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Total Synthesis of (−)-Orthodiffenes A and C

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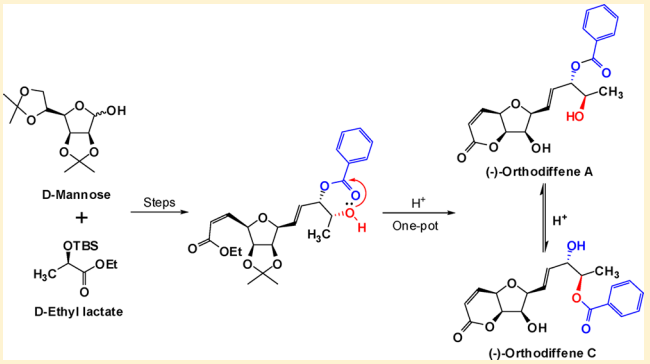
Supporting Information

ABSTRACT: The efficient and concise synthesis of (−)-orthodiffenes A and C has been accomplished for the first time in eight steps from readily available chiral synthons, D-mannose and D-ethyl lactate. Our work confirmed the complete structure of orthodiffenes A and C, including their absolute stereochemistry. The key steps of our total synthesis involved cis-fused tetrahydrofuran cyclization, one-pot deprotection−lactonization, and intramolecular benzoyl migration according to a biosynthetic hypothesis of orthodiffenes.



INTRODUCTION

Bioactive natural products have long been recognized as the major source of drugs and lead structures in the field of anticancer drug discovery.[1] About 75% of anticancer agents under clinical trials are either natural products or derived from natural products.[2] Very recently, Das and co-workers reported the isolation and structure elucidation of four novel furanopyrans, named as orthodiffenes A−D (Figure 1), from

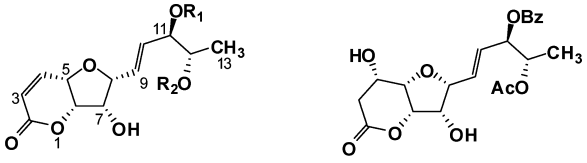


Figure 1. Structures of orthodiffenes A−D.

the Indian herb *Orthosiphon diffuses*.[3] The orthodiffenes A−C exhibit high cytotoxic activities against various tumor cell lines in vitro, and orthodiffene A (**1**) and orthodiffene B (**2**) were found to possess activity comparable to camptothecin against HL-60 and Jurkat cells, respectively. The structures of these compounds were established based on extensive spectroscopic analysis including 2D NMR experiments. In addition, the relative stereochemistry of orthodiffene A (Figure 1) was determined by using X-ray crystallographic diffraction analysis, whereas the absolute configuration is still unknown. Orthodiffenes A−D are composed of a similar unusual furanopyrone skeleton with an extra olefinic side chain connecting at C8−C9. Furthermore, the four consecutive stereogenic centers (C5−C8) on tetrahydrofuran framework were determined to be cis to each other from the coupling relationship. These all-syn tetrasubstituted furanopyrans are relatively rare in nature.

Despite the promising biological activity of orthodiffenes, the mode of action in terms of pharmacology remains unknown. To the best of our knowledge, the total synthesis of orthodiffenes has not been reported yet. The impressive biological activity, novel structural features, and the lack of structure−activity relationship (SAR) studies on orthodiffenes encouraged us to undertake a total synthesis of these novel natural products. Owing to the intriguing structural features of the unusual furanopyrone and consecutive all-syn tetrasubstituted tetrahydrofuran structural framework, the total synthesis of these compounds represents a challenge.

Orthodiffenes A and C have the same carbon backbone and stereochemistry, except for the benzoyl ester on the side chain which attaches to C-11 and C-12, respectively. This phenomenon is usually ascribed to the esterase involved in the natural biosynthetic process, suggesting that orthodiffenes A and C could be isomerized through an intramolecular ester migration at C-11 and C-12 via orthoester intermediates with retention of chirality.[4] Accordingly, we expected that orthodiffenes A and C could be prepared from the same

