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Diastereoselective Total Synthesis of (−)-Galiellalactone

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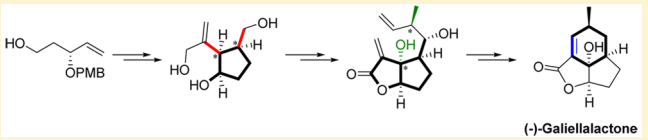
Supporting Information

ABSTRACT: An enantioselective total synthesis of (−)-galiellalactone has been accomplished. The key features of the synthesis involve the highly stereoselective construction of the *cis*-trisubstituted cyclopentane intermediate by a Pd(0)-catalyzed cyclization, the stereospecific introduction of an angular hydroxyl group by Riley oxidation, and the efficient construction of the tricyclic system of (−)-galiellalactone via a combination of diastereoselective Hosomi−Sakurai crotylation and ring-closing metathesis (RCM)



INTRODUCTION

(−)-Galiellalactone (**1**), a fungal metabolite originally isolated from the ascomycete *Galiella rufa*[1] (Figure 1), has been

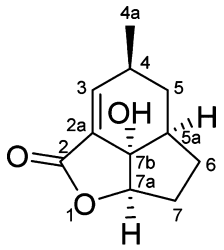


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Figure 1. Structure of (−)-galiellalactone (**1**).

reported to be a potent and specific inhibitor of signal transducer and activator of transcription 3 (STAT3), which is involved in numerous signaling pathways.[2] (−)-Galiellalactone covalently binds to one or more cysteine residues in STAT3 and subsequently blocks the DNA binding of phosphorylated STAT3 without inhibition of phosphorylation and dimerization.[3] Importantly, persistent and aberrant activation of STAT3 has been detected in several human solid and hematological cancer cells,[2,4] whereas it is tightly regulated in normal cells,[5] which supports STAT3 as a promising molecular target for cancer therapy. (−)-Galiellalactone also induces apoptosis and growth inhibition of human prostate cancer cells expressing constitutively active STAT3 both *in vitro* and *in vivo*[6] and suppresses stem cell-like ALDH+ prostate cancer cells.[7] For these reasons, (−)-galiellalactone has recently been considered to be a potential therapeutic agent against hormone-refractory prostate cancer.

The structure of (−)-galiellalactone (**1**) features a unique and highly congested [5,5,6]-tricyclic ring system that consists of a reactive α,β-unsaturated lactone functionality and four stereocenters. The tertiary stereogenic center possesses an angular hydroxyl group, which is essential for the biological activity of **1**.[8] Sterner and Johansson reported the first and efficient synthesis of (−)-galiellalactone and established the absolute configuration of the natural product.[9] However, the stereoselective introduction of a tertiary hydroxyl group remains a formidable task[10] because introduction of an epoxide, as a precursor of the tertiary hydroxyl group, into the hydrindane system of **1** has only been reported with moderate diastereoselectivity.[9a] In addition, chemical hydroxylation at the central angular position could not directly elaborate the tertiary hydroxyl group.[10a]

Recently, we have been interested in studies on (−)-galiellalactone, particularly on the cyclohexene system for which the role in its biological activity has not been explored much; however, the [3.3] bicyclic lactone system has been extensively studied.[10c,11] Thus, we envisioned a unique and versatile synthetic strategy, in which the [3.3] bicyclic lactone system and the cyclohexene moiety are sequentially constructed starting from cyclopentane **4** because most of the previous synthetic studies pursued the strategy. From the viewpoint of medicinal chemistry, we realized that the structural variation of the cyclohexene system is restricted because early construction of the hydrindane system would limit late steps of the synthesis. Herein, we report our enantioselective total synthesis of (−)-galiellalactone (**1**).

RESULTS AND DISCUSSION

Our synthetic approach for **1** is outlined in Scheme 1, which includes stereoselective construction of the tricyclic intermediate containing three contiguous stereocenters as well as a methyl substituent. (−)-Galiellalactone (**1**) was anticipated to be obtained from homoallylic alcohol **2**, which comprises all four stereocenters of the natural product, by ring-closing metathesis (RCM) and subsequent Barton−McCombie deox-

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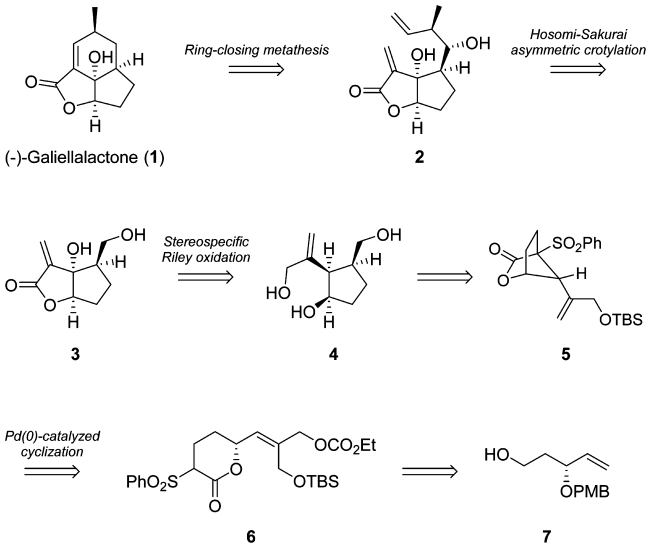
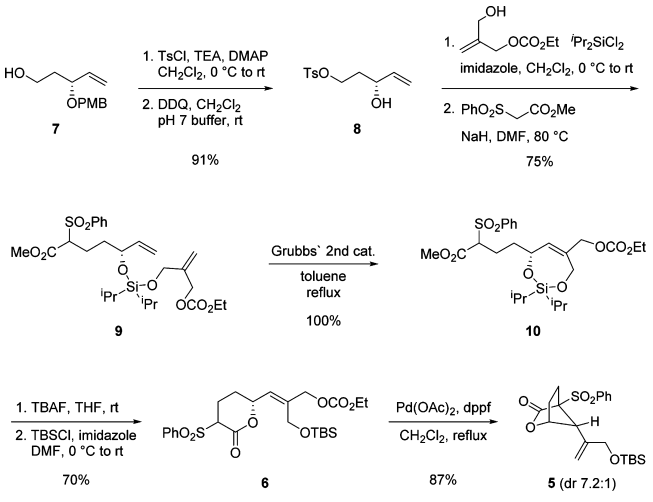
Scheme 1. Retrosynthetic Analysis of (−)-Galiellalactone (1)



ygenation of the secondary hydroxyl group at the final stage. The C5a-side chain of **2** can be installed into the key bicyclic intermediate **3** by oxidation of the alcohol followed by a substrate-controlled stereoselective crotylation. The stereochemistry of the C7b-stereocenter was predicted based on the stereospecific introduction of an angular hydroxyl group by a substrate-controlled oxidation of the *cis*-fused 5,5-bicyclic lactone system, which can be efficiently produced from the *cis*-trisubstituted cyclopentanetriol **4**. Cyclopentanetriol **4** is accessible by reduction of the [2.2.1] bridged bicyclic lactone **5**, which can be efficiently prepared by a diastereoselective Pd(0)-catalyzed cyclization of *δ*-valerolactone **6** that was developed by our group although the substituents are quite different.[12] *δ*-Valerolactone **6** was expected to be conveniently prepared from the known alcohol **7**.

