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Stereodivergent Synthesis of (+)- and (−)-Isolineatin

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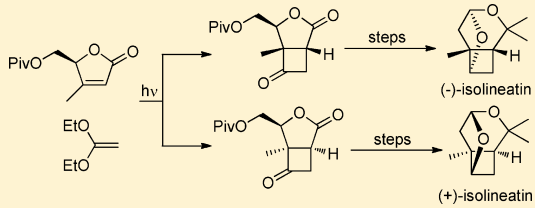
Supporting Information

ABSTRACT: A stereodivergent approach to (+)- and (−)-isolineatin using (*S*)-4-methyl-5-pivaloyloxymethyl-2(5*H*)-furanone as the single source of asymmetry by exploiting the inherent chirality at the C-5 stereocenter is described.



INTRODUCTION

(+)-Lineatin, **1**, is the main component of the aggregation pheromone produced by the female ambrosia beetle *Trypodendron lineatum* Olivier, which is a damaging pest to coniferous forest in Europe and North America (Figure 1).[1] Because of its challenging structure and significant biological activity, much attention has been given to the synthesis of (+)-lineatin, and several research groups, including ours, have developed different approaches for the preparation of this attractive natural product.[2] Isolineatin, **2**, a constitutional isomer of **1** also featuring a tricyclic acetal, has often been described as a byproduct in the syntheses of racemic **1**.[3] However, to date, only one publication, reported by Askani and Keller,[4] describes the synthesis of isolineatin through a sequence specifically devoted to this target and yet in racemic form.

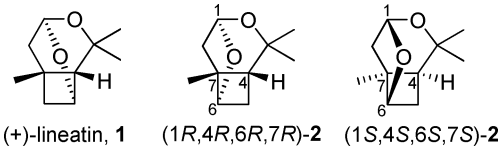
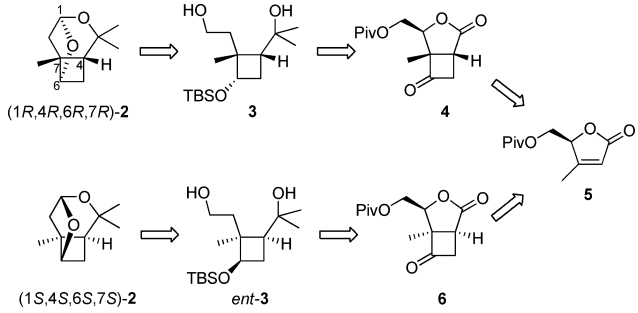


Figure 1. Lineatin, **1**, and isolineatin, **2**.

As part of our investigations of the stereochemical course of the photochemical cycloaddition of substituted homochiral 2(5*H*)-furanones to different olefins[5] and acetylenes,[6] we obtained some products that were seen as potential precursors for isolineatin.[7] Hence, though isolineatin is devoid until now of any known biological activity, the lack of any previous enantioselective synthesis coupled with the interest in this class of compounds prompted us to select **2** as a synthetic target. Herein, we report our successful enantiodivergent synthesis of both enantiomers of isolineatin.

The retrosynthetic analysis of each enantiomer of isolineatin led us back to the enantiomeric diols **3** and *ent*-**3**, which in turn can be derived from the diastereomeric ketolactones **4** and **6**, respectively (Scheme 1). Lactones **4** and **6** had been previously prepared from the 2(5*H*)-furanone **5** as a chiral platform through its regioselective [2+2] photochemical cycloaddition reaction with 1,1-diethoxyethylene, **7**.

Scheme 1. Retrosynthetic Analysis



RESULTS AND DISCUSSION

Accordingly, our initial task focused on the preparation of the diastereomeric cyclobutanones **4** and **6** on a multigram scale. We had previously performed a study on the stereochemical course of the photochemical cycloaddition of **7** to different 5-*O*-acyl-substituted 2(5*H*)-furanones, including lactone **5**.[5c] This cycloaddition could lead to the formation of up to four adducts: the head-to-tail (HT) *anti* and *syn* isomers and the head-to-head (HH) *anti* and *syn* isomers (Scheme 2).[8] When the reaction of **5** and **7** is performed in diethyl ether, the process occurs with excellent regioselectivity giving the HT *anti* and *syn* isomers in similar amounts. Taking this into account, our synthesis commenced with 2(5*H*)-furanone **5**, which was obtained in three steps from (*S*)-5-hydroxymethyl-2(5*H*)-furanone. We scaled the photochemical process up to 2 g of lactone. Thus, irradiation of a solution of **5** and a 10-fold excess of freshly prepared[9] olefin **7** in diethyl ether with a 400 W medium pressure mercury lamp through a quartz filter at −40 °C for 3 h afforded the photoadducts **8**, **9**, **10**, and **11** in a 51:42:4:3 ratio determined by GC. Without further purification, the cycloadduct mixture was treated with *p*-TsOH in acetone to

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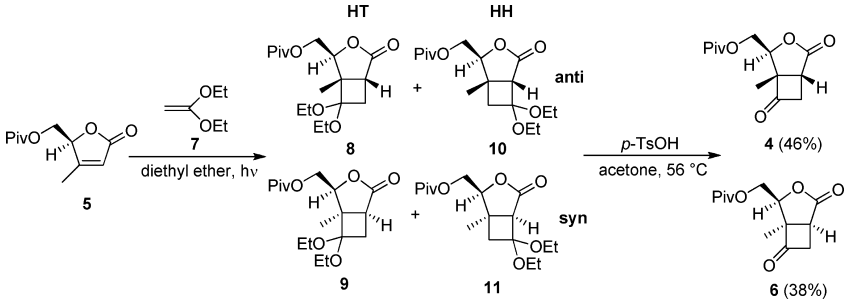
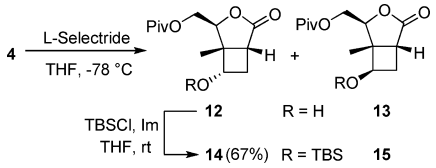
Scheme 2. Synthesis of Cyclobutanones 4 and 6



furnish, after column chromatography, the cyclobutanones **4** and **6** in 46% and 38% yield, respectively. The regioisomeric cyclobutanones of **4** and **6** could not be isolated.