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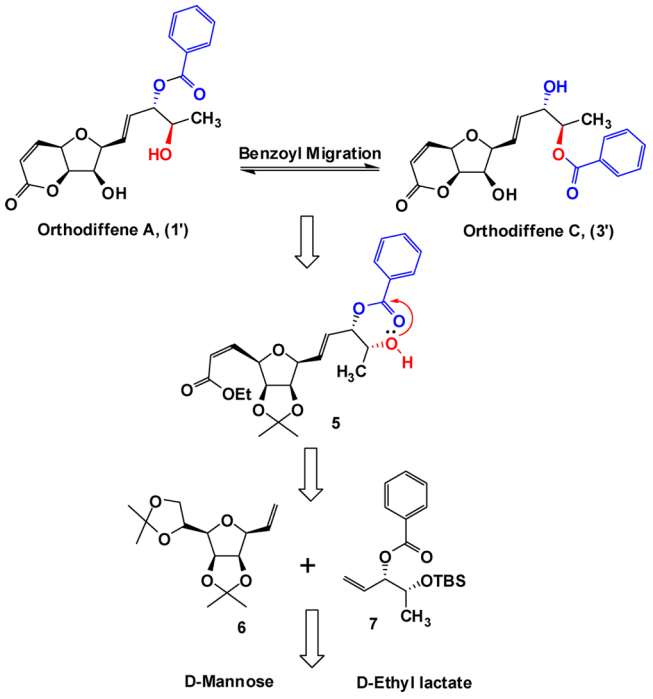
precursor and transformed to each other under a controlled benzoyl migration condition.

Due to the structural similarities between L-mannofuranoside and the desired furanopyrone skeleton (C3−C10) of orthodiffenes (Figure 1), we initially imagined that the natural orthodiffenes could be derived from unnatural L-mannose. Given the prohibitive cost of L-mannose and the unknown absolute configurations of the orthodiffenes, we were interested in synthesizing both the natural (**1**−**4**) and unnatural enantiomer (**1′**−**4′**) for structural determination and further biological studies. Consequently, our synthetic blueprint required swift access to either enantiomer of the orthodiffenes, based on the readily available natural carbohydrate D-mannose. Herein, we report the first total synthesis of (−)-orthodiffenes A and C by a short and efficient route.

RESULTS AND DISCUSSION

The retrosynthetic analysis of orthodiffenes A and C is outlined in Scheme 1. We envisaged that orthodiffenes A and C could be elaborated from well functionalized (*Z*)-*α*,*β*-unsaturated ethyl ester **5** by one-pot acetonide deprotection/lactonization accompanied by benzoyl migration (Scheme 1). The *trans*-olefin moiety at C9/C10 could be installed by coupling of *β*-D-*C*-furanoside subunit **6** with the olefinic side chain **7** involving an olefin cross-metathesis strategy. The *β*-D-*C*-furanoside subunit **6**, in which all four cis stereocenters are in place, could be readily accessible from the natural carbohydrate 2,3:5,6-di-*O*-isopropylidene-*α*-D-mannofuranose (**8**). The Bz and TBS group protected allylic alchol **7** can be easily prepared from D-ethyl lactate through reduction and Grignard addition by a one-pot sequence in three steps. Details of the studies thus undertaken are described below.

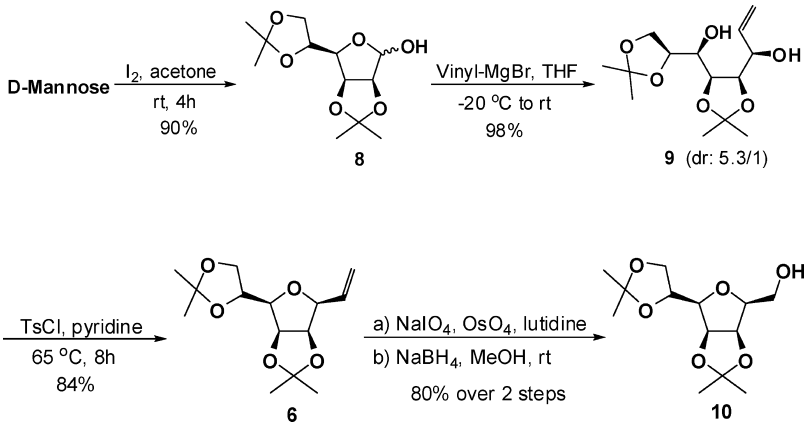
Scheme 1. Retrosynthetic Analysis of Orthodiffenes A and C