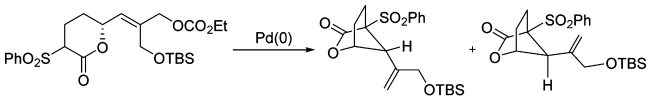
The synthesis commenced with the preparation of bicyclic lactone **5**, as shown in Scheme 2. Tosylation of the known alcohol **7**[13] and PMB deprotection with DDQ afforded the allylic alcohol **8**, which was converted to *bis*-alkoxysilane **9** via a sequence of double silylation with another allylic alcohol fragment and tosylate substitution with the anion of benzenesulfonyl acetate.[14] Ring closing metathesis (RCM)[15] of diene **9** in the presence of a second generation Grubbs catalyst afforded a cyclic *bis*-alkoxysilane **10** in a quantitative yield. Cleavage of the silicon tether of **10** resulted in a spontaneous lactonization of the resulting dihydroxy ester, followed by TBS-protection of the allylic alcohol to produce *δ*-valerolactone **6**.

Scheme 2. Synthesis of [2.2.1] Bridged Bicyclic Lactone 5



After intensive optimization of the cyclization conditions including various ligands and solvents as summarized in Table 1, it was determined that the intramolecular allylic alkylation of

Table 1. Pd(0)-Catalyzed Cyclization of *δ*-Valerolactone 6[a]



entry	catalyst	solvent	yield[b] (%)	ratio (5:5′)[c]
1	$Pd(dppf)_2$	CH_2Cl_2	99	7.2:1
2	$Pd(dppf)_2$	THF	80	1:1
3	$Pd(PPh_3)_4$	CH_2Cl_2	90	5:1
4	$Pd(PPh_3)_4$	DCE	85	3:1
5	$Pd(PPh_3)_4$	DMSO[d]	76	3:1
6	$Pd(dppe)_2$	CH_2Cl_2	90	1.3:1
7	$Pd(dppe)_2$	THF	82	1.3:1
8	$Pd(dppp)_2$	THF	73	1:1.5
9	$Pd(dppb)_2$	THF	61	2:1

[a]All reactions were conducted with 5 mol % catalyst in 0.05 M solution under reflux conditions except entry 5. [b]Isolated yield of the diastereomeric mixture. [c]Determined by ^1H NMR spectra of the diastereomeric mixtures. [d]Reaction was conducted at 80 °C. dppe: 1,2-bis(diphenylphosphino)ethane. dppp: 1,3-bis(diphenylphosphino)-propane. dppb: 1,4-bis(diphenylphosphino)butane. dppf: 1,1′-ferrocenediyl-bis(diphenylphosphine).

6 in the presence of $Pd(dppf)_2$ in CH_2Cl_2 afforded the bicyclic lactone **5** in an 87% yield with the best diastereoselectivity (entry 1), which was determined by the isolation of each isomer. Cyclization of **6** in the presence of $Pd(PPh_3)_4$ resulted in low stereoselectivity regardless of the solvents (entries 3−5). Cyclization in the presence of $Pd(OAc)_2$ with dppe or dppb also showed a disappointingly low stereoselectivity (entries 6−7, 9). Interestingly, the cyclization in the presence of $Pd(dppp)_2$ showed the opposite diastereoselectivity, although the yield was slightly lower (entry 8). The observed high diastereoselectivity is presumably due to the Pd(0)-catalyzed cyclization through the transition state with the least steric interaction between the benzenesulfonyl group and the *π*-allylpalladium complex (Figure 2).[12b,16]

Having successfully prepared the optically pure bicyclic intermediate **5**, we executed the construction of the *cis*-fused 5,5-bicylic lactone **12** and the stereoselective introduction of the angular hydroxyl group as shown in Scheme 3. To the best of our knowledge, direct introduction of the angular hydroxyl group to the bicyclic or tricyclic backbone of **1** has not been reported. Thus, we undertook the stereoselective construction of the functionalized *cis*-fused 5,5-bicyclic lactone system. We first transformed the bridged bicyclic lactone **5** into the *cis*-1,2,3-trisubstituted cyclopentanetriol **4**, which is difficult to access by conventional cyclization procedures.[17]

Desulfonylation of **5** with 5% Na/Hg in the presence of $B(OH)_3$ afforded the desulfonylated bridged bicyclic lactone **11** in a 93% yield.[18] Reduction of **11** with $LiBH_4$ in the presence of MeOH and subsequent TBS deprotection afforded the

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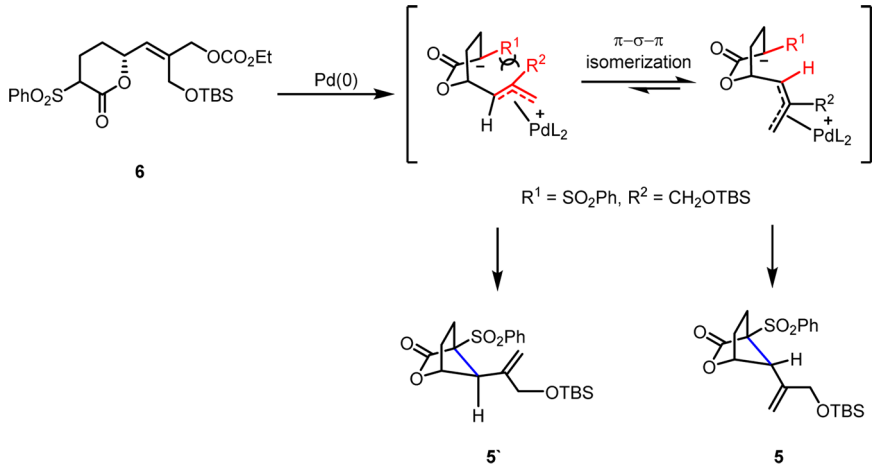
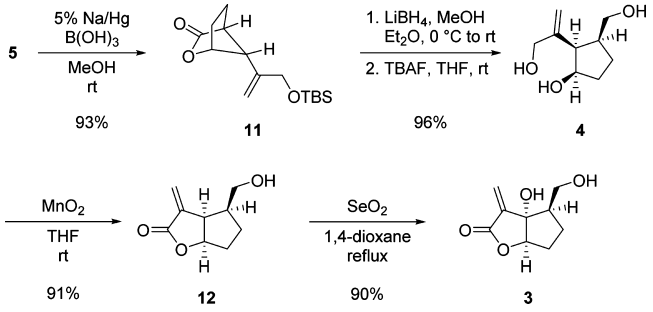


Figure 2. Plausible mechanism for Pd(0)-catalyzed cyclization.

Scheme 3. Synthesis of Dihydroxy Bicyclic Lactone 3

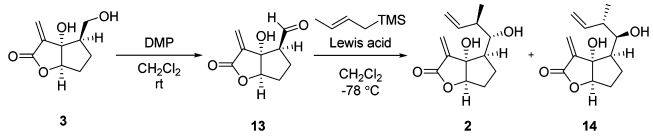


thermodynamically less favorable *cis*-1,2,3-trisubstituted cyclopentanetriol **4**. Allylic oxidation of **4** with excess MnO_2[19] followed by spontaneous lactonization of the resulting lactol effectively produced the bicyclic lactone **12**. For the pivotal introduction of the angular hydroxyl group, we envisioned the stereoselective oxidation of the *exo*-methylene moiety of the *cis*-fused bicyclic lactone system because of its inherent convex-face selectivity. Indeed, Riley oxidation[20] of **12** with SeO_2 in 1,4-dioxane provided the dihydroxy bicyclic lactone **3** as a single diastereomer in a 90% yield (Scheme 3).

Next, we turned our attention to the stereoselective elaboration of the C5a-side chain as summarized in Table 2. To our delight, Dess-Martin oxidation[21] of **3** afforded aldehyde **13** without epimerization of the labile C5a stereocenter. We originally anticipated an efficient elaboration of the C5a-side chain unit that utilized the Brown[22] or Roush[23] crotylation procedure. However, our attempts to directly install the C5a-side chain unit were not successful. The aldehyde was unexpectedly intact under those conditions. Thus, we employed the diastereoselective Hosomi–Sakurai crotylation[24] to directly introduce the C5a-side chain unit, which contains both the C4 unit and a requisite terminal alkene for RCM at a later stage. We expected a diastereoselective coupling in a chelation-controlled fashion to elaborate the C4-stereocenter of **1**.

