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Total Synthesis of Eupomatilones 1, 2, and 5 by Enantioselective [2,3]-Wittig Rearrangement

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In this study, the asymmetric total synthesis of eupomatilones 1, 2, and 5 has been accomplished. These compounds are lignan congeners containing a biaryl system bearing an α-methylene γ-lactone. They were isolated from the Australian shrub *Eupomatia bennettii*. Two chiral centers were constructed enantioselectively by the asymmetric [2,3]-Wittig rearrangement of highly oxygenated biaryl compounds, using a bis(oxazoline) chiral ligand. Optimization of the key reaction using *n*BuLi as the base and ether as the co-solvent increased the enantioselectivity to 88–91 % *ee*.

Introduction

In 1991, Carroll and Taylor isolated structurally new lignans from the Australian shrub *Eupomatia bennettii*, which is found in the tropical and subtropical forests of New South Wales and Queensland, and elucidated their stereostructures.[1] The stereochemistry of eupomatilone 6 was revised later by Coleman et al.[2] The eupomatilone 1–7 family of lignans (Figure 1) possess an unusual biaryl skeleton with a γ-lactone ring, and the compounds are presumably formed by phenolic oxidative coupling and cleavage of a propyl chain from the aromatic ring. The highly oxygenated biaryl structure causes hindered rotation around the biaryl linkage, and eupomatilones 5–7 exist as a mixtures of inseparable atropisomers.

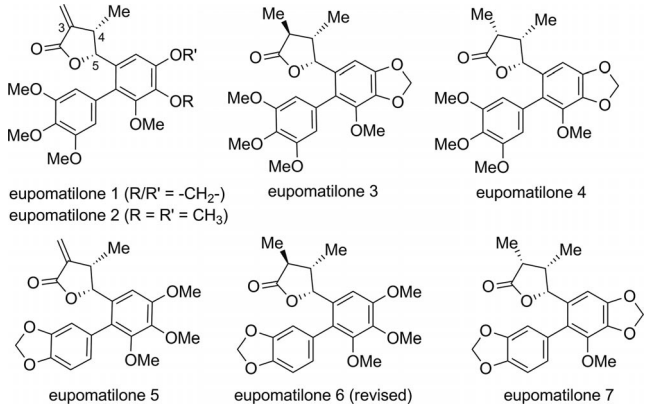
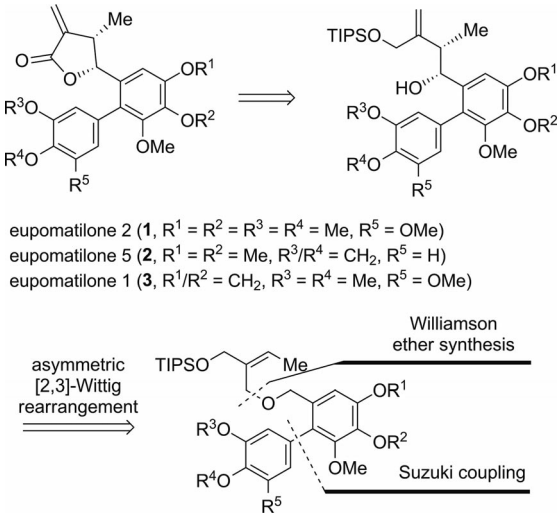


Figure 1. Structures of eupomatilones 1–7.

Eupomatilones 1, 2, and 5 are members of the eupomatilone family that contain an α-methylene γ-lactone, and they are expected to form covalent bonds with biomolecules by Michael addition, and thus, to exhibit biological activity.[3] Although syntheses of eupomatilones containing a saturated C-3 substituent have been reported,[4] there have been few studies on the total syntheses of these natural products. One paper describes the synthesis of racemic eupomatilones 2 and 5 using an allylindium reagent,[5] and another reports the asymmetric synthesis of eupomatilones using a chiral methoxycarbonylcrotyl boronate reagent.[2] In the latter work, the enantioselectivity was still moderate (76–88 % *ee*),



Scheme 1. Synthetic plan for the synthesis of eupomatilones 1, 2, and 5.

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and the formation of an inseparable diastereoisomer of eupomatilone 1 remained as a problem to be solved.

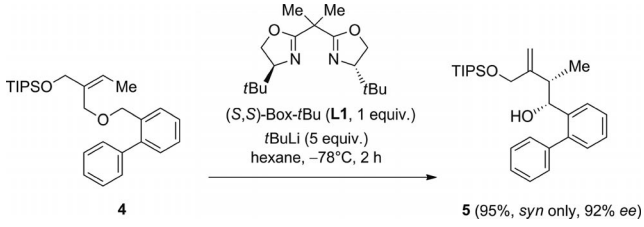
We have investigated the highly enantioselective asymmetric [2,3]-Wittig rearrangement of allyl benzyl ether derivatives, using an external chiral ligand.[6] The application of this methodology with highly oxygenated biarylmethyl ethers as substrates was considered for the synthesis of eupomatilone 2 (**1**), eupomatilone 5 (**2**), and eupomatilone 1 (**3**).[7] The synthetic plan is shown in Scheme 1. The two stereogenic centers would be constructed stereoselectively by the asymmetric [2,3]-Wittig rearrangement, and the resulting homoallylic alcohol would be used for the construction of the α-methylene γ-lactone moiety.

Previously,[7] we reported the asymmetric total synthesis of eupomatilone 2. In this paper, we report full details of our research into the synthesis of eupomatilones 1, 2, and 5.

