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Formal synthesis of (+)-3-*epi*-eupomatilone-6 and the 3,5-bis-epimer†

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The formal synthesis of (+)-3-*epi*-eupomatilone-6 (**1**) and the 3,5-bis-epimer (**2**) has been accomplished. The key synthetic strategy involved the stereoselective construction of (3*R*,4*S*,5*R*)- and (3*R*,4*S*,5*S*)-trisubstituted γ-butyrolactones **3** and **4** from (2*R*,3*R*)-2,3-dimethyl-4-pentenoic acid derivative **7**, which was readily obtained *via* stereoselective conjugate addition of vinylmagnesium chloride to a chiral α,β-unsaturated *N*-acyl oxazolidinone (Evans' auxiliary) followed by α-methylation.

Introduction

Lignans, a class of secondary plant metabolites, have been found in a wide variety of plants and were reported to possess a broad range of important biological activities, including antioxidant, anti-inflammatory, antitumor, antifungal, and antiviral activities.[1] Biosynthetically, lignans are formed by the dimerization of two phenylpropanoid units (C6–C3) with a variety of structural differences. Eupomatilones-1–7 (Fig. 1), belonging to a structurally novel subclass of lignans, were first isolated from the Australian shrub *Eupomatia bennettii* in 1991 by Carroll and Taylor.[2] Among the lignan family, the eupomatilones are structurally unusual in that they possess a substituted γ-butyrolactone connected to one of the aromatic rings of the highly oxygenated biaryl skeleton. These unique structural features of eupomatilones have attracted the attention of the organic synthetic community.[3] Despite numerous literature reports, it is still of interest to develop a new asymmetric strategy towards the synthesis of this structurally novel subclass of lignans.

Our interest in the synthesis of eupomatilones and their epimers stems from the relative orientation of three substituents on the lactone core, particularly the adjacent *syn*-dimethyl relationship. Several asymmetric approaches, including asymmetric Sharpless dihydroxylation,[3c] diastereoselective reduction,[3e] and enantioselective desymmetrization of cyclic *meso*-anhydrides,[3i] have been employed as efficient strategies to install such a relative stereochemistry for the synthesis of 3-*epi*-eupomatilone-6 (**1**) as well as eupomatilone-4 and -7. While several asymmetric approaches to **1** have been reported, there have been few reports on the diastereoselective synthesis of **2**. We report herein the asymmetric strategy towards the synthesis of **1** and the 3,5-bis-epimer (**2**) *via* a stereoselective construction of trisubstituted γ-butyrolactone cores bearing the *syn*-dimethyl stereocenters.

The synthetic plan is outlined in Scheme 1. The oxygenated biaryl motifs of **1** and **2** could be obtained by a halogenation/Suzuki cross-coupling sequence of the key (3*R*,4*S*,5*R*)- and (3*R*,4*S*,5*S*)-γ-butyrolactones **3** and **4**, which in turn should be

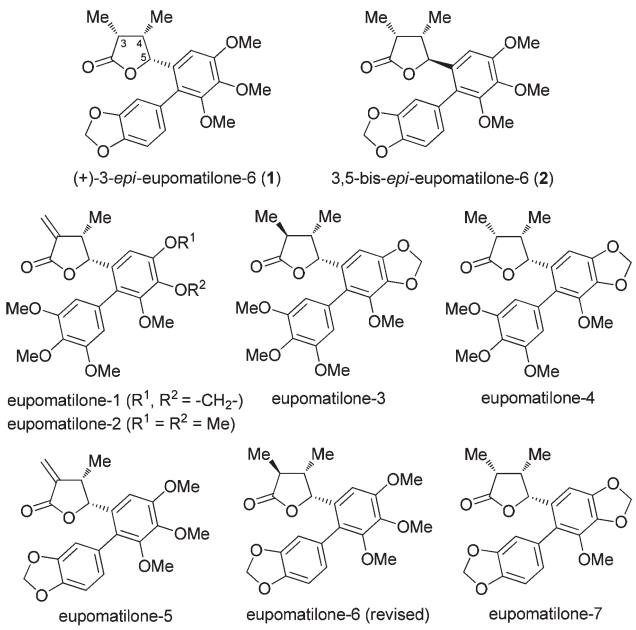

Fig. 1 Structures of eupomatilones.

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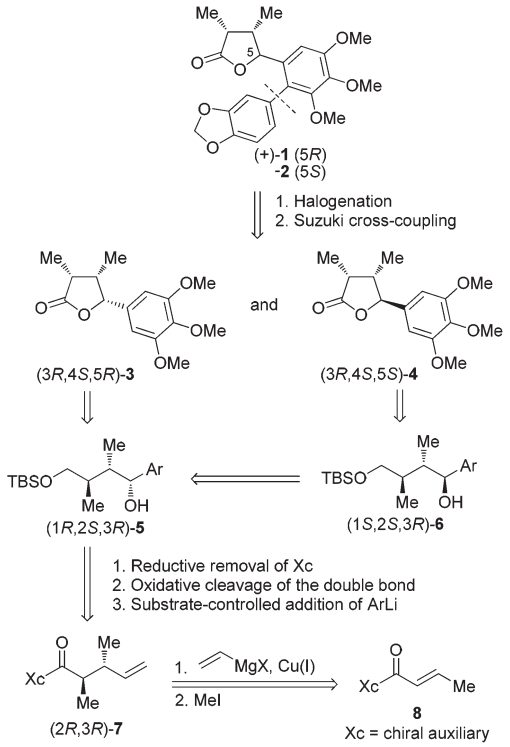
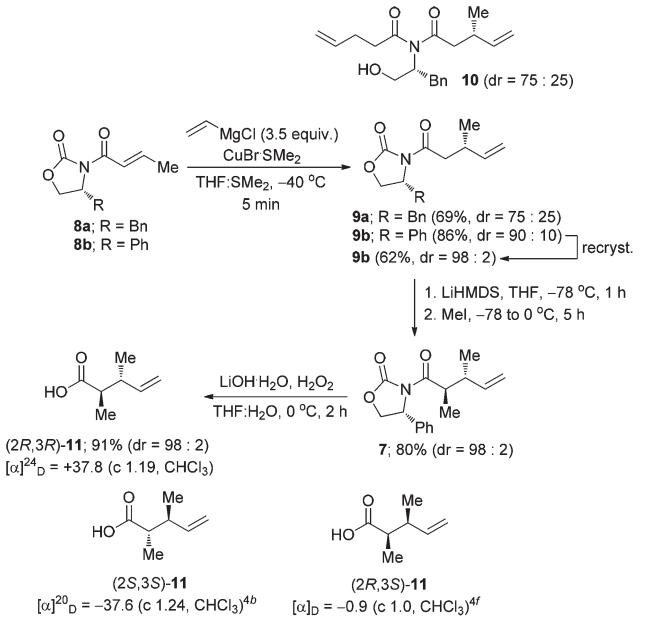
† Electronic supplementary information (ESI) available: Spectroscopic data of all compounds (copies of ^{1}H and ^{13}C NMR), and NOE of compounds **3**, **4**, **16**, **18**, and **19**. See DOI: 10.1039/c4ob01078g



Scheme 1 Synthetic plan for the synthesis of (+)-3-*epi*-eupomatilone-6 (**1**) and the 3,5-bis-epimer (**2**).