Interestingly, the treatment of **13** with (*E*)-crotyltrimethylsilane and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 afforded the isomer **14** as a major product, along with the desired isomer **2**, in an 88% yield (entry 1). The undesired diastereoselectivity can be explained by Felkin–Anh control as shown in Figure 3. However, diastereoselective Hosomi–Sakurai crotylation in the presence of $TiCl_4$ provided a reversed diastereoselectivity with a ratio of

Table 2. Diastereoselective Hosomi–Sakurai Crotylation of Aldehyde 13[a]



entry	Lewis acid	yield[b] (%)	ratio (**2**:**14**)[c]
1	$BF_3{\cdot}Et_2O$	88	1:5
2	$TiCl_4$	78	5:1
3	$SnCl_4$	97	1:1
4	$MgBr_2{\cdot}Et_2O$		NR[d]
5	Et_2AlCl		NR
6	$AlCl_3$		complex mixture

[a]All reactions were conducted with (*E*)-crotyltrimethylsilane (10 equiv) and Lewis acid (2 equiv) in 0.1 M solution at −78 °C for 12 h. [b]Isolated yield of the diastereomeric mixture. [c]Determined by isolation of each isomer after TES protection (See Scheme 4). [d]No reaction.

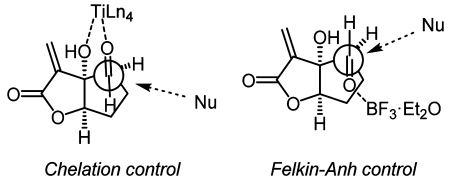


Figure 3. Diastereoselectivity in the Hosomi–Sakurai crotylation of aldehyde **13**.

5:1 presumably via chelation-controlled asymmetric induction as we anticipated (entry 2). Crotylation in the presence of $SnCl_4$ resulted in low diastereoselectivity (entry 3), although the yield was quantitative. The variation in diastereoselectivity is likely due to complexation of the lactone moiety with Lewis acids, although it is not clear at this stage.

The structure of the C4-stereocenter was confirmed by comparison of its spectral data with that of the natural (−)-galiellalactone after completion of the synthesis.

The diastereomeric mixture of homoallylic alcohols **2** and **14**, which were prepared in the presence of $TiCl_4$ and inseparable by column chromatography, was purified after TES protection of the alcohol to afford optically pure RCM precursor **15**[25] in a 59% yield in three steps (Scheme 4). The tricyclic lactone **17** was obtained in a high yield from **15** by RCM in the presence

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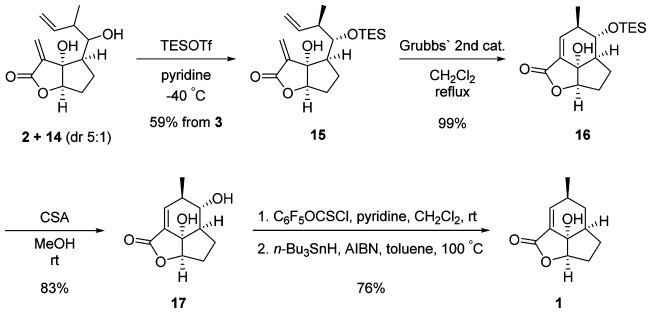
Scheme 4. Completion of (−)-Galiellalactone (1) Synthesis



of a second generation Grubbs catalyst, followed by TES deprotection of the resulting tricyclic lactone **16** with CSA in MeOH. We originally anticipated facile deoxygenation of the secondary hydroxyl group right after stereoselective crotylation reaction. However, preparation of the deoxygenation precursor under a variety of reaction conditions was not successful because of the steric congestion on the concave face. Thus, we carried out the deoxygenation reaction after constructing the tricyclic lactone system of **1**. After intensive screening of the deoxygenation conditions, deoxygenation of **17** with the Barton−McCombie reaction[26] via careful acylation with pentafluorophenyl chlorothionoformate[27] and *n*-Bu_3SnH treatment of the resulting xanthate finally furnished (−)-galiellalactone (**1**) in a 76% yield in two steps. Synthetic **1** was identical to the natural product in all aspects, including optical rotation.[9a,10a,28]

■ CONCLUSION

In summary, we have achieved the enantioselective total synthesis of (−)-galiellalactone (**1**). Our unique strategy based on substrate-controlled stereocontrol involves the diastereoselective construction of the contra-thermodynamic tri-*cis*-substituted cyclopentanetriol, the stereospecific introduction of an angular hydroxyl group, and its efficient transformation into the tricyclic system of (−)-galiellalactone via a sequence of stereoselective Hosomi−Sakurai crotylation and RCM of the resulting diene. Our versatile and straightforward procedure is widely applicable to the syntheses of (−)-galiellalactone and its structural variants including the cyclohexene-modified analogs, which are quite useful in terms of synthetic and medicinal chemistry.

■ EXPERIMENTAL SECTION

General Experimental Procedure. Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, triethylamine, and pyridine were freshly distilled from calcium hydride. All solvents used for the routine isolation of products and chromatography were reagent grade and glass distilled. Reaction flasks were dried at 100 °C. Air and moisture sensitive reactions were performed under an argon atmosphere. Flash column chromatography was performed using silica gel (230−400 mesh) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates. Optical rotations were measured with a digital polarimeter at ambient temperature using a 100 nm cell of 2 mL capacity. Infrared spectra were recorded on a FT-IR spectrometer. Mass spectra were obtained with a double focusing mass spectrometer (electrostatic analyzer and magnetic analyzer). ^1H and ^{13}C NMR spectra were recorded on a 300, 400, 500, or 600 MHz spectrometers as solutions in deuteriochloroform ($CDCl_3$) or tetradeuteromethanol (methanol-d_4). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent ($CDCl_3$ or CD_3OD). ^1H NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; dd, doublet of doublets; dt, doublet of triplet; td, triplets of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; qtd, quartet of triplet of doublets; br, broad; m, multiplet and/or multiple resonance), number of protons, and coupling constant in hertz (Hz).

(*R*)-3-Hydroxypent-4-en-1-yl 4-methylbenzenesulfonate (8). To a mixture of alcohol **7** (4.09 g, 18 mmol) and triethylamine (5.1 mL, 36.8 mmol) in CH_2Cl_2 (46 mL) were added *p*-toluenesulfonyl chloride (5.27 g, 27.6 mmol) and 4-dimethylaminopyridine (674 mg, 5.5 mmol) at 0 °C. After stirring for 3 h at ambient temperature, the reaction mixture was quenched with saturated NH_4Cl solution (30 mL) and diluted with CH_2Cl_2 (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:6) to afford *p*-methoxybenzyl ether (6.44 g, 93%) as a colorless oil: $[\alpha]_D^{20}$+11.46 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, 2H, *J* = 8.3 Hz), 7.30 (d, 2H, *J* = 8.1 Hz), 7.14 (d, 2H, *J* = 8.5 Hz), 6.83 (d, 2H, *J* = 8.6 Hz), 5.65 (m, 1H), 5.21 (d, 1H, *J* = 1.7 Hz), 5.18 (d, 2H, *J* = 9.5 Hz), 4.43 (d, 1H, *J* = 11.0 Hz), 4.18 (m, 1H), 4.14 (d, 1H, *J* = 11.1 Hz), 4.06 (dt, 1H, *J* = 9.7 Hz, *J* = 5.6 Hz), 3.84 (td, 1H, *J* = 7.7 Hz, *J* = 5.3 Hz), 3.78 (s, 3H), 2.41 (s, 3H), 1.89−1.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.1, 144.7, 137.7, 133.0, 130.2, 129.8, 129.3, 127.8, 117.9, 113.7, 70.0, 67.1, 55.2, 34.8, 21.5; IR (neat) ν_{max} 2957, 1613, 1514, 1465, 1361, 1303, 1249, 1189, 1177, 1097, 1035, 916, 817, 770, 664 cm^{-1}; LR-MS (FAB+) *m*/*z* 376 (M^+); HR-MS (FAB+) calcd for $C_{20}H_{24}O_5S$ (M^+) 376.1344, found 376.1351.