Our synthesis commenced with transformation of D-mannose to the diol **9** in two steps according to a modified procedure from Singh (Scheme 2).[5] The known 2,3:5,6-di-*O*-isopropylidene-*α*-D- mannofuranose (**8**), easily obtained from D-mannose in 90% yield using iodine as catalyst in dry acetone,[6] was treated with 5.0 equiv of vinylmagnesium bromide, leading to a known compound **9** as a separable 5.3:1 mixture of diastereoisomers in almost quantitative yield (98%). Attempts to improve the diastereoselectivity of this reaction by changing solvents or running at lower temperature (−20 °C to −80 °C) were fruitless. Chemoselective tosylation of diol **9**, with 1.1 equiv of *p*-toluenesulfonyl chloride (TsCl) in pyridine at 65 °C,[7] initiated a favorable regioselective intramolecular S_N2 substitution at the allylic position to form the configuration-inversed and cis-fused cyclization compound **6** in 84% yield. Other methods using triflic anhydride,[8] $FeCl_3$,[9] $SOCl_2$,[10] and Mitsunobu reaction[11] did not show an acceptable yield improvement. It is noteworthy that cis-fused tetrahydrofuran **6** was obtained as a single diastereomer, and the other isomers were not observed even when adding excessive TsCl (up to 2.2 equiv). The stereochemistry of the resulting *β*-*C*-glycosides was confirmed by NOE experiments and derivatization of **6** to the known compound **10**[12] in two steps (oxidative cleavage of olefins with osmium tetraoxide−sodium periodate[13] followed by sodium borohydride reduction).

With the completion of the *β*-*C*-furanoside subunit, our attention was then focused on the synthesis of the olefinic side chain **7** as shown in Scheme 3. The protected allylic alchol **7** was prepared from D-ethyl lactate via the known TBS-protected ethyl lactate **11**.[14] Reduction of **11** with DIBAL-H to the corresponding lactaldehyde and subsequent treatment with vinylmagnesium chloride delivered the required (*R*,*S*)-**12** as a

Scheme 2. Synthesis of *β*-*C*-Glycosides 6



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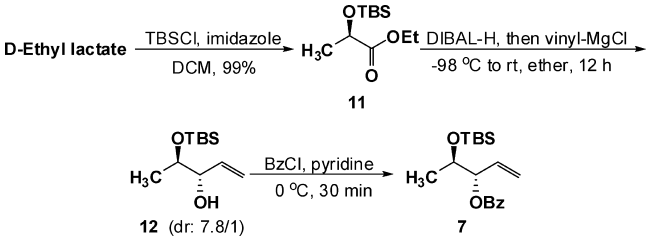
Scheme 3. Synthesis of 7