Results and Discussion

Synthesis of Substrates for [2,3]-Wittig Rearrangement

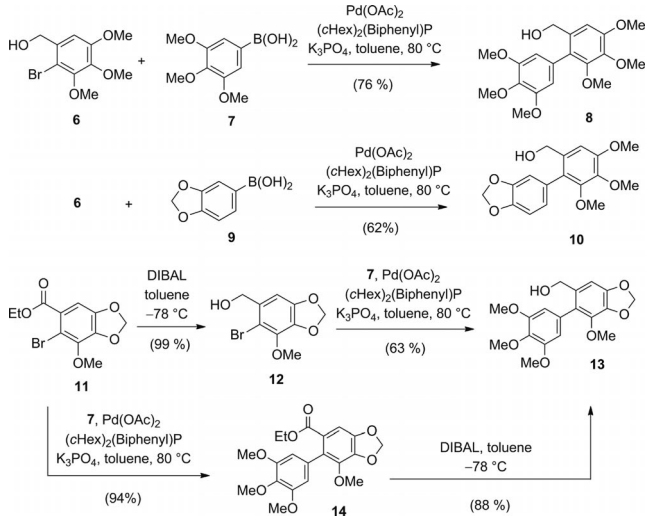
In preliminary research, we found that simple biarylmethyl ether **4** underwent the [2,3]-Wittig rearrangement to give **5** in 95% yield with high enantioselectivity and diastereoselectivity (92% *ee*, *syn* only), as shown in Scheme 2.[6,8] The promising results encouraged us to apply this strategy to highly oxygenated biaryl-type substrates.



Scheme 2. Model study of the key step.

The synthesis of congested biarylmethyl ethers, which are key intermediates in the synthesis of the eupomatilones, is shown in Scheme 3. Buchwald's modified Suzuki coupling[9] was used for the construction of the highly congested biaryl moiety of eupomatilones 1, 2, and 5.

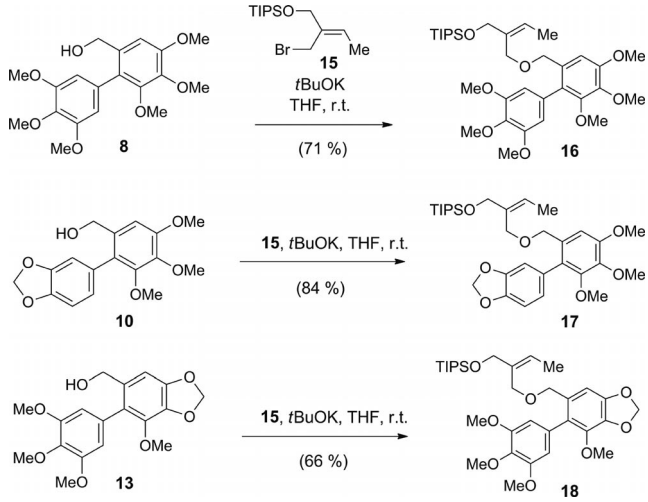
The Suzuki coupling of 2-bromo-3,4,5-trimethoxybenzyl alcohol (**6**)[10] and 3,4,5-trimethoxyphenylboronic acid (**7**) in the presence of $Pd(OAc)_2$ (2 mol-%), $(tBu)_2$(Biphenyl)P (2 mol-%), and KF in THF at 50 °C for 7 h gave the coupling product in 6% yield. However, the use of $Pd(OAc)_2$, $(c\text{Hex})_2$(Biphenyl)P, and K_3PO_4 in toluene at 80 °C for 7 h, gave biarylmethyl alcohol **8** in an increase in the yield to 76%. Suzuki coupling of bromide **6** and 3,4-(methylenedioxy)phenylboronic acid (**9**) furnished coupling product **10** in 62% yield under the optimized conditions. The biarylmethyl alcohol (i.e., **13**) required for the synthesis of eupomatilone 1 was prepared from bromo ester **11**[11] by DIBAL (diisobutylaluminium hydride) reduction in toluene (99%) and subsequent Suzuki coupling of the resulting bromo alcohol (i.e., **12**) with boronic acid **7** (63%). We found that the yield of the Suzuki coupling was improved to 94% when



Scheme 3. Synthesis of biarylmethyl alcohols **8**, **10**, and **13**.

bromide **11** was treated with boronic acid **7** under the same conditions.[12] Ester **14** was then reduced with DIBAL in toluene to give alcohol **13** in 88% yield.

The substrates for the [2,3]-Wittig rearrangement were synthesized by Williamson ether synthesis from biarylmethyl alcohols **8**, **10**, and **13** with allylic bromide **15**[6] in the presence of *t*BuOK, resulting in the formation of the biarylmethyl ethers **16**, **17**, and **18** in 71, 84, and 66% yields, respectively (Scheme 4).

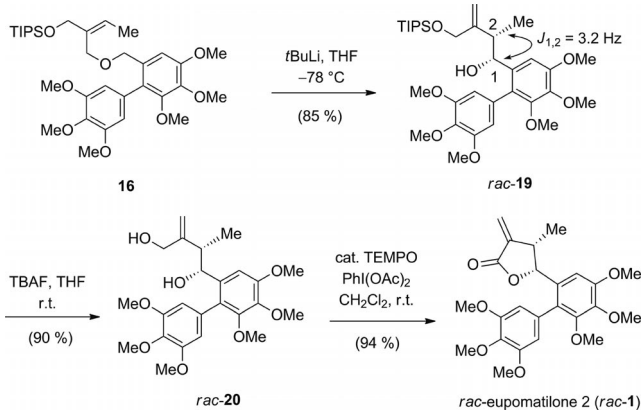


Scheme 4. Synthesis of biarylmethyl ethers **16**–**18**.

