NMO) followed by $NaIO_4$ to provide the corresponding aldehyde **6**.[6c] After purification, **6** was further treated with [4-(benzyloxy)-3-methoxyphenyl]lithium (1.5 equiv.) [freshly prepared from bromine-lithium exchange between 1-(benzyloxy)-4-bromo-2-methoxybenzene and *n*-BuLi] in THF at −78 °C for 4 h to give the corresponding lithium alkoxide **7**. Similar to the previously reported results,[6c] when **7** was quenched with a saturated aqueous NH_4Cl solution, a trisubstituted tetrahydrofuran **8**, containing 2,3-*anti*-3,4-*syn* stereochemistries, was obtained in 59% yield (from **5**) (dr = 89 : 8 : 3, ^{1}H NMR analysis). The chemical structure of **8** and its stereochemistry were established on the basis of mass spectrometry, NMR analyses, and NOESY experiments (see ESI). Interestingly, when **7**, derived from **5** (dr = 9 : 1), was quenched with a saturated aqueous $NaHCO_3$ solution, the corresponding alcohol adducts **4A** and **4B** were obtained in 55% yield as a mixture of diastereomers (dr = 67 : 33) after column chromatography without the formation of furan **8**. The mechanism for the formation of **8** was proposed to proceed *via* the formation of an intermediate oxonium ion **I** followed by an intramolecular cyclization (Scheme 3). The observed stereochemical outcome of **8** (2,3-*anti*-3,4-*syn*) can be explained by the more favorable transition state **III** possessing a minimal steric interaction between the aryl ring and the adjacent methyl group (**II** vs. **III**).

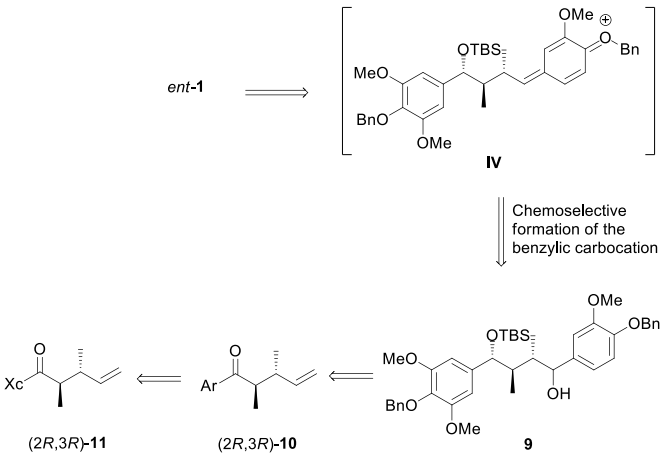


Scheme 2. The selective formation of alcohols **4** and furan **8**.



Scheme 3. Proposed mechanism for the formation of furan **8**.

The observed chemoselective formation of the benzylic carbocation under mildly acidic reaction conditions leading to the formation of furan **8** with high stereoselectivity encouraged us to revise our synthetic plan to *ent*-**1**. As shown in Scheme 4, we anticipated that an intramolecular cyclization of an intermediate oxonium ion **IV** would lead to *ent*-**1** after debenzylation. The oxonium ion **IV** would be generated from an alcohol **9**, which in turn should be readily prepared from (2*R*,3*R*)-**10** and (2*R*,3*R*)-**11**, respectively.



Scheme 4. Synthetic plan to *ent*-**1** *via* the chemoselective formation of the benzylic carbocation.

Based on the revised synthetic plan, the requisite (2*R*,3*R*)-aryl ketone **10** was readily prepared starting from (2*R*,3*R*)-**11** (Scheme 5). Removal of the chiral auxiliary moiety of (2*R*,3*R*)-**11**[6c] (dr = 96 : 4) yielded (2*R*,3*R*)-2,3-dimethyl-4-pentenoic acid **12**[9] (92% yield, dr = 96 : 4) which was then converted to the corresponding Weinreb amide **13** in 74% yield. Treatment of **13** with [4-(benzyloxy)-3,5-dimethoxyphenyl]lithium (1.5 equiv.) [freshly prepared from the bromine-lithium exchange between 2-(benzyloxy)-5-bromo-1,3-dimethoxybenzene with *n*-BuLi] in THF at −78 °C and the reaction mixture was allowed to stir at room temperature for 2 h gave the expected (2*R*,3*R*)-ketone **10** in 75% yield (dr = 96 : 4). The (2*R*,3*R*)-ketone **10** was subjected to stereoselective reduction using $NaBH_4$ in MeOH at −78 to 0 °C for 4 h to give the desired alcohol (1*R*,2*R*,3*R*)-**14** in 87% yield as an inseparable mixture of diastereoisomers (dr = 84 : 11 : 5). Similar results were observed when DIBALH was employed as a reducing agent in THF at −78 °C.[10] The stereochemical outcome of the hydride reduction of (2*R*,3*R*)-**10** to give (1*R*,2*R*,3*R*)-**14** as a major diastereomer could be explained on the basis of the Felkin–Ahn model.[11] The relative stereochemistry at the C-1 and C-2 of (1*R*,2*R*,3*R*)-**14** was assigned by the analysis of the coupling constant between H-1 and H-2; H-1 appeared as a doublet at δ 4.27 (d, ^3J = 9.2 Hz) ppm.[12] Next, treatment of alcohol **14** (as a mixture of diastereomers, dr = 84 : 11 : 5) with TBSCl gave TBS-ether **15**, containing (1*R*,2*R*,3*R*)-**15** as a major isomer, in 82% yield. The second aromatic ring was installed *via* dihydroxylation of the terminal alkene of (1*R*,2*R*,3*R*)-**15** by using OsO_4 and NMO followed by oxidative cleavage using $NaIO_4$ to provide the corresponding aldehyde. Without isolation, the

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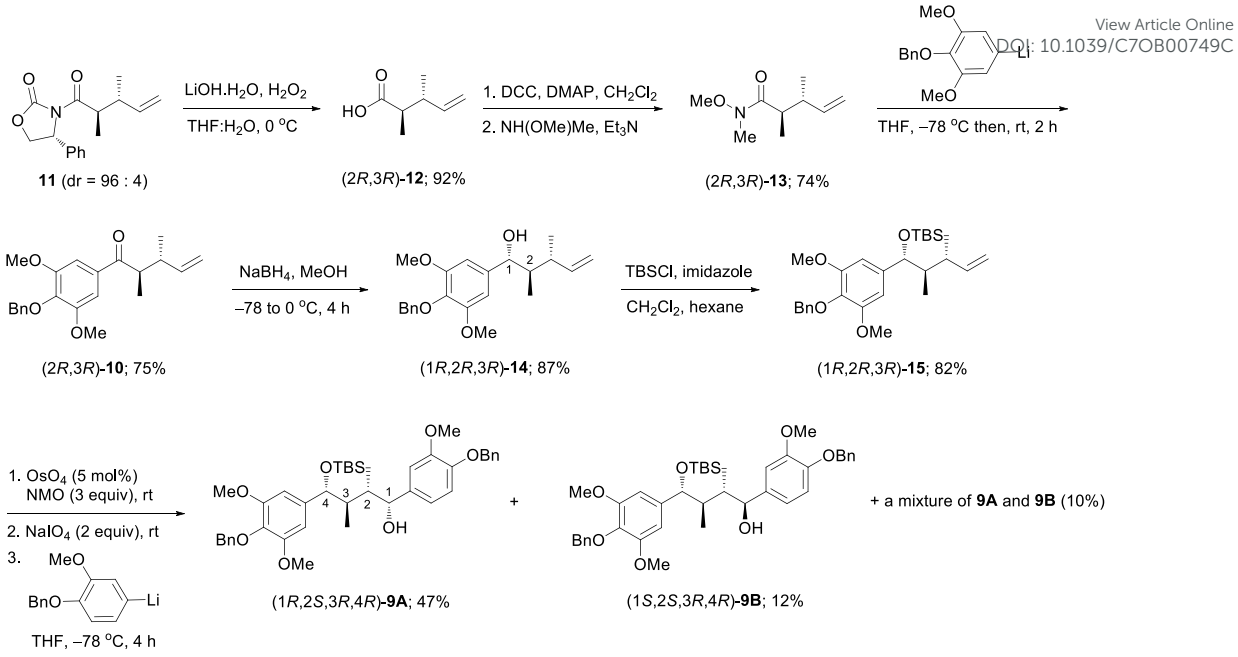

