JOC The Journal of Organic Chemistry

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Total Synthesis of the Marine Polyketide (−)-Gracilioether F

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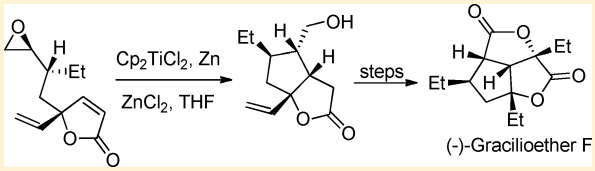
Supporting Information

ABSTRACT: First asymmetric synthesis of the marine natural product (−)-gracilioether F is described from a D-mannitol derived known compound. The key step involves intramolecular 1,4-conjugate addition of a hydroxymethyl radical generated from Ti (III) mediated ring opening of a terminal epoxy ring tethered to a butenolide to produce stereoselectively a five-membered ring fused bicyclic lactone, the core structure present in gracilioether F.



Marine sponges are rich sources of polyketide natural products of diverse structures. A number of structurally novel compounds have recently been isolated[1] from the family of *plakortins*. A few representative examples are gracilioether A **1**, gracilioether E **2**, gracilioether F **3**, gracilioether G **4**, gracilioether I **5**, hippolachnin A **6**, etc. (Figure 1). A few

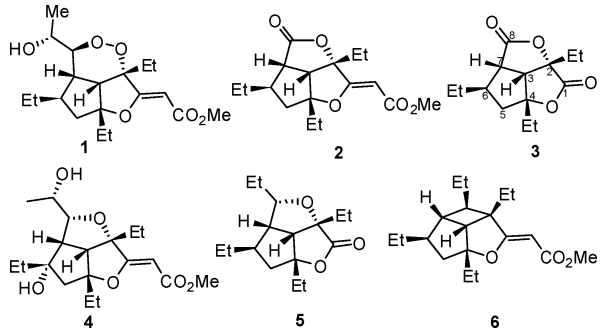


Figure 1. Structures of gracilioethers and hippolachnin A.

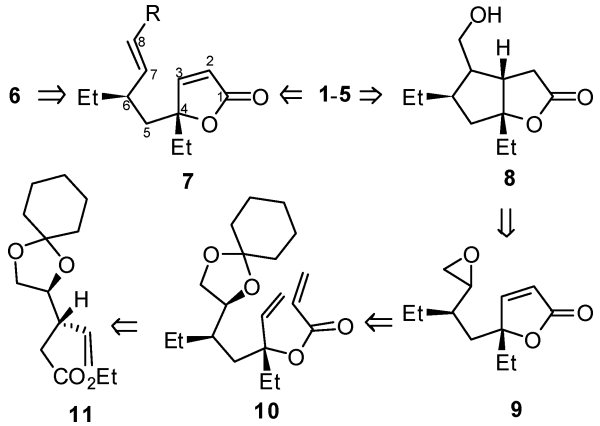
members of this family exhibit significant biological activities.[2] These compounds are characterized mainly by the presence of a densely functionalized bridged tricyclic backbone with at least five contiguous stereocenters. Intrigued by the unique structures and promising medicinal properties we[3] and others[4−6] became interested in the synthesis of some members of this family.

We visualized 4-substituted butenolide **7** as the common precursor for access to hippolachnin A **6** and gracilioethers. Quite some time back we reported our preliminary work on the synthesis of the tricyclic core structure of hippolachnin A through intramolecular [2 + 2] photocycloaddition of the butenolide **7** (R = Et).[3] In that communication we invoked that this reaction plausibly proceeded through initial 1, 4-conjugate addition of a radical generated during irradiation to provide a cyclopentannulated butanolide biradical intermediate which collapsed to lead to tricyclic core structure of hippolachnin A.

We envisioned that a similar concept involving 1,4-conjugate addition of a radical generated at C-7 to the butenolide **7** might be employed to give rise to the bicyclic lactone **8**, the structural unit present in the gracilioether F **3**. While our work was near completion, Xu and Wu[6] reported synthesis of gracilioethers E and F using an analogous concept.

The concept we thought for generating a radical at C-7 involves Cp_2TiCl mediated opening of epoxy ring reaction developed by RajanBabu[7] and extensively employed[8] in many natural products synthesis. The epoxide **9**, to be derivable in principle, from the butenolide **7** was envisioned as the substrate for initiating the radical reaction (Scheme 1). The advantage of

Scheme 1. Retrosynthetic Plan

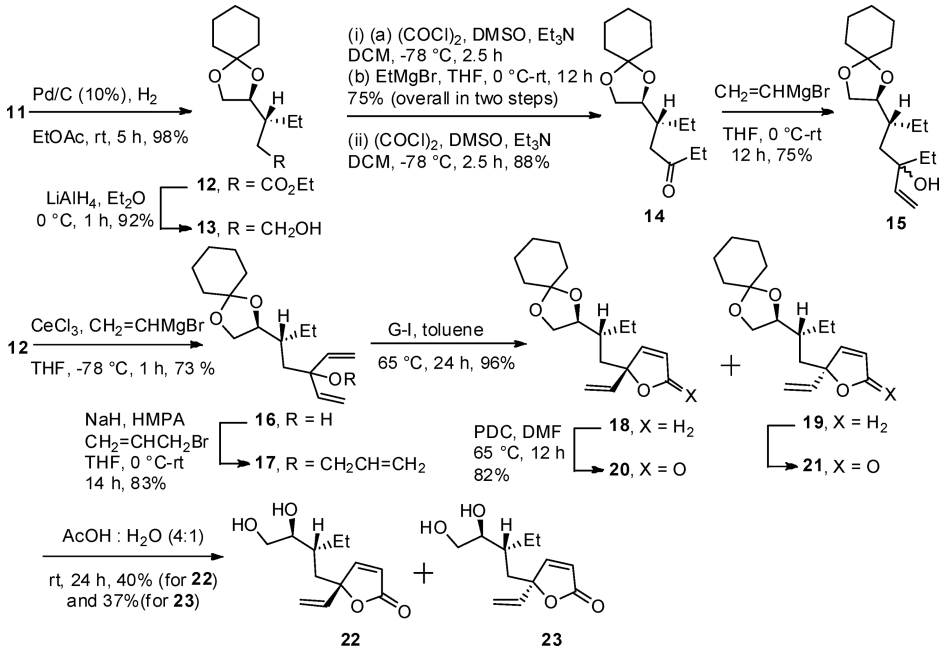


this process is that it will generate directly a CH_2OH group with simultaneous annulation of a 5-membered ring on to the butenolide to form the bicyclic lactone **8**, an advanced intermediate for synthesis of gracilioethers. Annulation of a ring on to a butenolide in this way to construct fused bicyclic lactone systems for natural products synthesis has not been explored.[9] The hydroxymethyl group in **8** can be manipulated to construct either the second lactone unit present in **3** or the furan moieties of the gracilioethers **4** and **5** after stereo-

Received: May 15, 2017
Published: June 21, 2017

DOI: 10.1021/acs.joc.7b01179
J. Org. Chem. 2017, 82, 7675−7682

Scheme 2. Synthesis of the Butenolides 22 and 23



controlled addition of the Et group to the carbonyl group to be available on oxidation of the methylene α to the lactone carbonyl. The butenolide moiety in compound **9** should in principle be available from ring closing metathesis (RCM)[10] of the diene unit in **10**. The masked diol in **10** will be the source of the epoxide ring. Compound **10** in turn will be available from D-mannitol-derived known unsaturated ester **11**[11] which was employed by us earlier in several chiral syntheses.[12] The present route will thus accomplish synthesis of gracilioethers in enantiomerically pure form, unlike the other reported approaches which provided only the racemates. We herein report the results of our investigation based on this concept culminating in the first asymmetric synthesis of (−)-gracilioether F **3**.