Synthesis of Racemic Eupomatilone 2

To establish the synthetic route to the eupomatilones before the asymmetric synthesis was investigated, efforts were directed towards the conversion of biarylmethyl ether **16** into racemic eupomatilone 2. On treatment of **16** with *t*BuLi (5 equiv.) in THF at –78 °C, the [2,3]-Wittig rearrangement proceeded smoothly to give *rac*-**19** in 85% yield. Formation of the [1,2]-Wittig rearranged product was not observed.

The relative stereochemistry of the resulting alcohol (i.e., *rac*-**19**) was assumed to be *syn* based on the coupling constant between the two methine protons at the C-1 and C-2 positions ($J_{1,2}$ = 3.2 Hz).[13] After deprotection of the TIPS (triisopropylsilyl) group with TBAF (tetrabutylammonium fluoride), the resulting diol (i.e., *rac*-**20**) was converted to *rac*-eupomatilone 2 (*rac*-**1**) by TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) oxidation in the presence of $PhI(OAc)_2$ as a co-oxidant[14] in 85% yield over two steps (Scheme 5). The spectroscopic data (IR, ^1H and ^{13}C NMR) were consistent with those reported for the natural product.[1,2]

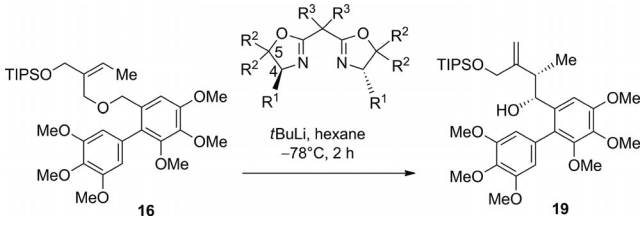


Scheme 5. Synthesis of racemic eupomatilone 2.

Asymmetric [2,3]-Wittig Rearrangement

Next, we examined the asymmetric [2,3]-Wittig rearrangement, using **16** as substrate and a bis(oxazoline) as the external chiral ligand.[6,15] The results are summarized in Table 1.

Table 1. Effect of the chiral ligand on the asymmetric [2,3]-Wittig rearrangement.[a]



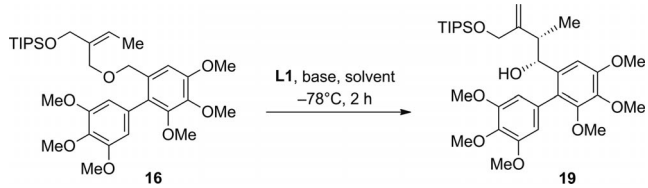
Entry	Ligand	R^1	R^2	R^3	Yield [%][b]	*ee* [%][c]
1	**L1**	*t*Bu	H	Me	92	68
2	**L2**	*i*Pr	H	Me	72	38
3	**L3**	*t*Bu	Me	Me	0	–
4	**L4**	*i*Pr	Me	Me	38	22
5	**L5**	*t*Bu	H	Et	43	12

[a] The reactions were performed in the presence of chiral ligand (1 equiv.) and *t*BuLi (5 equiv.) in dry hexane at –78 °C for 2 h under Ar atmosphere unless otherwise stated. [b] Isolated yields. [c] Determined by chiral HPLC.

Arylmethyl ether **16** was subjected to the asymmetric [2,3]-Wittig rearrangement, using 1 equiv. of the chiral ligand and 5 equiv. of base at –78 °C for 2 h. Investigation of potentially suitable chiral bis(oxazoline) ligands revealed that the enantiomeric excess was significantly dependent on the structure of the ligand. Bulkiness at the C-4 position was important for a high *ee* (entries 1 and 2), while bulkiness at the C-5 position and on the methylene bridge reduced both the yield and the enantioselectivity (entries 3–5). The best ligand of those examined was bis(oxazoline) **L1** [(*S*,*S*)-Box-*t*Bu]. However, the *ee* was moderate (68% *ee*), despite the high yield (92%). In contrast, the simple biphenylmethyl ether with no methoxy substituents (i.e., **4**) had reacted under these conditions with excellent enantioselectivity (92% *ee*, see Scheme 2).

During attempts to improve the enantioselectivity, it was found that highly oxygenated substrate **16** underwent slow [2,3]-Wittig rearrangement, even with bases weaker than *t*BuLi. Importantly, *s*BuLi and *n*BuLi showed better enantioselectivity than *t*BuLi, but gave reduced yields of the product (Table 2, entries 1–3). The yield was improved to 77% when the reaction ran for 4 h (entry 4). The co-solvent also plays an important role in accelerating the reaction rate. When toluene was used as the co-solvent, the reaction was complete within 2 h, and the rearranged product (i.e., **19**) was obtained in 92% yield and with 80% *ee* (entry 5). Finally, optimal selectivity was obtained when ether was added as the co-solvent, and both the yield and the enantioselectivity were optimized to 98 and 89%, respectively (entry 6). The selectivity did not improve further, even when the proportion of ether in the solvent mixture was increased, but this resulted in a decrease in the yields (entries 8 and 9). Addition of the more polar THF suppressed the reaction significantly, and resulted in a lower yield and selectivity (entry 7). The addition of THF presumably interfered with the coordination of the chiral ligand to *n*BuLi, thus preventing the formation of a reactive chiral base.