Scheme 5. Synthesis of chiral alcohols **9**.

aldehyde formed was further reacted with [4-(benzyloxy)-3-methoxyphenyl]lithium (1.5 equiv.) in THF at –78 °C for 4 h to yield, after column chromatography, the corresponding alcohols (1*R*,2*S*,3*R*,4*R*)-**9A** (47% yield, single isomer) and (1*S*,2*S*,3*R*,4*R*)-**9B** (12% yield, single isomer) along with a mixture of **9A** and **9B** (10% yield).[13] The stereochemical outcome of the addition of aryllithium to aldehyde derived from (1*R*,2*R*,3*R*)-**15** to give (1*R*,2*S*,3*R*,4*R*)-**9A** as a major diastereomer[14] could be explained by the Felkin–Ahn model.[11]

The chemoselective generation of the oxonium ion intermediate **IV** was then planned to be generated *via* a methane sulfonate derivative **16** (Scheme 6).[15] Unexpectedly, upon treatment of (1*R*,2*S*,3*R*,4*R*)-**9A** with methane sulfonyl chloride and dry Et_3N in THF at room temperature for 1 h, the aryltetralin **17** was obtained in 54% yield as a single diastereomer without the formation of the desired furan **18**. The chemical structure of **17** and its stereochemistry were established based on mass spectrometry, the NMR analyses, and the NOESY experiments (see ESI). The relative stereochemistry at the 3,4-position was assigned by the analysis of the coupling constant between H-3 and H-4; H-4 appeared as a doublet at δ 3.55 (d, ^3J = 9.8 Hz) ppm.[16] The reaction mechanism for the formation of **17** was proposed (Scheme 6). Indeed, the chemoselective generation of the oxonium ion intermediate **IV** *via* methane sulfonate derivative **16** was achieved as expected. However, **IV** rapidly underwent an intramolecular Friedel–Crafts reaction (route *a* vs. route *b*) to form an intermediate **V** leading to **17** after re-aromatization process. It is also worth mentioning here that the observed stereoselective formation of aryltetralin **17** could be useful for the synthesis of a variety of biologically active aryltetralin lignans.[17]

To circumvent the formation of aryltetralin **17**, it was anticipated that the increase in the nucleophilicity of the oxygen atom at the C-1 would both facilitate the C–O bond formation (route *b*) and suppress the competitive Friedel–Crafts reaction (route *a*). Thus, (1*R*,2*S*,3*R*,4*R*)-**9A** was subjected to TBS deprotection using TBAF to give diol (1*R*,2*R*,3*S*,4*R*)-**19A** in 87% yield (Scheme 6). To our delight, it was found that diol (1*R*,2*R*,3*S*,4*R*)-**19A** underwent stereoselective intramolecular cyclization *via* the C–O bond formation (furan formation) to form the desired furan (2*R*,3*R*,4*S*,5*S*)-**20** in 92% yield as a single diastereomer by simply treatment with a catalytic amount of *p*-TsOH in dry CH_2Cl_2 at room temperature for 1.5 h. The NOESY experiments confirmed that (2*R*,3*R*,4*S*,5*S*)-**20** possessed 2,3-*anti*-3,4-*syn*-4,5-*anti* stereochemistries (see ESI).

At this stage, the observed stereoselective formation of (2*R*,3*R*,4*S*,5*S*)-**20** from (1*R*,2*R*,3*S*,4*R*)-**19A** should be discussed (Scheme 7). According to the experimental results described above, it was proposed that the chemoselective formation of benzylic carbocation is governed by the substitution pattern in the aromatic rings. Upon treatment of (1*R*,2*R*,3*S*,4*R*)-**19A** with *p*-TsOH, the oxonium ion **VI** was chemoselectively generated. Intramolecular cyclization of **VI** *via* the more favorable transition state **VIII** led to the formation of furan (2*R*,3*R*,4*S*,5*S*)-**20** as a single isomer. On the contrary, furan **21** was not detected in the ^{1}H NMR analysis of the crude mixture[18] implying that the oxonium **IX** was not formed under our reaction conditions presumably due to the developing steric interaction between the adjacent methoxy and benzyloxy substituents on the aromatic ring of **IX**. Alternatively, the formation of **20** from **21** *via* an acid-catalyzed ring opening of the furan ring of **21** followed by cyclization *via* the more favorable transition state **VIII** should not be excluded.[10] The chemoselective formation of the oxonium ion **VI** and stereoselective cyclization were further confirmed when (1*S*,2*S*,3*R*,4*R*)-**9B** was readily converted to (2*R*,3*R*,4*S*,5*S*)-**20** as a single isomer in 89% yield (Scheme 6).

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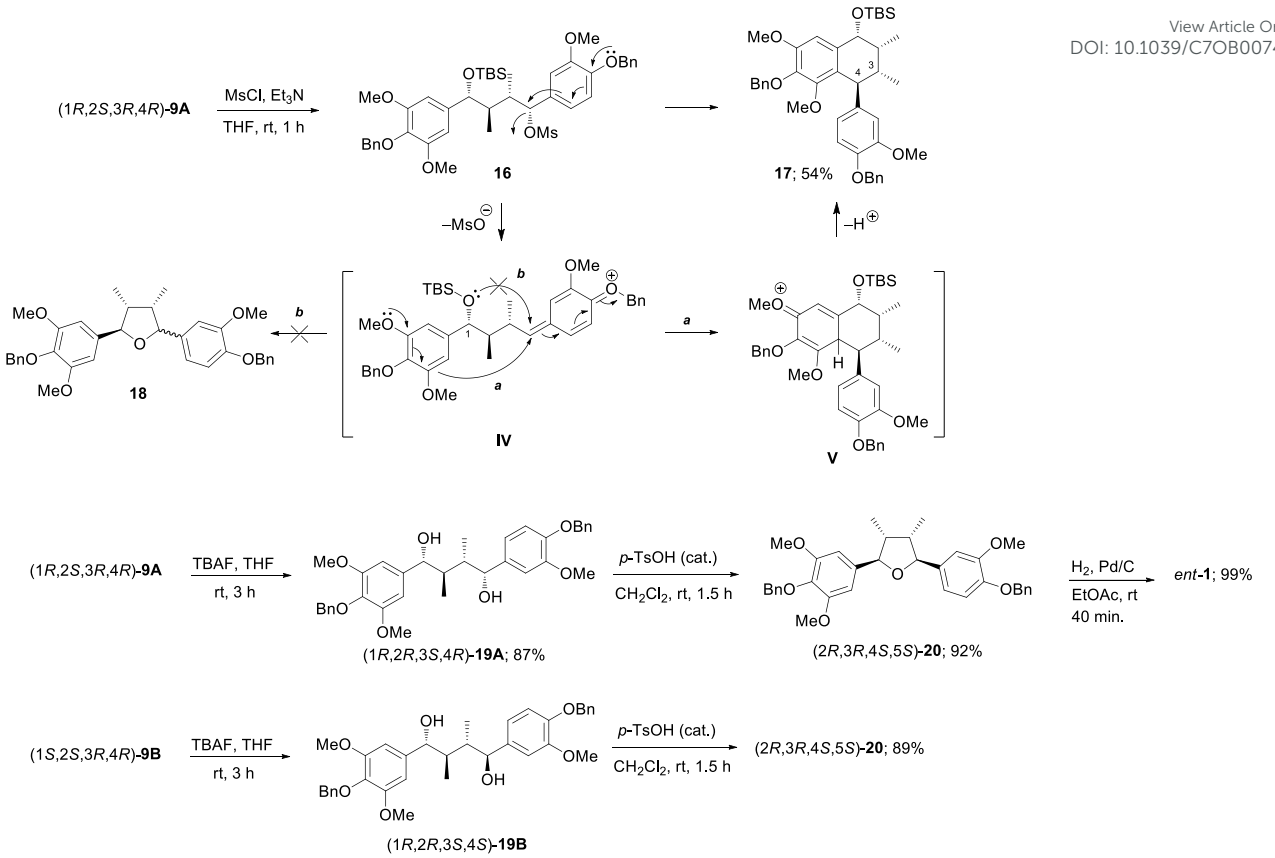
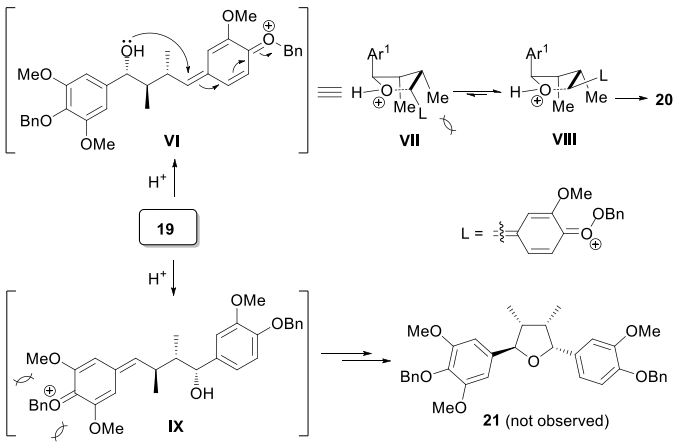