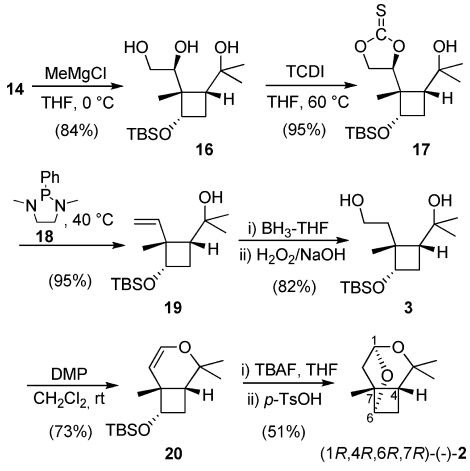
The synthetic sequence was first continued with the *anti* cyclobutanone **4**. Our approach required an efficient and stereoselective reduction of the carbonyl group into the corresponding endo alcohol **12**, where the hydroxyl group is correctly positioned to allow a facile intramolecular acetalization in a later stage of the synthesis (Scheme 3). In a first attempt, the reduction of cyclobutanone **4** with $NaBH_4$ in MeOH at 0 °C delivered a chromatographically inseparable 1:2.7 mixture of the *endo* and *exo* alcohols **12** and **13** in 97% overall yield. The unfavorable proportion of the necessary *endo* alcohol **12** prompted us to investigate other reducing agents. Satisfyingly, when the reaction was performed with L-Selectride in THF at −78 °C, the stereoselectivity was reversed, affording a 9:1 mixture of **12** and **13** in 88% yield. Other attempts, using NB-Enantride or $LiAl(^tBuO)_3H$, improved neither the yield nor the ratio of epimers. The subsequent protection of the secondary alcohol of the mixture as the *tert*-butyldimethylsilyl ether under standard conditions provided compound **14** that was isolated, after purification by column chromatography, in 67% yield over the two steps.

Scheme 3. Stereoselective Reduction of the Cyclobutanone 4 and Protection of the Resulting Secondary Alcohol



Next, exposure of **14** to an excess of methylmagnesium chloride in THF led to the addition of two methyl groups to the lactone and concurrent cleavage of the pivaloyl ester providing triol **16** in 84% yield (Scheme 4).[10] Combination of methylmagnesium chloride with THF was critical for completing the conversion of **14** to triol **16**. The use of MeLi as the nucleophile or diethyl ether as the solvent gave lower yields of triol **16**. The stage was now set for the preparation of intermediate **3.** Initially, we intended to remove the secondary hydroxyl group of **16** by the Barton−McCombie procedure, which involved the formation of a cyclic thionocarbonate followed by a radical reduction with Bu_3SnH.[11] As expected, condensation of **16** with *N*,*N*′-thiocarbonyldiimidazole (TCDI) in THF provided the thionocarbonate **17** in excellent yield. However, all attempts to carry out the radical deoxygenation of the secondary hydroxyl group of **17** met with failure. As a consequence, we

Scheme 4. Synthesis of (−)-Isolineatin



assayed an alternative pathway for the preparation of **3**. Thus, treatment of the thionocarbonate **17** with the Corey−Hopkins reagent, **18**,[12] delivered the olefin **19**, which was submitted to hydroboration with BH_3−THF followed by standard oxidative workup to provide the desired diol **3** in 82% yield for the two steps.

From diol **3**, the envisioned final steps of our approach were oxidation of the primary alcohol to the corresponding aldehyde and then desilylation with simultaneous ketal formation. Accordingly, for the oxidation of the primary alcohol, compound **3** was treated with Dess−Martin periodinane.[13] However, instead of the expected aldehyde, this reaction led to the formation of the dihydropyran **20** as a result of an oxacyclization process leading to an intermediate lactol followed by in situ dehydration. Some attempts to circumvent this elimination were unsuccessful. Nevertheless, enol ether **20** was synthetically equivalent to the expected lactol. Hence, it was also a suitable precursor of the target ketal if an acid-promoted intramolecular addition of the secondary alcohol to the dihydropyran moiety could be efficiently accomplished. To that end, removal of the silyl protecting group was immediately followed by acid treatment to afford the target isolineatin, **2**, in 51% yield, that was found to be the (−)-isomer, $[\alpha]_D$ −22.9 (*c* 0.7, $CDCl_3$), and whose spectral data were in accordance with those previously reported in the literature.[3] Because byproducts were not isolated from this reaction, it was reasoned that the low efficiency of the process was, in part, due to the volatility of **2**.[14]

Turning next to (+)-isolineatin, we attempted to apply the same reaction sequence to cyclobutanone **6**, derived from the *syn* photocycloaddduct (Scheme 5). Unexpectedly, the reduction of **6** with L-Selectride, under identical conditions as

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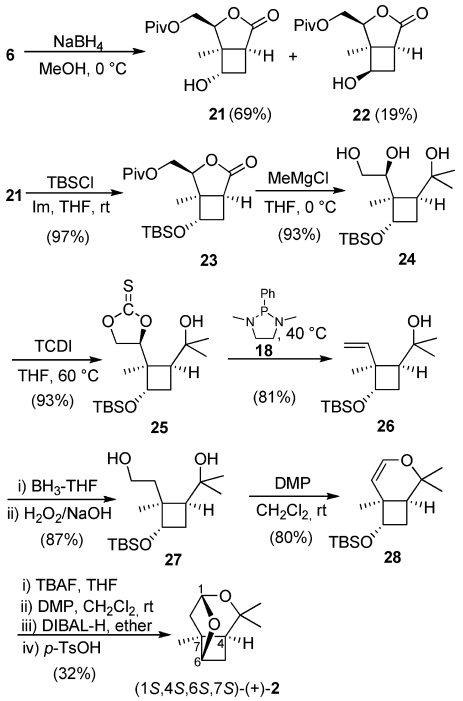
Scheme 5. Synthesis of (+)-Isolineatin



before, resulted in a complex product mixture containing considerable amounts of inseparable byproducts. On the contrary, it was eventually found that the reduction of **6** with $NaBH_4$ in MeOH followed a similar trend as before, showing a moderate *exo* selectivity, and delivering a mixture of the *exo* alcohol **21** and the *endo* isomer **22** in an overall 88% yield and a 3.6:1 ratio. Because these isomeric alcohols were readily separated, we continued the synthesis with the major *exo* isomer **21**. We planned to invert the configuration of this center later, through an oxidation−reduction sequence.