Table 2. Effect of base and solvent on the asymmetric [2,3]-Wittig rearrangement.[a]

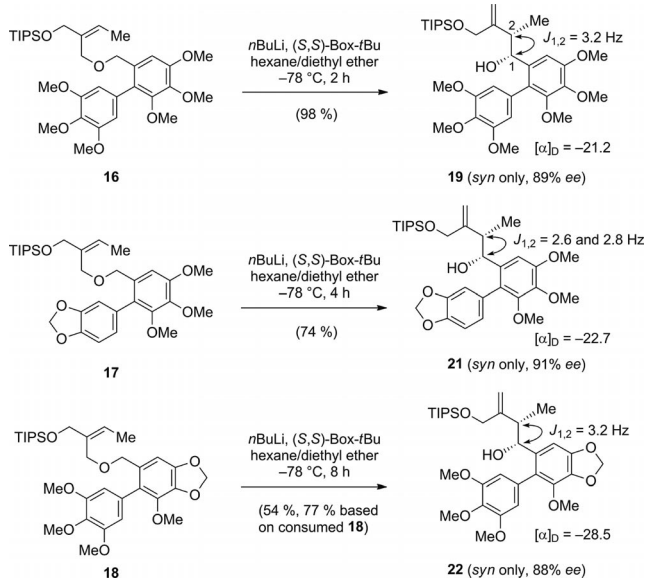


Entry	Conditions	Yield [%][b]	*ee* [%][c]
1	*t*BuLi, hexane	92	68
2	*s*BuLi, hexane	50	71
3	*n*BuLi, hexane	46	77
4[d]	*n*BuLi, hexane	77	77
5	*n*BuLi, hexane/toluene (4:1)[e]	92	80
6	*n*BuLi, hexane/ether (4:1)[e]	98	89
7	*n*BuLi, hexane/THF (4:1)[e]	7	5
8	*n*BuLi, hexane/ether (1:1)[e]	83	89
9	*n*BuLi, ether	26	87

[a] Reactions were carried out in the presence of chiral ligand **L1** (1 equiv.) and base (5 equiv.) in dry solvent at –78 °C for 2 h under Ar atmosphere, unless otherwise stated. [b] Isolated yields. [c] Determined by chiral HPLC. [d] The reaction was run for 4 h. [e] The solvent ratio before the addition of *n*BuLi solution is indicated.

Confirmation of the absolute configuration at the chiral center of the secondary alcohol was then attempted using the modified Mosher method,[16] but owing to the arbitrary distribution of the $\Delta\delta^{SR}$ sign, an assignment was difficult.[17] Thus, the modified Mosher method was not suitable for this compound. However, we assumed the absolute configuration to be (1*R*,2*S*) by analogy to our previous results for the asymmetric [2,3]-Wittig rearrangement.[18] This assumed assignment was later confirmed by transformation of **16** to the natural product.

Next, the optimum reaction conditions described above were applied to the rearrangement of synthetic intermediates **17** and **18** (Scheme 6). The intermediate (i.e., **17**) for eupomatilone 5 gave rearranged product **21** in 74% yield and with 91% *ee*. The signals due to the protons around the biaryl moiety in the ^{1}H and ^{13}C NMR spectra were doubled, indicating the existence of atropisomers.

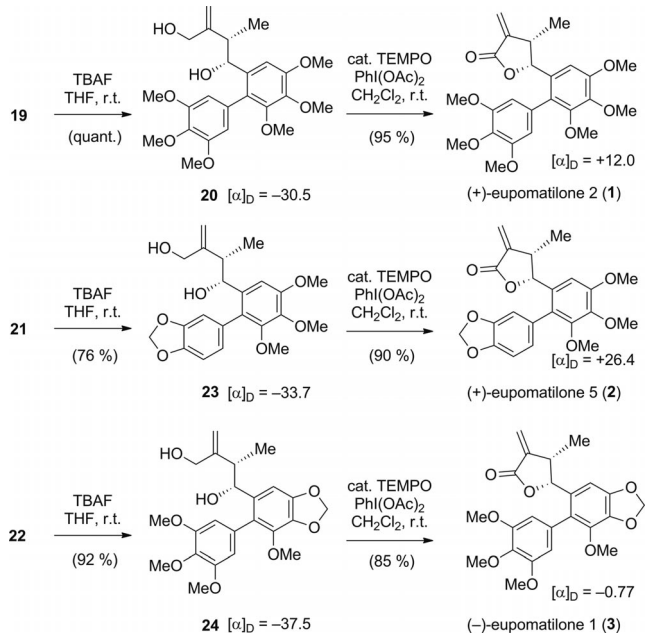


Scheme 6. Asymmetric [2,3]-Wittig rearrangement.

However, the reaction of intermediate **18** was sluggish, and a considerable amount of starting material was recovered, despite the use of 10 equiv. of *n*BuLi. When the stronger bases *s*BuLi and *t*BuLi were used, a decrease in the *ee* and yield was observed, due to decomposition. This problem was solved to some extent by using 10 equiv. of *n*BuLi and a longer reaction time (8 h); also, the quantity of hexane was reduced to maintain the final solvent ratio and concentration of substrate **18** after addition of the *n*BuLi hexane solution. Under these conditions, product **22** was obtained in 54% yield (77% based on consumed **18**) and with 88% *ee*. All of the rearranged products were formed as single diastereomers with coupling constants of approximately 3 Hz between the two methine protons at the C-1 and C-2 positions.[13] This indicates a *syn* relationship between the hydroxy and methyl substituents at the C-1 and C-2 positions, respectively.