Scheme 6. Synthesis of aryltetralin **17** and furan **20**.

With (2*R*,3*R*,4*S*,5*S*)-**20** in hand, it was converted to *ent*-**1** (99% yield) by hydrogenation using Pd/C in dry ethyl acetate. The spectroscopic data of the synthesized *ent*-**1** are in good agreement with those reported (see ESI).



Scheme 7. Proposed mechanism for the formation of **20**.

Conclusions

The first asymmetric synthesis of *ent*-fragransin C_1 was described using an intramolecular C–O bond formation *via* the chemoselective formation of the benzylic carbocation as a key step. On this basis, *ent*-fragransin C_1 bearing the 2,3-*anti*-3,4-*syn*-4,5-*anti* stereochemistires was synthesized in good yield as a single diastereomer. Our synthesis confirms the 2*R*,3*R*,4*S*,5*S* configurations assigned for the natural *ent*-fragransin C_1. The biological activity evaluation is currently under investigation. Moreover, aryltetralin derivative was also synthesized with high stereoselectivity *via* an intramolecular C–C bond formation. This approach could be useful for asymmetric synthesis of various biologically active aryltetralin derivatives.

Experimental

General information

The ^{1}H NMR spectra were recorded on a Bruker-400 (400 MHz) spectrometer in acetone-d_6 or $CDCl_3$ using tetramethylsilane as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker-400 (100 MHz) spectrometer in acetone-d_6 or $CDCl_3$ using residual non-deuterated solvent peaks as an internal standard. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Dichloromethane (CH_2Cl_2), ethyl acetate (EtOAc), and ethanol (EtOH) were distilled over calcium hydride and stored over

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activated molecular sieves (4 Å). Methanol (MeOH) was distilled over Mg powder. Other common solvents [CH_2Cl_2, hexanes, and EtOAc] were distilled before use. All glassware including needles and syringes were oven-dried and kept in a desiccator before use. Purification of the reaction products was carried out by column chromatography on silica gel.

***tert*-Butyl{[(2*R*,3*R*)-2,3-dimethylpent-4-en-1-yl]oxy}dimethylsilane (5).**[6c] $[\alpha]^{24}_D$ +21.2 (c 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75–5.66 (m, 1H, C*H*), 5.00–4.91 (m, 2H, CH_2), 3.49 (dd, *J* = 9.8, 6.5 Hz, 1H, C*H*H), 3.39 (dd, *J* = 9.8, 6.5 Hz, 1H, CH*H*), 2.35–2.26 (m, 1H, C*H*), 1.61–1.52 (m, 1H, C*H*), 1.00 (d, *J* = 6.9 Hz, 3H, CH_3), 0.89 [s, 9H, SiC(CH_3)$_3$], 0.81 (d, *J* = 6.9 Hz, 3H, CH_3), 0.03 (s, 6H, 2 × SiCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8 (CH), 113.9 (CH_2), 66.3 (CH_2), 40.5 (CH), 38.8 (CH), 25.9 (3 × CH_3), 18.4 (C), 17.9 (CH_3), 12.9 (CH_3), −5.4 (2 × CH_3). IR ($CHCl_3$): ν_{max} 1472w, 1257m, 1091m, 838s cm^{-1}. MS: m/z (%) relative intensity 229 [(M + H)$^+$, 2], 220 (100), 204 (53), 190 (85), 148 (76), 98 (32). HRMS (ESI-TOF) calcd for $C_{13}H_{29}OSi$ [M + H]$^+$: 229.1988, found: 229.1986.

(2*S*,3*S*,4*R*)-2-[4-(Benzyloxy)-3-methoxyphenyl]-3,4-dimethyltetrahydrofuran (8). To a solution of **5** (dr = 90 : 10) (63 mg, 0.28 mmol) and NMO (113.7 mg, 0.84 mmol) in CH_2Cl_2 (11 mL) were added OsO_4 (2.5% w/v in *t*-butanol, 0.14 mL, 0.014 mmol) and water (0.14 mL). After stirring for 14 h at room temperature, $NaIO_4$ (119.3 mg, 0.56 mmol) was added, and stirring of the reaction mixture continued for 1 h. Then it was quenched with a saturated aqueous $Na_2S_2O_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The crude mixture was filtered through a short column (50% Et_2O in pentane) to give **6**. A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with 1-(benzyloxy)-4-bromo-2-methoxybenzene (123 mg, 0.42 mmol) and dry THF (1 mL). The solution was cooled at −78 °C and then a solution of *n*-BuLi (1.6 M in hexane, 0.26 mL, 0.42 mmol) was added dropwise. The resulting mixture was stirred for 10 min and then a solution of **6** in dry THF (0.7 mL) was added dropwise. After stirring at −78 °C for 2 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (10% EtOAc in hexanes) gave **8** as a colorless oil (51.4 mg, 59% yield) as a mixture of diasteromers (dr = 89 : 8 : 3, 400 MHz ^{1}H NMR analysis). R_f 0.31 (20% EtOAc in hexanes); $[\alpha]^{24}_D$ +14.8 (c 0.99, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.25 (m, 5H, Ar*H*), 6.90 (d, *J* = 1.8 Hz, 1H, Ar*H*), 6.83 (d, *J* = 8.2 Hz, 1H, Ar*H*), 6.77 (dd, *J* = 1.8, 8.2 Hz, 1H, Ar*H*), 5.14 (s, 2H, CH_2), 4.36 (d, *J* = 8.2 Hz, 1H, C*H*), 4.24 (dd, *J* = 6.4, 8.3 Hz, 1H, C*H*H), 3.90 (s, 3H, OCH_3), 3.61 (dd, *J* = 4.6, 8.3 Hz, 1H, CH*H*), 2.50–2.30 (m, 1H, C*H*), 2.20–2.00 (m, 1H, C*H*), 1.00 (d, *J* = 7.2 Hz, 3H, CH_3), 0.95 (d, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7 (C), 147.5 (C), 137.3 (C), 135.9 (C), 128.5 (2 × CH), 127.8 (CH), 127.3 (2 × CH), 118.3 (CH), 113.8 (CH), 109.6 (CH), 86.4 (CH), 75.3 (CH_2), 71.1 (CH_2), 56.0 (OCH_3), 45.2 (CH), 36.8 (CH), 13.5 (CH_3), 11.9 (CH_3). IR (neat): ν_{max} 1513s, 1454m, 1383m, 1264s, 1226m, 1139m, 1012m cm^{-1}. MS (ISCID): m/z (%) relative intensity 335 [(M + Na)$^+$, 48], 276 (3), 244 (100), 229 (7). HRMS (ESI-TOF) calcd for $C_{20}H_{25}O_3$ [M + H]$^+$: 313.1804, found: 313.1792.