To a solution of *p*-methoxybenzyl ether (5.30 g, 14.1 mmol) in CH_2Cl_2/pH 7.2 buffer solution (9:1, 140 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (6.39 g, 28.2 mmol) in one portion at ambient temperature. After stirring for 3 h, the reaction mixture was filtered and quenched with a saturated $NaHCO_3$ solution (100 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 2:3) to afford allylic alcohol **8** (3.57 g, 99%) as a colorless oil: $[\alpha]_D^{20}$ +3.50 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, 2H, *J* = 8.2 Hz), 7.30 (d, 2H, *J* = 8.0 Hz), 5.74 (m, 1H), 5.14 (d, 1H, *J* = 17.2 Hz), 5.04 (d, 1H, *J* = 10.5 Hz), 4.20−4.14 (m, 2H), 4.08−4.03 (m, 1H), 2.39 (s, 3H), 2.21 (br, 1H), 1.87−1.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.8, 139.7, 132.7, 129.8, 127.8, 115.3, 68.8, 67.3, 35.7, 21.5; IR (neat) ν_{max} 3412, 2961, 1599, 1496, 1424, 1358, 1308, 1293, 1190, 1176, 1142, 1098, 1068, 996, 969, 916, 832, 816, 766, 664 cm^{-1}; LR-MS (FAB+) *m*/*z* 257 (M + H^+); HR-MS (FAB+) calcd for $C_{12}H_{17}O_4S$ (M + H^+) 257.0848, found 257.0860.

Methyl (12*R*)-10,10-Diisopropyl-7-methylene-4-oxo-15-(phenylsulfonyl)-12-vinyl-3,5,9,11-tetraoxa-10-silahexadecan-16-oate (9). To a solution of imidazole (5.88 g, 86.4 mmol) in CH_2Cl_2 (140 mL) was added dichlorodiisopropylsilane (5.8 mL, 31.7 mmol) at 0 °C. After stirring for 10 min, a solution of allylic alcohol **8** (7.38 g, 28.8 mmol) in CH_2Cl_2 (20 mL) was added dropwise. After stirring for 10 min at the same temperature, a solution of another allylic alcohol (5.53 g, 34.6 mmol) in CH_2Cl_2 (20 mL) was added at 0 °C. The reaction mixture was warmed to ambient temperature and stirred for 12 h. The resulting mixture was quenched with a saturated NH_4Cl solution (30 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:8) to afford *bis*-alkoxysilane (14.62 g, 96%) as a colorless oil: $[\alpha]_D^{20}$ −7.68 (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, 2H, *J* = 8.3 Hz), 7.29 (d, 2H, *J* = 8.2 Hz), 5.68 (m, 1H), 5.21 (s, 1H), 5.13 (s, 1H), 5.03 (dd, 2H, *J* = 18.3 Hz, *J* = 10.4 Hz), 4.58 (s, 2H), 4.36 (q, 1H, *J* = 6.2 Hz),

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4.20 (s, 2H), 4.16 (q, 2H, J = 7.2 Hz), 4.11−4.02 (m, 2H), 2.40 (s, 3H), 1.89−1.78 (m, 2H), 1.26 (t, 3H, J = 7.1 Hz), 0.94−0.93 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.9, 144.6, 142.2, 139.6, 133.0, 129.7, 127.8, 115.2, 113.2, 70.1, 67.6, 67.0, 63.9, 63.3, 36.8, 21.5, 17.2, 14.2, 12.1; IR (neat) ν_{max} 2946, 2868, 1748, 1599, 1466, 1367, 1259, 1189, 1178, 1097, 1000, 920, 885, 816, 664 cm^{-1}; LR-MS (FAB+) m/z 529 (M + H$^+$); HR-MS (FAB+) calcd for $C_{25}H_{41}O_8SSi$ (M + H$^+$) 529.2291, found 529.2297.

To a suspension of 60% sodium hydride (727 mg, 18.2 mmol) in DMF (38 mL) was added methyl phenylsulfonylacetate (3.89 g, 18.2 mmol) in DMF (10 mL) at 0 °C. After stirring for 1 h at 0 °C, a solution of *bis*-alkoxysilane (3.95 g, 7.48 mmol) in DMF (10 mL) was added. The reaction mixture was heated to 80 °C, stirred for 9 h, and cooled to ambient temperature. The resulting mixture was quenched with a saturated NH_4Cl solution (30 mL) and diluted with ethyl acetate (100 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford benzenesulfonyl *bis*-alkoxysilane **9** (3.32 g, 78%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of diastereomers) δ 7.82 (d, 2H, J = 7.3 Hz), 7.64 (t, 1H, J = 7.4 Hz), 7.52 (t, 2H, J = 11.9 Hz), 5.73−5.64 (m, 1H), 5.21 (d, 1H, J = 0.9 Hz), 5.13−5.08 (m, 2H), 5.04−5.00 (m, 1H), 4.58 (s, 2H), 4.29−4.20 (m, 3H), 4.15 (q, 2H, J = 7.1 Hz), 3.96 (ddd, 1H, J = 25.6 Hz, J = 11.2 Hz J = 4.0 Hz), 3.63 (d, 3H, J = 0.9 Hz), 2.08−1.87 (m, 2H), 1.53−1.45 (m, 2H), 1.26 (t, 3H, J = 7.1 Hz), 0.98−0.90 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz, a mixture of diastereomers) δ 166.2, 154.9, 142.2, 139.8, 139.6, 137.1, 136.9, 134.1, 129.2, 128.9, 115.1, 115.0, 113.2, 72.5, 72.4, 70.6, 67.6, 64.0, 63.2, 52.8, 34.5, 34.4, 22.4, 22.1, 17.3, 17.2, 14.2, 12.2, 12.1; IR (neat) ν_{max} 2947, 2868, 1746, 1448, 1375, 1328, 1260, 1150, 1085, 1011, 924, 884, 772, 724, 689 cm^{-1}; LR-MS (FAB+) m/z 571 (M + H$^+$); HR-MS (FAB+) calcd for $C_{27}H_{43}O_9SSi$ (M + H$^+$) 571.2397, found 571.2383.