Thus, starting from alcohol **21** and following the same step sequence as described above, the dihydropyran **28** was synthesized in 47% overall yield. The bicyclic compound **28** was desilylated, and the free alcohol was submitted to epimerization by reaction with Dess−Martin periodinane followed by in situ reduction of the corresponding ketone with DIBAL-H. Finally, acid-catalyzed ketalization furnished (+)-isolineatin in 32% yield over the four steps, $[\alpha]_D$ +21.0 (*c* 0.7, $CDCl_3$).

CONCLUSIONS

In summary, we have achieved the total synthesis of both enantiomers of isolineatin through a stereodivergent approach starting from a 2(5*H*)-furanone **5** as a sole chiral precursor. Our route features a regioselective [2+2] photochemical reaction and led to (−)- and (+)-isolineatin in 7% and 5% overall yield, respectively.

EXPERIMENTAL SECTION

General Methods. Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying agents. All reactions were performed avoiding moisture by standard procedures and under a nitrogen atmosphere. Flash column chromatography was performed using silica gel (230−400 mesh). ^1H NMR and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, 360 and 90 MHz, or 500 and 125 MHz. NMR signals were assigned with the help of DEPT, COSY, HMBC, HMQC, and NOESY experiments. Proton chemical shifts are reported in parts per million (δ) ($CDCl_3$, δ 7.26; acetone-d_6, δ 2.05). Carbon chemical shifts are reported in parts per million (δ) ($CDCl_3$, δ 77.2). NMR signals were assigned with the help of COSY, HSQC, HMBC, and NOESY experiments. Melting points were determined on a hot stage and are uncorrected. Optical rotations were measured at 22 ± 2 °C.

(1*R*,4*S*,5*S*)-5-Methyl-4-pivaloyloxymethyl-3-oxabicyclo-[3.2.0]heptan-2,6-dione (4) and (1*S*,4*S*,5*R*)-5-Methyl-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2,6-dione (6). A solution of 2(5*H*)-furanone **5** (2.08 g, 9.8 mmol) and 1,1-diethoxyethylene **7** (12.9 mL, 98 mmol) in diethyl ether (800 mL) was placed in a photochemical reactor (two-necked vessel fitted with a Quartz immersion type cooling jacket). The reactor was immersed in a cooling bath at −20 °C, and a stream of MeOH at −15 °C was circulated throughout the refrigeration jacket. The reaction mixture was initially degassed by passage of oxygen-free argon through the solution for 10 min and then irradiated under an atmosphere of argon using a medium pressure 400 W mercury lamp for 3 h. Evaporation of the solvent and column chromatography (hexanes:EtOAc, 12:1) afforded a 51:42:4:3 mixture of **8**, **9**, **10**, and **11**. The resulting crude was diluted in a solution of *p*-toluenesulfonic acid in acetone (0.01 M, 120 mL). The mixture was stirred overnight at the reflux temperature. Evaporation of the solvent and purification by column chromatography (from 10:1 hexane:EtOAc to 5:1 hexane:EtOAc) afforded the *anti* isomer **4** (1.45 g, 5.70 mmol, 46% yield) as a white solid and the *syn* isomer **6** (946 mg, 3.72 mmol, 38% yield) as a white solid.[5c]

(1*R*,4*S*,5*R*,6*S*)-6-Hydroxy-5-methyl-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (12) and Its (1*R*,4*S*,5*S*,6*R*)-Isomer (13). To a solution of **4** (280 mg, 1.10 mmol) in dry THF (24 mL) at −78 °C was added dropwise a 1.0 M solution of L-Selectride in THF (1.65 mL, 1.65 mmol). After the mixture had been stirred for 3 h at −78 °C, the reaction was quenched by the slow addition of saturated NH_4Cl solution, and the mixture was allowed to warm to room temperature. The two layers were separated, and the aqueous layer was extracted twice with EtOAc. The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated to dryness. The crude residue was purified by column chromatography (hexane:EtOAc, 4:1) to afford a mixture (89:11) of the two isomeric alcohols **12** and **13** (248 mg, 0.97 mmol, 88% yield) as a white solid.

From the mixture: MS (ESI+, MeOH) 279.0 ($[M + Na]^+$, 100); IR (ATR) 3386, 2972, 1726, 1280, 1145, 1043, 970 cm^{-1}. Anal. Calcd for ($C_{13}H_{20}O_5$): C, 60.92; H, 7.87. Found: C, 60.77; H, 7.93. **12**: ^1H NMR (500 MHz, $CDCl_3$) δ 5.08 (dd, $J_{4,8}$ = 4.2 Hz, $J_{4,8}$ = 3.5 Hz, 1H, H-4), 4.38 (dd, J_{gem} = 12.3 Hz, $J_{8,4}$ = 3.5 Hz, 1H, H-8), 4.12 (dd, J_{gem} = 12.3 Hz, $J_{8,4}$ = 4.2 Hz, 1H, H-8), 4.11 (m, 1H, H-6), 2.90 (m, 1H, H-7), 2.58 (m, 2H, H-1, OH), 2.09 (m, 1H, H-7), 1.29 (s, 3H, CH_3), 1.20 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5 (C═O), 178.5 (C═O, C-2), 77.7 (CH, C-4), 72.0 (CH, C-6), 63.5 (CH_2, C-8), 48.4 (C, C-5), 39.7 (CH, C-1), 38.8 (C, $\underline{C}(CH_3)_3$), 32.4 (CH_2, C-7), 27.1 (CH_3, $C(\underline{C}H_3)_3$), 17.7 (CH_3). **13**: ^1H NMR (250 MHz, $CDCl_3$) δ 4.51 (dd, $J_{4,8}$ = 2.8 Hz, $J_{4,8}$ = 2.2 Hz, 1H, H-4), 4.40 (m, 1H, H-6), 4.35 (dd, J_{gem} = 12.4 Hz, $J_{8,4}$ = 2.8 Hz, 1H, H-8), 4.05 (dd, J_{gem} = 12.4 Hz, $J_{8,4}$ = 2.2 Hz, 1H, H-8), 2.60 (m, 2H, H-1, H-7), 2.37 (m, 1H, H-7), 1.27 (s, 3H, CH_3), 1.17 (s, 9H, $(C\underline{H}_3)_3C$).