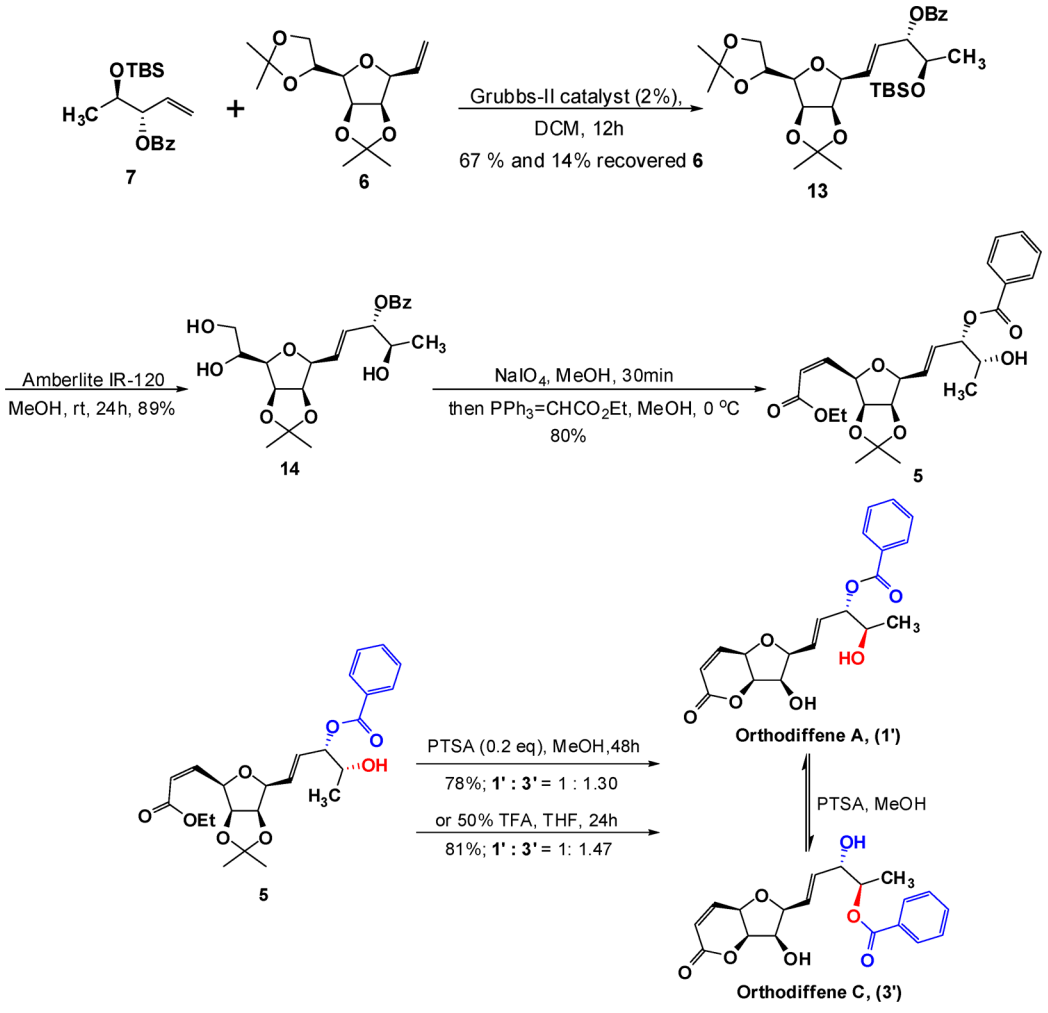


7.8:1 mixture of diastereoisomers in a one-pot process.[15] Blocking of the corresponding allylic alcohol as a benzoyl ester provided **7**. This approach afforded the desired protected allylic alchol **7** in a yield of 74% over three steps from D-ethyl lactate (Scheme 3).

With both key fragments in hand, we then investigate the olefin cross metathesis of *β*-*C*-furanoside **6** with **7** (Scheme 4). This reaction carried out smoothly using an excess of **7** (4.8 equiv) and a catalytic amount of Grubbs-II in DCM at room temperature for 12 h generated the desired olefin **13** in a yield of 67% with excellent *E*:*Z* selectivity (>15:1).[16] Selective hydrolysis of the 1,2-acetonide and TBS protecting group with Amberlite IR-120 (H^+) ion-exchange resin in methanol afforded **14** in 89% yield. Oxidative cleavage of the diol in **14** with $NaIO_4$, followed by immediate Wittig olefination with (ethoxycarbonylmethylene)triphenylphosphorane, afforded predominantly (*Z*)-*α*,*β*-unsaturated ester **5** in 80% yield with cis:trans > 13:1.[17]

After screening several conditions, we achieved one-pot acetonide deprotection/lactonization by treatment of **5** with a catalytic amount of *p*-toluenesulfonic acid (PTSA) in methanol, or 50% trifluoroacetic acid (TFA) aqueous solution in THF;[18] both approaches furnished a mixture of orthodiffenes A (**1′**) and C (**3′**) which were readily separated by column chromatography (Scheme 4). Interestingly, treatment of either pure orthodiffene A (**1′**) or orthodiffene C (**3′**) with a catalytic amount of PTSA in methanol at room temperature for 72 h afforded a mixture of orthodiffenes A (**1′**) and C (**3′**) in a balanced ratio from 1:1.3 to 1:1.7 (Scheme 4). We assumed that such an acidolysis equilibrium between orthodiffene A (**1′**) and orthodiffene C (**3′**) probably resulted from a process of intramolecular transesterification via dioxolane intermediate.[4c] The spectroscopic data (^1H, ^{13}C NMR, IR, and HRMS) of both synthetic orthodiffene A (**1′**) and orthodiffene C (**3′**) were in good agreement with those of the natural products (see the Supporting Information). However, the optical rotation obtained for synthetic samples are opposite in sign to the value reported for the natural products, which shows that our synthetic (−)-orthodiffene A (**1′**) and C (**3′**) are the enantiomers of the natural products.[19]

Scheme 4. Total Synthesis of Orthodiffenes A and C



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CONCLUSION

We have completed the first total synthesis of compounds **1′** and **3′**, the enantiomers of natural orthodiffenes A and C, respectively, in eight steps from readily available D-mannose and D-ethyl lactate. The key transformations involved in this work are the tosylation-mediated, one-pot, cis-fused tetrahydrofuran cyclization, olefin cross metathesis, and one-pot tandem deprotection/lactonization. In addition, we observed intramolecular benzoyl migration between orthodiffene C_{11} and C_{12} under acidic conditions in methanol, supporting a possible biotransformation of orthodiffenes through esterase-promoted ester migration. The current method offers an opportunity to prepare orthodiffenes A and C with the same process at the same time. We believe our strategy also provides a short and efficient approach for the syntheses of other orthodiffene-like natural products.