Methyl 4-((*R*)-6-(((Ethoxycarbonyl)oxy)methyl)-2,2-diisopropyl-4,7-dihydro-1,3,2-dioxasilepin-4-yl)-2-(phenylsulfonyl)-butanoate (10). To a refluxing solution of benzenesulfonyl *bis*-alkoxysilane **9** (765 mg, 1.6 mmol) in toluene (160 mL, 0.01 M) was added a second generation Grubbs catalyst (135 mg, 0.2 mmol). After stirring for 30 min, the reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to afford the cyclic *bis*-alkoxysilane **10** (720 mg, 100%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of diastereomers) δ 7.85 (d, 2H, J = 7.8 Hz), 7.66 (t, 1H, J = 7.4 Hz), 7.54 (t, 2H, J = 7.7 Hz), 5.55 (s, 1H), 4.66 (d, 1H, J = 18.4 Hz), 4.56 (d, 1H, J = 15.6 Hz), 4.44 (t, 2H, J = 15.3 Hz), 4.26 (dd, 1H, J = 15.5 Hz, J = 4.8 Hz), 4.17 (m, 2H), 4.09−4.02 (m, 1H), 3.67 (d, 3H, J = 6.8 Hz), 2.28−1.85 (m, 2H), 1.62−1.53 (m, 2H), 1.28 (td, 3H, J = 7.1 Hz, J = 1.5 Hz), 0.99 (s, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz, a mixture of diastereomers) δ 170.9, 166.3, 166.2, 154.7, 137.1, 137.0, 136.6, 136.5, 134.1, 133.6, 133.4, 129.2, 128.9, 70.5, 70.4, 70.3, 69.9, 69.3, 64.1, 62.8, 62.7, 60.2, 52.8, 34.7, 34.5, 23.8, 22.9, 20.9, 17.3, 17.2, 17.1, 16.9, 14.1, 12.1, 12.0; IR (neat) ν_{max} 2949, 1746, 1259, 1220, 1149, 772, 688 cm^{-1}; LR-MS (FAB+) m/z 543 (M + H$^+$); HR-MS (FAB+) calcd for $C_{25}H_{39}O_9SSi$ (M + H$^+$) 543.2084, found 543.2077.

(*Z*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-((2*R*)-6-oxo-5-(phenylsulfonyl)tetrahydro-2*H*-pyran-2-yl)allyl Ethyl Carbonate (6). To a solution of the cyclic *bis*-alkoxysilane **10** (10.04 g, 18.5 mmol) in THF (185 mL) was added tetra-*n*-butylammonium fluoride (1.0 M solution in THF, 37.0 mL, 37.0 mmol) at ambient temperature. After stirring for 12 h, the reaction mixture was quenched with a saturated NH_4Cl solution (50 mL) and diluted with ethyl acetate (100 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 3:1) to afford hydroxyl valerolactone (5.83 g, 79%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of diastereomers) δ 7.93−7.90 (m, 2H), 7.69−7.65 (m, 1H), 7.56 (td, 2H, J = 7.9 Hz, J = 2.9 Hz), 5.83 (d, 0.5H, J = 8.8 Hz), 5.72 (d, 0.5H, J = 8.7 Hz), 5.46−5,41 (m, 0.5H), 5.34−5.27 (m, 0.5H), 4.79 (dd, 1H, J = 12.7 Hz, J = 3.7 Hz), 4.65 (dd, 1H, J = 12.7 Hz, J = 7.4 Hz), 4.22−4.00 (m, 5H), 2.90−2.86 (m, 0.5H), 2.72−2.64 (m, 0.5H), 2.47−2.38 (m, 0.5H), 2.36−2.13 (m, 1H), 1.99−1.93 (m, 0.5H), 1.86−1.70 (m, 1H), 1.33−1.27 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, a mixture of diastereomers) δ 162.9, 162.7, 154.9, 139.0, 138.6, 138.0, 137.5, 134.5, 134.3, 129.3, 129.2, 129.1, 129.0, 128.4, 127.7, 77.2, 76.3, 68.6, 68.4, 64.4, 63.4, 58.6, 27.4, 25.9, 20.0, 19.5, 14.2; IR (neat) ν_{max} 2994, 1758, 1374, 1246, 1059 cm^{-1}; LR-MS (FAB+) m/z 399 (M + H$^+$); HR-MS (FAB+) calcd for $C_{18}H_{23}O_8S$ (M + H$^+$) 399.1114, found 399.1105.

To a mixture of hydroxyl valerolactone (260 mg, 0.7 mmol) and imidazole (67 mg, 1.0 mmol) in DMF (7 mL) was added *tert*-butyldimethylsilyl chloride (148 mg, 1.0 mmol) at 0 °C. After stirring for 10 min at ambient temperature, the reaction mixture was quenched with H_2O (10 mL) and diluted with ethyl acetate (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford δ-valerolactone **6** (334 mg, 89%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of diastereomers) δ 7.90 (m, 2H), 7.67−7.63 (m, 1H), 7.56−7.52 (m, 1H), 5.74 (dd, 0.5H, J = 34.3 Hz, J = 8.8 Hz), 5.60 (dd, 0.5H, J = 38.5 Hz, J = 8.5 Hz), 5.46−5.38 (m, 0.5 H), 5.29 (td, 0.5H, J = 9.5 Hz, J = 3.7 Hz), 4.73 (dd, 0.5H, J = 12.5 Hz, J = 3.7 Hz), 4.68−4.53 (m, 1.5H), 4.30−4.00 (m, 5H), 2.83−2.78 (m, 0.5H), 2.67−2.59 (m, 0.5H), 2.44−2.08 (m, 2H), 1.95−1.90 (m, 0.5H), 1.77−1.66 (m, 0.5H), 1.30−1.24 (m, 3H), 0.88−0.85 (m, 9H), 0.08−0.02 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz, a mixture of diastereomers) δ 171.0, 162.7, 154.8, 138.9, 138.6, 138.4, 138.1, 137.6, 134.3, 129.3, 129.0, 126.9, 126.1, 125.9, 77.4, 76.2, 68.2, 68.0, 64.3, 63.8, 63.5, 62.5, 60.3, 59.4, 27.5, 25.9, 25.8, 20.9, 20.0, 19.5, 18.2, 14.1, −5.5; IR (neat) ν_{max} 2955, 1745, 1448, 1321, 1255, 1147, 1085, 838, 773, 724, 688 cm^{-1}; LR-MS (FAB+) m/z 513 (M + H$^+$); HR-MS (FAB+) calcd for $C_{24}H_{37}O_8SSi$ (M + H$^+$) 513.1978, found 513.1967.

(1*R*,4*R*,7*R*)-7-(3-(((*tert*-Butyldimethylsilyl)oxy)prop-1-en-2-yl)-4-(phenylsulfonyl)-2-oxabicyclo[2.2.1]heptan-3-one (5). To a refluxing solution of δ-valerolactone **6** (5.38 g, 10.5 mmol) in CH_2Cl_2 (210 mL) was added a mixture of palladium acetate (118 mg, 0.5 mmol) and 1,1′-bis(diphenylphosphino)ferrocene (582 mg, 1.1 mmol) in CH_2Cl_2 (2 mL). After stirring for 6 h, the reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to afford [2.2.1] bridged bicyclic lactone **5** (3.84 g, 87%) as a colorless oil and the minor product **5′** (533 mg, 12%) as a white solid: $[\alpha]_D^{20}$ −44.13 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (d, 2H, J = 7.9 Hz), 7.65 (t, 1H, J = 7.4 Hz), 7.53 (t, 1H, J = 8.0 Hz), 5.34 (d, 2H, J = 19.1 Hz), 4.82 (s, 1H), 4.17 (q, 2H, J = 13.6 Hz), 3.20 (s, 1H), 2.54 (td, 1H, J = 12.0 Hz, J = 4.6 Hz), 2.08 (m, 1H), 1.89 (m, 1H), 1.69 (m, 1H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.1, 139.8, 137.2, 134.4, 130.2, 128.8, 116.1, 83.2, 73.0, 65.7, 57.1, 29.1, 28.0, 25.9, 18.3, −5.4; IR (neat) ν_{max} 2954, 2929, 2856, 1791, 1463, 1448, 1326, 1256, 1158, 1119, 1076, 1037, 924, 839, 782, 759, 717, 688, 604 cm^{-1}; LR-MS (FAB+) m/z 423 (M + H$^+$); HR-MS (FAB+) calcd for $C_{21}H_{31}O_5SSi$ (M + H$^+$) 423.1661, found 423.1663.