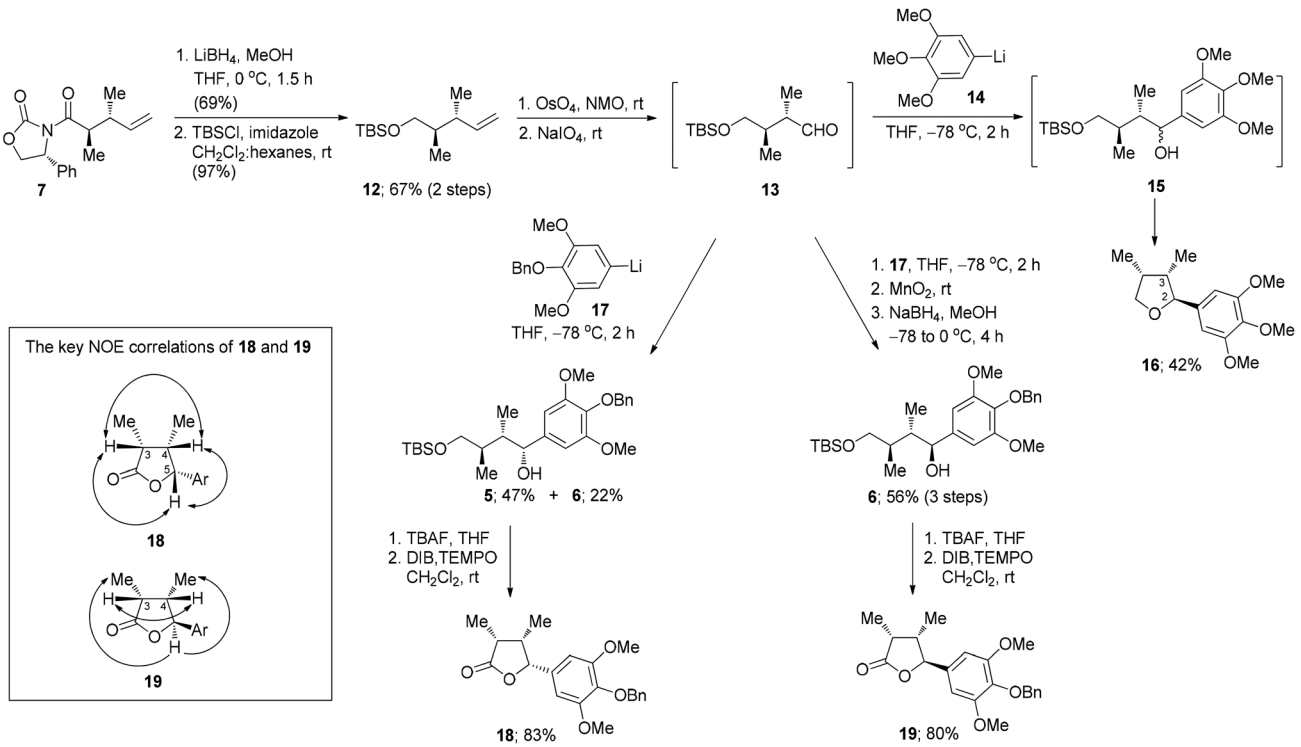


Scheme 2 Asymmetric synthesis of (2*R*,3*R*)-**7**.

readily prepared from (1*R*,2*S*,3*R*)-**5** and (1*S*,2*S*,3*R*)-**6**, respectively, *via* oxidative lactonization reaction. Compounds **5** and **6** could be synthesized stereoselectively from the substrate-controlled addition of aryllithium (ArLi) to an aldehyde derived from (2*R*,3*R*)-2,3-dimethyl-4-pentenoic acid derivatives **7**.[4] Finally, it was envisioned that the (2*R*,3*R*)-**7** could be synthesized by a copper-mediated conjugate addition of vinylmagnesium halides to chiral α,β-unsaturated *N*-acyl oxazolidinones **8** (Evans' chiral auxiliary)[5] followed by α-methylation. Notably, even though the stereoselective conjugate additions of Grignard reagents to *N*-enoyl oxazolidinones[6] and α-enolate alkylations[7] have been studied, less attention has been paid to the stereoselective conjugate addition of vinylmagnesium halides to **8** followed by α-methylation to construct *anti*-2,3-dimethyl-4-pentenoic acid derivatives found in (2*R*,3*R*)-**7**.[8]

Results and discussion

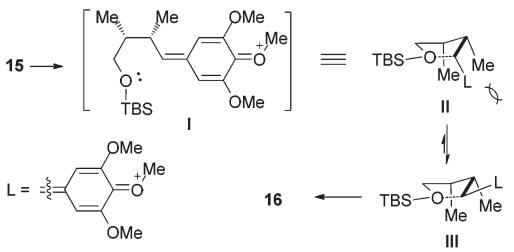
At the outset, asymmetric conjugate addition of vinylmagnesium chloride to compounds **8**[9] was carried out. Initially, the reactions of **8a** with vinylmagnesium chloride under various reaction conditions were screened.[6q–y] In contrast to the reactions using alkyl and arylmagnesium halides,[6a–p] which usually give the corresponding products in good yields with high diastereoselectivity, asymmetric conjugate addition of vinylmagnesium halides often gave lower yields and diastereoselectivity.[6q,y] After a thorough screening, it was found that the reaction of **8a** with commercially available vinylmagnesium chloride (3.5 equiv.) in the presence of CuBr·SMe_2 in THF–SMe_2 (4 : 1) at −40 °C for 1 h gave the desired product **9a** (21%) along with a by-product **10** (19%) (Scheme 2). The structure of compound **10** was confirmed based on its spectroscopic data (see ESI†). Compound **10** was presumably derived from a subsequent reaction of product **9a** with an excess quantity of vinylmagnesium chloride through the addition of vinyl nucleophile to the carbonyl carbon of the oxazolidinone ring of **9a** leading to the ring-opened adduct, which subsequently underwent the second conjugate addition with vinylmagnesium chloride. Significant improvement in the yield of **9a** was obtained by shortening the reaction time (Hughes' procedure).[6w] Thus, the reaction of **8a** with vinylmagnesium chloride at −40 °C for 5 min provided **9a** (69% yield, dr = 75 : 25, 500 MHz ^{1}H NMR analysis) without the detection of **10**. Under similar reaction conditions to those for **8a**, compound **8b** yielded **9b** in good yield with high diastereoselectivity (86% yield, dr = 90 : 10). The diastereomeric ratio (dr) of **9b** was enhanced to 98 : 2 (500 MHz ^{1}H NMR analysis) after a single recrystallization from CH_2Cl_2–hexanes (1 : 9, v/v). Having obtained a precursor **9b** with good yield and high stereoselectivity, we next studied the α-methylation reaction. Thus, compound **9b** (dr = 98 : 2) was treated with LiHMDS in THF at −78 °C followed by methylation using methyl iodide at −78 to 0 °C for 5 h. Gratifyingly, the methylation reaction proceeded stereoselectively to give the desired *anti*-dimethylated product **7** in 80% yield (dr = 98 : 2, 400 MHz ^{1}H NMR analysis). The absolute configuration of **7** was later confirmed after removal of the chiral auxiliary upon hydrolysis to yield chiral 2,3-dimethyl-4-pentenoic acid **11**. Our synthesized compound **11** (dr = 98 : 2, 400 MHz ^{1}H NMR analysis) showed a specific optical rotation value of $[\alpha]_D^{24}$ +37.8 (*c* 1.19, $CHCl_3$) while the known (2*S*,3*S*)-**11**[4b] and (2*R*,3*S*)-**11**[4f] show the values of $[\alpha]_D^{20}$ −37.6 (*c* 1.24, $CHCl_3$) and



Scheme 3 Synthesis of (3*R*,4*S*,5*R*)-**18** and (3*R*,4*S*,5*S*)-**19**.