(1*R*,2*S*,3*R*)-1-[4-(Benzyloxy)-3-methoxyphenyl]-4-[(*tert*-butyldimethylsilyl)oxy]-2,3-dimethylbutan-1-ol (4A) and (1*S*,2*S*,3*R*)-1-[4-(Benzyloxy)-3-methoxyphenyl]-4-[(*tert*-butyldimethylsilyl)oxy]-2,3-dimethylbutan-1-ol (4B). According to the same procedure as for **8**, oxidative cleavage of **5** (dr = 90 : 10) (89.5 mg, 0.4 mmol) provided **6**, which was further reacted with [4-(benzyloxy)-3-methoxyphenyl]lithium [prepared from 1-(benzyloxy)-4-bromo-2-methoxybenzene (176 mg, 0.6 mmol) and *n*-BuLi (1.6 M in hexane, 0.4 mL, 0.6 mmol)]. After stirring at −78 °C for 2 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (10% EtOAc in hexanes) gave a mixture of **4A** (major) and **4B** (minor) (96.6 mg, 55% yield, dr = 67 : 33) as a colorless oil. R_f 0.10 (10% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, interpreted equally for both isomers): δ 7.50–7.20 (m, 10H, Ar*H* of **4A** and **4B**), 6.98 (d, *J* = 1.2 Hz, 1H, Ar*H* of **4A**), 6.94 (d, *J* = 1.8 Hz, 1H, Ar*H* of **4B**), 6.85–6.74 (m, 4H, Ar*H* of **4A** and **4B**), 5.14 (s, 4H CH_2 of **4A** and **4B**), 4.80 (s, 2H, O*H* of **4A** and **4B**), 4.44 (s, 2H, C*H* of **4A** and **4B**), 3.90 (s, 6H, 2 × OCH_3 of **4A** and **4B**), 3.65–3.55 (m, 2H, CH*H* of **4A** and **4B**), 3.55–3.45 (m, 2H, C*H*H of **4A** and **4B**), 2.15–2.05 (m, C*H* of **4B**), 2.05–1.98 (m, C*H* of **4A**), 1.98–1.89 (m, C*H* of **4B**), 1.82–1.73 (m, C*H* of **4A**), 0.94 [s, 9H, SiC(CH_3)$_3$ of **4B**], 0.93 [s, 9H, SiC(CH_3)$_3$ of **4A**], 0.91 (d, *J* = 7.1 Hz, 3H, CH_3 of **4A**), 0.85 (d, *J* = 7.2 Hz, 3H, CH_3 of **4B**), 0.80 (d, *J* = 7.1 Hz, 3H, CH_3 of **4B**), 0.74 (d, *J* = 7.2 Hz, 3H, CH_3 of **4A**), 0.13 (s, 6H, 2 × SiCH_3 of **4A**), 0.12 (s, 6H, 2 × SiCH_3 of **4B**). ^{13}C NMR (100 MHz, $CDCl_3$, **4A** marked *): δ 149.5 (C), 149.2 (C*), 147.0 (C), 146.6 (C*), 138.1 (C), 138.0 (C*), 137.6 (C*), 137.4 (C), 128.5 (2 × CH of **4A** and **4B**), 127.7 (CH of **4A** and **4B**), 127.3 (2 × CH of **4A** and **4B**), 118.9 (CH), 118.1 (CH*), 113.7 (CH of **4A** and **4B**), 110.0 (CH of **4A** and **4B**), 76.8 (CH*), 76.6 (CH), 71.2 (CH_2 of **4A** and **4B**), 65.5 (CH_2), 65.0 (CH_2*), 56.0 (OCH_3 of **4A** and **4B**), 46.0 (CH*), 44.9 (CH), 40.3 (CH*), 35.2 (CH), 29.7 (C of **4A** and **4B**), 25.9 (3 × CH_3 of **4A** and **4B**), 17.5 (CH_3*), 15.6 (CH_3), 12.6 (CH_3), 5.7 (CH_3*), −5.4 (CH_3), −5.5 (CH_3*). IR (neat): ν_{max} 3398br, 1593m, 1514s, 1456s, 1258s, 1226s, 1138s, 1078s, 1035s cm^{-1}. MS (ISCID): m/z (%) relative intensity 467 [(M + Na)$^+$, 100], 413 (2), 376 (9). HRMS (ESI-TOF) calcd for $C_{26}H_{40}NaO_4Si$ [M + Na]$^+$: 467.2594, found: 467.2609.

(2*R*,3*R*)-2,3-Dimethylpent-4-enoic acid (12).[9] A solution of **11** (dr = 96 : 4, 533 mg, 1.95 mmol) in a mixture of THF (9 mL) and water (3 mL) cooled at 0 °C was treated with a 30% (v/v) aqueous solution of H_2O_2 (0.9 mL, 7.8 mmol) followed by dropwise addition of a solution of LiOH·H_2O (131 mg, 3.1 mmol) in water (4 mL). After stirring at 0 °C for 2 h, two phases of the reaction mixture were separated. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo* to give the recovered chiral auxiliary. The aqueous phase was acidified (pH 1) by using 10% HCl aqueous solution and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (20% EtOAc in hexanes) gave **12** (230.4 mg, 92% yield, dr = 96 : 4, 400 MHz ^{1}H NMR analysis) as a colorless liquid. R_f 0.33 (30% EtOAc in hexanes); $[\alpha]^{24}_D$ +37.8 (c 1.19, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65 (ddd, *J* = 17.1, 10.2, 8.2 Hz, 1H, C*H*), 5.04–4.93 (m, 2H, CH_2), 2.60–2.40 (m, 1H, C*H*), 2.40–2.30 (m, 1H, C*H*), 1.13 (d, *J* = 7.0 Hz, 3H, CH_3), 1.07 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ

182.2 (CO), 140.5 (CH), 115.4 (CH_2), 44.8 (CH), 40.8 (CH), 18.4 (CH_3), 14.3 (CH_3). MS: m/z (%) relative intensity 129 [(M + H)$^+$, 20], 128 (M+, 8), 113 (40), 83 (49), 67 (53).