(1*R*,4*R*,7*S*)-7-(3-(((*tert*-Butyldimethylsilyl)oxy)prop-1-en-2-yl)-4-(phenylsulfonyl)-2-oxabicyclo[2.2.1]heptan-3-one (5′). $[\alpha]_D^{20}$ +40.16 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, 2H, 7.6 Hz), 7.67 (t, 1H, J = 7.5 Hz), 7.53 (t, 1H, J = 7.9 Hz), 5.65 (s, 1H), 5.50 (s, 1H), 4.84 (s, 1H), 4.12 (q, 2H, J = 13.0 Hz), 3.10 (s, 1H), 2.90−2.84 (m, 1H), 2.39−2.33 (m, 1H), 2.08−1.96 (m, 2H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.4, 139.0, 137.3, 134.4, 130.2, 128.8, 116.6, 81.1, 74.2, 67.2, 55.6, 28.8, 25.9, 23.2, 18.3; IR (neat) ν_{max} 2954, 2857, 1794, 1471, 1448, 1326, 1254, 1155, 1119, 1055, 1008, 943, 838, 779, 720, 688, 603 cm^{-1}; LR-MS (FAB+) m/z 423 (M + H$^+$); HR-MS (FAB+) calcd for $C_{21}H_{31}O_5SSi$ (M + H$^+$) 423.1661, found 423.1666.

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(1*R*,4*S*,7*R*)-7-(3-((*tert*-Butyldimethylsilyl)oxy)prop-1-en-2-yl)-2-oxabicyclo[2.2.1]heptan-3-one (11). To a mixture of [2.2.1] bridged bicyclic lactone **5** (324 mg, 0.8 mmol) and boric acid (475 mg, 7.7 mmol) in MeOH (8 mL) was added 5% sodium mercury amalgam (2.35 g, 6.1 mmol) at ambient temperature. After stirring for 3 h, the reaction mixture was decanted with diethyl ether and quenched with a saturated NH_4Cl solution (30 mL). The organic layer was separated, and an aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:6) to afford desulfonylated bicyclic lactone **11** (200 mg, 93%) as a white solid: $[\alpha]_D^{20}$ −8.35 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.18 (s, 1H), 5.04 (s, 1H), 4.86 (s, 1H), 4.13 (t, 2H, J = 14.7 Hz), 2.94 (d, 1H, *J* = 3.4 Hz), 2.66 (s, 1H), 2.05−1.92 (m, 3H), 1.81−1.75 (m, 1H), 0.88 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.7, 142.4, 113.1, 82.0, 66.1, 53.7, 45.5, 29.0, 25.8, 23.1, 18.3, −5.4; IR (neat) ν_{max} 2954, 2857, 1789, 1471, 1333, 1255, 1149, 1097, 1047, 955, 907, 839, 778 cm^{-1}; LR-MS (FAB+) *m*/*z* 283 (M + H$^+$); HR-MS (FAB+) calcd for $C_{15}H_{27}O_3Si$ (M + H$^+$) 283.1729, found 283.1736.

(1*R*,2*R*,3*S*)-3-(Hydroxymethyl)-2-(3-hydroxyprop-1-en-2-yl)-cyclopentan-1-ol (4). To a solution of desulfonylated bicyclic lactone **11** (212 mg, 0.8 mmol) in diethyl ether (8 mL) were added lithium borohydride (3.0 M in THF, 1.0 mL, 3.0 mmol) and methanol (0.18 mL, 4.5 mmol) at 0 °C. After stirring for 4 h, the reaction mixture was quenched with H_2O (10 mL) and diluted with diethyl ether (10 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 10 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford cyclopentane silyl ether (206 mg, 96%) as a colorless oil: $[\alpha]_D^{20}$ −5.00 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.28 (s, 1H), 5.13 (s, 1H), 4.30−4.26 (m, 1H), 4.18 (d, 1H, *J* = 12.2 Hz), 4.10 (d, 1H, *J* = 12.2 Hz), 3.62 (dd, 1H, *J* = 12.5 Hz, *J* = 3.4 Hz), 3.35 (dd, 1H, *J* = 11.1 Hz, *J* = 5.5 Hz), 2.69 (dd, 1H, *J* = 8.6 Hz, *J* = 4.3 Hz), 2.40 (m, 1H), 1.89−1.73 (m, 4H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0, 116.4, 74.0, 68.2, 62.4, 51.0, 43.2, 33.6, 25.8, 24.5, 18.3, −5.3; IR (neat) ν_{max} 3278, 2954, 2858, 1472, 1255, 1083, 1022, 837, 775 cm^{-1}; LR-MS (FAB+) *m*/*z* 287 (M + H$^+$); HR-MS (FAB+) calcd for $C_{15}H_{31}O_3Si$ (M + H$^+$) 287.2042, found 287.2038.

To a solution of cyclopentane silyl ether (206 mg, 0.7 mmol) in THF (15 mL) was added tetra-*n*-butylammonium fluoride (1.0 M solution in THF, 0.8 mL, 0.8 mmol) at ambient temperature. After stirring for 30 min, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 9:1) to afford cyclopentanetriol **4** (124 mg, 100%) as a colorless oil: $[\alpha]_D^{20}$ +37.84 (*c* 0.5, MeOH); ^{1}H NMR (CD_3OD, 400 MHz) δ 5.25 (d, 2H, *J* = 18.4 Hz), 4.26 (q, 1H, *J* = 4.4 Hz), 4.01 (s, 2H), 3.51 (m, 2H), 2.63 (dd, 1H, *J* = 8.2 Hz, *J* = 4.5 Hz), 2.40−2.38 (m, 1H), 1.89−1.82 (m, 2H), 1.79−1.69 (m, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 147.8, 114.7, 76.2, 68.4, 64.3, 51.3, 44.0, 35.4, 26.6; IR (neat) ν_{max} 3313, 2942, 1648, 1472, 1338, 1129, 1019, 945, 908, 798 cm^{-1}; LR-MS (FAB+) *m*/*z* 173 (M + H$^+$); HR-MS (FAB+) calcd for $C_9H_{17}O_3$ (M + H$^+$) 173.1178, found 173.1177.

(3a*R*,4*S*,6a*R*)-4-(Hydroxymethyl)-3-methylenehexahydro-2*H*-cyclopenta[*b*]furan-2-one (12). To a solution of cyclopentanetriol **4** (52.5 mg, 0.3 mmol) in THF (12 mL) was added manganese dioxide (1.06 g, 12.2 mmol) at ambient temperature. After stirring for 12 h, the reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 2:1) to afford *cis*-fused 5,5-bicyclic lactone **12** (46.7 mg, 91%) as a colorless oil: $[\alpha]_D^{20}$ +39.36 (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.39 (d, 1H, *J* = 1.8 Hz), 5.85 (d, 1H, *J* = 1.0 Hz), 5.00 (t, 1H, *J* = 5.9 Hz), 3.69 (dd, 1H, *J* = 10.5 Hz, *J* = 5.6 Hz), 3.64−3.56 (m, 2H), 2.32−2.24 (m, 1H), 2.14 (dd, 1H, *J* = 13.4 Hz, *J* = 6.4 Hz), 1.79−1.69 (m, 2H), 1.29−1.18 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.1, 134.7, 125.6, 83.5, 62.2, 46.2, 44.3, 32.9, 25.9; IR (neat) ν_{max} 3460, 2962, 1757, 1313, 1268, 1220, 1158, 1026, 985, 772 cm^{-1}; LR-MS (FAB+) *m*/*z* 169 (M + H$^+$); HR-MS (FAB+) calcd for $C_9H_{13}O_3$ (M + H$^+$) 169.0865, found 169.0874.