$[\alpha]_D$ −0.9 (*c* 1.0, $CHCl_3$), respectively. Thus, our synthesized compound **11** was confirmed to be (2*R*,3*R*)-2,3-dimethyl-4-pentenoic acid [(2*R*,3*R*)-**11**)], and compound 7 was confirmed to possess (2*R*,3*R*) configurations. At this stage, it is worth noting that, among the preceding methods that allowed for stereoselective construction of the 2,3-dimethyl stereocenters, our reported procedure serves as a practical approach to create the *anti*-2,3-dimethyl stereocenters found in 2,3-dimethyl-4-pentenoic acid derivatives, such as (2*R*,3*R*)-7.

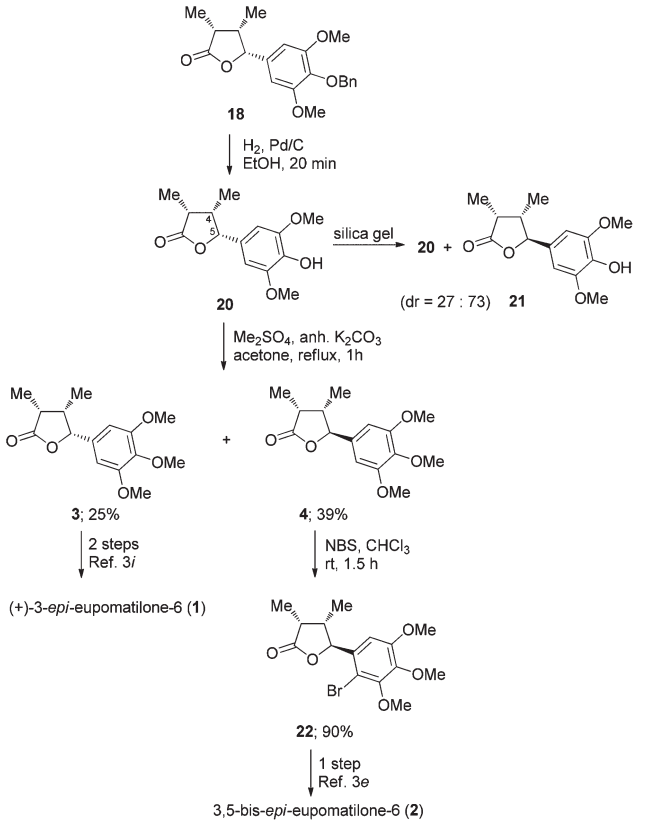
After obtaining the required (2*R*,3*R*)-7 with high stereoselectivity, we next focused our attention on its conversion to compounds **5** and **6** (Scheme 3). Thus, compound 7 (dr = 98 : 2) was subjected to a reductive cleavage of the chiral auxiliary by using $LiBH_4$ in THF with a catalytic amount of methanol[10] at 0 °C for 1.5 h to provide the corresponding alcohol[11] and the recovered chiral auxiliary in 69% and 72% yields, respectively.[12] Subsequently, protection of the initially formed alcohol as a TBS-ether gave compound **12**[13] in 97% yield. Next, oxidative cleavage of the double bond of **12** by using OsO_4 (5 mol%), *N*-methylmorpholine-*N*-oxide (NMO) (3 equiv.) and then $NaIO_4$ (2 equiv.) provided the corresponding aldehyde **13**, which proved to be unstable. Thus, the aldehyde intermediate **13** was further reacted with (3,4,5-trimethoxyphenyl)lithium (**14**; 1.5 equiv.) in THF at −78 °C for 2 h to provide the expected alcohol adduct **15** as a mixture of diastereomers as revealed by ^1H NMR analysis. It was found that the adduct **15** rapidly underwent an intramolecular cyclization to give a trisubstituted tetrahydrofuran **16** in 42% yield (from **12**) as a single diastereomer. The chemical structure of **16** and its stereochemistry were established based on NMR analyses, mass spectrometry, and NOE experiments (see ESI†). The mechanism for the formation of **16** was proposed to proceed *via* the formation of an intermediate oxonium ion **I** followed by an intramolecular cyclization (Scheme 4). The observed stereochemical outcome of **16** (2,3-*anti*-3,4-*syn*) can be explained by the energetically favorable transition state **III** possessing minimized steric interaction between the aryl ring and the adjacent methyl group. To our delight, under similar reaction conditions to those for **14**, the substrate-controlled addition of [4-(benzyloxy)-3,5-dimethoxyphenyl]lithium (**17**; 1.5 equiv.) to aldehyde **13** gave diastereomerically pure adduct **5** (47% yield, major isomer) along with its diastereomer **6** (22% yield, minor isomer); they could be easily separated by simple column chromatography. Alternatively, diastereomeri-



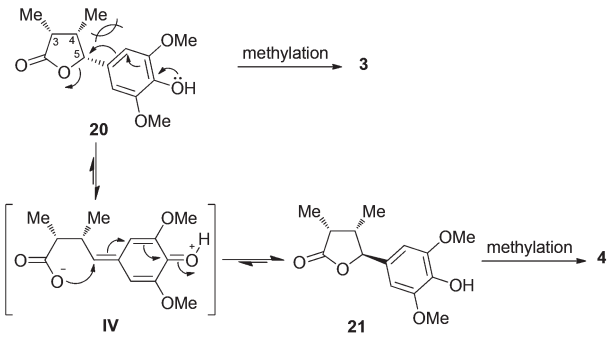
Scheme 4 Proposed reaction mechanism for the formation of **16**.

cally pure compound **6** could be efficiently prepared by the oxidation of a mixture of **5** and **6** to the corresponding ketone followed by stereoselective hydride reduction. In a synthetic sequence, a mixture of **5** and **6** (obtained in 69% yield from the reaction of aldehyde **13** with aryllithium **17**) was treated with MnO_2 at room temperature for 13 h yielding the corresponding ketone (89% yield), which was subsequently subjected to reduction using $NaBH_4$ in MeOH at −78 to 0 °C for 4 h to give the desired compound **6** as a single diastereomer in 89% yield (56% yield, 3 steps). The stereochemical outcome of the addition reaction of **17** to **13** providing **5** as a major diastereomer as well as the hydride reduction of the respective ketone to give **6** as a single diastereomer could be explained on the basis of the Felkin–Ahn model.[14] The stereochemistries of **5** and **6** were also confirmed by the NOE experiments of their corresponding γ-butyrolactone derivatives **18** and **19**, respectively. Desilylation of **5** followed by oxidative lactonization of the corresponding diol using (diacetoxyiodo)benzene (DIB) and 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO)[15] in CH_2Cl_2 at room temperature provided **18** in 83% yield as a single diastereomer. Upon a similar treatment, compound **6** was converted to **19** in 80% yield albeit contaminated with its C-3 epimer (dr = 95 : 5). The NOE experiments confirmed that compound **18** possessed the all-*syn* stereochemistries while compound **19** possessed the 3,4-*syn*-4,5-*anti* stereochemistries (Scheme 3) (see ESI†). Furthermore, the 4,5-*syn* stereochemistry of **18** was further confirmed by the chemical shift of the methyl group at C-4. The influence exerted by an anisotropic effect of the aromatic ring at C-5 (Ar-5) made the methyl group at C-4 of **18** appear at a higher field region (δ = 0.49 ppm) while that of **19** appeared at δ = 1.04 ppm.