We initially focused on preparation of the RCM precursor **10**. The unsaturated ester **11** was first transformed to the hydroxy-compound **13** in 92% yield through hydrogenation of the vinyl group followed by $LiAlH_4$ reduction of the ester unit (Scheme 2). The hydroxy-compound **13** was then converted to the ethyl ketone **14** in 88% yield through a three-step sequence involving oxidation of the hydroxyl group-addition of ethyl magnesium bromide to the resulting aldehyde and oxidation of the carbinol thus obtained. Reaction of vinyl magnesium bromide to **14** resulted in a 1:1 diastereoisomeric mixture of the carbinol **15** in 75% yield. Attempted coupling of the hydroxyl group with acryloyl chloride to prepare the RCM precursor **10** failed. Even allylation (NaH-allyl bromide) of the carbinol **15** was unsuccessful. The failure of the carbinol to undergo coupling was possibly due to the steric crowding around the tertiary hydroxyl group. We thought that steric crowding can be reduced by replacing the Et group with a less steric demanding vinyl group which can be easily converted to ethyl at a suitable stage of the synthesis. Reaction of the ester **12** with excess vinyl magnesium bromide in the presence of anhydrous ceric chloride afforded the divinyl carbinol **16** in 73% yield. Unfortunately the carbinol **16** was also found to be inert toward coupling with acryloyl chloride. At this stage we decided to change the protocol. The carbinol **16** could be allylated smoothly to afford the allyl ether **17** in excellent (83%) yield. RCM of **17** in toluene at 65 °C in the presence of Grubbs' catalyst **G-I** [$Cl_2(PCy_3)_2Ru$ = CHPh] afforded a mixture of the dihydrofuran derivatives **18** and **19** in ca. 1:1 ratio in 96% yield. Separation of these compounds through silica gel column chromatography was unsuccessful. So we decided to proceed with this mixture anticipating that the desired isomer could be separated in a subsequent step. Oxidation of this mixture of dihydrofurans with PDC in DMF produced again an inseparable mixture of the butenolides **20** and **21** in 82% yield. This mixture was then treated with HOAc-H_2O to form a mixture of the diols **22** and **23**. To our delight the diols could be separated by column chromatography to produce the pure diols **22** and **23** in 40% and 37% yields, respectively. However, assignment of stereochemistry to them became a daunting task.

We decided to proceed for the preparation of the epoxide required for carrying out the crucial radical cyclization. The diol **22** was treated with tosyl chloride to produce the monotosylate **24** in 90% yield (Scheme 3). Treatment of the monotosylate **24** with NaH afforded the epoxide **25**. Attempted purification of the epoxide caused extensive decomposition. Thus, without purification and further characterization the epoxide **25** was treated with in situ generated Cp_2TiCl. Cyclization proceeded efficiently to afford stereoselectively the bicyclic lactone **26** in 61% yield as the only isolable product. The structure of **26** was established through 2D NMR spectroscopy (HSQC, COSY and ROESY) (Figure 2). The compound **26** obtained from the butenolide **22** was found to possess the desired stereochemistry for synthesis of gracilioethers. Additional evidence in support of the structure **26** was obtained from its subsequent transformation (Scheme 4) to the diol **37** whose structure was established through single crystal X-ray crystallography. The other diastereoisomer **27** which could arise from the epoxide **25** during radical cyclization was not formed at all probably due to the steric repulsion between the two vicinal substituents Et and hydroxymethyl group. This transformation led to the assignment of the structure of the butenolides as **22** and **23**.

DOI: 10.1021/acs.joc.7b01179
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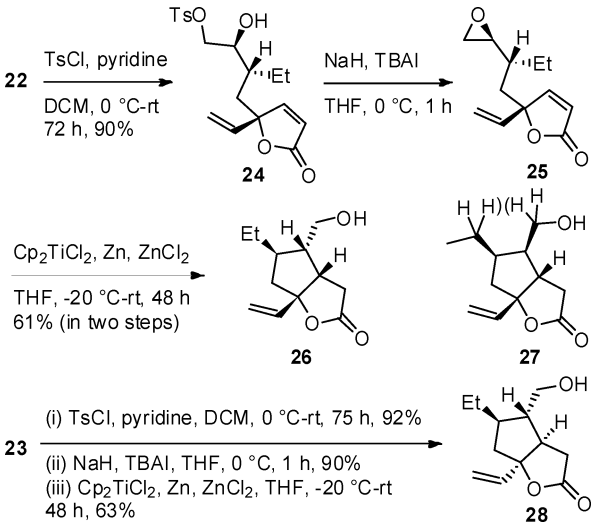
Scheme 3. Synthesis of the Bicyclic Lactones 26 and 28



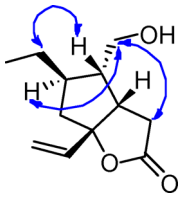
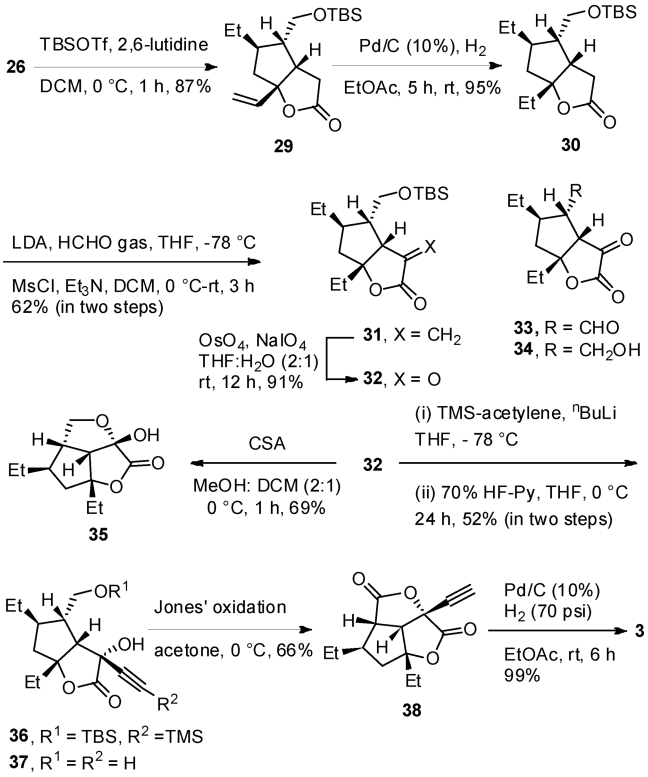


Figure 2. ROESY of **26**.

Scheme 4. Synthesis of Gracilioether F



The butenolide **23** was similarly transformed through the corresponding epoxide to give after reaction with Cp_2TiCl the bicyclic lactone **28**. Needless to say, compound **28** appeared to have the undesired stereochemistry (Figure 3) at the ring junction (from analysis of 2 D NMR spectra) for transformation to gracilioethers.

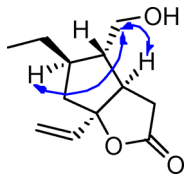


Figure 3. ROESY of **28**.

Thus, we proceeded with the bicyclic lactone **26** for synthesis of gracilioethers. The hydroxyl group was first protected to give the TBS ether **29** (Scheme 4). Compound **29** was then hydrogenated over 10% Pd−C to afford the lactone **30**. Oxidation of the methylene unit α to the lactone carbonyl was the next target. Attempt to introduce a hydroxyl group α to the lactone carbonyl through the corresponding enolate using 2-sulfonyloxaziridine[13a] or with molecular oxygen[13b] failed. The lactone **30** was then transformed to the α-methylene lactone **31** in good yield as delineated in Scheme 4. The methylene lactone **31** was then converted to the α-keto lactone **32** [OsO_4 (cat.)-$NaIO_4$].

An attempt to convert the silyl ether **32** to gracilioether I **5** required transformation of **32** to the aldehyde **33** so that EtMgBr can be added to the aldehyde unit as well as to the keto group next to the lactone carbonyl in a single operation. The resulting diol could then be expected to cyclize to provide **5**.[14] However, removal of the silyl protecting group with camphor sulfonic acid to form the hydroxy-compound **34** resulted in its concomitant ring closure to form the tricyclic ether **35**, a structural analogue of gracilioether I **5** in 69% yield.