(1*R*,4*S*,5*S*,6*S*)-6-*tert*-Butyldimethylsilyloxy-5-methyl-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (14). To an ice-cooled solution of a (89:11) mixture of **12** and **13** (100 mg, 0.39 mmol) in CH_2Cl_2 (4 mL) were added imidazole (54 mg, 0.79 mmol) and *tert*-butyldimethylsilyl chloride (121 mg, 0.78 mmol) . The mixture was stirred overnight at room temperature and then was diluted with CH_2Cl_2 (5 mL) and washed with water (5 mL). The organic layer was dried, filtered, and concentrated to dryness. The reaction crude was purified by column chromatography (hexane:EtOAc, 12:1) to afford **14** (125 mg, 0.34 mmol, 86% yield) as a white solid and **15** (12 mg, 0.03 mmol, 8% yield).

14: mp 114−116 °C (from pentane−EtOAc); $[\alpha]_D$ +11.4 (*c* 0.65, $CHCl_3$); MS (ESI+, MeOH) 393.1 ($[M + Na]^+$, 100); IR (ATR) 2953, 1759, 1731, 1152, 1079 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.10 (dd, $J_{4,8}$ = 4.9 Hz, $J_{4,8}$ = 3.3 Hz, 1H, H-4), 4.38 (dd, J_{gem} = 12.3 Hz, $J_{8,4}$ = 3.3 Hz, 1H, H-8), 4.11 (dd, J_{gem} = 12.3 Hz, $J_{8,4}$ = 4.9 Hz, 1H,

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H-8), 4.06 (m, 1H, H-6), 2.84 (m, 1H, H-7), 2.55 (m, 1H, H-1), 2.09 (m, 1H, H-7), 1.29 (s, 3H, C$\underline{H}_3$), 1.22 (s, 9H, $(CH_3)_3C$), 0.90 (s, 9H, $(CH_3)_3C$), 0.06 (s, 6H, 2C$\underline{H}_3$-Si); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.2 (C═O), 178.0 (C═O, C-2), 77.9 (CH, C-4), 71.9 (CH, C-6), 63.6 (CH_2, C-8), 49.1 (C, C-5), 39.5 (CH, C-1), 38.7 (C, $\underline{C}(CH_3)_3$), 33.0 (CH_2, C-7), 27.1 (CH_3, $C(\underline{C}H_3)_3$), 25.6 (CH_3, $C(\underline{C}H_3)_3$), 18.1 (C, $\underline{C}(CH_3)_3$), 18.0 (CH_3), −4.7 (CH_3−Si), −4.9 (CH_3−Si). Anal. Calcd for ($C_{19}H_{34}O_5Si$): C, 61.58; H, 9.25. Found: C, 61.88; H, 9.41.

15: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.40 (m, 1H, H-6), 4.31 (m, 2H, H-4, H-8), 4.04 (dd, J_{gem} = 12.4 Hz, $J_{8,4}$ = 2.2 Hz, 1H, H-8), 2.61 (m, 1H, H-1), 2.48 (m, 1H, H-7), 2.32 (m, 1H, H-7), 1.19 (s, 3H, C$\underline{H}_3$), 1.17 (s, 9H, $(CH_3)_3C$), 0.86 (s, 9H, $(CH_3)_3C$), 0.02 (s, 6H, 2C$\underline{H}_3$-Si).

(1*S*)-1-[(1*S*,2*S*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-(1-hydroxy1-methylethyl)-1-methylcyclobutyl]-1,2-ethanediol (16). To a solution of **14** (200 mg, 0.54 mmol) in anhydrous THF (20 mL) was added dropwise MeMgCl 3 M in ether (1.8 mL, 5.4 mmol), and the mixture was heated to reflux for 2 h. Following the careful addition of a saturated solution of NH_4Cl (15 mL), the organic layer was separated, and the aqueous phase was extracted successively with CH_2Cl_2 (2 × 15 mL) and EtOAc (2 × 15 mL). The organic extracts were washed with brine and dried, and the solvents were removed. The crude residue was purified by column chromatography (hexane:EtOAc, 3:1) to afford triol **16** (145 mg, 0.46 mmol, 84% yield) as a white solid: mp 98−100 °C (from EtOAc−pentane); $[\alpha]_D$ +29.2 (*c* 1.3, $CHCl_3$); MS (ESI+, MeOH) 341.2 ($[M + Na]^+$, 100); IR (ATR) 3287, 2927, 1462, 1116, 835 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.22 (dd, $J_{1,2}$ = 9.0 Hz, $J_{1,2}$ = 2.9 Hz, 1H, H-1), 4.02 (dd, J_{gem} = 10.7 Hz, $J_{2,1}$ = 2.9 Hz, 1H, H-2), 3.66 (dd, $J_{2',3'}$ = 8.8 Hz, $J_{2',3'}$ = 6.9 Hz, 1H, H-2′), 3.53 (dd, J_{gem} = 10.7 Hz, $J_{2,1}$ = 9.0 Hz, 1H, H-2), 2.12 (ddd, J_{gem} = 10.3 Hz, $J_{3',4'}$ = 8.0 Hz, $J_{3',2'}$ = 6.9 Hz, 1H, H-3′), 2.00 (ddd, $J_{3',4'}$ = 12.5 Hz, J_{gem} = 10.3 Hz, $J_{3',2'}$= 8.8 Hz, 1H, H-3′), 1.41 (dd, $J_{4',3'}$ = 12.5 Hz, $J_{4',3'}$ = 7.8 Hz, 1H, H-4′), 1.32 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 0.87 (s, 9H, $(CH_3)_3C$), 0.03 (s, 6H, CH_3−Si); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 71.9 (CH, C-2′), 71.6 (CH, C-1), 70.8 (C, C-1″), 64.4 (CH_2, C-2), 52.4 (C, C-1′), 49.5 (CH, C-4′), 31.2 (CH_2, C-3′), 29.0 (CH_3), 28.7 (CH_3), 25.8 (C, $C(\underline{C}H_3)_3$), 22.6 (CH_3), 18.0 (C, $\underline{C}(CH_3)_3$), −4.6 (CH_3−Si), −5.1 (CH_3−Si). Anal. Calcd for ($C_{16}H_{34}O_4Si$): C, 60.33; H, 10.76. Found: C, 60.63; H, 11.09.