Having accomplished the stereoselective synthesis of γ-butyrolactones **18** and **19** containing all requisite absolute stereochemistries, we then paid attention to their synthetic conversions directed toward **1** and **2** (Scheme 5). Debenzylation of **18** was carried out by hydrogenation using Pd/C in dry EtOH at room temperature for 20 min providing the debenzylated product **20** in a quantitative yield. Upon purification using silica gel, compound **20** underwent epimerization at C-5, providing an inseparable mixture of **20** and **21** with a 27 : 73 diasteromeric ratio as determined by ^{1}H NMR analysis. Therefore, after debenzylation, compound **20** was subsequently subjected to the methylation reaction (Me_2SO_4, anhydrous K_2CO_3, acetone, reflux, 1 h). The corresponding γ-butyrolactone **3** together with its diastereomer **4**, which could be easily separated by simple column chromatography, were obtained in 25% and 39% yields, respectively. The stereochemistries of **3** and **4** were confirmed by the NOE experiments (see ESI†). These results implied that epimerization at C-5 of **20** followed by methylation leading to **4** readily took place and competed with a simple methylation to provide **3** (Scheme 6). The observed C-5 epimerization of **20** leading to the thermodynamically more stable **21** was proposed to occur through a lactone ring-opening, facilitated by a hydroxy group on the aromatic ring, to give an intermediate **IV**. Cyclization of the carboxylate intermediate **IV** provided the lactone **21** with *anti*-orientation



Scheme 5 Formal synthesis of (+)-3-*epi*-eupomatilone-6 (**1**) and the 3,5-bis-epimer (**2**).



Scheme 6 Proposed reaction mechanism for the epimerization at C-5 of **20**.

between the methyl group at C-4 and the aromatic ring at C-5 in order to minimize the steric interaction between the two groups. It is worth mentioning that under the reaction conditions, epimerization at C-3 of **20** was not observed. Our synthesized γ-butyrolactones **3** and **4** show the specific optical rotation values of $[\alpha]_D^{27}$ +51.4 (*c* 0.34, $CHCl_3$) {lit.[3i] $[\alpha]_D^{23}$ +57.1 (*c* 0.2, $CHCl_3$)} and $[\alpha]_D^{28}$ +8.3 (*c* 0.35, $CHCl_3$), respectively.

With compounds **3** and **4** in hand, they can be converted to (+)-3-*epi*-eupomatilone-6 (**1**) and the 3,5-bis-epimer (**2**) by following the previously reported studies by Rovis[3i] and Hall,[3e] respectively.

Conclusion

In summary, we accomplished a formal synthesis of (+)-3-*epi*-eupomatilone-6 (**1**) and the 3,5-bis-epimer (**2**). The synthesis scheme involved stereoselective construction of (3*R*,4*S*,5*R*)- and (3*R*,4*S*,5*S*)-trisubstituted γ-butyrolactones **3** and **4** from (2*R*,3*R*)-2,3-dimethyl-4-pentenoic acid derivative **7**. The stereoselective conjugate addition of vinylmagnesium chloride to a chiral α,β-unsaturated *N*-acyl oxazolidinone (Evans' auxiliary) followed by α-methylation was employed to create the *anti*-2,3-dimethyl orientation in (2*R*,3*R*)-**7** leading to the *syn*-3,4-dimethyl relationship present in the target natural molecules.

Experimental

General information

The ^{1}H NMR spectra were recorded on a Bruker DPX-300 (300 MHz), a Bruker-400 (400 MHz) or a Bruker-500 (500 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The ^{13}C NMR spectra were recorded on a Bruker DPX-300 (75 MHz) or a Bruker-400 (100 MHz) spectrometer in $CDCl_3$ using residual non-deuterated solvent peaks as an internal standard. The IR spectra were recorded on a Perkin Elmer Spectrum GX FT-IR infrared spectrometer. The mass spectra were recorded using a Thermo Finnigan Polaris Q mass spectrometer. The high resolution mass spectra were recorded on a HR-TOF-MS Micromass model VQ-TOF2 mass spectrometer. Melting points were recorded using a Buchi 510 melting Point Apparatus and are uncorrected. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Dichloromethane (CH_2Cl_2), pentane, and ethanol were distilled over calcium hydride and stored over activated molecular sieves (4 Å). Methanol (MeOH) was distilled over Mg powder. Column chromatography was performed using Merck silica gel 60 (0.063–0.200 mm) (Art 7734). Other common solvents [CH_2Cl_2, hexanes, and ethyl acetate (EtOAc)] were distilled before use.

(*R*,*E*)-3-(But-2-enoyl)-4-phenyloxazolidin-2-one (8b). Compound **8b** was obtained as a white solid according to the reported procedures;[9] mp 75–77 °C (20% CH_2Cl_2 in hexanes); R_f 0.45 (30% EtOAc in hexanes); $[\alpha]_D^{24}$ −143.1 (*c* 1.0, EtOAc) {lit.[9h] $[\alpha]_D^{20}$ −121.2 (*c* 1.0, EtOAc)}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.27 (m, 6H, 5 × Ar*H* and C*H*), 7.17–7.05 (m, 1H, C*H*), 5.50 (dd, *J* = 8.8, 3.9 Hz, 1H, C*H*N), 4.71 (dd, *J* = 8.8, 8.8 Hz, 1H, C*H*H), 4.28 (dd, *J* = 8.8, 3.9 Hz, 1H, CH*H*), 1.95 (dd, *J* = 6.8, 1.5 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.4 (CO), 153.7 (CO), 147.2 (CH), 139.1 (C), 129.1 (2 × CH), 128.6 (CH), 125.8 (2 × CH), 121.7 (CH), 69.9 (CH_2), 57.6 (CH), 18.4 (CH_3). IR ($CHCl_3$): ν_{max} 1780s, 1689s, 1638s, 1385s, 1340s cm^{-1}. MS: *m*/*z* (%) relative intensity 232 [(M + H)$^+$, 26], 211 (24), 172 (100), 159 (30), 144 (25), 117 (27), 104 (31), 91 (36), 77 (27). HRMS (ESI-TOF) calcd for $C_{13}H_{13}NO_3Na$ [M + Na]$^+$: 254.0793, found: 254.0781.

(*R*)-3-[(*S*)-3-Methylpent-4-enoyl]-4-phenyloxazolidin-2-one (9b).[6w] In a glove box, CuBr·SMe_2 (360 mg, 1.76 mmol) was placed in an oven-dried round bottom flask containing a magnetic stirring bar. The flask was sealed with a rubber septum and removed from the glove box. To the reaction flask, dry THF (6 mL) and SMe_2 (3 mL) were added under argon, and the resulting yellow solution was cooled at −40 °C. Vinylmagnesium chloride (1.6 M in THF, 4.4 mL, 7.0 mmol) was then added dropwise to give a dark green suspension. After stirring at −40 °C for 10 min, a solution of **8b** (463 mg, 2.0 mmol) in dry THF (6 mL) was added as rapidly as possible, and the resulting dark brown solution was vigorously stirred for 5 min. The reaction mixture was then quenched at −40 °C with a saturated aqueous NH_4Cl solution (5 mL), followed by the addition of 30% (v/v) aqueous ammonia solution (5 mL). After stirring for 30 min at room temperature, the resulting solution was diluted with brine. The organic phase was then collected, and the aqueous phase was 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 (30% EtOAc in hexanes) provided **9b** as a colorless solid (444 mg, 86% yield, dr = 90 : 10 as determined by 500 MHz ^{1}H NMR analysis). Recrystallization (10% CH_2Cl_2 in hexanes) yielded **9b**[6q,y] (320 mg, 62% yield) with a 98 : 2 diastereomeric ratio. mp 59–61 °C (10% CH_2Cl_2 in hexanes); R_f 0.54 (30% EtOAc in hexanes); $[\alpha]_D^{24}$ −62.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43–7.28 (m, 5H, 5 × Ar*H*), 5.78 (ddd, *J* = 17.2, 10.6, 7.0 Hz, 1H, C*H*), 5.46 (dd, *J* = 8.7, 3.7 Hz, 1H, C*H*N), 4.99–4.90 (m, 2H, CH_2), 4.71 (dd, *J* = 8.8, 8.8 Hz, 1H, C*H*H), 4.30 (dd, *J* = 8.8, 3.7 Hz, 1H, CH*H*), 3.12 (dd, *J* = 15.9, 6.6 Hz, 1H, C*H*H), 2.87 (dd, *J* = 15.9, 7.4 Hz, 1H, CH*H*), 2.79–2.69 (m, 1H, C*H*), 1.04 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5 (CO), 153.7 (CO), 142.4 (CH), 139.0 (C), 129.1 (2 × CH), 128.7 (CH), 126.0 (2 × CH), 113.4 (CH_2), 69.9 (CH_2), 57.6 (CH), 41.8 (CH_2), 33.8 (CH), 19.6 (CH_3). IR (KBr): ν_{max} 1772s, 1705s, 1386s, 1364m, 1309s, 1196s cm^{-1}. MS: *m*/*z* (%) relative intensity 260 [(M + H)$^+$, 100], 121 (19), 104 (15), 96 (21), 82 (15). HRMS (ESI-TOF) calcd for $C_{15}H_{17}NO_3Na$ [M + Na]$^+$: 282.1106, found: 282.1105.