For synthesis of gracilioether F **3** we first tried to introduce an Et group. All attempts to add a two-carbon nucleophile such as EtMgBr or vinyl magnesium bromide to **32** was of no use. Finally lithium trimethylsilyl acetylide was found to add smoothly to produce the lactone **36**. Global desilylation of **36** could be achieved only with HF·Py to produce the diol **37**. Structure of the diol **37** was unequivocally established through single crystal X-ray (see Page S3 in Supporting Information).[15] Jones oxidation of the diol **37** afforded the lactone **38** in 66% yield. Catalytic hydrogenation (H_2, 10% Pd/C, EtOAc, 70 psi) of the acetylinic moiety finally afforded (−)-gracilioether F **3** in 99% yield. The observed spectral data and optical rotation were found to be closely comparable (see Table S1 in Supporting Information) to those reported in literature.

In conclusion we have accomplished the first total synthesis of (−)-gracilioether F. The key step involves annulation of a five-membered ring on to an appropriately constructed butenolide through intramolecular 1,4-conjugate addition of a radical generated through Cp_2TiCl mediated ring opening of an epoxy ring. The present strategy can also be extended for synthesis of gracilioethers **1**, **2** and **4** through transformation of the lactone carbonyl to the unsaturated ester following the procedure of McCallum et al.[4a] used for synthesis of hippolachnin A.

EXPERIMENTAL SECTION

General Experimental Methods. All air and moisture sensitive reactions were performed in oven-dried glassware under argon atmosphere with freshly distilled anhydrous solvents. Reactions were monitored by thin layer chromatography (Silica gel 60 F_{254}) with

DOI: 10.1021/acs.joc.7b01179
J. Org. Chem. 2017, 82, 7675−7682

ethanolic anisaldehyde as developing agent. Organic extracts were dried over anhydrous sodium sulfate. Column chromatography was performed with 60−120 mesh silica gel unless otherwise stated. PE refers to the fraction of petroleum ether having bp 60−80 °C. EA refers to ethyl acetate. Optical rotations were measured using sodium (589, D line) lamp and reported as follows: $[\alpha]_D^{25}$ (c = g/100 mL, solvent). IR spectra for liquids were recorded as thin films. Unless otherwise stated NMR spectra were recorded in $CDCl_3$ at 300 MHz for ^1H and 75 MHz for ^{13}C using residual chloroform as an internal standard and the chemical shifts are reported in δ ppm scale. High resolution mass spectra (HRMS) were recorded on a QTOF I (quardrupole-hexapole-TOF) mass spectrometer with an orthogonal Z-spray-electrospray interface.

Bruker SMART APEX diffractometer equipped with a CCD area detector at 298 K was used for collecting single crystal X-ray data. Intensity data of the crystal was collected using Mo Kα irradiation (λ = 0.7107 Å). To process data integration and reduction SAINT software was used. The structure was solved by direct methods using SHELXTL and was refined on F^2 by the full-matrix least-squares technique using the SHELXL-2014/6. MERCURY 3.9 was used for graphics. The non-hydrogen atoms were refined anisotropically until convergence.

*(R)-Ethyl 3-((S)-1,4-dioxaspiro[4.5]decan-2-yl)pentanoate (**12**).* The ester **11** (2.43 g, 9.1 mmol) in EtOAc (20 mL) was stirred with 10% Pd/C (61 mg) under hydrogen atmosphere at room temperature for 5 h. The reaction mixture was filtered through Celite. The Celite bed was washed with Et_2O (2 × 100 mL). The combined organic layers were dried and evaporated. Purification by column chromatography (8% EA/PE) provided the ester **12** as a liquid (2.4 g, 98%): $[\alpha]_D^{25}$ −25.6 (c 3.1, $CHCl_3$); IR (neat) ν_{max} 1733 cm^{-1}; ^1H NMR δ 4.12−4.02 (m, 3H), 3.92 (dd, J = 7.8, 6.3 Hz, 1H), 3.54 (t, J = 7.8 Hz, 1H), 2.35−2.28 (m, 1H), 2.18−2.07 (m, 2H), 1.55−1.52 (m, 7H), 1.48−1.41 (m, 2H), 1.36−1.29 (m, 3H), 1.21 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 173.1, 109.3, 77.2, 66.4, 60.4, 39.3, 36.2, 34.9, 34.7, 25.3, 24.1, 23.9, 23.7, 14.3, 11.3; HRMS (ESI) m/z calcd for $C_{15}H_{26}O_4Na$ $(M + Na)^+$, 293.1729; found 293.1728.

*(R)-3-((S)-1,4-Dioxaspiro[4.5]decan-2-yl)pentan-1-ol (**13**).* A solution of the ester **12** (503 mg, 1.86 mmol) in Et_2O (15 mL) was added dropwise to a magnetically stirred suspension of $LiAlH_4$ (71 mg, 1.86 mmol) in Et_2O (10 mL). Stirring was continued for 1 h at 0 °C. The reaction was quenched by saturated aqueous Na_2SO_4 (5 mL) and filtered through Celite. The Celite bed was washed with Et_2O (150 mL). The combined organic layers were dried and evaporated under reduced pressure. Purification by column chromatography (30% EA/PE) provided **13** (391 mg, 92%) as oil: $[\alpha]_D^{25}$ +21.0 (c 1.3, $CHCl_3$); ^1H NMR δ 4.15−4.11 (m, 1H), 3.97 (dd, J = 8.1, 6.6 Hz, 1H), 3.75−3.68 (m, 1H), 3.64−3.56 (m, 2H), 2.35 (brs, 1H), 1.73−1.66 (m, 3H), 1.64−1.56 (m, 8H), 1.50−1.35 (m, 4H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 109.4, 77.8, 66.6, 61.0, 39.4, 36.3, 34.9, 32.4, 25.3, 24.1, 24.0, 23.1, 11.5; HRMS (ESI) m/z calcd for $C_{13}H_{24}O_3Na$ $(M + Na)^+$, 251.1623; found 251.1620.

(5R)-5-((S)-1,4-Dioxaspiro[4.5]decan-2-yl)heptan-3-ol. A solution of DMSO (0.29 mL, 4.1 mmol) in DCM (8 mL) was added slowly to a solution of oxalyl chloride (0.17 mL, 1.97 mmol) in DCM (8 mL) at −78 °C and was stirred for 30 min at this temperature. A solution of the alcohol **13** (374 mg, 1.64 mmol) in DCM (10 mL) was added dropwise and stirred at −78 °C for 1 h. Et_3N (0.91 mL, 6.56 mmol) was added to this solution and the solution was allowed to attain room temperature. Stirring was continued for 1h at rt. The reaction mixture was quenched by addition of water (5 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layer was washed with brine (20 mL) and dried. The residual mass after removal of solvent under reduced pressure was chromatographed (10% EA/PE) to afford the aldehyde (337 mg). The aldehyde thus obtained was used for the next step without any further characterization.

Ethylmagnesium bromide [3 M in Et_2O] (0.6 mL, 1.8 mmol) was added dropwise to a solution of the above aldehyde (337 mg, 1.49 mmol) in THF (10 mL) at 0 °C and was allowed to attain room temperature slowly. After stirring for additional 12 h, the reaction mixture was quenched by saturated aqueous NH_4Cl (1 mL). The reaction mixture was then filtered through Celite bed. The Celite bed was washed with Et_2O (100 mL). The combined organic layer was dried and concentrated under reduced pressure. Purification by column chromatography (15% EA/PE) afforded the carbinol (liquid) (314 mg, 75%): ^1H NMR (for the mixture of diastereoisomers) δ 4.18−4.06 (m, 1H), 3.95−3.89 (m, 1H), 3.62−3.45 (m, 2H), 2.77 (brs, 1H), 1.85−1.70 (m, 1H), 1.58−1.53 (m, 8H), 1.44−1.34 (m, 8H), 0.93−0.86 (m, 6H); ^{13}C NMR (of the mixture) δ 109.3 (×2), 78.0, 77.6, 72.1, 70.1, 66.3 (×2), 39.4, 38.2, 37.0, 36.2 (×2), 36.1, 34.8, 34.6, 31.2, 30.4, 25.2 (×2), 24.4, 24.1, 24.0, 23.9, 23.8, 22.9, 11.7, 11.3, 10.2, 10.0; HRMS (ESI) m/z calcd for $C_{15}H_{28}O_3Na$ $(M + Na)^+$, 279.1936; found 279.1938.