(4*S*)-4-[(1*S*,2*S*,4*R*)-2-(*tert*-Butyldimethylsilyloxy)-4-(1-hydroxy-1-methylethyl)-1-methylcyclobutyl]-1,3-dioxolane-2-thione (17). A mixture of triol **16** (130 mg, 0.41 mmol) and *N*,*N*-thiocarbonyldiimidazole (243 mg, 1.23 mmol) in dry THF (7 mL) was heated at 60 °C for 5 h under an Ar atmosphere. After being cooled, the solvent was evaporated, and the residue was purified by column chromatography (hexane:EtOAc, 6:1) to afford **17** (140 mg, 0.40 mmol, 95% yield) as a colorless oil: $[\alpha]_D$ +21.8 (*c* 0.55, $CHCl_3$); IR (ATR) 3429, 2973, 1784, 1484, 1289 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.79 (dd, $J_{4,5}$ = 9.1 Hz, $J_{4,5}$ = 7.0 Hz, 1H, H-4), 4.67 (dd, J_{gem} = 9.4 Hz, $J_{5,4}$ = 9.1 Hz, 1H, H-5), 4.47 (dd, J_{gem} = 9.4 Hz, $J_{5,4}$ = 7.0 Hz, 1H, H-5), 3.80 (dd, $J_{2',3'}$ = 8.7 Hz, $J_{2',3'}$ = 7.0 Hz, 1H, H-2′), 2.22 (m, 1H, H-3′), 2.04 (m, 1H, H-3′), 1.58 (dd, $J_{4',3'}$ = 12.1 Hz, $J_{4',3'}$ = 8.0 Hz, 1H, H-4′), 1.43 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 0.86 (s, 9H, $(CH_3)_3C$), 0.04 (s, 6H, 2CH_3−Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4 (C═S), 82.3 (CH, C-4), 72.3 (CH_2, C-5), 71.2 (CH, C-2′), 70.7 (C, C-1″), 51.8 (C, C-1′), 47.0 (CH, C-4′), 30.8 (CH_2, C-3′), 28.9 (CH_3), 28.6 (CH_3), 25.6 (C, $C(\underline{C}H_3)_3$), 19.9 (CH_3), 17.8 (C, $\underline{C}(CH_3)_3$), −4.8 (CH_3−Si), −5.2 (CH_3−Si); HRMS (ESI-TOF) calcd for $[(C_{17}H_{32}O_4SSi) + Na]^+$ 383.1683, found 383.1672.

2-((1*R*,2*R*,3*S*)-3-*tert*-Butyldimethylsilyloxy-2-methyl-2-vinylcyclobutyl)-2-propanol (19). A solution of **17** (144 mg, 0.40 mmol) in 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine, **18** (223 μL, 1.21 mmol), was stirred at 40 °C for 24 h under an Ar atmosphere. After being cooled, the contents were directly chromatographed (pentane:ether, 7:1). The solvent was removed by distillation at atmospheric pressure to afford **19** (108 mg, 0.38 mmol, 95% yield) as a colorless volatile oil: $[\alpha]_D$ +34.0 (*c* 0.9, $CHCl_3$); IR (ATR) 3570, 2973, 1630, 1550, 1462 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.59 (dd, J_{trans} = 17.9 Hz, J_{cis} = 10.9 Hz, 1H, H-1″), 5.25 (dd, J_{cis} = 10.9 Hz, J_{gem} = 1.8 Hz, 1H, H-2″), 5.14 (dd, J_{trans} = 17.9 Hz, J_{gem} = 1.8 Hz, 1H, H-2″), 3.77 (dd, $J_{3',4'}$ = 8.5 Hz, $J_{3',4'}$ = 7.2 Hz, 1H, H-3′), 2.16 (m, 2H, 2H-4′), 1.56 (dd, $J_{1',4'}$ = 11.4 Hz, $J_{1',4'}$ = 8.3 Hz, 1H, H-1′), 1.28 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 0.85 (s, 9H, $(CH_3)_3C$), 0.01 (s, 3H, CH_3−Si), −0.02 (s, 3H, CH_3−Si); ^{13}C NMR (90 MHz, $CDCl_3$) δ 139.7 (CH, C-1″), 114.8 (CH_2, C-2″), 72.7 (CH, C-3′), 71.7 (C, C-2), 51.9 (C, C-2′), 48.2 (CH, C-1′), 30.2 (CH_2, C-4′), 28.4 (CH_3), 28.2 (CH_3), 25.7 (C, $C(\underline{C}H_3)_3$), 24.8 (CH_3), 18.0 (C, $\underline{C}(CH_3)_3$), −4.7 (CH_3−Si), −4.8 (CH_3−Si); HRMS (ESI-TOF) calcd for $[(C_{16}H_{32}O_2Si) + Na]^+$ 307.2064, found 307.2053.