Total Synthesis of Eupomatilones 1, 2, and 5

The construction of the α-methylene γ-lactone moiety of the eupomatilones (Scheme 7) was the final task. For the completion of the total synthesis, alcohol **19** was subjected to deprotection with TBAF in THF, followed by selective oxidation in the presence of a primary alcohol using a catalytic amount of TEMPO and $PhI(OAc)_2$ as the co-oxidant.[14] This process provided eupomatilone 2 (**1**) in 95% yield over two steps. Similarly, alcohol **21** was converted into eupomatilone 5 (**2**) in 68% yield over two steps. Eupomatilone 1 (**3**) was also synthesized in 78% yield over two steps.



Scheme 7. Asymmetric total synthesis of eupomatilones 1, 2, and 5.

The ^{1}H and ^{13}C NMR spectroscopic data for these synthetic eupomatilones were identical to the reported data.[1,2] Eupomatilone 5 was found to exist as a 1:1 mixture of atropisomers, as reported. The optical purity of the synthetic eupomatilones was determined by chiral HPLC (Daicel CHIRALPAK® AD-H), and was in agreement with that of the corresponding [2,3]-Wittig products.[19] The signs of the specific rotations of all of the [2,3]-Wittig products and diols were negative, and the signs were reversed to positive after formation of the γ-lactone moiety in eupomatilones 2 and 5. The signs of the specific rotations of synthetic eupomatilones 2 and 5 matched those of the natural products, and the values were greater than those reported in previous studies [eupomatilone 2: $[\alpha]_D^{25}$ = +12.0 (*c* = 0.60, $CHCl_3$), ref.[1] $[\alpha]_D$ = +3.3 (*c* = 0.5, $CHCl_3$); eupomatilone 5: $[\alpha]_D^{24}$ = +26.4 (*c* = 1.04, $CHCl_3$), ref.[1] $[\alpha]_D$ = +6.5 (*c* = 1.50, $CHCl_3$)]. On the other hand, the specific rotation of our synthetic eupomatilone 1 was very small, despite its high optical purity [eupomatilone 1: $[\alpha]_D^{25}$ = –0.77 (*c* = 0.80, $CHCl_3$), ref.[1] $[\alpha]_D$ = –10.0 (*c* = 0.50, $CHCl_3$)].

Conclusions

We have accomplished the total synthesis of eupomatilones 1, 2, and 5 using the asymmetric [2,3]-Wittig rearrangement of highly oxygenated biaryl compounds as the key reaction. The [2,3]-Wittig rearrangement proceeded, even though the substrates were highly oxygenated, to give the rearranged products with high diastereo- and enantioselectivities. This concise synthetic route should be applicable to the synthesis of other congeners and unnatural derivatives.

Experimental Section

General Remarks: Optical rotations were measured with a JASCO P-1020 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 400 and 100 MHz, respectively, with a JEOL JNM-AL-400 spectrometer. Chemical shifts in ^{1}H NMR spectra are expressed in ppm downfield from tetramethylsilane as an internal standard (δ = 0 ppm). Chemical shifts in ^{13}C NMR spectra are expressed as ppm using $CDCl_3$ as an internal standard (δ = 77 ppm). IR absorption spectra (FT: diffuse reflectance spectroscopy) were recorded with KBr powder with a JASCO FT-6300 IR spectrophotometer, and only noteworthy absorptions (cm^{-1}) are listed. Mass spectra were obtained with a JEOL GC-Mate II mass spectrometer. Purification of the crude products was carried out by flash column chromatography. Fuji Silysia Silica Gel BW-300 was used as the adsorbent for column chromatography. For preparative TLC (PTLC), silica gel 60F_{254} (Merck) was used. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under an atmosphere of Ar or N_2. All organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure with a rotary evaporator, unless otherwise stated.

General Procedure for Suzuki Coupling

(3′,4,4′,5,5′,6-Hexamethoxybiphenyl-2-yl)methanol (8): $Pd(OAc)_2$ (20 mg, 0.093 mmol, 1.0 mol-%), 2-(dicyclohexylphosphanyl)biphenyl (65 mg, 0.186 mmol, 2.0 mol-%), 2-bromo-3,4,5-trimethoxybenzyl alcohol (**6**; 2.57 g, 9.30 mmol), (3,4,5-trimethoxyphenyl)-boronic acid (**7**; 2.97 g, 14.0 mmol), and K_3PO_4 (3.95 g, 18.6 mmol) were placed in an oven-dried three-necked flask. After the flask was evacuated and backfilled with Ar, dry toluene (26 mL) was added to the mixture. The suspension was then sonicated, evacuated, and backfilled with Ar, and this cycle was repeated three times. The flask was then heated at 80–90 °C with stirring for 10 h. After cooling, the reaction mixture was diluted with diethyl ether and washed with NaOH (1 N). The aqueous phase was extracted twice with ether, and the combined organic extracts were washed with brine prior to drying and solvent evaporation. The residue was purified by chromatography on silica gel with hexane/EtOAc (1:2) to give **8** (2.57 g, 76%) as a colorless oil. ^{1}H NMR: δ = 1.63 (t, J = 5.6 Hz, 1 H), 3.69 (s, 3 H), 3.84 (s, 6 H), 3.90 (s, 3 H), 3.91 (s, 3 H), 3.93 (s, 3 H), 4.44 (d, J = 5.6 Hz, 2 H), 6.48 (s, 2 H), 6.90 (s, 1 H) ppm. ^{13}C NMR: δ = 56.00, 56.04 (2 C), 60.83, 60.85, 61.22, 63.00, 106.95, 107.05 (2 C), 127.86, 131.41, 134.48, 136.93, 141.43, 151.23, 152.83 (2 C), 152.87 ppm. IR (KBr): $\tilde{\nu}$ = 3496, 3066, 1584 cm^{-1}. MS (FAB): m/z = 365 [M + H]$^+$. HRMS (FAB): calcd. for $C_{19}H_{25}O_7$ [M + H]$^+$ 365.1600; found 365.1583.