EXPERIMENTAL SECTION

1. General Experimental. Unless noted otherwise, commercially available materials were used without further purification. All solvents were dried according to the established procedures ahead of use. All reagents were purchased from commercial corporations. Flash chromatography (FC) was performed using silica gel (200−300 mesh) according to the standard protocol. All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on gel F254 plates. Optical rotations were measured using a polarimeter with a thermally jacketed 5 cm cell at approximately 25 °C. Infrared spectra were recorded as KBr discs using a FT-IR spectrophotometer with wave numbers expressed in cm^{-1}. High-resolution mass spectrometry data (HRMS) were acquired using a Q-TOF analyzer in acetone as solvent. ^1H NMR and ^{13}C NMR were measured on 400 or 100 MHz spectrometers (in $CDCl_3$ with TMS as an internal standard). Chemical shifts (δ) are given in ppm relative to residual solvent (usually chloroform; δ 7.26 for ^1H NMR or 77.0 for proton-decoupled ^{13}C NMR), and coupling constants (J) in hertz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, m for multiplet, and br when the signal in question is broadened.

2. Experimental Procedures. *Synthesis of (3aS,4R,6S,6aR)-4-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-vinyltetrahydrofuro[3,4-d][1,3]dioxole (**6**).* To a solution of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (6.9 g, 26.54 mmol) in dry THF (60 mL) was added vinylmagnesium bromide (133 mmol) via syringe in three portions at −20 °C under N_2 protection. After 90 min, the solution was warmed to room temperature and stirred for another 20 h. The reaction was quenched by the slow addition of aq NH_4Cl (50 mL, Caution!). The aqueous layer was extracted with ether (3 × 100 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The crude diol could be used for the next step without further purification. To a solution of crude diol (ca. 26.54 mmol) in dry pyridine (60 mL) was added TsCl (11.2 g, 58.4 mmol) in three portions at rt under N_2 protection. After 10 min, the solution was warmed to 65 °C and stirred for a further 8−10 h. The reaction was quenched at rt by the addition of MeOH (20 mL). The solution was concentrated with toluene and poured into saturated aqueous $CuSO_4$ (100 mL) and then extracted with DCM (3 × 120 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The crude was purified by flash column chromatography (hexanes/EtOAc 7:1) to give compound **6** as a yellow oil (5.01 g, 70% for two steps). $[\alpha]_D^{25}$ −16.1 (*c* 3.2, $CHCl_3$); ^1H NMR (400 MHz): δ 1.31 (s, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 1.47 (s, 3H), 3.52 (dd, J = 7.6 Hz, J = 3.6 Hz, 1H), 3.97 (dd, J = 7.2 Hz, J = 3.6 Hz, 1H), 4.04−4.11 (m, 2H), 4.38−4.43 (m, 1H), 4.65 (dd, J = 6.0 Hz, J = 3.6 Hz, 1H), 4.76 (dd, J = 6.0 Hz, J = 3.6 Hz, 1H), 5.29 (dd, J = 10.4 Hz, J = 0.8 Hz, 1H), 5.35 (dd, J = 17.2 Hz, J = 0.8 Hz, 1H), 5.95 (ddd, J = 17.2 Hz, J = 10.4 Hz, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz) δ 24.5, 25.2, 25.7, 26.9, 66.9, 73.0, 80.8, 81.6, 82.5, 83.2, 108.9, 112.5, 119.2, 132.1; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{22}O_5Na$ 293.1365; Found 293.1376.

*Synthesis of ((3aR,4S,6R,6aS)-6-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (**10**).*[12] To a mixture of compound **6** (108 mg, 0.4 mmol), 2,6-lutidine (0.1 mL, 0.79 mmol), and solid $NaIO_4$ (129 mg, 0.6 mmol) in dioxane (8 mL) and deionized H_2O (2 mL) was added a solution of OsO_4 (5 mg) in ^{t}BuOH and stirred at rt for 12 h. After completion, the reaction was quenched by the addition of saturated aq NH_4Cl (10 mL). The reaction mixture was extracted with DCM (3 × 10 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The crude aldehyde was used for the next step without further purification. To a solution of crude aldehyde (ca. 0.4 mmol) in MeOH (5 mL) was added solid $NaBH_4$ (31 mg, 0.8 mmol) in two portions at 0 °C. After 5 min, the solution was warmed to rt and stirred for a further 15 min. The mixture was concentrated under vacuum. The residue was added into saturated aqueous NaCl (10 mL) and extracted with DCM (3 × 50 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The crude material was purified by flash column chromatography (hexanes/EtOAc 1:1) to give compound **10** as a colorless oil (88 mg, 80% for two steps). Data are consistent with a previously characterized compound.[12]