Compound 10. A pale yellow solid; mp 64–66 °C (30% EtOAc in hexanes); R_f 0.35 (30% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$, major isomer): δ 7.27–7.09 (m, 5H, 5 × Ar*H*), 5.83–5.69 (m, 1H, C*H*), 5.69–5.58 (m, 1H, C*H*), 5.58–5.45 (m, 1H, O*H*), 5.05–4.83 (m, 4H, 2 × CH_2), 4.45–4.32 (m, 1H, C*H*N), 4.05–3.95 (m, 2H, CH_2), 2.86–2.77 (m, 1H, C*H*H), 2.77–2.68 (m, 1H, CH*H*), 2.60–2.50 (m, 1H, C*H*), 2.44–2.36 (m, 2H, CH_2), 2.36–2.29 (m, 2H, CH_2), 2.18–1.95 (m, 2H, CH_2), 0.94 (d, *J* = 6.8 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, major isomer): δ 173.0 (CO), 171.3 (CO), 142.6 (CH), 136.9 (C), 136.6 (CH), 129.2 (2 × CH), 128.6 (2 × CH), 126.8 (CH), 115.7 (CH_2), 113.5 (CH_2), 64.7 (CH_2), 49.4 (CH), 43.8 (CH_2), 37.6 (CH_2), 34.7 (CH), 33.4 (CH_2), 28.8 (CH_2), 19.6 (CH_3). IR (KBr): ν_{max} 3293s, 1726s, 1648s, 1552s, 1190m, 918m cm^{-1}. MS: *m*/*z* (%) relative intensity 329 (M$^+$, 12), 237 (17), 230 (13), 178 (17), 156 (13), 138 (30), 91 (81), 77 (30). HRMS (ESI-TOF) calcd for $C_{20}H_{27}NO_3Na$ [M + Na]$^+$: 352.1889, found: 352.1902.

(*R*)-3-[(2*R*,3*R*)-2,3-Dimethylpent-4-enoyl]-4-phenyloxazolidin-2-one (7). A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum

was charged with hexamethyldisilazane (HMDS) (0.5 mL, 2.1 mmol) and dry THF (5 mL). The solution was cooled at −78 °C and then a solution of *n*-BuLi (1.64 M in hexanes, 1.1 mL, 1.8 mmol) was added dropwise. After stirring at −78 °C for 1 h, a solution of **9b** (dr = 98 : 2, 518 mg, 2.0 mmol) in dry THF (3 mL) was added dropwise, and the reaction mixture was stirred at −78 °C for 1 h. To the resulting lithium enolate solution, MeI (0.24 mL, 4.0 mmol) was then added dropwise. The reaction mixture was slowly warmed up to 0 °C over 3 h, and the stirring was continued at 0 °C for 2 h. Then it was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc (3 × 25 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (30% EtOAc in hexanes) gave **7** as a colorless oil (437 mg, 80% yield, dr = 98 : 2 as determined by 400 MHz ^{1}H NMR analysis). R_f 0.66 (30% EtOAc in hexanes); $[\alpha]_D^{23}$ −89.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.17 (m, 5H, 5 × Ar*H*), 5.66–5.55 (m, 1H, C*H*), 5.36 (dd, *J* = 8.8, 3.5 Hz, 1H, C*H*N), 4.98–4.90 (m, 2H, CH_2), 4.60 (dd, *J* = 8.8, 8.8 Hz, 1H, C*H*H), 4.17 (dd, *J* = 8.8, 3.5 Hz, 1H, CH*H*), 3.65 (dq, *J* = 7.0, 7.0 Hz, 1H, C*H*), 2.41 (dq, *J* = 14.9, 7.0 Hz, 1H, C*H*), 0.96 (d, *J* = 7.0 Hz, 6H, 2 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8 (CO), 153.4 (CO), 140.8 (CH), 139.2 (C), 129.2 (2 × CH), 128.6 (CH), 125.6 (2 × CH), 115.2 (CH_2), 69.7 (CH_2), 57.7 (CH), 42.4 (CH), 40.6 (CH), 18.7 (CH_3), 15.2 (CH_3). IR (neat): ν_{max} 1781s, 1704s, 1456m, 1383s, 1319s, 1199s cm^{-1}. MS: *m*/*z* (%) relative intensity 274 [$(M + H)^+$, 74], 258 (24), 218 (32), 200 (24), 164 (21), 146 (40), 120 (69), 104 (100), 95 (61), 77 (62). HRMS (ESI-TOF) calcd for $C_{16}H_{19}NO_3Na$ $[M + Na]^+$: 296.1263, found: 296.1263.

(2*R*,3*R*)-2,3-Dimethyl-4-pentenoic acid (11).[4b,f] A solution of **7** (dr = 98 : 2, 235 mg, 0.9 mmol) in a 1 : 1 mixture of THF and water (12 mL) cooled at 0 °C was treated with an aqueous 30% solution of H_2O_2 (0.39 mL, 3.4 mmol) and $LiOH{\cdot}H_2O$ (70 mg, 1.7 mmol). 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 in 83% yield (117 mg). The aqueous phase was acidified (pH 1) by using 1 M HCl and extracted with CH_2Cl_2 (3 × 10 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 **11** (100 mg, 91% yield, dr = 98 : 2 as determined by 400 MHz ^{1}H NMR analysis) as a colorless liquid. R_f 0.30 (20% EtOAc in hexanes); $[\alpha]_D^{24}$ +37.8 (*c* 1.19, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59 (ddd, *J* = 17.2, 10.3, 8.2 Hz, 1H, C*H*), 5.04–4.93 (m, 2H, CH_2), 2.40 (dq, *J* = 14.7, 7.1 Hz, 1H, C*H*), 2.27 (dq, *J* = 7.1, 7.1 Hz, 1H, C*H*), 1.06 (d, *J* = 7.1 Hz, 3H, CH_3), 1.00 (d, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.6 (CO), 140.5 (CH), 115.3 (CH_2), 44.9 (CH), 40.8 (CH), 18.3 (CH_3), 14.3 (CH_3). IR (neat): ν_{max} 3081s, 1707s, 1460m, 1419m, 1289m, 1220m, 917m cm^{-1}. MS: *m*/*z* (%) relative intensity 129 [$(M + H)^+$, 20], 128 (M^+, 8), 113 (40), 83 (49), 67 (53).