*(R)-5-((S)-1,4-Dioxaspiro[4.5]decan-2-yl)heptan-3-one (**14**).* Following the procedure described above for oxidation of the hydroxy-compound **13**, the carbinol (292 mg, 1.14 mmol) was oxidized to afford the ketone **14** (liquid) (255 mg, 88%); $[\alpha]_D^{25}$ −6.7 (c 1.2, $CHCl_3$); IR (neat) ν_{max} 1716 cm^{-1}; ^1H NMR δ 4.07−4.01 (m, 1H), 3.86 (dd, J = 8.1, 6.6 Hz, 1H), 3.51 (t, J = 7.8 Hz, 1H), 2.45−2.35 (m, 3H), 2.27−2.14 (m, 2H), 1.53−1.50 (m, 8H), 1.39−1.23 (m, 4H), 0.99 (t, J = 7.2 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 210.6, 109.2, 77.1, 66.2, 42.4, 37.7, 36.4, 36.2, 34.8, 25.3, 24.0, 23.8, 23.6, 11.5, 7.8; HRMS (ESI) m/z calcd for $C_{15}H_{26}O_3Na$ $(M + Na)^+$, 277.1780; found 277.1782.

*(3S,5R)-3-Ethyl-5-((S)-1,4-dioxaspiro[4.5]decan-2-yl)hept-1-en-3-ol (**15**).* Vinylmagnesium bromide [1 M in THF] (1.05 mL, 1.05 mmol) was added slowly to **14** (241 mg, 0.95 mmol) in THF (6 mL) at 0 °C. The reaction mixture was allowed to attain room temperature slowly and stirred additionally for 12 h. The reaction mixture on quenching with saturated aqueous NH_4Cl (1 mL) was filtered through Celite. The Celite bed was washed with Et_2O (100 mL). The combined organic layers were dried and evaporated under reduced pressure. Purification by column chromatography (10% EA/PE) provided **15** (201 mg, 75%) as a liquid as an inseparable 1:1 mixture. ^1H NMR (of the mixture) δ 5.83−5.59 (m, 1H), 5.35−5.20 (m, 1H) 5.12−5.01 (m, 1H), 4.24−4.16 (m, 1H), 3.92−3.87 (m, 1H), 3.77 and 3.13 (s, 1H), 3.60−3.51 (m, 1H), 2.04−1.91 (m, 1H), 1.76−1.65 (m, 2H), 1.60−1.56 (m, 6H), 1.50−1.43 (m, 2H), 1.39−1.27 (m, 4H), 1.23−1.08 (m, 2H), 0.95−0.80 (m, 6H); ^{13}C NMR (of the mixture) δ 145.0, 143.8, 113.5, 112.0, 109.5, 109.4, 77.5, 77.4, 74.6, 74.5, 65.6, 65.3, 39.2, 38.2, 36.1 (×2), 36.0, 35.8, 35.7, 34.7, 34.5, 32.9, 26.3, 25.8, 25.2, 25.1, 24.0 (×2), 23.8, 23.7, 12.2, 12.0, 8.1 (×2); HRMS (ESI) m/z calcd for $C_{17}H_{30}O_3Na$ $(M + Na)^+$,305.2093; found 305.2096.

*(R)-5-((S)-1,4-Dioxaspiro[4.5]decan-2-yl)-3-vinylhept-1-en-3-ol (**16**).* $CeCl_3$, $7H_2O$ (9.85 g, 26.43 mmol) was heated under vacuum for 2 h in an oil bath preset at 150 °C. On cooling to rt THF (25 mL) was added to it and stirred for 2 h. The ethyl ester **12** (2.38 g, 8.81 mmol) in THF (25 mL) was added to it and stirred for 1 h. To this mixture cooled at −78 °C, vinylmagnesium bromide [1 M in THF] (29.1 mL, 29.1 mmol) was slowly added over 15 min. The reaction mixture was stirred for 1 h at this temperature. Saturated aqueous NH_4Cl (5 mL) was added to quench the reaction. The reaction mixture was filtered through Celite. The Celite bed was washed with Et_2O (250 mL). The filtrate was dried and evaporated under reduced pressure. Purification by column chromatography (10% EA/PE) of the residual mass provided the carbinol **16** (1.8 g, 73%) as a pale yellow liquid: $[\alpha]_D^{25}$ −1.2 (c 2.1, $CHCl_3$); ^1H NMR δ 5.93 (dd, J = 17.4, 10.8 Hz, 1H), 5.79 (dd, J = 17.1, 10.5 Hz, 1H), 5.39 (dd, J = 17.1, 1.8 Hz, 1H), 5.29 (dd, J = 17.1, 1.5 Hz, 1H), 5.13 (dd, J = 10.5, 2.1 Hz, 1H), 5.00 (dd, J = 10.5, 1.5 Hz, 1H), 4.26−4.20 (m, 1H), 4.01 (s, 1H), 3.95−3.90 (m, 1H), 3.58 (t, J = 8.1 Hz, 1H), 2.04−1.96 (m, 1H), 1.77−1.55 (m, 10H), 1.49−1.39 (m, 2H), 1.32−1.12 (m, 2H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 144.6, 142.5, 113.5, 111.7, 109.7, 77.3, 74.8, 65.4, 39.2, 36.0, 35.9, 34.6, 26.1, 25.3, 24.0, 23.8, 12.2; HRMS (ESI) m/z Calcd for $C_{17}H_{28}O_3Na$ (M + Na)+, 303.1936; found, 303.1933.

*(S)-2-((R)-5-(Allyloxy)-5-vinylhept-6-en-3-yl)-1,4-dioxaspiro[4.5]decane (**17**).* A solution of the hydroxy-compound **16** (1.78 g, 6.36 mmol) in THF (18 mL) was added slowly to a magnetically stirred suspension of NaH (1.83 g, 38.16 mmol) (50% in oil) in THF (20 mL) cooled at 0 °C and was stirred for 30 min. HMPA (5.53 mL, 31.8 mmol) was slowly added at this temperature and stirred for 15 min.

DOI: 10.1021/acs.joc.7b01179
J. Org. Chem. 2017, 82, 7675−7682

Then allyl bromide (3.30 mL, 38.16 mmol) was added at this temperature and was allowed to stir for 14 h. Saturated aqueous NH_4Cl (20 mL) was slowly added to quench the reaction and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layer was washed with brine (20 mL), dried and evaporated under reduced pressure. The residual mass was purified by column chromatography (5% EA/PE) to obtain the triene **17** (1.69 g, 83%) as oil: $[\alpha]_D^{25}$ +0.46 (c 4.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 5.95−5.76 (m, 3H), 5.32−5.20 (m, 4H), 5.12−4.99 (m, 2H), 4.18−4.12 (m, 1H), 3.96−3.79 (m, 3H), 3.59 (t, J = 7.8 Hz, 1H), 1.81−1.76 (m, 1H), 1.74−1.65 (m, 1H), 1.60−1.56 (m, 9H), 1.39−1.25 (m, 4H), 0.88 (t, J = 7.8 Hz, 3H); ^{13}C NMR δ 140.5, 140.4, 135.9, 115.8, 115.7, 115.2, 109.1, 80.9, 77.5, 67.0, 64.3, 38.6, 36.9, 36.5, 35.0, 25.5, 24.5, 24.2, 24.0, 11.1; HRMS (ESI) m/z Calcd for $C_{20}H_{32}O_3Na$ (M + Na)+, 343.2249; found 343.2246.