(3a*S*,4*R*,6a*R*)-3a-Hydroxy-4-(hydroxymethyl)-3-methylene-hexahydro-2*H*-cyclopenta[*b*]furan-2-one (3). To a refluxing solution of bicyclic lactone **12** (27.0 mg, 0.1 mmol) in 1,4-dioxane (2 mL) was added selenium dioxide (178.0 mg, 1.6 mmol). After stirring for 24 h, the reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc only) to afford dihydroxy bicyclic lactone **3** (26.5 mg, 90%) as a colorless oil: $[\alpha]_D^{20}$ +16.25 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.60 (s, 1H), 6.20 (s, 1H), 4.70 (d, 1H, *J* = 2.0 Hz), 3.83 (dd, 1H, *J* = 10.1 Hz, *J* = 5.0 Hz), 3.58 (t, 1H, *J* = 10.0 Hz), 2.81 (s, 1H), 2.44−2.36 (m, 1H), 2.06−2.01 (m, 2H), 1.78−1.72 (m, 1H), 1.60 (br, 1H), 1.17−1.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.5, 138.4, 128.4, 89.8, 85.1, 62.1, 53.3, 31.0, 25.7; IR (neat) ν_{max} 3420, 2967, 1748, 1408, 1300, 1220, 1193, 1146, 1089, 1024, 984, 819, 772 cm^{-1}; LR-MS (FAB+) *m*/*z* 185 (M + H$^+$); HR-MS (FAB+) calcd for $C_9H_{13}O_4$ (M + H$^+$) 185.0814, found 185.0810.

Diastereomeric Mixture of (3a*S*,4*R*,6a*R*)-3a-Hydroxy-4-((1*S*,2*R*)-1-hydroxy-2-methylbut-3-en-1-yl)-3-methylenehexahydro-2*H*-cyclopenta[*b*]furan-2-one (2) and (1*R*,2*S*) Isomer (14). To a solution of dihydroxy bicyclic lactone **3** (23.0 mg, 0.1 mmol) in CH_2Cl_2 (1 mL) was added Dess-Martin periodinane (106.0 mg, 0.3 mmol) at ambient temperature. After stirring for 30 min, the reaction mixture was filtered through a pad of anhydrous sodium sulfate and concentrated *in vacuo*. The residue was used in the next step without further purification.

To a solution of crude aldehyde **13** in CH_2Cl_2 (1.3 mL, 0.1 M) were added titanium tetrachloride (0.25 mL, 0.3 mmol) and (*E*)-crotyltrimethylsilane (160 mg, 1.3 mmol) at −78 °C. After stirring for 6 h, the reaction mixture was quenched with a saturated $Na_2S_2O_3$ solution (5 mL) and diluted with ethyl acetate (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford a diastereomeric mixture of homoallylic alcohol **2**/**14** (23.2 mg, 78%, dr 5:1) as a colorless oil. The diastereomeric ratio was determined after the separation of each diastereomer as the silyl ethers **15** and **15′** followed by desilylation.

Major Product **2**. $[\alpha]_D^{20}$ +50.16 (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.33 (s, 1H), 5.86 (s, 1H), 5.67 (ddd, 1H, *J* = 17.9 Hz, *J* = 9.6 Hz, *J* = 8.4 Hz), 5.09−5.03 (m, 2H), 4.52 (d, 1H, *J* = 4.3 Hz), 3.51 (m, 1H), 2.35 (td, 1H, *J* = 10.7 Hz, *J* = 2.8 Hz), 2.26 (q, 1H, *J* = 7.2 Hz), 2.13−2.09 (m, 1H), 1.96−1.89 (m, 1H), 1.83−1.77 (m, 1H), 1.76 (s, 1H), 1.33 (d, 1H, *J* = 5.2 Hz), 1.23 (s, 1H), 1.05 (d, 3H, *J* = 1.7 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 168.7, 142.7, 140.7, 122.4, 115.5, 90.4, 85.6, 72.2, 54.5, 43.2, 29.7, 22.5, 16.2; IR (neat) ν_{max} 3503, 2926, 1749, 1220, 773 cm^{-1}; LR-MS (FAB+) *m*/*z* 239 (M + H$^+$); HR-MS (FAB+) calcd for $C_{13}H_{19}O_4$ (M + H$^+$) 239.1283, found 239.1290.

Minor Product **14**. $[\alpha]_D^{20}$ +23.28 (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.60 (s, 1H), 6.24 (s, 1H), 5.86 (m, 1H), 5.24 (d, 1H, *J* = 10.7 Hz), 5.15 (d, 1H, *J* = 7.6 Hz), 4.72 (s, 1H), 3.57 (d, 1H, *J* = 10.4 Hz), 3.39 (s, 1H), 2.32 (s, 1H), 2.20 (ddd, 1H, *J* = 13.6 Hz, *J* = 7.0 Hz, *J* = 5.8 Hz), 2.05−2.02 (m, 1H), 1.78 (s, 1H), 1.71−1.68 (m, 1H), 1.25−1.13 (m, 1H), 1.02 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 140.2, 138.6, 128.7, 116.8, 88.8, 85.2, 72.9, 54.5, 39.5, 31.3, 25.1, 9.7; IR (neat) ν_{max} 3472, 2970, 1702, 1284, 1197, 1144, 1099, 987 cm^{-1}; LR-MS (FAB+) *m*/*z* 239 (M + H$^+$); HR-MS (FAB+) calcd for $C_{13}H_{19}O_4$ (M + H$^+$) 239.1283, found 239.1282.

(3a*S*,4*R*,6a*R*)-3a-Hydroxy-4-((1*S*,2*R*)-2-methyl-1-((triethylsilyl)oxy)but-3-en-1-yl)-3-methylenehexahydro-2*H*-cyclopenta[*b*]furan-2-one (15). To a solution of a diastereomeric mixture of homoallylic alcohol **2**/**14** (5:1) (23.2 mg, 0.1 mmol) in pyridine (1 mL) was added triethylsilyl trifluoromethanesulfonate (0.1 mL, 0.3 mmol) at −40 °C. After stirring for 30 min, the reaction mixture was quenched with H_2O (1 mL) and diluted with ethyl acetate (5 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 5 mL). The combined organic layer was

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washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:10 to 1:6) to afford the bicyclic lactone silyl ether **15** (25.7 mg, 75%) as a white solid and the minor (1*R*, 2*S*) isomer **15′** (5.2 mg, 15%) as a white solid.

Major Product ***15***. $[\alpha]_D^{20}$ +37.60 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.48 (s, 1H), 5.90 (s, 1H), 5.87 (m, 1H), 5.04−4.97 (m, 2H), 4.57 (d, 1H, *J* = 3.5 Hz), 3.69 (dd, 1H, *J* = 7.0 Hz, *J* = 2.0 Hz), 2.55−2.51 (m, 1H), 2.26−2.20 (m, 1H), 2.03−1.99 (m, 1H), 1.92−1.83 (m, 2H), 1.83 (s, 1H), 1.49−1.43 (m, 1H), 1.01 (d, 3H, *J* = 6.8 Hz), 0.90 (t, 9H, *J* = 8.0 Hz), 0.53 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 168.6, 141.6, 140.2, 126.3, 114.1, 91.1, 84.8, 74.6, 53.9, 41.6, 29.9, 26.8, 12.6, 7.0, 5.5; IR (neat) ν_{max} 3434, 2958, 1749, 1261, 1220, 1011, 772 cm^{-1}; LR-MS (FAB+) *m*/*z* 353 (M + H^+); HR-MS (FAB+) calcd for $C_{19}H_{33}O_4Si$ (M + H^+) 353.2148, found 353.2138.