(2*R*,3*R*)-*N*-Methoxy-*N*,2,3-trimethylpent-4-enamide (13).[19] A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with **12** (dr = 96 : 4) (228 mg, 1.78 mmol), DMAP (22 mg, 0.18 mmol), and dry CH_2Cl_2 (7 mL). The solution was cooled at 0 °C then *N*,*N*'-dicyclohexylcarbodiimide (404 mg, 1.96 mmol) was added. The mixture was stirred for 15 min and *N*,*O*-dimethylhydroxylamine hydrochloride (208 mg, 2.13 mmol) and NEt_3 (0.3 mL, 2.13 mmol) were subsequently added. The reaction was slowly warmed up to room temperature, and the stirring was continued at room temperature for 15 h. The reaction mixture was quenched with H_2O (10 mL) and the suspension was filtered. The filter cake was washed with CH_2Cl_2 (3 x 10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4. After removal of solvent in *vacuo*, the crude product was purified by column chromatography (20% EtOAc in hexane] to afford **13** (226.5 mg, 74% yield) as a colorless oil (dr = 96 : 4). R_f 0.40 (20% EtOAc in hexanes); $[\alpha]^{30}_D$ −15.0 (c 1.02, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72–5.60 (m, 1H, C*H*), 5.10–4.98 (m, 2H, C*H*H), 3.69 (s, 3H, OC*H*$_3$), 3.20 (s, 3H, C*H*$_3$), 2.80–2.66 (m, 1H, C*H*), 2.50–2.35 (m, 1H, C*H*), 1.07 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 0.97 (d, *J* = 6.6 Hz, 3H, C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4 (CO), 141.7 (CH), 114.9 (CH_2), 61.4 (OCH_3), 41.3 (CH_3), 40.1 (CH), 32.1 (CH), 19.0 (CH_3), 16.0 (CH_3). MS (ISCID): m/z (%) relative intensity 194 [(M + Na)$^+$, 100], 172 [(M + H)$^+$, 23], 126 (3), 118 (3). HRMS (ESI-TOF) calcd for $C_9H_{18}NO_2$ [M + H]$^+$: 172.1338, found: 172.1346.

(2*R*,3*R*)-1-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-2,3-dimethylpent-4-en-1-one (10). A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with 2-(benzyloxy)-5-bromo-1,3-dimethoxybenzene (521 mg, 1.6 mmol) and dry THF (4.5 mL). The solution was cooled at −78 °C then a solution of *n*-BuLi (1.6 M in hexane, 0.93 mL, 1.5 mmol) was added dropwise. After stirring for 10 min, a solution of the amide **13** in dry THF (4.5 mL) was added dropwise at −78 °C. The reaction was slowly warmed up to room temperature, and the stirring was continued at room temperature for 2 h. The reaction mixture was quenched with H_2O (15 mL) and extracted with EtOAc (3 × 25 mL). The combined organic phase was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After removal of solvent in *vacuo*, the crude product was purified by column chromatography (10% Et_2O in hexanes) to afford **10** (330.5 mg, 75% yield) as a colorless oil with a 96 : 4 diastereomeric ratio (400 MHz ^{1}H NMR analysis). R_f 0.40 (20% EtOAc in hexanes); $[\alpha]^{24}_D$ −47.4 (c 0.51, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55–7.45 (m, 2H, Ar*H*), 7.40–7.25 (m, 3H, Ar*H*), 7.20 (s, 2H, Ar*H*), 5.80–5.65 (m, 1H, C*H*), 5.10 (s, 2H, C*H*$_2$), 5.10–5.00 (m, 2H, C*HH*), 3.89 (s, 6H, 2 × OC*H*$_3$), 3.35–3.25 (m, 1H, C*H*), 2.70–2.25 (m, 1H, C*H*), 1.14 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.00 (d, *J* = 6.7 Hz, 3H, C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.1 (CO), 153.4 (2 × C), 141.5 (C), 141.2 (CH), 137.4 (C), 132.7 (C), 128.4 (2 × CH), 128.2 (2 × CH), 128.0 (CH), 115.0 (CH_2), 105.9 (2 × CH), 75.1 (CH_2), 56.3 (2 × OCH_3), 45.4 (CH), 41.2 (CH), 19.0 (CH_3), 15.9 (CH_3). IR ($CHCl_3$): ν_{max} 1672m, 1584m, 1501m, 1463m, 1415m, 1324m, 1131s cm^{-1}. MS (ISCID): m/z (%) relative intensity 377 [(M + Na)$^+$, 20], 355 [(M + H)$^+$, 5], 306 (49), 286 (100). HRMS (ESI-TOF) calcd for $C_{22}H_{27}O_4$ [M + H]$^+$: 355.1909, found: 355.1906.

(1*R*,2*R*,3*R*)-1-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-2,3-dimethylpent-4-en-1-ol (14). A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with **10** (318.7 mg, 0.9 mmol) and dry MeOH (6 mL). The solution was cooled at −78 °C and then $NaBH_4$ (137 mg, 3.6 mmol) was added. The reaction was slowly warmed up to 0 °C over 3 h, and the stirring was continued at 0 °C for 1 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phase was dried over anhydrous Na_2SO_4. After removal of solvent in *vacuo*, the crude product was purified by column chromatography (1% EtOAc in CH_2Cl_2) to afford **14** (277.9 mg, 87% yield) as a colorless oil with 84 : 11 : 5 diastereomeric ratio (400 MHz ^{1}H NMR analysis). R_f 0.24 (20% EtOAc in hexanes); $[\alpha]^{28}_D$ −7.5 (c 0.53, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55–7.45 (m, 2H, Ar*H*), 7.40–7.20 (m, 3H, Ar*H*), 6.52 (s, 2H, Ar*H*), 5.95–5.80 (m, 1H, C*H*), 5.20–5.05 (m, 2H, C*HH*), 5.00 (s, 2H, C*H*$_2$), 4.27 (d, *J* = 9.2 Hz, 1H, C*H*), 3.82 (s, 6H, 2 × OC*H*$_3$), 2.90–2.80 (m, 1H, C*H*), 1.90–1.80 (m, 1H, C*H*), 1.09 (d, *J* = 7.0 Hz, 3H, C*H*$_3$), 0.57 (d, *J* = 7.0 Hz, 3H, C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4 (2 × C), 140.6 (CH), 139.8 (C), 137.8 (C), 136.1 (C), 128.5 (2 × CH), 128.1 (2 × CH), 127.8 (CH), 115.1 (CH_2), 103.7 (2 × CH), 77.8 (CH), 74.9 (CH_2), 56.1 (2 × OCH_3), 45.1 (CH), 37.3 (CH), 18.4 (CH_3), 11.0 (CH_3). IR ($CHCl_3$): ν_{max} 3602m, 1593s, 1504m, 1464s, 1422m, 1328m, 1237s, 1131s cm^{-1}. MS (ISCID): m/z (%) relative intensity 379 [(M + Na)$^+$, 100], 357 [(M + H)$^+$, 3], 339 (23). HRMS (ESI-TOF) calcd for $C_{22}H_{28}O_4Na$ [M + Na]$^+$: 379.1885, found: 379.1888.