*(S)-2-((R)-5-(Allyloxy)-5-vinylhept-6-en-3-yl)-1,4-dioxaspiro[4.5]-decane (**18** and **19**).* A solution of the triene **17** (1.6 g, 5.0 mmol) in deoxygenated toluene (130 mL) was heated with Grubbs' first generation catalyst **G-I** (412 mg, 0.5 mmol) at 65 °C for 24 h. On cooling, toluene was removed under vacuum and the residual mass was purified by column chromatography (7% EA/PE) to afford the dihydrofuran derivatives **18** and **19** (liquid) (1.4 g, 96%) as an inseparable 1:1 diastereoisomeric mixture; ^{1}H NMR (of the mixture) δ 5.95−5.83 (m, 2H), 5.73−5.69 (m, 1H), 5.26−5.18 (m, 1H), 5.05−4.99 (m, 1H), 4.66−4.62 (m, 2H), 4.14−4.03 (m, 1H), 3.98−3.92 (m, 1H), 3.64−3.54 (m, 1H), 1.61−1.56 (m, 12H), 1.40−1.36 (m, 3H), 0.93−0.86 (m, 3H); ^{13}C NMR (of the mixture) δ 142.0, 141.7, 132.2, 132.1, 126.2, 126.0, 112.7, 112.4, 109.1, 109.0, 92.7, 92.5, 78.0, 77.7, 75.0, 74.8, 67.5, 66.9, 38.8, 38.2, 37.9, 37.8, 36.6, 36.5, 35.1, 35.0, 25.4 (×2), 25.0, 24.6, 24.2 (×2), 24.1, 24.0, 11.3, 11.0; HRMS (ESI) m/z Calcd for $C_{18}H_{28}O_3Na$ (M + Na)+, 315.1936; found, 315.1933.

*5-((R)-2-((S)-1,4-Dioxaspiro[4.5]decan-2-yl)butyl)-5-vinylfuran-2(5H)-one (**20** and **21**).* A mixture of the dihydrofurans **18** and **19** (1.36 g, 4.66 mmol) in DMF (20 mL) was treated with PDC (8.77 g, 23.3 mmol) for 12 h at 65 °C. On cooling the reaction mixture was filtered through neutral alumina. The alumina bed was washed with Et_2O (200 mL). The combined organic layers were washed with water (50 mL), brine (15 mL) and dried. The residual mass after removal of solvent under reduced pressure was chromatographed (30% EA/PE) to provide a mixture (1:1) of the butenolides **20** and **21** (1.17 g, 82%) as oil; IR (neat) ν_{max} 1760 cm^{-1}; ^{1}H NMR (of the mixture) δ 7.40-7.32 (m, 1H), 6.03−5.97 (m, 1H), 5.92−5.80 (m, 1H), 5.37−5.28 (m, 1H), 5.21−5.14 (m, 1H), 4.16−4.08 (m, 1H), 3.94−3.87 (m, 1H), 3.54−3.48 (m, 1H), 1.98−1.90 (m, 1H), 1.77−1.70 (m, 1H), 1.58−1.53 (m, 8H), 1.36−1.32 (m, 5H), 0.90−0.84 (m, 3H); ^{13}C NMR (of the mixture) δ 172.5, 172.4, 159.0, 158.7, 136.1, 135.1, 120.3, 119.6, 116.5, 116.0, 109.2, 109.1, 90.6 (×2), 76.8 (×2), 66.1, 65.8, 37.0, 36.6, 36.5, 36.3, 36.2, 35.9, 34.6, 34.5, 25.3 (×2), 25.0, 24.4, 24.1, 24.0, 23.8, 23.7, 11.5, 11.2; HRMS (ESI) m/z calcd for $C_{18}H_{26}O_4Na$ (M + Na)$^+$, 329.1729; found 329.1726.

*(S)-5-((2R,3S)-2-Ethyl-3,4-dihydroxybutyl)-5-vinylfuran-2(5H)-one (**22**) and (R)-5-((2R,3S)-2-Ethyl-3,4-dihydroxybutyl)-5-vinylfuran-2(5H)-one (**23**).* A mixture of the butenolides **20** and **21** (784 mg, 2.56 mmol) was treated with AcOH (48 mL) and water (12 mL) at room temperature for 24 h. The solvent was removed under vacuum and the residue was purified by flash column chromatography (SiO_2, 230−400 mesh) (80% EA/PE) to afford the pure butenolides **22** (R_f 0.3, 80% EA/PE) (liquid) (231 mg, 40%) and **23** (R_f 0.27, 80% EA/PE) (liquid) (214 mg, 37%). For **22**: $[\alpha]_D^{25}$ +32.2 (c 0.8, $CHCl_3$); IR (neat) ν_{max} 1745 cm^{-1}; ^{1}H NMR δ 7.42 (d, J = 5.4 Hz, 1H), 6.00 (d, J = 5.4 Hz, 1H), 5.86 (dd, J = 17.4, 10.8 Hz, 1H), 5.34 (d, J = 17.4 Hz, 1H), 5.19 (d, J = 10.8 Hz, 1H), 3.80−3.47 (m, 3H), 3.03 (brs, 2H), 2.00−1.93 (m, 1H), 1.81−1.75 (m, 1H), 1.66−1.23 (m, 3H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 172.9, 159.4, 135.2, 119.8, 116.4, 91.2, 73.4, 64.4, 37.9, 36.9, 23.2, 11.9; HRMS (ESI) m/z calcd for $C_{12}H_{18}O_4Na$ (M + Na)$^+$, 249.1103; found 249.1105. For **23**: $[\alpha]_D^{25}$ −76.2 (c 0.14, $CHCl_3$); IR (neat) ν_{max} 1745 cm^{-1}; ^{1}H NMR δ 7.39 (d, J = 5.7 Hz, 1H), 6.04 (d, J = 5.7 Hz, 1H), 5.89 (dd, J = 17.1, 10.8 Hz, 1H), 5.36 (d, J = 17.4 Hz, 1H), 5.21 (d, J = 10.8 Hz, 1H), 3.76−3.47 (m, 3H), 2.69 (brs, 2H), 2.19−2.08 (m, 1H), 1.63−1.57 (m, 1H), 1.47−1.35 (m, 3H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR δ 172.7, 158.9, 135.4, 120.2, 116.5, 90.9, 73.7, 64.1, 37.5, 37.0, 23.4, 11.6; HRMS (ESI) m/z calcd for $C_{12}H_{18}O_4Na$ (M + Na)$^+$, 249.1103; found 249.1102.

*(2S,3R)-2-Hydroxy-3-(((S)-5-oxo-2-vinyl-2,5-dihydrofuran-2-yl)-methyl)pentyl 4-methylbenzenesulfonate (**24**).* The diol **22** (219 mg, 0.97 mmol) in DCM (10 mL) was treated with pyridine (0.2 mL, 2.43 mmol) and TsCl (222 mg, 1.16 mmol) at 0 °C and was allowed to attain room temperature slowly. The reaction mixture was stirred for additional 72 h. Aqueous saturated $NaHCO_3$ (2 mL) was added to quench the reaction and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL). Combined organic layers were washed with brine (10 mL) and dried. Evaporation of organic layer under reduced pressure followed by purification by column chromatography (40% EA/PE) furnished the monotosylate **24** (330 mg, 90%) as an oil: $[\alpha]_D^{25}$ +28.3 (c 0.13, $CHCl_3$); IR (neat) ν_{max} 1755 cm^{-1}; ^{1}H NMR δ 7.79 (d, J = 8.4 Hz, 2H), 7.38−7.35 (m, 3H), 6.01 (d, J = 5.7 Hz, 1H), 5.83 (dd, J = 17.4, 10.8 Hz, 1H), 5.34 (d, J = 17.4 Hz, 1H), 5.20 (d, J = 10.8 Hz, 1H), 4.09−3.87 (m, 3H), 2.46 (s, 3H), 2.29 (brs, 1H), 1.97−1.90 (m, 1H), 1.82−1.76 (m, 1H), 1.66−1.65 (m, 1H), 1.53−1.44 (m, 1H), 1.35−1.28 (m, 1H), 0.84 (t, J = 6 Hz, 3H); ^{13}C NMR δ 172.4, 158.8, 145.3, 135.1, 132.8, 130.1, 130.1, 128.1, 128.1, 120.1, 116.5, 90.6, 72.2, 70.5, 37.7, 36.6, 22.7, 21.8, 11.8; HRMS (ESI) m/z calcd for $C_{19}H_{24}O_6SNa$ (M + Na)$^+$, 403.1191; found 403.1194.