General Procedure for Williamson Ether Synthesis

(*E*)-1-[(3′,4,4′,5,5′,6-Hexamethoxybiphenyl-2-yl)methoxy]-2-(triisopropylsilyloxymethyl)but-2-ene (16): *t*BuOK (300 mg, 2.67 mmol) was added to a solution of biarylmethyl alcohol **8** (720 mg, 1.98 mmol) and bromide **15** (640 mg, 1.98 mmol) in dry THF (10 mL) with stirring at room temp. under Ar. After stirring for 1 d, the reaction was quenched with saturated NH_4Cl. The mixture was partitioned between EtOAc and water. The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with water and brine prior to drying and solvent evaporation. The residue was purified by chromatography on silica gel with hexane/EtOAc (4:1) to give ether **16** (860 mg, 71%) as a colorless powder. M.p. 51–52 °C (hexane). ^{1}H NMR: δ = 1.00–1.10 (m, 21 H), 1.64 (d, J = 7.1 Hz, 3 H), 3.67 (s, 3 H), 3.84 (s, 6 H), 3.899 (s, 3 H), 3.903 (s, 3 H), 3.91 (s, 3 H), 4.00 (s, 2 H), 4.18 (s, 2 H), 4.23 (m, 2 H), 5.76 (q, J = 7.1 Hz, 1 H), 6.47 (s, 2 H), 6.87 (s, 1 H) ppm. ^{13}C NMR: δ = 11.98 (3 C), 13.01, 17.97 (6 C), 55.88, 56.02 (2 C), 60.86 (2 C), 61.19, 65.38, 65.41, 69.63, 107.13, 107.20 (2 C), 123.57, 128.31, 131.53, 132.32, 135.67, 136.89, 141.39, 151.10, 152.68 (2 C), 152.77 ppm. IR (KBr): $\tilde{\nu}$ = 1583 cm^{-1}. MS (FAB): m/z = 605 [M + H]$^+$. HRMS (FAB): calcd. for $C_{33}H_{53}O_8Si$ [M + H]$^+$ 605.3510; found 605.3500. $C_{33}H_{52}O_8Si$: calcd. C 65.53, H 8.67; found C 65.30, H 8.52.

General Procedure for the [2,3]-Wittig Rearrangement Without a Chiral Ligand

(1*RS*,2*SR*)-1-(3′,4,4′,5,5′,6-Hexamethoxybiphenyl-2-yl)-2-methyl-3-[(triisopropylsilyloxy)methyl]but-3-en-1-ol (*rac*-19): *t*BuLi (1.59 M in pentane; 2.10 mL, 3.30 mmol) was added dropwise to a suspension of ether **16** (400 mg, 0.66 mmol) in THF (3.3 mL) with stirring at –78 °C under Ar. Stirring was continued at this temperature for 2 h. Then the reaction was quenched with saturated NH_4Cl, and the mixture was partitioned between EtOAc and water. The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with water and brine prior to drying and solvent evaporation. The residue was purified by chromatography on silica gel with hexane/EtOAc (2:1) to give alcohol *rac*-**19** (340 mg, 85%) as a colorless powder. M.p. 94–95 °C (hexane). ^{1}H NMR: δ = 0.96 (d, J = 7.1 Hz, 3 H), 1.00–1.10 (m, 21 H), 2.35 (qd, J = 7.1, 3.2 Hz, 1 H), 3.50 (br., 1 H), 3.67 (s, 3 H), 3.80 (s, 3 H), 3.85 (s, 3 H), 3.82 (d, J = 12.7 Hz, 1 H), 3.89 (s, 6 H), 3.93 (s, 3 H), 4.03 (d, J = 12.7 Hz, 1 H), 4.52 (s, 1 H), 4.77 (d, J = 3.2 Hz, 1 H), 4.97 (d, J = 1.2 Hz, 1 H), 6.42 (d, J = 1.7 Hz, 1 H), 6.47 (d, J = 1.7 Hz, 1 H), 7.04 (s, 1 H) ppm. ^{13}C NMR: δ = 11.16, 11.86 (3 C), 17.85 (6 C), 43.80, 55.93, 55.97, 56.16, 60.77, 60.84, 61.25, 65.09, 72.61, 105.74, 106.59, 108.01, 113.05, 127.31, 131.92, 136.39, 136.94, 140.86, 150.51, 150.96, 152.39, 152.79, 153.00 ppm. IR (KBr): $\tilde{\nu}$ = 3477, 3097, 1586 cm^{-1}. MS (FAB): m/z = 605 [M + H]$^+$. HRMS (FAB): calcd. for $C_{33}H_{53}O_8Si$ [M + H]$^+$ 605.3510; found 605.3528. $C_{33}H_{52}O_8Si$: calcd. C 65.53, H 8.67; found C 65.58, H 8.62.