*Synthesis of (3S,4R)-4-(tert-Butyldimethylsilyloxy)pent-1-en-3-yl Benzoate (**7**).* To a solution of TBS-protected lactate **11** (2.33 g, 10 mmol) in dry ether (50 mL) was added DIBAL-H (11.7 mL, 14 mmol) via syringe in three portions at −98 °C under N_2 atmosphere. After 15 min, vinylmagnesium chloride (28.6 mL, 20 mmol) was added into the mixture via syringe. The solution was then warmed to room temperature and stirred overnight. The reaction was quenched by the slow addition of a saturated solution of K/Na tartrate. (80 mL, Caution!). The aqueous layer was extracted with ether (3 × 80 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The crude allylic alcohol **12** was used for next step without further purification. To a solution of crude allylic alcohol (ca. 10 mmol) in dry pyridine (25 mL) was added BzCl (1.74 mL, 15 mmol) by two portions at 0 °C. After 15 min, the solution was warmed to rt and stirred for a further 15 min. The reaction was quenched by the addition of MeOH (10 mL) and concentrated with toluene. The residue was poured into saturated aqueous $CuSO_4$ (50 mL) and extracted with DCM (3 × 50 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The crude was purified by flash column chromatography (hexanes/EtOAc 30:1) to give compound **7** as a colorless oil (2.36 g, 74% for two steps). $[\alpha]_D^{25}$ −24.8 (*c* 1.7, $CHCl_3$); ^1H NMR (400 MHz): δ 0.04 (s, 6H), 0.89 (s, 9H), 1.20 (d, J = 6.4 Hz, 3H), 4.02−4.09 (m, 1H), 5.26−5.45 (m, 3H), 5.96−6.05 (ddd, J = 17.2 Hz, J = 10.4 Hz, J = 6.8 Hz, 1H); 7.44 (t, J = 7.6 Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 8.07 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz) δ −4.8, −4.5, 18.0, 19.8, 25.7, 69.7, 79.4, 118.7, 128.3, 129.7, 130.6, 132.9, 133.1, 165.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{28}O_3SiNa$ 343.1705; Found 343.1708.

*Synthesis of (3S,4R,E)-4-(tert-Butyldimethylsilyloxy)-1-((3aR,4S,6R,6aS)-6-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydrofuro[3, 4-d][1,3]dioxol-4-yl)pent-1-en-3-yl Benzoate (**13**).* Grubbs second catalyst (15 mg, 0.018 mmol) was added to a mixture of **7** (1.38 g, 4.3 mmol) and **6** (243 mg, 0.9 mmol) in dry DCM (75 mL). The reaction was stirred for 12 h at rt. The solution was concentrated and purified by flash column chromatography (hexanes/EtOAc 6:1) to give compound **13** as a colorless oil (339 mg, 67%) and **6** (34 mg, 14%). $[\alpha]_D^{25}$ 13.8 (*c* 2.1, $CHCl_3$); ^1H NMR (400 MHz): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 1.19 (d, J = 6.0 Hz, 3H), 1.29 (s, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 1.44 (s, 3H), 3.52 (dd, J = 7.6 Hz, J = 3.6 Hz, 1H), 4.01 (dd, J = 6.4 Hz, J = 3.6 Hz, 1H), 4.03−4.10 (m, 3H), 4.38−4.42 (m, 1H), 4.65 (dd, J = 6.0 Hz, J = 3.6 Hz, 1H), 4.76 (dd, J = 6.0 Hz, J = 3.6 Hz, 1H), 5.41 (dd, J = 6.4 Hz, J = 4.0 Hz, 1H), 5.90 (dd, J = 16.0 Hz, J = 6.4 Hz, 1H), 5.97 (dd, J = 16.0 Hz, J = 6.4 Hz, 1H), 7.41−7.45 (m, 2H), 7.54 (dt, J = 7.6 Hz, J = 1.2 Hz, 1H), 8.05−8.07 (m, 2H); ^{13}C NMR (100 MHz) δ −4.8, −4.5, 18.0, 19.9, 24.7, 25.3, 25.7, 25.8, 26.9, 67.0, 69.7, 73.1, 78.4, 80.9, 81.7, 82.2,

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82.5, 109.0, 112.6, 128.2, 128.5, 129.3, 129.7, 130.6, 132.8, 165.6; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{46}O_8SiNa$ 585.2860; Found 585.2863.