***tert*-Butyl{[(2*R*,3*R*)-2,3-dimethylpent-4-en-1-yl]oxy}dimethylsilane (12).** A solution of $LiBH_4$ (231 mg, 10 mmol) in dry THF (13 mL) was added to a solution of **7** (dr = 98 : 2, 1.23 g, 4.5 mmol) in dry THF (18 mL) in the presence of MeOH (0.5 mL) cooled at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h, then carefully quenched with an aqueous NaOH solution (1 M, 10 mL) and extracted with Et_2O (3 × 30 mL). The combined organic phase was dried over anhydrous Na_2SO_4. Purification by column chromatography (70% Et_2O in pentane) gave the corresponding alcohol as a colorless liquid (354 mg, 69% yield) and the recovered chiral auxiliary as a white solid (529 mg, 72% yield). The obtained alcohol was dissolved in dry CH_2Cl_2 (6 mL) and then imidazole (530 mg, 6.2 mmol) and a solution of TBSCl (1.0 g, 6.2 mmol) in dry hexanes (0.9 mL) were added. The reaction mixture was allowed to stir at room temperature overnight and then quenched with a saturated aqueous $NaHCO_3$ solution (10 mL). The organic phase was collected, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (10% Et_2O in pentane) gave **12** as a colorless liquid (687 mg, 97% yield, dr = 98 : 2 as determined by 400 MHz ^{1}H NMR analysis). R_f 0.80 (10% Et_2O in pentane); $[\alpha]_D^{24}$ +21.2 (*c* 1.1, $CHCl_3$). ^{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.

(1*R*,2*S*,3*R*)-1-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-4-[(*tert*-butyldimethylsilyl)oxy]-2,3-dimethylbutan-1-ol (5) and (1*S*,2*S*,3*R*)-1-[4-(benzyloxy)-3,5-dimethoxyphenyl]-4-[(*tert*-butyldimethylsilyl)oxy]-2,3-dimethylbutan-1-ol (6). To a solution of **12** (dr = 98 : 2, 457 mg, 2.0 mmol) and NMO (812 mg, 6.0 mmol) in CH_2Cl_2 (80 mL) were added OsO_4 (2.5% w/v in *t*-butanol, 1 mL, 0.1 mmol) and water (1 mL). After stirring for 10 h at room temperature, $NaIO_4$ (852 mg, 4.0 mmol) was added, and stirring of the reaction mixture continued for 30 min. 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 **13**. 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 (986 mg, 3.0 mmol) and dry THF (5 mL). The solution was cooled at −78 °C and then a solution of *n*-BuLi (1.77 M in hexanes, 1.70 mL, 3.0 mmol) was added dropwise. The resulting mixture was stirred for 10 min and then a solution of **13** in dry THF (5 mL) was added dropwise. After stirring at −78 °C for 2 h, the reaction mixture was quenched with a saturated

aqueous NH_4Cl solution 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 (20% EtOAc in hexanes) gave **5** (446 mg, 47% yield) and **6** (209 mg, 22% yield).

5: a colorless oil; R_f 0.34 (20% EtOAc in hexanes); $[\alpha]_D^{22}$ +20.1 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 6.9 Hz, 2H, 2 × Ar*H*), 7.21–7.12 (m, 3H, 3 × Ar*H*), 6.46 (s, 2H, 2 × Ar*H*), 4.85 (s, 2H, CH_2), 4.66 (s, 1H, C*H*), 4.42 (br s, 1H, O*H*), 3.69 (s, 6H, 2 × OCH_3), 3.45 (dd, *J* = 10.3, 9.9 Hz, 1H, C*H*H), 3.35 (dd, *J* = 10.3, 4.0 Hz, 1H, CH*H*), 1.94–1.88 (m, 1H, C*H*), 1.68–1.63 (m, 1H, C*H*), 0.81 [s, 9H, SiC(CH_3)$_3$], 0.79 (d, *J* = 7.3 Hz, 3H, CH_3), 0.61 (d, *J* = 7.3 Hz, 3H, CH_3), 0.00 (s, 6H, 2 × SiCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1 (2 × C), 140.5 (C), 138.1 (C), 135.4 (C), 128.5 (2 × CH), 128.1 (2 × CH), 127.7 (CH), 103.2 (2 × CH), 77.1 (CH), 75.0 (CH_2), 65.0 (CH_2), 56.1 (2 × CH_3), 46.0 (CH), 40.4 (CH), 25.9 (3 × CH_3), 18.4 (C), 17.5 (CH_3), 5.6 (CH_3), −5.4 (CH_3), −5.5 (CH_3). IR ($CHCl_3$): ν_{max} 3357w, 1592m, 1505m, 1464m, 1418m 1131s, 1068m, 837w cm^{-1}. MS: *m*/*z* (%) relative intensity 476 [$(M + H)^+$, 1], 271 (19), 251 (39), 223 (41), 218 (35), 191 (25), 181 (27), 152 (33), 91 (100), 77 (31). HRMS (ESI-TOF) calcd for $C_{27}H_{42}O_5SiNa$ $[M + Na]^+$: 497.2699, found: 497.2701.

6: a colorless oil; R_f 0.41 (20% EtOAc in hexanes); $[\alpha]_D^{22}$ −14.8 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.0 Hz, 2H, 2 × Ar*H*), 7.23–7.10 (m, 3H, 3 × Ar*H*), 6.42 (s, 2H, 2 × Ar*H*), 4.85 (s, 2H, CH_2), 4.44 (d, *J* = 5.8 Hz, 1H, O*H*), 4.30 (dd, *J* = 5.8, 5.8 Hz, 1H, C*H*), 3.68 (s, 6H, 2 × OCH_3), 3.45 (dd, *J* = 10.1, 9.0 Hz, 1H, C*H*H), 3.36 (dd, *J* = 10.1, 3.6 Hz, 1H, CH*H*), 1.98–1.87 (m, 1H, C*H*), 1.86–1.76 (m, 1H, C*H*), 0.82 [s, 9H, SiC(CH_3)$_3$], 0.72 (d, *J* = 7.4 Hz, 3H, CH_3), 0.70 (d, *J* = 7.4 Hz, 3H, CH_3), 0.00 (s, 6H, 2 × SiCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3 (2 × C), 140.8 (C), 138.0 (C), 135.7 (C), 128.5 (2 × CH), 128.1 (2 × CH), 127.7 (CH), 103.6 (2 × CH), 77.0 (CH), 75.0 (CH_2), 65.6 (CH_2), 56.1 (2 × CH_3), 44.9 (CH), 35.1 (CH), 25.9 (3 × CH_3), 18.3 (C), 15.7 (CH_3), 12.7 (CH_3), −5.5 (CH_3), −5.6 (CH_3). IR ($CHCl_3$): ν_{max} 3337w, 1593m, 1506m, 1464m, 1419m, 1259m, 1130s, 1066m, 839s cm^{-1}. MS: *m*/*z* (%) relative intensity 475 (M^+, 1), 363 (24), 334 (21), 304 (21), 273 (15), 251 (16), 247 (37), 232 (100), 218 (77), 201 (25), 188 (49), 91 (51). HRMS (ESI-TOF) calcd for $C_{27}H_{42}O_5SiNa$ $[M + Na]^+$: 497.2699, found: 497.2697.