Minor Product ***15′***. $[\alpha]_D^{20}$ −29.78 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ, 6.54 (s, 1H), 6.03 (ddd, 1H, *J* = 17.4 Hz, *J* = 10.8 Hz, *J* = 4.6 Hz), 5.99 (s, 1H), 5.16 (dt, 1H, *J* = 11.0 Hz, *J* = 1.4 Hz), 5.09 (dt, 1H, *J* = 17.4 Hz, *J* = 1.8 Hz), 4.62 (d, 1H, *J* = 5.5 Hz), 3.81 (dd, 1H, *J* = 9.6 Hz, *J* = 2.8 Hz), 3.69 (s, 1H), 2.55−2.50 (m, 1H), 2.17 (m, 1H), 1.97−1.86 (m, 2H), 1.68 (quint, 1H, *J* = 6.0 Hz), 1.18−1.10 (m, 1H), 1.00−0.97 (m, 12H), 0.74−0.65 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 169.6, 139.8, 137.9, 127.1, 115.2, 88.2, 85.2, 77.9, 55.9, 42.3, 31.4, 25.1, 14.6, 7.0, 6.0; IR (neat) ν_{max} 3442, 2959, 2877, 1747, 1415, 1338, 1113, 1007, 977, 914, 819, 741 cm^{-1}; LR-MS (FAB+) *m*/*z* 353 (M + H^+); HR-MS (FAB+) calcd for $C_{19}H_{33}O_4Si$ (M + H^+) 353.2148, found 353.2155.

(2a*R*,2a1*S*,4a*R*,5*S*,6*R*)-2a1-Hydroxy-6-methyl-5-((triethylsilyl)oxy)-2a1,3,4,4a,5,6-hexahydroindeno[1,7-*bc*]furan-1-(2a*H*)-one (16). To a refluxing solution of bicyclic lactone silyl ether **15** (6.5 mg, 0.02 mmol) in CH_2Cl_2 (2 mL, 0.01 M) was added a second generation Grubbs catalyst (0.9 mg, 0.9 μmol). After stirring for 6 h, the reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:5) to afford the tricyclic lactone **16** (6.0 mg, 99%) as a white solid: $[\alpha]_D^{20}$ −22.84 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.75 (d, 1H, *J* = 2.4 Hz), 4.81 (d, 1H, *J* = 8.4 Hz), 3.95 (d, 1H, *J* = 2.5 Hz), 3.83 (s, 1H), 2.65−2.60 (m, 1H), 2.46 (ddd, 1H, *J* = 12.4 Hz, *J* = 6.7 Hz, *J* = 3.0 Hz), 2.14−2.06 (m, 1H), 1.76−1.67 (m, 2H), 1.30−1.21 (m, 1H), 1.15 (d, 3H, *J* = 8.1 Hz), 0.96 (t, 9H, *J* = 7.9 Hz), 0.63 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.9, 141.6, 129.6, 88.3, 80.0, 74.6, 48.4, 39.2, 30.8, 26.5, 19.1, 6.6, 4.6; IR (neat) ν_{max} 3414, 2958, 2877, 1761, 1673, 1459, 1283, 1221, 1193, 1096, 1051, 1029, 836, 745 cm^{-1}; LR-MS (FAB+) *m*/*z* 325 (M + H^+); HR-MS (FAB+) calcd for $C_{17}H_{29}O_4Si$ (M + H^+) 325.1835, found 325.1840.

(2a*R*,2a1*S*,4a*R*,5*S*,6*R*)-2a1,5-Dihydroxy-6-methyl-2a1,3,4,4a,5,6-hexahydroindeno[1,7-*bc*]furan-1(2a*H*)-one (17). To a solution of tricyclic lactone **16** (17.7 mg, 0.1 mmol) in MeOH (1 mL) was added camphor-10-sulfonic acid (β) (1.3 mg, 5 μmol) at ambient temperature. After stirring for 1 min, the reaction mixture was quenched with a saturated $NaHCO_3$ solution (1.0 mL) and diluted with ethyl acetate (5.0 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (5 × 5.0 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 4:1) to afford hydroxygaliellalactone **17** (9.5 mg, 83%) as a white solid: $[\alpha]_D^{20}$ −39.44 (*c* 0.5, MeOH); ^1H NMR (CD_3OD, 500 MHz) δ 6.81 (d, 1H, *J* = 3.2 Hz), 4.62 (t, 1H, *J* = 4.7 Hz), 3.06 (dd, 1H, *J* = 7.0 Hz, *J* = 5.0 Hz), 2.59 (m, 1H), 2.23 (dd, 1H, *J* = 10.7 Hz, *J* = 4.5 Hz), 2.18−2.11 (m, 1H), 2.09−2.04 (m, 1H), 1.58−1.48 (m, 1H), 1.25 (d, 3H, *J* = 5.7 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 177.6, 149.1, 134.5, 92.1, 84.5, 82.1, 54.5, 39.3, 33.0, 30.8, 18.0; IR (neat) ν_{max} 3413, 2928, 1743, 1220, 1047, 772 cm^{-1}; LR-MS (FAB+) *m*/*z* 211 (M + H^+); HR-MS (FAB+) calcd for $C_{11}H_{15}O_4$ (M + H^+) 211.0970, found 211.0971.

(−)-Galiellalactone (1). To a mixture of hydroxygaliellalactone **17** (5.0 mg, 0.02 mmol) and pyridine (10 μL, 0.1 mmol) in CH_2Cl_2 (0.5 mL) was added pentafluorophenyl chlorothionoformate (13 μL, 0.1 mmol) at ambient temperature. After stirring for 3 h, the reaction mixture was quenched with H_2O (1 mL) and diluted with CH_2Cl_2 (1 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:2) to afford the crude xanthate.

To a mixture of tributyltin hydride (13 μL, 0.05 mmol) and azobis(isobutyronitrile) (0.4 mg, 2 μmol) in toluene (0.5 mL) was added the crude xanthate in toluene (0.5 mL) at 80 °C. The reaction mixture was heated to 100 °C. After stirring for 1 h, the resulting mixture was cooled to ambient temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:3) to afford (−)-galiellalactone **1** (3.5 mg, 76% in 2 steps) as a white solid: $[\alpha]_D^{20}$ −47.56 (*c* 0.25, $CHCl_3$) (lit.[1,2] $[\alpha]_D^{20}$ −52.80 (*c* 0.20, $CHCl_3$)); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.03 (d, 1H, *J* = 3.0 Hz), 4.76 (dd, 1H, *J* = 7.5 Hz, *J* = 2.0 Hz), 2.62 (qdt, 1H, *J* = 14.6 Hz, *J* = 7.4 Hz, *J* = 3.1 Hz), 2.43 (dddd, 1H, *J* = 10.5 Hz, *J* = 7.4 Hz, *J* = 7.2 Hz, *J* = 4.8 Hz), 2.24 (dt, 1H, *J* = 14.0 Hz, *J* = 7.4 Hz), 2.07 (dddd, 1H, *J* = 14.6 Hz, *J* = 11.2 Hz, *J* = 7.6 Hz, *J* = 7.3 Hz), 1.93 (s, 1H) 1.85 (dddd, 1H, *J* = 13.2 Hz, *J* = 7.2 Hz, *J* = 7.2 Hz, *J* = 2.9 Hz), 1.74 (m, 1H), 1.18 (1H, m), 1.18 (d, 3H, *J* = 7.4 Hz), 1.07 (ddd, 1H, *J* = 13.6 *J* = 8.0 Hz, *J* = 4.7 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.5, 150.2, 130.6, 89.7, 81.9, 43.1, 33.0, 31.3, 29.0, 20.9; IR (neat) ν_{max} 2959, 2931, 1759, 1744, 1188, 1017, 971, 896 cm^{-1}; LR-MS (FAB+) *m*/*z* 195 (M + H^+); HR-MS (FAB+) calcd for $C_{11}H_{15}O_3$ (M + H^+) 195.1021, found 195.1013.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02121.

^1H and ^{13}C NMR spectra of all novel compounds and synthetic natural product (PDF)

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Notes

The authors declare no competing financial interest.

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