*(3aS,4S,5R,6aS)-5-Ethyl-4-(hydroxymethyl)-6a-vinylhexahydro-2H-cyclopenta[b]furan-2-one (**26**).* A solution of the monotosylate **24** (317 mg, 0.83 mmol) in THF (6 mL) was added to a suspension of NaH (50% in oil) (1.25 mmol, 60 mg) and TBAI (20 mg) in THF (9 mL) at 0 °C. The reaction was quenched by saturated aqueous NH_4Cl (1 mL) after 1 h and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (10 mL) and dried. Evaporation of organic layer under reduced pressure provided the epoxide **25** as a liquid (156 mg). The liquid thus obtained was used directly without further purification and characterization in the next step.

To a suspension of Cp_2TiCl_2 (622 mg, 2.50 mmol), Zn (326 mg, 4.98 mmol) and freshly fused $ZnCl_2$ (340 mg, 2.50 mmol) in THF (16 mL), the epoxide **25** (156 mg) in THF (3 mL) was slowly added over 20 min at −20 °C. The reaction mixture was stirred for 2 h at this temperature and was allowed to warm up slowly to room temperature and stirred for additional 48 h. The reaction mixture was filtered through Celite. The Celite bed was washed with Et_2O (150 mL). The combined organic layers were washed with brine (10 mL), dried and concentrated under reduced pressure. The residual mass was purified by column chromatography (50% EA/PE) to afford the bicyclic lactone **26** (liquid) (105 mg, 61% overall in two steps): $[\alpha]_D^{25}$ −9.4 (c 0.3, $CHCl_3$); IR (neat) ν_{max} 1762 cm^{-1}; ^{1}H NMR δ 5.92 (dd, J = 17.1, 10.8 Hz, 1H), 5.32 (d, J = 17.1 Hz, 1H), 5.13 (d, J = 11.1 Hz, 1H), 3.84 (dd, J = 10.8, 4.2 Hz, 1H), 3.58 (dd, J = 10.8, 9 Hz, 1H), 2.87−2.77 (m, 1H), 2.72−2.58 (m, 2H), 2.32−2.26 (m, 1H), 2.02−1.97 (m, 1H), 1.79−1.76 (m, 2H), 1.65−1.59 (m, 1H), 1.49−1.41 (m, 1H), 1.20−1.15 (m, 1H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 177.8, 138.8, 113.9, 94.9, 61.6, 49.2, 46.0, 43.8, 41.1, 30.1, 26.3, 12.4; HRMS (ESI) m/z calcd for $C_{12}H_{18}O_3Na$ (M + Na)$^+$, 233.1154; found 233.1156.

*(3aR,4S,5R,6aR)-5-Ethyl-4-(hydroxymethyl)-6a-vinylhexahydro-2H-cyclopenta[b]furan-2-one (**28**).* Following the procedure described for preparation of the monotosylate **24**, the diol **23** (179 mg, 0.79 mmol) was converted to the corresponding monotosylate (273 mg, 92%) as oil; $[\alpha]_D^{25}$ −32.7 (c 0.17, $CHCl_3$); IR (neat) ν_{max} 1743 cm^{-1}; ^{1}H NMR δ 7.77 (d, J = 8.1 Hz, 2H), 7.37−7.33 (m, 3H), 5.98 (d, J = 5.4 Hz, 1H), 5.84 (dd, J = 17.4, 10.8 Hz, 1H), 5.33 (d, J = 17.1 Hz, 1H), 5.18 (d, J = 10.8 Hz, 1H), 4.05−4.00 (m, 1H), 3.98−3.91 (m, 2H), 2.51 (brs, 1H), 2.43 (s, 3H), 2.15−2.07 (m, 1H), 1.56−1.46 (m, 2H), 1.44−1.37 (m, 1H), 1.29−1.22 (m, 1H), 0.81 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 172.3, 158.7, 145.3, 135.0, 132.7, 130.1, 130.1, 128.0, 128.0, 119.9, 116.5, 90.5, 72.2, 70.8, 37.8, 36.8, 22.9, 21.7, 11.5; HRMS (ESI) m/z calcd for $C_{19}H_{24}O_6SNa$ (M + Na)$^+$, 403.1191; found 403.1190.

DOI: 10.1021/acs.joc.7b01179
J. Org. Chem. 2017, 82, 7675−7682

The monotosylated compound obtained as above from the diol **23** (266 mg, 0.7 mmol) was transformed to the corresponding epoxide (131 mg, 90%) as a liquid: $[\alpha]_D^{25}$ −22.6 (c 1.36, $CHCl_3$); IR (neat) ν_{max} 1758 cm^{-1}; ^1H NMR δ 7.35 (d, J = 5.4 Hz, 1H), 6.01 (d, J = 5.7 Hz, 1H), 5.86 (dd, J = 17.4, 10.8 Hz, 1H), 5.35 (d, J = 17.4 Hz, 1H), 5.20 (d, J = 10.8 Hz, 1H), 2.79−2.72 (m, 2H), 2.44−2.42 (m, 1H), 1.95 (dd, J = 15.0, 6.6 Hz, 1H), 1.74 (dd, J = 15.0, 5.4 Hz, 1H), 1.59−1.44 (m, 2H), 1.27−1.21 (m, 1H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 172.3, 158.3, 135.5, 120.3, 116.4, 90.2, 55.6, 47.2, 37.9, 37.6, 26.1, 10.9; HRMS (ESI) m/z calcd for $C_{12}H_{16}O_3Na$ $(M + Na)^+$, 231.0997; found 231.0995.

Following the procedure described above for Cp_2TiCl reaction of the epoxide **25**, the epoxide obtained as above (129 mg, 0.62 mmol) was treated with Cp_2TiCl to afford the bicyclic lactone **28** (81 mg, 63%) as an oil: $[\alpha]_D^{25}$ −9.47 (c 5.7, $CHCl_3$); IR (neat) ν_{max} 1762 cm^{-1}; ^1H NMR δ 5.90 (dd, J = 17.1, 10.8 Hz, 1H), 5.27 (d, J = 17.1 Hz, 1H), 5.10 (d, J = 10.8 Hz, 1H), 3.79 (dd, J = 10.8, 3.9 Hz, 1H), 3.66 (dd, J = 10.8, 6 Hz, 1H), 2.72 (dd, J = 17.7, 8.4 Hz, 1H), 2.54−2.43 (m, 2H), 2.33−2.24 (m, 1H), 1.89−1.80 (m, 2H), 1.65−1.59 (m, 3H), 1.29−1.27 (m, 1H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 176.9, 139.4, 112.9, 94.3, 63.1, 53.3, 48.1, 43.5, 42.4, 34.4, 26.7, 12.4; HRMS (ESI) m/z calcd for $C_{12}H_{18}O_3Na$ $(M + Na)^+$, 233.1154; found 233.1152.