Synthesis of (3S,4R,E)-1-((3aR,4S,6R,6aS)-6-((Z)-3-Ethoxy-3-oxoprop-1-enyl)-2, 2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-4-hydroxypent-1-en-3-yl Benzoate (5). Amberlite IR-120 acidic resin (25 mg) was added to the solution of **13** (175 mg, 0.31 mmol) in MeOH (15 mL). The reaction was stirred for 24 h at rt. The solid resin was filtered with cotton wool. The solution was concentrated under vacuum to afford **14** as a colorless oil. The crude triol **14** could be used for the next step without any purification. A small sample was purified on a silica gel column to get the physical data of **14**: $[\alpha]_D^{25}$ 31.0 (c 1.0, $CHCl_3$); ^1H NMR (400 MHz): δ 1.25 (d, J = 6.4 Hz, 3H), 1.30 (s, 3H), 1.40 (s, 3H), 2.56 (br s, 3H), 3.56 (dd, J = 8.0 Hz, J = 3.6 Hz, 1H), 3.74 (dd, J = 11.6 Hz, J = 5.6 Hz, 1H), 3.85 (dd, J = 11.6 Hz, J = 3.2 Hz, 1H), 4.00−4.09 (m, 3H), 4.66 (dd, J = 6.0 Hz, J = 3.6 Hz, 1H), 4.83 (dd, J = 6.0 Hz, J = 4.0 Hz, 1H), 5.48 (dd, J = 4.8 Hz, J = 0.4 Hz, 1H), 5.92 (dd, J = 16.0 Hz, J = 5.6 Hz, 1H), 6.00 (dd, J = 16.0 Hz, J = 5.6 Hz, 1H), 7.42−7.46 (m, 2H), 7.58 (dt, J = 7.2 Hz, J = 1.2 Hz, 1H), 8.05−8.07 (m, 2H); ^{13}C NMR (100 MHz) δ 18.5, 24.8, 25.8, 64.5, 69.0, 70.1, 77.9, 80.9, 81.3, 81.6, 82.2, 112.8, 127.8, 128.4, 129.1, 129.7, 130.1, 133.1, 165.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{28}O_8Na$ 431.1682; Found 431.1671. To a solution of triol **14** (102 mg, 0.25 mmol) in MeOH (20 mL) was added solid $NaIO_4$ (80 mg, 0.375 mmol) at rt. The mixture was stirred for 30 min and filtered with Celite. To the resulting solution was added (ethoxycarbonylmethylene)triphenylphosphorane (174 mg, 0.5 mmol) at 0 °C. After being stirred at 0 °C for 60 min, the reaction was concentrated under vacuum. The crude material was purified by flash column chromatography (hexanes/EtOAc 2:1) to give compound **5** as a colorless oil (89 mg, 80%). $[\alpha]_D^{25}$ −41.4 (c 3.5, $CHCl_3$); ^1H NMR (400 MHz): δ 1.25 (s, 3H), 1.26 (t, J = 6.8 Hz, 3H), 1.27 (d, J = 6.0 Hz, 3H), 1.40 (s, 3H), 2.42 (br s, 1H), 4.00−4.08 (m, 1H), 4.10 (dd, J = 5.6 Hz, J = 4.0 Hz, 1H), 4.16 (q, J = 6.8 Hz, 2H), 4.68 (dd, J = 5.6 Hz, J = 4.0 Hz, 1H), 5.03 (dd, J = 6.0 Hz, J = 3.6 Hz, 1H), 5.05−5.08 (m, 1H), 5.51 (dd, J = 6.0 Hz, J = 4.0 Hz, 1H), 5.94−6.01 (m, 2H), 6.05 (dd, J = 16.0 Hz, J = 5.6 Hz, 1H), 6.35 (dd, J = 12.0 Hz, J = 6.4 Hz, 1H), 7.43 (t, J = 8.0 Hz, 2H), 7.54−7.58 (m, 1H), 8.05−8.07 (m, 2H); ^{13}C NMR (100 MHz) δ 14.1, 18.5, 24.8, 25.8, 60.4, 69.0, 78.0, 78.6, 81.5, 82.4, 82.9, 112.5, 120.9, 127.8, 128.3, 129.4, 129.7, 130.1, 133.1, 144.8, 165.7; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{30}O_8Na$ 469.1838; Found 469.1810.