{[(1*R*,2*R*,3*R*)-1-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-2,3-dimethylpent-4-en-1-yl]oxy}(*tert*-butyl)dimethylsilane (15). A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with **14** (270 mg, 0.76 mmol), imidazole (103.5 mg, 1.52 mmol), and dry CH_2Cl_2 (2.7 mL). A solution of TBSCl (230 mg, 1.52 mmol) in dry hexane (0.27 mL) was added. The reaction mixture was allowed to stir at room temperature overnight. After the complete consumption of **14**, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After removal of solvent in *vacuo*, the crude product was purified by column chromatography (10% EtOAc in hexanes) to afford **15** (160.3 mg, 82% yield) as a colorless oil with a 82 : 13 : 5 diastereomeric ratio (400 MHz ^{1}H NMR analysis). R_f 0.54 (20% EtOAc in hexanes); $[\alpha]^{27}_D$ +25.8 (c 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.40 (m, 2H, Ar*H*), 7.35–7.20 (m, 3H, Ar*H*), 6.45 (s, 2H, Ar*H*), 5.90–5.80 (m, 1H, C*H*), 5.10–5.00 (m, 2H, C*HH*), 5.01 (s, 2H, C*H*$_2$), 4.20 (d, *J* = 8.6 Hz, 1H, C*H*), 3.78 (s, 6H, 2 × OC*H*$_3$), 2.75–2.90 (m, 1H, C*H*), 1.65–1.75 (m, 1H, C*H*), 1.04 (d, *J* = 7.0 Hz, 3H, C*H*$_3$), 0.85 [s, 9H, SiC(C*H*$_3$)$_3$], 0.49 (d, *J* = 7.0 Hz, 3H, C*H*$_3$), 0.01 (s, 3H, SiC*H*$_3$), −0.34 (s, 3H, SiC*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1 (2 × C), 140.5 (CH), 137.8 (C), 136.4 (C), 135.5 (C), 128.6 (2 × CH), 128.0 (2 × CH), 127.8 (CH), 114.4 (CH_2), 104.1 (2 × CH), 78.3 (CH), 74.9 (CH_2), 56.1 (2 × OCH_3), 46.7 (CH), 36.4 (CH), 25.9 (3 × CH_3), 18.9 (CH_3), 18.2 (C), 10.8 (CH_3), −4.4 (CH_3), −4.9 (CH_3). IR ($CHCl_3$): ν_{max} 1593m, 1464s, 1129s cm^{-1}. MS (ISCID): m/z (%) relative intensity 493 [(M + Na)$^+$, 100], 402 (15), 339 (6), 319 (12). HRMS (ESI-TOF) calcd for $C_{28}H_{42}O_4SiNa$ [M + Na]$^+$: 493.2750, found: 493.2752.

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(1*R*,2*S*,3*R*,4*R*)-4-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-1-[4-(benzyloxy)-3-methoxyphenyl]-4-[(*tert*-butyldimethylsilyl)oxy]-2,3-dimethylbutan-1-ol (9A) and (1*S*,2*S*,3*R*,4*R*)-4-[4-(benzyloxy)-3,5-dimethoxyphenyl]-1-[4-(benzyloxy)-3-methoxyphenyl]-4-[(*tert*-butyldimethylsilyl)oxy]-2,3-dimethylbutan-1-ol (9B). To a stirred suspension of **15** (dr = 91 : 5 : 4) (128.6 mg, 0.27 mmol) and *N*-methylmorpholine-*N*-oxide (110 mg, 0.81 mmol) in CH_2Cl_2 (12 mL), osmium tetroxide (2.5% w/v in *t*-butanol, 0.14 mL, 0.014 mmol) and water (0.14 mL) were added. After stirring at room temperature for 14 h, the $NaIO_4$ (115 mg, 0.54 mmol) was added. The stirring was continued for 1.5 h then it was quenched with a saturated aqueous $Na_2S_2O_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents in *vacuo*, the aldehyde crude product was obtained. A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with 1-(benzyloxy)-4-bromo-2-methoxybenzene (119 mg, 0.4 mmol) and dry THF (2 mL). The solution was cooled at −78 °C then a solution of *n*-BuLi (1.6 M in hexane, 0.25 mL, 0.4 mmol) was added dropwise. After stirring for 10 min, a solution of the above obtained aldehyde in dry THF (2 mL) was added dropwise. After stirring at −78 °C for 4 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents in *vacuo*, the crude product was purified by column chromatography (20% EtOAc in hexanes) to afford **9A** (87 mg, 47% yield), **9B** (22.1 mg, 12% yield), and a mixture of **9A** and **9B** (19.1 mg, 10%).

9A; a colorless oil; R_f 0.16 (20% EtOAc in hexanes); $[\alpha]^{26}_D$ +25.6 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.20 (m, 10H, 2 × Ar*H*), 6.97 (s, 1H, Ar*H*), 6.84 (s, 2H, Ar*H*), 6.45 (s, 2H, Ar*H*), 5.14 (s, 2H, CH_2), 5.10–5.00 (m, 1H, C*H*), 5.01 (s, 2H, CH_2), 4.42 (d, *J* = 8.2 Hz, 1H, C*H*), 3.89 (s, 3H, OCH_3), 3.76 (s, 6H, 2 × OCH_3), 2.00–1.90 (m, 1H, C*H*), 1.90–1.80 (m, 1H, C*H*), 0.94 (d, *J* = 6.9 Hz, 3H, CH_3), 0.90 [s, 9H, SiC(CH_3)$_3$], 0.76 (d, *J* = 7.0 Hz, 3H, CH_3), 0.09 (s, 3H, CH_3), −0.27 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2 (2 × C), 149.4 (C), 147.0 (C), 139.9 (C), 138.2 (C), 137.7 (C), 137.4 (C), 135.8 (C), 128.6 (2 × CH), 128.5 (2 × CH), 128.1 (2 × CH), 127.8 (CH), 127.7 (CH), 127.3 (2 × CH), 118.4 (CH), 113.7 (CH), 110.2 (CH), 104.5 (2 × CH), 78.8 (CH), 76.0 (CH), 74.9 (CH_2), 71.2 (CH_2), 56.1 (2 × OCH_3), 56.0 (OCH_3), 44.4 (CH), 44.3 (CH), 26.0 (3 × CH_3), 18.3 (C), 17.2 (CH_3), 9.4 (CH_3), −4.3 (CH_3), −4.7 (CH_3). IR ($CHCl_3$): ν_{max} 3358br, 1593s, 1508s, 1464s, 1258s, 1130s cm^{-1}. MS (ISCID): m/z (%) relative intensity 709 [(M + Na)$^+$, 100], 669 (2), 618 (2), 537 (6), 525 (11), 446 (3). HRMS (ESI-TOF) calcd for $C_{41}H_{54}O_7SiNa$ [M + Na]$^+$: 709.3537, found: 709.3538.

9B; a colorless oil; R_f 0.20 (20% EtOAc in hexanes). $[\alpha]^{26}_D$ +19.4 (c 1.04, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.20 (m, 10H, 2 × Ar*H*), 6.88 (s, 1H, Ar*H*), 6.82 (d, *J* = 8.3 Hz, 1H, Ar*H*), 6.75 (d, *J* = 8.1 Hz, 1H, Ar*H*), 6.62 (s, 2H, Ar*H*), 5.16 (s, 2H, CH_2), 5.08 (s, 2H, CH_2), 4.77 (d, *J* = 5.0 Hz, 1H, C*H*), 4.31 (d, *J* = 9.8 Hz, 1H, C*H*), 3.89 (s, 3H, OCH_3), 3.85 (s, 6H, 2 × OCH_3), 2.10–2.00 (m, 1H, C*H*), 2.00–1.90 (m, 1H, C*H*), 1.10 (d, *J* = 7.1 Hz, 3H, CH_3), 0.98 [s, 9H, SiC(CH_3)$_3$], 0.54 (d, *J* = 6.92 Hz, 3H, CH_3), 0.17 (s, 3H, CH_3), −0.10 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2 (2 × C), 149.6 (C), 147.3 (C), 139.3 (C), 138.2 (C), 137.7 (C), 137.4 (C), 135.3 (C), 128.6 (2 × CH), 128.5 (2 × CH), 128.0 (2 × CH), 127.8 (CH), 127.7 (CH), 127.2 (2 × CH), 119.6 (CH), 113.8 (CH), 110.7 (CH), 103.7 (2 × CH), 79.2 (CH), 75.6 (CH), 74.8 (CH_2), 71.1 (CH_2), 56.1 (2 × OCH_3), 55.9 (OCH_3), 45.7 (CH), 40.0 (CH), 25.9 (3 × CH_3), 18.3 (C), 18.1 (CH_3), 13.3 (CH_3), −4.5 (CH_3), −5.0 (CH_3). IR ($CHCl_3$): ν_{max} 3355br, 1594m, 1507s, 1464s, 1131s cm^{-1}. MS (ISCID): m/z (%) relative intensity 709 [(M + Na)$^+$, 100], 669 (3), 618 (2), 537 (4), 446 (2), 319 (4). HRMS (ESI-TOF) calcd for $C_{41}H_{54}O_7SiNa$ [M + Na]$^+$: 709.3537, found: 709.3535.