2-[(1*R*,2*R*,3*S*)-3-*tert*-Butyldimethylsilyloxy-2-(2-hydroxyethyl)-2-methylcyclobutyl]-2-propanol (3). To a stirred solution of BH_3−THF (2.5 mL, 1 M in THF, 2.5 mmol) in THF (6 mL) at −15 °C was added dropwise a solution of **19** (150 mg, 0.53 mmol) in THF (4 mL). The mixture was stirred further at −15 °C for 4 h. H_2O (0.4 mL), a 3 M NaOH solution (2.5 mL), and 30% H_2O_2 (1.4 mL) were successively added, and the mixture was stirred for 1 h at room temperature. The mixture was poured into brine containing 2% hydrochloric acid (5 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated to give a residue that was purified by column chromatography (pentane:ether, 3:1) to give **3** (132 mg, 0.44 mmol, 82% yield) as a colorless oil: $[\alpha]_D$ +14.8 (*c* 0.8, $CHCl_3$); IR (ATR) 3335, 2931, 1110 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (m, 3H, 2H-2″, H-3′), 2.28 (m, 1H, H-1″), 2.14 (m, 1H, H-4′), 1.90 (m, 1H, H-4′), 1.86 (m, 1H, H-1″), 1.43 (m, 1H, H-1′), 1.42 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 0.91 (s, 9H, $(CH_3)_3C$), 0.09 (s, 3H, CH_3−Si), 0.08 (s, 3H, CH_3−Si); ^{13}C NMR (90 MHz, $CDCl_3$) δ 72.8 (CH, C-3′), 71.4 (C, C-2), 58.9 (CH_2, C-2″), 49.3 (C, C-2′), 47.8 (CH, C-1′), 31.4 (CH_2, C-1″), 30.7 (CH_2, C-4′), 30.3 (CH_3), 30.1 (CH_3), 28.3 (CH_3), 25.8 (C, $C(\underline{C}H_3)_3$), 18.1 (C, $\underline{C}(CH_3)_3$), −4.5 (CH_3−Si), −5.0 (CH_3−Si); HRMS (ESI-TOF) calcd for $[(C_{16}H_{34}O_3Si) + Na]^+$ 325.2169, found 325.2167.

(1*R*,6*R*,7*S*)-7-*tert*-Butyldimethylsilyloxy-2,2,6-trimethyl-3-oxabicyclo[4.2.0]oct-4-ene (20). To a solution of alcohol **3** (132 mg, 0.44 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dropwise a solution of Dess−Martin periodinane 15 wt % in CH_2Cl_2 (1.90 mL, 0.90 mmol) under an Ar atmosphere. The reaction mixture was stirred at room temperature for 4 h and then diluted with CH_2Cl_2 (10 mL). The organic layer was washed successively with a solution of $Na_2S_2O_3$ (2.6 g) in saturated aqueous $NaHCO_3$ (8 mL), a saturated $NaHCO_3$ solution, and brine. The organic layer was dried, filtered, and concentrated under atmospheric pressure. The crude residue was purified by column chromatography (pentane:ether, 8:1). The solvent was removed by distillation at atmospheric pressure to give **20** (90 mg, 0.32 mmol, 73% yield) as a colorless volatile oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.34 (d, $J_{4,5}$ = 6.4 Hz, 1H, H-4), 4.54 (dd, $J_{5,4}$ = 6.4 Hz, $J_{5,1}$ = 1.5 Hz, 1H, H-5), 3.84 (dd, $J_{7,8}$ = 8.4 Hz, $J_{7,8}$ = 7.0 Hz, 1H, H-7), 2.08 (m, 1H, H-8), 1.58 (m, 1H, H-8), 1.49 (m, 1H, H-1), 1.14 (s, 6H, 2CH_3), 1.10 (s, 3H, CH_3), 0.86 (s, 9H, $(C\underline{H}_3)_3C$), 0.01 (s, 3H, CH_3−Si), 0.00 (s, 3H, CH_3−Si); ^{13}C NMR (90 MHz, $CDCl_3$) δ 140.5 (CH, C-4), 103.5 (CH, C-5), 73.5 (CH, C-7), 72.4 (C, C-2), 42.0 (C, C-6), 41.6 (CH, C-1), 34.1 (CH_2, C-8), 26.0 (CH_3), 25.9 (CH_3), 25.8 (C, $C(\underline{C}H_3)_3$), 24.0 (CH_3), 18.1 (C, $\underline{C}(CH_3)_3$), −4.6 (CH_3−Si), −4.6 (CH_3−Si); HRMS (ESI-TOF) calcd for $[(C_{16}H_{30}O_2Si) + Na]^+$ 305.1907, found 305.1900.

(1*R*,4*R*,6*S*,7*R*)-3,3,7-Trimethyl-2,9-dioxatricyclo[4.2.1.0^{4,7}]-nonane, (−)-Isolineatin. To a solution of **20** (20 mg, 0.07 mmol) in THF (4 mL) was added a 1.0 M solution of TBAF in THF (210 μL, 0.21 mmol), and the resulting solution was stirred for 12 h at room temperature. Then *p*-TsOH (68 mg, 0.35 mmol) was added, and the mixture was stirred further for 2 h. CH_2Cl_2 (3 mL) was added, and the organic layer was washed successively with a saturated aqueous $NaHCO_3$ solution and brine and dried. The solvent was removed by distillation at atmospheric pressure. The crude residue was purified by column chromatography (pentane:ether, 7:1). The solvent was removed by distillation at atmospheric pressure to give isolineatin, **2** (6 mg, 0.035 mmol, 51% yield), as a colorless oil: $[\alpha]_D$ −22.9 (*c* 0.7, $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 (d, $J_{1,8}$ = 3.6 Hz, 1H, H-1), 4.05 (t, $J_{6,5}$ = 4.0 Hz, $J_{6,5}$ = 4.0 Hz, 1H, H-6), 2.42 (ddd, J_{gem} = 13.0 Hz, $J_{5,4}$ = 8.8 Hz, $J_{5,6}$ = 4.0 Hz, H-5), 2.17 (d, J_{gem} = 12.2 Hz, 1H, H-8),