General Procedure for the [2,3]-Wittig rearrangement with a Chiral Ligand

(1*R*,2*S*)-1-(3′,4,4′,5,5′,6-Hexamethoxybiphenyl-2-yl)-2-methyl-3-[(triisopropylsilyloxy)methyl]but-3-en-1-ol (19): *n*BuLi (1.6 M in hexane; 1.25 mL, 2.00 mmol) was added dropwise to a suspension of ether **16** (240 mg, 0.40 mmol) and bis(oxazoline) ligand **L1** (118 mg, 0.40 mmol) in a mixture of dry hexane (1.6 mL) and dry ether (0.4 mL) with stirring at –78 °C under Ar. Stirring was continued at this temperature for 2 h. The reaction was then quenched with saturated NH_4Cl, and the mixture was partitioned between EtOAc and water. The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with water and brine prior to drying and solvent evaporation. The residue was purified by chromatography on silica gel with hexane/EtOAc (1:1) to give alcohol **19** (235 mg, 98%) as

a colorless oil. *ee* 89% (column: Daicel CHIRALPAK® AD-H, *i*PrOH/hexane = 98:2, flow rate: 1 mL/min, λ = 254 nm). $[\alpha]_D^{25}$ = –21.2 (*c* = 0.72, $CHCl_3$).

General Procedure for TIPS Deprotection

(1*R*,2*S*)-1-(3′,4,4′,5,5′,6-Hexamethoxybiphenyl-2-yl)-2-methyl-3-methylenebutane-1,4-diol (20): Tetrabutylammonium fluoride (1 M in THF, 1.54 mL, 1.54 mmol) was added to a solution of **19** (310 mg, 0.51 mmol) in THF (5 mL) at room temp. under Ar, and the mixture was stirred for 2 h. The reaction was then quenched with saturated aqueous NH_4Cl, and the mixture was partitioned between EtOAc and water. The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined extracts were washed with saturated aqueous NH_4Cl, water, and brine prior to drying and solvent evaporation. The crude residue was purified by chromatography on silica gel with hexane/EtOAc (1:2) to give diol **20** (228 mg, quant.) as a colorless oil. $[\alpha]_D^{26}$ = –30.5 (*c* = 0.54, $CHCl_3$). ^{1}H NMR: δ = 0.95 (d, *J* = 7.0 Hz, 3 H), 2.41 (qd, *J* = 7.0, 2.6 Hz, 1 H), 3.69 (s, 3 H), 3.70 (d, *J* = 12.7 Hz, 1 H), 3.82 (d, *J* = 12.7 Hz, 1 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 3.89 (s, 3 H), 3.90 (s, 3 H), 3.93 (s, 3 H), 4.60 (s, 1 H), 4.77 (d, *J* = 2.6 Hz, 1 H), 4.97 (s, 1 H), 6.44 (d, *J* = 1.7 Hz, 1 H), 6.47 (d, *J* = 1.7 Hz, 1 H), 7.02 (s, 1 H) ppm. ^{13}C NMR: δ = 10.53, 43.21, 55.91, 56.02, 56.14, 60.71, 60.80, 61.18, 64.12, 72.32, 105.63, 106.65, 108.12, 113.12, 127.05, 131.85, 136.26, 136.85, 140.77, 150.77, 150.81, 152.30, 152.80, 152.95 ppm. IR (KBr): $\tilde{\nu}$ = 3450, 3070, 1583 cm^{-1}. MS (FAB): *m*/*z* = 471 $[M + Na]^+$. HRMS (FAB): calcd. for $C_{24}H_{32}O_8Na$ $[M + Na]^+$ 471.1995; found 471.1985.

General Procedure for TEMPO Oxidation

(+)-Eupomatilone 2 (1): 2,2,6,6-Tetramethyl-1-piperidinyloxy (TEMPO; 6.7 mg, 0.043 mmol) and $PhI(OAc)_2$ (156 mg, 0.47 mmol) were added to a solution of diol **20** (192 mg, 0.43 mmol) in dry CH_2Cl_2 (2.2 mL) with stirring at room temp. under Ar. After continued stirring at room temp. for 1 h, additional $PhI(OAc)_2$ (227 mg, 0.68 mmol) was added to the mixture. The entire mixture was then stirred at room temp. for 3.5 h. Next, the mixture was diluted with $CHCl_3$, and the resulting solution was stirred with saturated $Na_2S_2O_3$. Then the organic phase was separated, and the aqueous phase was extracted with $CHCl_3$. The combined organic extracts were washed with saturated $NaHCO_3$ and brine prior to drying over Na_2SO_4 and solvent evaporation. The residue was purified by chromatography on silica gel with hexane/EtOAc (2:1) to give (+)-eupomatilone 2 (**1**; 180 mg, 95%) as a pale yellow oil. *ee* 89% (column: Daicel CHIRALPAK® AD-H, *i*PrOH/hexane = 85:15, flow rate: 1 mL/min, λ = 254 nm). $[\alpha]_D^{23}$ = +12.0 (*c* = 0.60, $CHCl_3$). ^{1}H NMR: δ = 0.84 (d, *J* = 7.3 Hz, 3 H), 2.88 (qnt, *J* = 7.3, 2.2 Hz, 1 H), 3.70 (s, 3 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 3.88 (s, 3 H), 3.92 (s, 6 H), 5.52 (d, *J* = 7.3 Hz, 1 H), 5.55 (d, *J* = 2.2 Hz, 1 H), 6.26 (d, *J* = 2.2 Hz, 1 H), 6.37 (d, *J* = 1.7 Hz, 1 H), 6.46 (d, *J* = 1.7 Hz, 1 H), 6.69 (s, 1 H) ppm. ^{13}C NMR: δ = 16.86, 38.31, 56.12, 56.16, 56.25, 60.88, 60.92, 61.37, 79.26, 104.86, 106.42, 107.42, 122.07, 127.64, 129.86, 131.02, 137.28, 140.90, 141.90, 151.25, 152.98, 153.06, 153.24, 170.14 ppm. IR (KBr): $\tilde{\nu}$ = 3097, 1767, 1664, 1592 cm^{-1}. MS (FAB): *m*/*z* = 445 $[M + H]^+$. HRMS (FAB): calcd. for $C_{24}H_{29}O_8$ $[M + H]^+$ 445.1862; found 445.1853.