*(3aS,4S,5R,6aS)-4-(((tert-Butyldimethylsilyl)oxy)methyl)-5-ethyl-6a-vinylhexahydro-2H-cyclopenta[b]furan-2-one (**29**).* 2,6-Lutidine (0.52 mL, 4.52 mmol) was added to a solution of the hydroxy-compound **26** (380 mg, 1.81 mmol) in DCM (15 mL) at 0 °C. After 10 min TBSOTf (0.36 mL, 2.17 mmol) was added slowly at this temperature and was stirred for 1 h. Water (1 mL) was used to quench the reaction and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (15 mL) and dried. The residual mass after evaporation of solvent under reduced pressure was purified by column chromatography (4% EA/PE) to afford the silyl ether **29** (510 mg, 87%) as an oil: $[\alpha]_D^{23}$ −13.8 (c 1.3, $CHCl_3$); IR (neat) ν_{max} 1777 cm^{-1}; ^1H NMR δ 5.91 (dd, J = 17.1, 10.8 Hz, 1H), 5.32 (d, J = 17.1 Hz, 1H), 5.12 (d, J = 11.1 Hz, 1H), 3.75 (dd, J = 10.5, 3.9 Hz, 1H), 3.54 (dd, J = 10.8, 8.4 Hz, 1H), 2.81−2.71 (m, 2H), 2.62−2.52 (m, 1H), 2.28 (dd, J = 13.8, 5.7 Hz, 1H), 1.95−1.87 (m, 1H), 1.83−1.78 (m, 1H), 1.65−1.63 (m, 1H), 1.42 (dd, J = 13.8, 12 Hz, 1H), 1.19−1.08 (m, 1H), 0.92−0.88 (m, 12H), 0.04 (s, 6H); ^{13}C NMR δ 177.6, 139.2, 113.6, 94.6, 61.6, 49.6, 46.3, 43.9, 40.7, 30.1, 26.2, 25.9, 18.3, 12.4, −5.4, −5.5; HRMS (ESI) m/z calcd for $C_{18}H_{32}O_3SiNa$ $(M + Na)^+$, 347.2018; found 347.2016.

*(3aS,4S,5R,6aR)-4-(((tert-Butyldimethylsilyl)oxy)methyl)-5,6a-diethylhexahydro-2H-cyclopenta[b]furan-2-one (**30**).* To a solution of the unsaturated lactone **29** (474 mg, 1.46 mmol) in EtOAc (30 mL), 10% Pd/C (48 mg) was added. The reaction mixture was stirred under hydrogen atmosphere at room temperature for 5 h. The mixture was filtered through Celite. The Celite bed was washed with Et_2O (100 mL), dried and evaporated under reduced pressure. The residual mass was purified by column chromatography (5% EA/PE) to afford the saturated lactone **30** (liquid) (453 mg, 95%): $[\alpha]_D^{25}$ −5.1 (c 0.56, $CHCl_3$); IR (neat) ν_{max} 1778 cm^{-1}; ^1H NMR δ 3.75 (dd, J = 10.8, 4.2 Hz, 1H), 3.52 (dd, J = 10.5, 8.7 Hz, 1H), 2.76−2.56 (m, 3H), 2.25 (dd, J = 13.8, 6.0 Hz, 1H), 1.86−1.81 (m, 1H), 1.76−1.70 (m, 2H), 1.58−1.55 (m, 1H), 1.33−1.21 (m, 2H), 1.13−1.08 (m, 1H), 0.98 (t, J = 7.5 Hz, 3H), 0.88 (t, J = 5.7 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 177.9, 96.5, 61.7, 49.7, 44.7, 43.1, 40.2, 32.6, 30.8, 26.0, 25.9, 18.3, 12.3, 8.6, −5.4, −5.5; HRMS (ESI) m/z calcd for $C_{18}H_{34}O_3SiNa$ $(M + Na)^+$, 349.2175; found 349.2173.

*(3aR,4S,5R,6aR)-4-(((tert-Butyldimethylsilyl)oxy)methyl)-5,6a-diethyl-3-methylenehexahydro-2H-cyclopenta[b]furan-2-one (**31**).* A solution of the lactone **30** (425 mg, 1.30 mmol) in THF (10 mL) was treated with LDA [1 M in THF] (3.3 mL, 3.26 mmol) at −78 °C for 45 min followed by bubbling HCHO gas into the solution for 5 min. The reaction was quenched by saturated aqueous NH_4Cl (5 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (20 mL) and dried. Concentration of organic layer under reduced pressure provided a viscous mass (399 mg). A solution of the mass (399 mg) in DCM (10 mL) was treated with Et_3N (0.48 mL, 3.39 mmol) followed by MsCl (0.13 mL, 1.69 mmol) at 0 °C and was allowed to stir for 3 h. The reaction was quenched by saturated aqueous $NaHCO_3$ (4 mL) and the layers were separated. The aqueous layer was washed with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (15 mL) and dried. The residual mass after evaporation of solvent under reduced pressure was purified by column chromatography (8% EA/PE) to afford **31** (273 mg, 62%, liquid): $[\alpha]_D^{25}$ −8.29 (c 0.82, $CHCl_3$); IR (neat) ν_{max} 1763 cm^{-1}; ^1H NMR δ 6.36 (t, J = 1.8 Hz, 1H), 5.86 (t, J = 1.5 Hz, 1H), 3.66 (dd, J = 10.5, 4.2 Hz, 1H), 3.48 (t, J = 10.2 Hz, 1H), 3.26 (dt, J = 9.3, 1.8 Hz, 1H), 2.25 (dd, J = 13.5, 5.4 Hz, 1H), 1.93−1.88 (m, 1H), 1.78−1.72 (m, 2H), 1.57−1.50 (m, 2H), 1.28−1.23 (m, 1H), 1.14−1.04 (m, 1H), 0.95 (t, J = 7.5 Hz, 3H), 0.91−0.88 (m, 12H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR δ 171.1, 136.1, 125.6, 93.6, 61.2, 51.7, 50.0, 43.0, 40.2, 32.5, 26.0, 25.8, 18.3, 12.1, 8.4, −5.3; HRMS (ESI) m/z calcd for $C_{19}H_{34}O_3SiNa$ $(M + Na)^+$, 361.2175; found 361.2177.

*(3aS,4S,5R,6aR)-4-(((tert-Butyldimethylsilyl)oxy)methyl)-5,6a-diethyltetrahydro-2H-cyclopenta[b]furan-2,3(3aH)-dione (**32**).* Sodium metaperiodate (658 mg, 3.08 mmol) was added to a solution of the lactone **31** (208 mg, 0.62 mmol) in THF (5 mL) and water (2.5 mL). A catalytic amount of OsO_4 (2.5% by wt in ^tBuOH) was added and allowed to stir for 12 h at room temperature. The solid mass was filtered and the filtrate was washed with Et_2O (3 × 30 mL). The combined organic layers were washed with water (1 × 5 mL), brine (5 mL), dried and evaporated under reduced pressure. The residual mass was purified by column chromatography (10% EA/PE) to give the keto-lactone **32** (190 mg, 91%) as a liquid: $[\alpha]_D^{25}$ +38.7 (c 1.0, $CHCl_3$); IR (neat) ν_{max} 1785, 1767 cm^{-1}; ^1H NMR δ 3.79 (dd, J = 11.1, 1.8 Hz, 1H), 3.65 (dd, J = 10.8, 2.4 Hz, 1H), 2.88 (d, J = 11.4 Hz, 1H), 2.45 (dd, J = 13.5, 5.7 Hz, 1H), 2.35−2.26 (m, 1H), 2.23−2.15 (m, 1H), 1.90−1.80 (m, 1H), 1.79−1.72 (m, 1H), 1.64−1.60 (m, 1H), 1.42 (dd, J = 13.5, 12 Hz, 1H), 1.18−1.08 (m, 1H), 0.94 (t, J = 7.5 Hz, two methyl groups merged together, 6H), 0.84 (s, 9H), 0.02 (s, 6H); ^{13}C NMR δ 197.0, 161.5, 93.8, 58.5, 54.7, 54.4, 42.5, 39.3, 32.7, 26.0, 25.7, 18.7, 12.5, 8.4, −5.7, −5.8; HRMS (ESI) m/z calcd for $C_{18}H_{32}O_4SiNa$ $(M + Na)^+$, 363.1967; found 363.1965.