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1.90 (m, 2H, H-4, H-5), 1.41 (dd, J_{gem} = 12.2 Hz, $J_{8,1}$ = 3.6 Hz, 1H, H-8), 1.40 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 1.14 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 101.1 (C, C-1), 80.4 (CH, C-6), 72.6 (C, C-3), 47.9 (CH, C-4), 45.1 (C, C-7), 37.9 (CH_2, C-8), 31.0 (CH_3), 29.1 (CH_2, C-5), 28.6 (CH_3), 20.3 (CH_3); HRMS (ESI-TOF) calcd for $[(C_{10}H_{16}O_2) + Na]^+$ 191.1043, found 191.1041.

(1*S*,4*S*,5*S*,6*S*)-6-Hydroxy-5-methyl-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (21) and Its (1*S*,4*S*,5*S*,6*R*)-Isomer (22). To an ice-cooled solution of **6** (200 mg, 0.79 mmol) in dry methanol (6 mL) was slowly added $NaBH_4$ (25 mg, 0.63 mmol). After the mixture had been stirred for 1 h at 0 °C, the reaction was quenched by the slow addition of a saturated NH_4Cl solution, and the mixture was allowed to warm to room temperature. The solvent was evaporated, and the residue was taken up with CH_2Cl_2. The organic layer was washed with brine and dried. The crude residue was purified by column chromatography (hexane:EtOAc, 3:1) to afford **22** (39 mg, 0.15 mmol, 19% yield) as a white solid and **21** (140 mg, 0.54 mmol, 69% yield) also as a white solid.

21: mp 92−94 °C (from pentane−EtOAc); $[\alpha]_D$ +86.7 (*c* 0.3, $CHCl_3$); MS (ESI+, MeOH) 279.0 ($[M + Na]^+$, 100); IR (ATR) 3404, 2957, 1728, 1127, 935 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.48 (m, 1H, H-6), 4.42 (dd, J_{gem} = 11.5 Hz, $J_{8,4}$ = 4.4 Hz, 1H, H-8), 4.30 (dd, $J_{4,8}$ = 6.9 Hz, $J_{4,8}$ = 4.4 Hz, 1H, H-4), 4.23 (dd, J_{gem} = 11.5 Hz, $J_{8,4}$ = 6.9 Hz, 1H, H-8), 2.64 (m, 1H, H-1), 2.48 (m, 1H, H-7), 2.32 (m, 1H, H-7), 1.29 (s, 3H, CH_3), 1.18 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 178.9 (C═O), 178.6 (C═O, C-2), 83.0 (CH, C-4), 65.3 (CH, C-6), 61.6 (CH_2, C-8), 50.9 (C, C-5), 38.8 (C, $\underline{C}(CH_3)_3$), 38.5 (CH, C-1), 32.5 (CH_2, C-7), 27.1 (CH_3, $C(\underline{C}H_3)_3$), 13.6 (CH_3). Anal. Calcd for ($C_{13}H_{20}O_5$): C, 60.92; H, 7.87. Found: C, 60.78; H, 7.92.

22: mp 132−134 °C (from pentane−EtOAc); $[\alpha]_D$ +65.2 (*c* 1.35, $CHCl_3$); IR (ATR) 3386, 2972, 1726, 1280, 1145, 1043, 970 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.68 (dd, J_{gem} = 12.8 Hz, $J_{8,4}$ = 8.0 Hz, 1H, H-8), 4.59 (dd, J_{gem} = 12.8 Hz, $J_{8,4}$ = 2.5 Hz, 1H, H-8), 4.36 (dd, $J_{4,8}$ = 8.0 Hz, $J_{4,8}$ = 2.5 Hz, 1H, H-4), 4.24 (m, 1H, H-6), 2.80 (m, 1H, H-7), 2.64 (m, 1H, H-1), 2.02 (m, 1H, H-7), 1.38 (s, 3H, CH_3), 1.20 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 178.8 (C═O), 178.6 (C═O, C-2), 86.5 (CH, C-4), 74.0 (CH, C-6), 63.5 (CH_2, C-8), 48.4 (C, C-5), 40.5 (CH, C-1), 38.7 (C, $\underline{C}(CH_3)_3$), 32.2 (CH_2, C-7), 27.1 (CH_3, $C(\underline{C}H_3)_3$), 21.7 (CH_3); HRMS (ESI-TOF) calcd for $[(C_{13}H_{20}O_5) + Na]^+$ 279.1203, found 279.1199.