An alternative method to synthesize compound 6. MnO_2 (260 mg, 3.0 mmol) was added to a solution of a 2 : 1 mixture of **5** and **6** (47 mg, 0.1 mmol) in dry pentane (1 mL) at room temperature. The resulting black suspension was stirred for 13 h, filtered through a Celite pad, and the residue was eluted with EtOAc (50 mL). Purification by column chromatography (100% CH_2Cl_2) gave the corresponding ketone in 89% yield (42 mg) as a colorless oil. R_f 0.62 (100% CH_2Cl_2); $[\alpha]_D^{22}$ +39.5 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.1 Hz, 2H, 2 × Ar*H*), 7.35–7.22 (m, 3H, 3 × Ar*H*), 7.20 (s, 2H, 2 × Ar*H*), 5.07 (s, 2H, CH_2), 3.85 (s, 6H, 2 × OCH_3), 3.64 (dd, *J* = 10.0, 4.9 Hz, 1H, C*H*H), 3.58–3.48 (m, 2H, CH*H* and C*H*), 2.04–1.90 (m, 1H, C*H*), 1.15 (d, *J* = 6.9 Hz, 3H, CH_3), 0.91 (d, *J* = 6.8 Hz, 3H, CH_3), 0.87 [s, 9H, SiC(CH_3)$_3$], 0.02 (s, 3H, SiCH_3), 0.00 (s, 3H, SiCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.7 (CO), 153.4 (2 × C), 141.3 (C), 137.4 (C), 133.0 (C), 128.4 (2 × CH), 128.2 (2 × CH), 128.0 (CH), 105.8 (2 × CH), 75.0 (CH_2), 65.0 (CH_2), 56.2 (2 × CH_3), 41.5 (CH), 38.8 (CH), 25.9 (3 × CH_3), 18.3 (C), 15.9 (CH_3), 15.4 (CH_3), −5.4 (CH_3), −5.5 (CH_3). IR ($CHCl_3$): ν_{max} 1671s, 1584s, 1501m, 1464s, 1415s, 1322s, 1131s, 838s cm^{-1}. MS: *m*/*z* (%) relative intensity 415 (100), 383 (5), 324 (18), 306 (9), 209 (15), 91 (40). HRMS (ESI-TOF) calcd for $C_{27}H_{40}O_5SiNa$ $[M + Na]^+$: 495.2543, found: 495.2546.

A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with the above obtained ketone (47 mg, 0.1 mmol) and dry MeOH (1.2 mL). $NaBH_4$ (38 mg, 1 mmol) was added at −78 °C, and the resulting white suspension was allowed to warm to 0 °C over 3 h and then stirred at 0 °C for an additional 1 h. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (100% CH_2Cl_2) gave **6** (42 mg, 89% yield) as a single diastereomer as determined by ^1H NMR (400 MHz) analysis.

(2*S*,3*S*,4*R*)-3,4-Dimethyl-2-(3,4,5-trimethoxyphenyl)tetrahydrofuran (16). According to the same procedure as for **5** and **6**, oxidative cleavage of **12** (dr = 98 : 2, 457 mg, 2.0 mmol) provided **13**, which was further reacted with (3,4,5-trimethoxyphenyl)lithium (**14**) [prepared from 5-bromo-1,2,3-trimethoxybenzene (741 mg, 3.0 mmol) and *n*-BuLi (1.77 M in hexanes, 1.70 mL, 3.0 mmol)] at −78 °C for 2 h. Purification by column chromatography (30% EtOAc in hexanes) gave a colorless oil of **16** (223 mg, 42% yield) as a single diastereomer as determined by ^1H NMR (400 MHz) analysis. R_f 0.45 (30% EtOAc in hexanes); $[\alpha]_D^{28}$ +29.2 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 6.54 (s, 2H, 2 × Ar*H*), 4.37 (d, *J* = 7.9 Hz, 1H, C*H*), 4.25 (dd, d, *J* = 8.3, 6.5 Hz, 1H, C*H*H), 3.87 (s, 6H, 2 × OCH_3), 3.83 (s, 3H, OCH_3), 3.63 (dd, *J* = 8.3, 4.8 Hz, 1H, CH*H*), 2.46–2.34 (m, 1H, C*H*), 2.11 (dq, *J* = 14.4, 6.9 Hz, 1H, C*H*), 1.01 (d, *J* = 6.9 Hz, 3H, CH_3), 1.00 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2 (2 × C), 138.6 (2 × C), 102.8 (2 × CH), 86.7 (CH), 75.3 (CH_2), 60.8 (CH_3), 56.1 (2 × CH_3), 45.3 (CH), 36.7 (CH), 13.4 (CH_3), 12.1 (CH_3). IR ($CHCl_3$): ν_{max} 1593m, 1508m, 1464m, 1421m, 1330m, 1234m, 1128s cm^{-1}. MS: *m*/*z* (%) relative intensity 266 (M^+, 100), 235 (31), 196 (64), 181 (59). HRMS (ESI-TOF) calcd for $C_{15}H_{22}O_4Na$ $[M + Na]^+$: 289.1416, found: 289.1427.

(3*R*,4*S*,5*R*)-5-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-3,4-dimethyldihydrofuran-2(3*H*)-one (18). A solution of TBAF (30 mg, 0.1 mmol) in dry THF (5 mL) was added to a solution of **5** (48 mg, 0.1 mmol) in dry THF (1 mL) at 25 °C under argon. After stirring for 2 h, the reaction mixture was diluted and extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. The obtained crude product was dissolved in dry CH_2Cl_2 (1 mL) under argon and then DIB (103 mg, 0.3 mmol) and TEMPO (3 mg, 0.02 mmol) were sequentially added at room temperature. After stirring for 3.5 h, the resulting suspension was quenched with a saturated aqueous $Na_2S_2O_3$ solu-

tion (5 mL) and diluted with EtOAc (5 mL). The organic phase was collected and then washed with a saturated aqueous $NaHCO_3$ solution and water. The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (30% EtOAc in hexanes) afforded a pale yellow solid of **18** (30 mg, 83% yield) as a single diastereomer as determined by ^{1}H NMR (400 MHz) analysis. mp 75–77 °C (10% CH_2Cl_2 in hexanes); R_f 0.40 (30% EtOAc in hexanes); $[\alpha]_D^{25}$ +50.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.4 Hz, 2H, 2 × Ar*H*), 7.30–7.16 (m, 3H, 3 × Ar*H*), 6.39 (s, 2H, 2 × Ar*H*), 5.38 (d, *J* = 5.0 Hz, 1H, C*H*), 4.94 (s, 2H, CH_2), 3.74 (s, 6H, 2 × OCH_3), 2.95–2.70 (m, 1H, C*H*), 2.75–2.60 (m, 1H, C*H*), 1.15 (d, *J* = 7.2 Hz, 3H, CH_3), 0.49 (d, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9 (CO), 153.7 (2 × C), 137.7 (C), 136.1 (C), 132.0 (C), 128.5 (2 × CH), 128.1 (2 × CH), 127.8 (CH), 102.1 (2 × CH), 82.2 (CH), 74.9 (CH_2), 56.2 (2 × CH_3), 41.1 (CH), 40.1 (CH), 10.1 (CH_3), 9.3 (CH_3). IR ($CHCl_3$): ν_{max} 1772s, 1594s, 1506m, 1463s, 1421m, 1363m, 1339m, 1175s, 1132s, 970m cm^{-1}. MS: *m*/*z* (%) relative intensity 356 (M^+, 2), 264 (100), 209 (48), 181 (11), 177 (19), 91 (22). HRMS (ESI-TOF) calcd for $C_{21}H_{24}O_5Na$ $[M + Na]^+$: 379.1521, found: 379.1521.