Synthesis of Orthodiffene A (1′) and Orthodiffene C (3′). To a solution of ester **5** (42 mg, 0.094 mmol) in MeOH (5 mL) was added PTSA·H_2O (3.6 mg, 0.019 mmol) at rt. The mixture was stirred for 48 and concentrated under vacuum. The crude was purified by flash column chromatography (hexanes/EtOAc 1:3) to give orthodiffene A (**1′**) (11.5 mg, 34%) and orthodiffene C (**3′**) (14.9 mg, 44%). Orthodiffene A (**1′**): white solid, $[\alpha]_D^{25}$ −35.2 (c 0.8, $CHCl_3$); ^1H NMR (400 MHz): δ 1.25 (d, J = 6.8 Hz, 3H), 3.05 (br s, 2H), 4.04 (dq, J = 6.8 Hz, J = 2.0 Hz, 1H), 4.47 (t, J = 4.8 Hz, 1H), 4.55 (dd, J = 4.8 Hz, J = 4.0 Hz, 1H), 4.61 (ddd, J = 6.8 Hz, J = 4.0 Hz, J = 1.2 Hz, 1H), 5.06 (dd, J = 6.8 Hz, J = 4.8 Hz, 1H), 5.39−5.42 (m, 1H), 5.90 (dd, J = 15.6 Hz, J = 4.4 Hz, 1H), 5.93 (dd, J = 15.6 Hz, J = 4.4 Hz, 1H), 6.08 (dd, J = 10.0 Hz, J = 1.2 Hz, 1H), 6.79 (dd, J = 10.0 Hz, J = 4.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 2H), 7.56−7.59 (m, 1H), 8.04−8.06 (m, 2H); ^{13}C NMR (100 MHz) δ 18.7, 67.1, 69.0, 73.6, 78.1, 79.1, 79.3, 121.9, 128.4, 128.6, 129.5, 129.7, 130.0, 133.3, 141.6, 161.1, 165.8; IR (film): 3410, 2923, 2852, 1713, 1633, 1452, 1261, 1106, 1025, 802 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{20}O_7Na$ 383.1107; Found 383.1093. Orthodiffene C (**3′**): white solid, $[\alpha]_D^{25}$ −33.7 (c 0.6, $CHCl_3$); ^1H NMR (400 MHz): δ 1.36 (d, J = 6.8 Hz, 3H), 2.48 (br s, 2H), 4.36 (t, J = 4.4 Hz, 1H), 4.38−4.41(m, 1H), 4.48 (dd, J = 4.8 Hz, J = 4.0 Hz, 1H), 4.60 (ddd, J = 6.0 Hz, J = 4.0 Hz, J = 0.8 Hz, 1H), 5.04 (dd, J = 6.0 Hz, J = 4.8 Hz, 1H), 5.18 (dq, J = 6.8 Hz, J = 4.4 Hz, 1H), 5.87 (dd, J = 15.6 Hz, J = 4.8 Hz, 1H), 5.92 (dd, J = 15.6 Hz, J = 4.8 Hz, 1H), 6.06 (dd, J = 10.0 Hz, J = 0.8 Hz, 1H), 6.74 (dd, J = 10.0 Hz, J = 4.0 Hz, 1H), 7.43 (t, J = 8.0 Hz, 2H), 7.53−7.58 (m, 1H), 8.02−8.04 (m, 2H); ^{13}C NMR (100 MHz) δ 15.1, 66.9, 73.5, 73.6, 74.1, 79.0, 79.4, 121.6, 127.5, 128.4, 129.6, 130.2, 132.8, 133.1, 141.9, 161.3, 166.2; IR (film): 3418, 2925, 2853, 1713, 1632, 1451, 1262, 1110, 802 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{20}O_7Na$ 383.1107; Found 383.1089;

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(19) Synthetic orthodiffene A and orthodiffene C exhibit physical properties (^{1}H, ^{13}C NMR, IR, and HRMS) that are in good agreement with those of natural orthodiffene A and orthodiffene C. See Supporting Information for detailed comparative ^{1}H and ^{13}C NMR of synthetic (−)-orthodiffenes A (**1′**) and C (**3′**) and natural orthodiffenes A and C. However, the measured optical rotation for the synthetic (−)-orthodiffenes A (**1′**) and C (**3′**) material does not compare well to the reported value for the natural orthodiffene A and orthodiffene C { (−)-orthodiffene A (**1′**): $[\alpha]_D^{25}$ −35.2 (*c* 0.8, $CHCl_3$); $[\alpha]_D^{25}$ +84.1 (*c* 0.5, $CHCl_3$) lit.;[3] (−)-orthodiffene C (**3′**): $[\alpha]_D^{25}$ −33.7 (*c* 0.6, $CHCl_3$); $[\alpha]_D^{25}$ +139.6 (*c* 1.0, $CHCl_3$) lit.[3]}. We are currently working to understand this discrepancy.