{[(1*R*,2*R*,3*R*,4*S*)-6-(Benzyloxy)-4-[4-(benzyloxy)-3-methoxyphenyl]-5,7-dimethoxy-2,3-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl]oxy}(*tert*-butyl)dimethylsilane (17). A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with **9A** (36.7 mg, 0.05 mmol) and dry THF (1.5 mL). A solution of methanesulfonyl chloride in dry THF (0.08 mL, 1.03 M, 0.07 mmol) was added at room temperature followed by the addition of Et_3N (0.02 mL, 0.085 mmol). After stirring for 1 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried over anhydrous Na_2SO_4. After removal of solvent in *vacuo*, the crude product was purified by column chromatography (10% EtOAc in hexanes) to afford **17** (19.3 mg, 54% yield) as a single diastereomer as determined by ^{1}H NMR (400 MHz) analysis. R_f 0.46 (20% EtOAc in hexanes); $[\alpha]^{26}_D$ −33.1 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.40 (m, 4H, Ar*H*), 7.40–7.25 (m, 6H, Ar*H*), 6.93 (s, 1H, Ar*H*), 6.76 (d, *J* = 8.2 Hz, 1H, Ar*H*), 6.68 (d, *J* = 1.8 Hz, 1H, Ar*H*), 6.53 (dd, *J* = 8.2, 1.9 Hz, 1H, Ar*H*), 5.11 (s, 2H, CH_2), 4.99 (d, *J* = 4.4 Hz, 1H, C*H*), 4.95–4.80 (m, 2H, CH_2), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.55 (d, *J* = 9.8 Hz, 1H, C*H*), 2.96 (s, 3H, OCH_3), 2.10–1.98 (m, 1H, C*H*), 1.98–1.89 (m, 1H, C*H*), 1.03 [s, 9H, Si(CH_3)$_3$], 1.01 (d, *J* = 7.0 Hz, 3H, CH_3), 0.76 (d, *J* = 6.8 Hz, 3H, CH_3), 0.25 (s, 3H, CH_3), 0.19 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.2 (C), 151.3 (C), 149.4 (C), 145.9 (C), 142.0 (C), 140.1 (C), 137.9 (C), 137.4 (C), 135.3 (C), 128.4 (2 × CH), 128.2 (2 × CH), 128.1 (2 × CH), 127.7 (2 × CH), 127.4 (2 × CH), 125.2 (C), 120.4 (CH), 114.5 (CH), 113.2 (CH), 104.4 (CH), 74.7 (CH_2), 73.8 (CH), 71.4 (CH_2), 59.5 (OCH_3), 56.3 (OCH_3), 55.5 (OCH_3), 46.4 (CH), 41.2 (CH), 40.8 (CH), 25.9 (3 × CH_3), 18.3 (C), 17.5 (CH_3), 6.4 (CH_3), −4.2 (CH_3), −4.9 (CH_3). IR ($CHCl_3$): ν_{max} 1513m, 1464m, 1258s, 1125s, 1085m, 1051m cm^{-1}. MS (ISCID): m/z (%) relative intensity 691 [(M + Na)$^+$, 100], 600 (2), 537 (34), 446 (3), 413 (3), 355 (2), 323 (4). HRMS (ESI-TOF) calcd for $C_{41}H_{52}O_6SiNa$ [M + Na]$^+$: 691.3431, found: 691.3431.

(1*R*,2*R*,3*S*,4*R*)-1-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-4-[4-(benzyloxy)-3-methoxyphenyl]-2,3-dimethylbutane-1,4-diol (19A). A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with **9A** (77 mg, 0.11 mmol) and dry THF (2 mL). A solution of TBAF in dry THF (0.25 mL, 0.5 M, 0.11 mmol) was added at room temperature. After stirring for 3 h, the reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvents in *vacuo*, the crude product was purified by column chromatography (50% EtOAc in hexanes) to afford **19A** as a white solid (55.6 mg, 87% yield) as a single diastereomer (400 MHz ^{1}H NMR analysis). R_f 0.17 (40% EtOAc in hexanes). R_f 0.17 (40% EtOAc in hexanes); mp 49-52 °C (50% EtOAc in hexanes). $[\alpha]^{26}_D$ −16.5 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$):

δ 7.50–7.30 (m, 10H, 2 × Ar*H*), 6.97 (d, *J* = 1.6 Hz, 1H, Ar*H*), 6.83 (d, *J* = 8.3 Hz, 1H, Ar*H*), 6.79 (dd, *J* = 1.6, 8.3 Hz, 1H, Ar*H*), 6.48 (s, 2H, Ar*H*), 5.14 (s, 2H, CH_2), 4.99 (s, 2H, CH_2), 4.85 (d, *J* = 1.5 Hz, 1H, C*H*), 4.25 (d, *J* = 9.9 Hz, 1H, C*H*), 3.90 (s, 3H, OCH_3), 3.80 (s, 6H, 2 × OCH_3), 2.10–2.00 (m, 1H, C*H*), 1.90–1.80 (m, 1H, C*H*), 0.90 (d, *J* = 7.2 Hz, 3H, CH_3), 0.64 (d, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4 (2 × C), 149.2 (C), 146.8 (C), 139.9 (C), 138.0 (C), 137.8 (C), 137.4 (C), 136.1 (C), 128.6 (2 × CH), 128.5 (2 × CH), 128.1 (2 × CH), 127.9 (CH), 127.8 (CH), 127.3 (2 × CH), 118.0 (CH), 113.6 (CH), 109.9 (CH), 103.8 (2 × CH), 77.3 (CH), 76.5 (CH), 75.0 (CH_2), 71.1 (CH_2), 56.1 (2 × OCH_3), 56.0 (OCH_3), 47.3 (CH), 45.4 (CH), 18.9 (CH_3), 6.0 (CH_3). IR ($CHCl_3$): ν_{max} 3383br, 1594s, 1509s, 1464s, 1131s cm^{-1}. MS (ISCID): m/z (%) relative intensity 595 [(M + Na)$^+$, 100], 577 (14), 504 (14), 205 (11). HRMS (ESI-TOF) calcd for $C_{35}H_{40}O_7Na$ [M + Na]$^+$: 595.2672, found: 595.2674.