*(2aS,2a1S,4aS,5R,6aR)-5,6a-Diethyl-2a-hydroxyhexahydro-1,3-dioxacyclopenta[cd]pentalen-2(2aH)-one (**35**).* A solution of the keto-lactone **32** (11 mg, 32.3 μmol) in MeOH (2 mL) and DCM (1 mL) was treated with catalytic amount of CSA at 0 °C and was stirred for 1 h at room temperature. The reaction was quenched with excess triethyl amine (0.1 mL). The residual mass after removal of solvent under reduced pressure was purified by column chromatography (20% EA/PE) to afford the lactol **35** (5 mg, 69%) as a colorless liquid: $[\alpha]_D^{27}$ +2.32 (c 0.44, $CHCl_3$); IR (neat) ν_{max} 1778 cm^{-1}; ^1H NMR δ 4.24 (dd, J = 8.7, 4.2 Hz, 1H), 4.02 (d, J = 8.7 Hz, 1H), 3.73 (brs, 1H), 3.05 (d, J = 8.7 Hz, 1H), 2.52 (dt, J = 9.3, 4.2 Hz, 1H), 2.28 (dd, J = 13.8, 5.7 Hz, 1H), 2.00−1.85 (m, 2H), 1.81−1.69 (m, 1H), 1.58−1.47 (m, 1H), 1.38−1.26 (m, 2H), 1.00 (t, J = 7.5 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 173.4, 107.0, 94.4, 75.0, 59.2, 54.2, 44.2, 43.6, 32.5, 26.9, 12.9, 8.5; HRMS (ESI) m/z calcd for $C_{12}H_{18}O_4Na$ $(M + Na)^+$, 249.1103; found 249.1105.

*(3R,3aR,4S,5R,6aR)-5,6a-Diethyl-3-ethynyl-3-hydroxy-4-(hydroxymethyl)hexahydro-2H-cyclopenta[b]furan-2-one (**37**).* A solution of the Keto-lactone **32** (39 mg, 0.11 mmol) in THF (2 mL) was slowly treated at −78 °C with lithium (trimethylsilyl) acetylide [prepared by adding ^nBuLi (0.36 mL, 0.57 mmol) to trimethylsilyl acetylene (89 μL, 0.63 mmol) in THF (2 mL) at 0 °C for 1 h]. The reaction mixture was stirred for 30 min at this temperature. Saturated aqueous NH_4Cl (1 mL) was added to quench the reaction and it was filtered through Celite. The Celite bed was washed with Et_2O (20 mL). The combined organic layer was washed with brine (5 mL) and dried. The residual mass (45 mg) after evaporation of solvent under reduced pressure was directly used for the next step without any further purification and characterization. A solution of this mass (45 mg) in THF (2 mL) in a plastic vial was treated with HF-pyridine (70%, 0.14 mL) at 0 °C and was stirred for 24 h. The reaction was quenched with saturated aqueous $NaHCO_3$

DOI: 10.1021/acs.joc.7b01179
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(10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layer was washed with brine (4 mL), dried and evaporated under reduced pressure. The residual mass was purified by column chromatography (30% EA/PE) to afford the diol **37** (15 mg, 52%) as a crystalline solid: mp 140−142 °C; $[\alpha]_D^{25}$ −50.58 (c 0.34, $CHCl_3$); IR (neat) ν_{max} 1774 cm^{-1}; ^1H NMR δ 4.88 (brs, 1H), 3.93 (brs, 2H), 3.03 (d, J = 8.1 Hz, 1H), 2.75 (dd, J = 20.7, 11.7 Hz merged with a singlet at 2.73 of acetylene, 2H), 2.33 (dd, J = 14.1, 6.0 Hz, 1H), 2.11−1.98 (m, 3H), 1.88−1.76 (m, 1H), 1.65 (brs, 1H), 1.62−1.55 (m, 1H), 1.43−1.33 (m, 1H), 1.02 (t, J = 7.2 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 173.5, 95.1, 83.0, 75.5, 71.9, 60.5, 56.2, 51.0, 42.2, 40.2, 31.9, 26.1, 12.2, 8.7; HRMS (ESI) m/z calcd for $C_{14}H_{20}O_4Na$ $(M + Na)^+$, 275.1259; found 275.1257.

*(2aR,2a1S,4aS,5R,6aR)-5,6a-Diethyl-2a-ethynyltetrahydro-1,3-dioxacyclopenta[cd]pentalene-2,4(2aH,2a1H)-dione (**38**).* A solution of the diol **37** (9.3 mg, 36.9 μmol) in acetone (3 mL) was treated with Jones' reagent (88.6 μL, 2.5 M) dropwise at 0 °C until the color of the reagent persisted and stirred for additional 30 min at this temperature. The excess reagent was quenched by adding excess EtOH (1 mL). Et_2O (20 mL) was added to the reaction mixture and washed with water (1 mL), brine (1 mL) and dried. The residual mass after evaporation of organic layer under reduced pressure was purified by column chromatography (20% EA/PE) to provide the bislactone **38** (6 mg, 66%) as a liquid: $[\alpha]_D^{25}$ −7.9 (c 0.78, $CHCl_3$); IR (neat) ν_{max} 1779 cm^{-1}; ^1H NMR δ 3.51 (d, J = 10.2 Hz, 1H), 2.92 (t, J = 9.9 Hz merged with a singlet at 2.91 of acetylene, 2H), 2.42 (dd, J = 13.8, 6.0 Hz, 1H), 2.27−2.18 (m, 1H), 2.01−1.93 (m, 1H), 1.91−1.79 (m, 2H), 1.57−1.53 (m, 1H), 1.49−1.39 (m, 1H), 1.07 (t, J = 7.5 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H); ^{13}C NMR δ 174.5, 168.4, 96.2, 79.4, 78.4, 76.8, 57.3, 50.5, 45.4, 44.9, 31.5, 27.1, 12.3, 8.8; HRMS (ESI) m/z calcd for $C_{14}H_{16}O_4Na$ $(M + Na)^+$, 271.0946; found 271.0948.

*Synthesis of (−)-Gracilioether F **3**.* To a solution of the bislactone **38** (4 mg, 16.1 μmol) in EtOAc (5 mL) was treated with 10% Pd/C (400 μg) under a positive pressure (70 psi) of hydrogen gas at room temperature in a parr hydrogenator for 6 h. The reaction mixture was filtered through Celite. The Celite bed was washed with Et_2O (10 mL). The combined organic layers were evaporated under reduced pressure. The residual mass was purified by column chromatography (20% EA/PE) to provide (−)-gracilioether F **3** (4 mg, 99%) as a viscous liquid: $[\alpha]_D^{25}$ −6.0 (c 0.38, MeOH); IR (neat) ν_{max} 1778 cm^{-1}; ^1H NMR (300 MHz, MeOD-d_4) δ 3.33 (d, J = 8.7 Hz, 1H), 2.96 (t, J = 9.6 Hz, 1H), 2.33 (dd, J = 13.8, 6.0 Hz, 1H), 2.14−1.99 (m, 2H), 1.94−1.75 (m, 4H), 1.64 (dd, J = 13.8, 11.7 Hz, 1H), 1.55−1.40 (m, 1H), 1.02 (t, J = 7.5 Hz, 3H), 1.02 (t, J = 7.5 Hz, 3H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 178.2, 175.1, 97.3, 89.1, 54.1, 53.0, 47.2, 45.0, 32.6, 28.8, 28.1, 12.6, 9.1, 7.4; HRMS (ESI) m/z calcd for $C_{14}H_{20}O_4Na$ $(M + Na)^+$, 275.1259; found 275.1258.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01179.

Copies of NMR spectra for compounds **3**, **12**−**24**, **26**, **28**−**32**, **35**, **37**, **38** (PDF)

X-ray crystal data for compound **37** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

S.G. is grateful to Department of Science and Technology, Government of India and Indian National Science Academy for support of this work through J. C. Bose National Fellowship (Award No. SR/S2/JCB-83/2011) and INSA Senior Scientist program, respectively. R.D. thanks Council of Scientific and Industrial Research for a Senior Research Fellowship. We thank Mr. Abhijit Mallick, Department of Inorganic Chemistry, IACS for analysis of X-ray crystallographic data. Single-crystal diffraction data were collected at the DST-funded National Single Crystal Diffractometer Facility at the Department of Inorganic Chemistry, IACS.

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(15) CCDC 1547432 contains the crystallographic data for **37** (available also in the Supporting Information). The data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

DOI: 10.1021/acs.joc.7b01179
J. Org. Chem. 2017, 82, 7675−7682