(3*R*,4*S*,5*S*)-5-[4-(Benzyloxy)-3,5-dimethoxyphenyl]-3,4-dimethyldihydrofuran-2(3*H*)-one (19). According to the same procedure as for **18**, desilylation of **6** (95 mg, 0.2 mmol) followed by oxidative lactonization of the crude product using DIB (186 mg, 0.6 mmol) and TEMPO (6 mg, 0.04 mmol), and purification by column chromatography (30% EtOAc in hexanes) provided a pale yellow solid of **19** (57 mg, 80% yield) with contamination of its C-3 epimer (dr = 95 : 5) as determined by ^{1}H NMR (400 MHz) analysis. mp 79–81 °C (10% CH_2Cl_2 in hexanes); R_f 0.55 (30% EtOAc in hexanes); $[\alpha]_D^{22}$ +14.0 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 7.6 Hz, 2H, 2 × Ar*H*), 7.35–7.15 (m, 3H, 3 × Ar*H*), 6.43 (s, 2H, 2 × Ar*H*), 4.93 (s, 2H, CH_2), 4.91 (d, *J* = 6.7 Hz, 1H, C*H*), 3.75 (s, 6H, 2 × OCH_3), 2.73 (dq, *J* = 7.4, 7.4 Hz, 1H, C*H*), 2.47 (dq, *J* = 14.3, 7.4 Hz, 1H, C*H*), 1.16 (d, *J* = 7.4 Hz, 3H, CH_3), 1.04 (d, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7 (CO), 153.8 (2 × C), 137.7 (C), 136.9 (C), 134.1 (C), 128.5 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 102.6 (2 × CH), 85.8 (CH), 75.0 (CH_2), 56.3 (2 × CH_3), 42.3 (CH), 38.3 (CH), 12.7 (CH_3), 10.2 (CH_3). IR ($CHCl_3$): ν_{max} 1769s, 1594m, 1507m, 1464m, 1132s cm^{-1}. MS: *m*/*z* (%) relative intensity 356 (M^+, 19), 265 (100), 209 (58), 181 (25), 177 (26), 149 (14), 91 (70). HRMS (ESI-TOF) calcd for $C_{21}H_{24}O_5Na$ $[M + Na]^+$: 379.1521, found: 379.1537.

(3*R*,4*S*,5*R*)-3,4-Dimethyl-5-(3,4,5-trimethoxyphenyl)dihydrofuran-2(3*H*)-one (3)[3i] and (3*R*,4*S*,5*S*)-3,4-dimethyl-5-(3,4,5-trimethoxyphenyl)dihydrofuran-2(3*H*)-one (4). A flame-dried round bottom flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with **18** (36 mg, 0.1 mmol), Pd/C (10% w/w, 11 mg, 0.1 mmol), and dry EtOH (2.5 mL). The argon inlet was replaced by a H_2 balloon, and the reaction mixture was stirred at room temperature for 20 min. The resulting mixture was filtered through a Celite pad and then the residue was eluted with EtOAc (25 mL) to yield **20** in a quantitative yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.48 (s, 2H, 2 × Ar*H*), 5.45 (d, *J* = 5.0 Hz, 1H, C*H*), 3.87 (s, 6H, 2 × OCH_3), 2.99 (dq, *J* = 7.2, 7.2 Hz, 1H, C*H*), 2.80–2.77 (m, 1H, C*H*), 1.21 (d, *J* = 7.2 Hz, 3H, CH_3), 0.56 (d, *J* = 7.2 Hz, 3H, CH_3).

Compound **20** was dissolved in dry acetone (1 mL) and then Me_2SO_4 (30 μL, 0.4 mmol) and anhydrous K_2CO_3 (69 mg, 0.5 mmol) were added. After stirring at reflux for 1 h, the reaction mixture was cooled to room temperature, quenched with water, and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4. Purification by column chromatography (10% EtOAc in hexanes) gave **3** (7 mg, 25% yield) and **4** (11 mg, 39% yield).

3: a colorless viscous oil; R_f 0.25 (30% EtOAc in hexanes); $[\alpha]_D^{27}$ +51.4 (*c* 0.34, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.48 (s, 2H, 2 × Ar*H*), 5.46 (d, *J* = 4.9 Hz, 1H, C*H*), 3.86 (s, 6H, 2 × OCH_3), 3.85 (s, 3H, OCH_3), 3.00 (dq, *J* = 7.2, 7.2 Hz, 1H, C*H*), 2.82–2.72 (m, 1H, C*H*), 1.22 (d, *J* = 7.2 Hz, 3H, CH_3), 0.58 (d, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9 (CO), 153.5 (2 × C), 137.4 (C), 131.9 (C), 102.1 (2 × CH), 82.2 (CH), 60.9 (CH_3), 56.2 (2 × CH_3), 41.2 (CH), 40.1 (CH), 10.1 (CH_3), 9.4 (CH_3). IR ($CHCl_3$): ν_{max} 1771s, 1594m, 1464m, 1173m, 1131s cm^{-1}. MS: *m*/*z* (%) relative intensity 280 (M^+, 58), 205 (11), 196 (100), 181 (36), 180 (12). HRMS (ESI-TOF) calcd for $C_{15}H_{20}O_5Na$ $[M + Na]^+$: 303.1208, found: 303.1207.

4: a colorless viscous oil; R_f 0.35 (30% EtOAc in hexanes); $[\alpha]_D^{28}$ +8.3 (*c* 0.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.51 (s, 2H, 2 × Ar*H*), 4.98 (d, *J* = 6.6 Hz, 1H, C*H*), 3.86 (s, 6H, 2 × OCH_3), 3.84 (s, 3H, OCH_3), 2.79 (dq, *J* = 7.4, 7.4 Hz, 1H, C*H*), 2.53 (dq, *J* = 14.1, 7.4 Hz, 1H, C*H*), 1.23 (d, *J* = 7.4 Hz, 3H, CH_3), 1.11 (d, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.6 (CO), 153.5 (2 × C), 137.9 (C), 134.0 (C), 102.5 (2 × CH), 85.7 (CH), 60.9 (CH_3), 56.2 (2 × CH_3), 42.3 (CH), 38.3 (CH), 12.7 (CH_3), 10.2 (CH_3). IR ($CHCl_3$): ν_{max} 1770s, 1594m, 1509m, 1464m, 1421m, 1239m, 1131s, 1002m cm^{-1}. MS: *m*/*z* (%) relative intensity 280 (M^+, 58), 279 (41), 205 (21), 196 (100), 181 (59), 178 (40). HRMS (ESI-TOF) calcd for $C_{15}H_{20}O_5Na$ $[M + Na]^+$: 303.1208, found: 303.1206.

(3*R*,4*S*,5*S*)-5-(2-Bromo-3,4,5-trimethoxyphenyl)-3,4-dimethyldihydrofuran-2(3*H*)-one (22).[3e] To a solution of **4** (25 mg, 0.09 mmol) in $CHCl_3$ (1 mL) was added NBS (17 mg, 0.1 mmol) at room temperature. After stirring for 1.5 h, the solvent was removed *in vacuo*, and the crude product was purified by column chromatography (30% EtOAc in hexanes) to give a colorless oil of **22** (29 mg, 90% yield) as a single diastereomer as determined by ^{1}H NMR (400 MHz) analysis. R_f 0.43 (30% EtOAc in hexanes); $[\alpha]_D^{27}$ −18.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.63 (s, 1H, Ar*H*), 5.34 (d, *J* = 2.2 Hz, 1H, C*H*), 3.92 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 2.75 (dq, *J* = 7.4, 7.4 Hz, 1H, C*H*), 2.63–2.55 (m, 1H, C*H*), 1.25 (d, *J* = 7.4 Hz, 3H, CH_3), 1.19 (d, *J* = 7.4 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.8 (CO), 153.1 (C), 151.2 (C), 142.7 (C), 133.9 (C), 107.4 (C), 104.7 (CH), 84.3 (CH), 61.1 (2 × CH_3), 56.3 (CH_3), 41.1 (CH), 36.4 (CH), 14.3 (CH_3), 9.6 (CH_3). IR ($CHCl_3$): ν_{max} IR ($CHCl_3$): ν_{max} 1773s, 1571m, 1484m, 1397s, 1331s, 1167s, 1111s, 999s cm^{-1}. MS: *m*/*z* (%) relative intensity 359

(M^+, 32), 358 (42), 357 (38), 276 (100), 275 (58), 274 (98), 273 (76), 259 (22), 204 (13), 124 (19). HRMS (ESI-TOF) calcd for $C_{15}H_{19}O_5BrNa$ $[M + Na]^+$: 381.0314, found: 381.0310.

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