(1*R*,2*R*,3*S*,4*S*)-1-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-4-[4-(benzyloxy)-3-methoxyphenyl]-2,3-dimethylbutane-1,4-diol (19B). According to the procedure for the synthesis of **19A**, **9B** (22 mg, 0.03 mmol) was converted to **19B** in 79 % yield (14.5 mg) as a colorless sticky oil. R_f 0.10 (40% EtOAc in hexanes); $[\alpha]^{27}_D$ –3.0 (c 0.82, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.30 (m, 10H, 2 × Ar*H*), 6.88 (d, *J* = 1.8 Hz, 1H, Ar*H*), 6.83 (d, *J* = 8.2 Hz, 1H, Ar*H*), 6.76 (dd, *J* = 1.8, 8.2 Hz, 1H, Ar*H*), 6.54 (s, 2H, Ar*H*), 5.14 (s, 2H, CH_2), 4.99 (s, 2H, CH_2), 4.52 (d, *J* = 7.9 Hz, 1H, C*H*), 4.49 (d, *J* = 8.5 Hz, 1H, C*H*), 3.88 (s, 3H, OCH_3), 3.81 (s, 6H, 2 × OCH_3), 2.15–2.05 (m, 2H, 2 × C*H*), 0.84 (d, *J* = 7.1 Hz, 3H, CH_3), 0.75 (d, *J* = 7.1 Hz, 3H, CH_3). IR ($CHCl_3$): ν_{max} 3376br, 1594s, 1508s, 1464s, 1421m, 1262m, 1232m, 1131s cm^{-1}. MS (ISCID): m/z (%) relative intensity 595 [(M + Na)$^+$, 100], 504 (30), 413 (4), 357 (7). HRMS (ESI-TOF) calcd for $C_{35}H_{40}NaO_7$ [M + Na]$^+$: 595.2672, found: 595.2676.

(2*R*,3*R*,4*S*,5*S*)-2-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-5-[4-(benzyloxy)-3-methoxyphenyl]-3,4-dimethyltetrahydrofuran (20). A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with **19A** (55.6 mg, 0.1 mmol), *p*-toluenesulfonic acid monohydrate (3 mg, 0.016 mmol), and dry CH_2Cl_2 (1.5 mL). The reaction mixture was stirred at room temperature for 1.5 h. Then it was quenched with a saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After removal of solvent in *vacuo*, the crude product was purified by column chromatography (40% EtOAc in hexanes) to afford **20** as a white solid (49.5 mg, 92% yield) as a single diastereomer as determined by ^{1}H NMR (400 MHz) analysis. R_f 0.46 (40% EtOAc in hexanes); mp 75–78 ^{o}C (40% EtOAc in hexanes). $[\alpha]^{26}_D$ –3.8 (c 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55–7.25 (m, 10H, 2 × Ar*H*), 7.01 (d, *J* = 1.8 Hz, 1H, Ar*H*), 6.91 (dd, *J* = 1.8, 8.3 Hz, 1H, Ar*H*), 6.86 (d, *J* = 8.3 Hz, 1H, Ar*H*), 6.63 (s, 2H, Ar*H*), 5.16 (s, 2H, CH_2), 4.99 (s, 2H, CH_2), 4.52 (d, *J* = 6.4 Hz, 1H, C*H*), 4.51 (d, *J* = 5.9 Hz, 1H, C*H*), 3.88 (s, 3H, OCH_3), 3.80 (s, 6H, 2 × OCH_3), 2.40–2.30 (m, 2H, 2 × C*H*), 1.07 (d, *J* = 6.6 Hz, 3H, CH_3), 1.03 (d, *J* = 6.5 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4 (2 × C), 149.6 (C), 147.6 (C), 138.2 (C), 137.9 (C), 137.2 (C), 136.2 (C), 135.1 (C), 128.5 (2 × CH), 128.4 (2 × CH), 128.1 (2 × CH), 127.8 (CH), 127.7 (CH), 127.2 (2 × CH), 118.6 (CH), 113.8 (CH), 100.4 (CH), 103.3 (2 × CH), 87.5 (CH), 87.1 (CH), 75.0 (CH_2), 71.0 (CH_2), 56.1 (2 × OCH_3), 55.9 (OCH_3), 44.6 (CH), 43.9 (CH), 13.2 (CH_3), 12.8 (CH_3). IR ($CHCl_3$): ν_{max} 1593s, 1513s, 1464s, 1262m, 1233s, 1131s cm^{-1}. MS (ISCID): m/z (%) relative intensity 577 [(M + Na)$^+$, 100], 555 (6), 537 (4), 486 (10). HRMS (ESI-TOF) calcd for $C_{35}H_{38}O_6Na$ [M + Na]$^+$: 577.2566, found: 577.2563.

4-[(2*R*,3*R*,4*S*,5*S*)-5-(4-Hydroxy-3-methoxyphenyl)-3,4-dimethyltetrahydrofuran-2-yl]-2,6-dimethoxyphenol (*ent*-1). A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with **20** (22.8 mg, 0.04 mmol), Pd/C (10% w/w, 9 mg, 0.08 mmol), and dry EtOAc (1 mL). The argon inlet was replaced by a H_2 balloon, and the reaction mixture was stirred at room temperature for 40 min. The resulting mixture was filtered through a Celite pad and then the residue was eluted with EtOAc (10 mL). After removal of the solvents in *vacuo*, the crude product was purified by column chromatography (60% EtOAc in hexanes) to afford *ent*-**1** as a sticky brownish oil (15.3 mg, 99% yield) as a single diastereomer (400 MHz ^{1}H NMR analysis). R_f 0.18 (40% EtOAc in hexanes); $[\alpha]^{27}_D$ –6.97 (c 0.60, $CHCl_3$) (lit. $[\alpha]_D$ +3.8 (c 0.60, $CHCl_3$);[4a] UV (MeOH) λ_{max} (log ε) 208 (0.85), 233 (0.24), 279 (0.07) nm; CD (MeOH) 226 (Δε –2.23), 250 (Δε +0.12). ^{1}H NMR (400 MHz, acetone-d_6): δ 7.51 (s, 1H, O*H*), 7.12 (s, 1H, O*H*), 7.10 (d, *J* = 1.8 Hz, 1H, Ar*H*), 6.92 (d, *J* = 8.1, 1.8 Hz, 1H, Ar*H*), 6.82 (d, *J* = 8.1 Hz, 1H, Ar*H*), 6.77 (s, 2H, 2 × Ar*H*), 4.43 (d, *J* = 5.4 Hz, 1H, 2 × C*H*), 3.86 (s, 3H, OCH_3), 3.83 (s, 6H, 2 × OCH_3), 2.20–2.45 (m, 2H, 2 × C*H*), 1.03 (d, *J* = 6.7 Hz, 3H, CH_3), 1.00 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, acetone-d_6): δ 149.0 (2 × C), 148.7 (C), 147.3 (C), 136.6 (C), 135.5 (C), 134.7 (C), 120.4 (CH), 115.9 (CH), 111.2 (CH), 105.1 (2 × CH), 88.7 (CH), 88.4 (CH), 57.0 (2 × CH_3), 56.6 (CH_3), 46.1 (CH), 45.7 (CH), 13.7 (CH_3), 13.5 (CH_3). IR ($CHCl_3$): ν_{max} 3542s, 1616m, 1517s, 1465s, 1117s cm^{-1}. MS (ISCID): m/z (%) relative intensity 397 [(M + Na)$^+$, 100], 357 (1). HRMS (ESI-TOF) calcd for $C_{21}H_{26}O_6Na$ [M + Na]$^+$: 397.1627, found: 397.1622.

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14 The relative stereochemistries at the C-1 and C-2 of **9A** and **9B** were assigned by the analysis of the coupling constants between H-1 and H-2 of their corresponding diols **19A** and **19B**, respectively. For **19A**, H-1 appeared as a doublet at 4.85 (d, ^3J = 1.5 Hz) ppm. For **19B**, H-1 appeared as a doublet at 4.52 (d, ^3J = 7.9 Hz) ppm. See also, for example, ref. 8*f*.

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Asymmetric Synthesis of *ent*-Fragransin C_1

Santikorn Chaimanee, Manat Pohmakotr, Chutima Kuhakarn, Vichai Reutrakul, and Darunee Soorukram*

Graphical abstract

The first asymmetric synthesis of *ent*-fragransin C_1 bearing the 2,3-*anti*-3,4-*syn*-4,5-*anti* stereochemistires is reported.