(+)-Eupomatilone 5 (2): (+)-Eupomatilone 5 (**2**) was prepared in a manner similar to that described for the preparation of (+)-eupomatilone 2 (**1**). Yield 90%. *ee* 91% (column: Daicel CHIRALPAK® AD-H, *i*PrOH/hexane = 80:20, flow rate: 1 mL/min, λ = 254 nm). Colorless oil. 1:1 Mixture of rotamers. $[\alpha]_D^{24}$ = +26.4 (*c* = 1.04, $CHCl_3$). ^{1}H NMR: δ = 0.80 (d, *J* = 7.6 Hz, 1.5 H), 0.82 (d, *J* = 7.3 Hz, 1.5 H), 2.81–2.92 (m, 1 H), 3.64 (s, 1.5 H), 3.65 (s, 1.5 H), 3.88 (s, 3 H), 3.91 (s, 3 H), 5.44 (d, *J* = 7.3 Hz, 0.5 H), 5.53 (d, *J* = 7.1 Hz, 0.5 H), 5.54 (d, *J* = 2.2 Hz, 1 H), 6.017 (br. s, 0.5 H), 6.024 (br. s, 0.5 H), 6.028 (br. s, 0.5 H), 6.043 (br. s, 0.5 H), 6.24 (d, *J* = 2.2 Hz, 1 H), 6.59 (dd, *J* = 7.8, 1.5 Hz, 0.5 H), 6.64 (d, *J* = 1.2 Hz, 0.5 H), 6.69 (s, 1 H), 6.70 (dd, *J* = 7.8, 1.2 Hz, 0.5 H), 6.73 (d, *J* = 1.5 Hz, 0.5 H), 6.87 (d, *J* = 7.8 Hz, 1 H) ppm. ^{13}C NMR: δ = 17.03 (0.5 C), 17.21 (0.5 C), 38.14 (0.5 C), 38.32 (0.5 C), 56.11, 60.85, 61.10 (0.5 C), 61.16 (0.5 C), 79.29 (0.5 C), 79.35 (0.5 C), 101.16 (0.5 C), 101.20 (0.5 C), 104.78 (0.5 C), 104.83 (0.5 C), 108.18 (0.5 C), 108.51 (0.5 C), 109.91 (0.5 C), 110.54 (0.5 C), 121.94, 122.72 (0.5 C), 123.31 (0.5 C), 127.12, 128.97, 130.03 (0.5 C), 130.06 (0.5 C), 141.06 (0.5 C), 141.14 (0.5 C), 141.83 (0.5 C), 146.94 (0.5 C), 147.04, 147.64 (0.5 C), 147.72 (0.5 C), 151.47, 152.90, 170.11 (0.5 C), 170.15 (0.5 C) ppm. IR (KBr): $\tilde{\nu}$ = 1767 cm^{-1}. MS (FAB): *m*/*z* = 399 $[M + H]^+$. HRMS (FAB): calcd. for $C_{22}H_{23}O_7$ $[M + H]^+$ 399.1444; found 399.1422.

(–)-Eupomatilone 1 (3): (–)-Eupomatilone 1 (**3**) was prepared in a manner similar to that described for the preparation of (+)-eupomatilone 2 (**1**). Yield 85%. *ee* 88% (column: Daicel CHIRALPAK® AD-H, *i*PrOH/hexane = 60:40, flow rate: 1 mL/min, λ = 254 nm). Colorless oil. $[\alpha]_D^{25}$ = –0.77 (*c* = 0.80, $CHCl_3$). ^{1}H NMR: δ = 0.88 (d, *J* = 7.3 Hz, 3 H), 2.86–2.98 (m, 1 H), 3.84 (s, 3 H), 3.845 (s, 3 H), 3.847 (s, 3 H), 3.91 (s, 3 H), 5.44 (d, *J* = 7.6 Hz, 1 H), 5.53 (d, *J* = 2.3 Hz, 1 H), 6.00 (s, 2 H), 6.25 (d, *J* = 2.3 Hz, 1 H), 6.33 (d, *J* = 1.7 Hz, 1 H), 6.43 (d, *J* = 1.7 Hz, 1 H), 6.56 (br. s, 1 H) ppm. ^{13}C NMR: δ = 16.42, 38.27, 56.09, 56.18, 59.98, 60.86, 79.26, 100.77, 101.37, 106.60, 107.61, 121.84, 127.37, 128.88, 130.97, 136.58, 137.26, 140.64, 140.89, 148.79, 152.99, 153.26, 170.07 ppm. IR (KBr): $\tilde{\nu}$ = 1766, 1618, 1583 cm^{-1}. MS (FAB): *m*/*z* = 429 $[M + H]^+$. HRMS (FAB): calcd. for $C_{23}H_{25}O_8$ $[M + H]^+$ 429.1549; found 429.1556.

Supporting Information (see footnote on the first page of this article): Characterization data of synthetic intermediates of eupomatilone 1 and 5, and ^{1}H and ^{13}C NMR spectra of all new compounds.

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[19] The enantiomeric excesses of the synthetic eupomatilones 1, 2, and 5 was confirmed by chiral HPLC to be 88, 89, and 91% *ee*, respectively.

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