(1*S*,4*S*,5*R*,6*S*)-6-*tert*-Butyldimethylsilyloxy-5-methyl-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (23). To an ice-cooled solution of **21** (100 mg, 0.39 mmol) in CH_2Cl_2 (4 mL) were added imidazole (54 mg, 0.79 mmol) and *tert*-butyldimethylsilyl chloride (121 mg, 0.78 mmol). The mixture was stirred for 24 h at room temperature and then was diluted with CH_2Cl_2 (5 mL) and washed with brine (5 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated to dryness. The reaction crude was purified by column chromatography (hexane:EtOAc, 10:1) affording **23** (140 mg, 0.38 mmol, 97% yield) as a white solid: mp 42−44 °C (from pentane−EtOAc); $[\alpha]_D$ +80.0 (*c* 0.75, $CHCl_3$); IR (ATR) 2928, 1777, 1729, 1167, 776 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.39 (m, 1H, H-6), 4.26 (m, 3H, H-4, 2H-8), 2.62 (m, 1H, H-1), 2.45 (m, 1H, H-7), 2.27 (ddd, J_{gem} = 11.8 Hz, *J* = 7.0 Hz, *J* = 1.9 Hz, 1H, H-7), 1.30 (s, 3H, CH_3), 1.21 (s, 9H, $(CH_3)_3C$), 0.86 (s, 9H, $(CH_3)_3C$), 0.04 (s, 3H, CH_3−Si), 0.03 (s, 3H, CH_3−Si); ^{13}C NMR (90 MHz, $CDCl_3$) δ 178.6 (C═O), 178.2 (C═O, C-2), 83.4 (CH, C-4), 65.6 (CH, C-6), 61.9 (CH_2, C-8), 51.4 (C, C-5), 38.7 (C, $\underline{C}(CH_3)_3$), 38.5 (CH, C-1), 34.3 (CH_2, C-7), 27.1 (CH_3, $C(\underline{C}H_3)_3$), 25.6 (CH_3, $C(\underline{C}H_3)_3$), 17.8 (C, $\underline{C}(CH_3)_3$), 18.0 (CH_3), −4.7 (CH_3−Si), −4.9 (CH_3−Si); HRMS (ESI-TOF) calcd for $[(C_{19}H_{34}O_5Si) + Na]^+$ 393.2068, found 393.2065.

(1*S*)-1-[(1*R*,2*S*,4*S*)-2-(*tert*-Butyldimethylsilyloxy)-4-(1-hydroxy-1-methylethyl)-1-methylcyclobutyl]-1,2-ethanediol (24). To an ice-cooled solution of **23** (100 mg, 0.27 mmol) in anhydrous THF (10 mL) was added dropwise MeMgCl 3 M in ether (0.8 mL, 2.4 mmol), and the mixture was heated to reflux for 2 h. Following the careful addition of a saturated solution of NH_4Cl (5 mL), the organic layer was separated, and the aqueous phase was extracted successively with CH_2Cl_2 (2 × 5 mL) and EtOAc (2 × 5 mL). The organic extracts were washed with brine and dried, and the solvents were removed. The crude residue was purified by column chromatography (hexane:EtOAc, 3:1) to afford triol **24** (80 mg, 0.25 mmol, 93% yield) as a white solid: mp 43−45 °C (from EtOAc−pentane); $[\alpha]_D$ +52.6 (*c* 1.75, $CHCl_3$); MS (ESI+, MeOH) 341.1 ($[M + Na]^+$, 100); IR (ATR) 3199, 2928, 1426, 1251, 1110, 835 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.48 (dd, $J_{2',3'}$ = 7.5 Hz, $J_{2',3'}$ = 7.1 Hz, 1H, H-2′), 3.82 (dd, $J_{1,2}$ = 5.6 Hz, $J_{1,2}$ = 3.2 Hz, 1H, H-1), 3.65 (dd, J_{gem} = 11.6 Hz, $J_{2,1}$ = 5.6 Hz, 1H, H-2), 3.62 (br s, 3H, OH), 3.59 (dd, J_{gem} = 11.6 Hz, $J_{2,1}$ = 3.2 Hz, 1H, H-2), 2.26 (ddd, J_{gem} = 11.2 Hz, $J_{3',4'}$ = 5.1 Hz, $J_{3',2'}$ = 8.2 Hz, 1H, H-3′), 1.97 (ddd, J_{gem} = 11.2 Hz, $J_{3',4'}$ = 10.7 Hz, $J_{3',2'}$ = 6.7 Hz, 1H, H-3′), 1.87 (dd, $J_{4',3'}$ = 10.7 Hz, $J_{4',3'}$ = 5.1 Hz, 1H, H-4′), 1.31 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.87 (s, 9H, $(C\underline{H}_3)_3C$), 0.04 (s, 6H, CH_3−Si); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 73.3 (CH, C-1), 70.7 (C, C-1″), 64.9 (CH, C-2′), 63.2 (CH_2, C-2), 52.4 (CH, C-4′), 50.1 (C, C-1′), 30.7 (CH_2, C-3′), 29.1 (CH_3), 29.0 (CH_3), 25.8 (C, $C(\underline{C}H_3)_3$), 20.9 (CH_3), 17.9 (C, $\underline{C}(CH_3)_3$), −4.1 (CH_3−Si), −5.0 (CH_3−Si). Anal. Calcd for ($C_{16}H_{34}O_4Si$): C, 60.33; H, 10.76. Found: C, 60.48; H, 10.79.

(4*S*)-4-[(1*R*,2*S*,4*S*)-2-*tert*-Butyl(dimethyl)silyloxy-4-(1-hydroxy-1-methylethyl)-1-methylcyclobutyl]-1,3-dioxolane-2-thione (25). A mixture of triol **24** (295 mg, 0.93 mmol) and *N*,*N*-thiocarbonyldiimidazole (567 mg, 2.87 mmol) in dry THF (20 mL) was heated at 60 °C for 4 h under an Ar atmosphere. After cooling, the solvent was evaporated and the residue was purified by column chromatography (hexane:ether, 1:1) to afford **25** (313 mg, 0.87 mmol, 93% yield) as a colorless oil: $[\alpha]_D$ +32.6 (*c* 0.8, $CHCl_3$); IR (ATR) 3432, 2966, 1793, 1484, 1175 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 5.60 (dd, $J_{4,5}$ = 8.6 Hz, $J_{4,5}$ = 6.1 Hz, 1H, H-4), 4.69 (dd, J_{gem} = 9.5 Hz, $J_{5,4}$ = 8.6 Hz, 1H, H-5), 4.59 (dd, J_{gem} = 9.5 Hz, $J_{5,4}$ = 6.1 Hz, 1H, H-5), 4.22 (ddd, $J_{2',3'}$ = 7.1 Hz, $J_{2',3'}$ = 4.4 Hz, $J_{2',4'}$ = 0.9 Hz, 1H, H-2′), 2.76 (br s, 1H, OH), 2.24 (ddd, J_{gem} = 11.8 Hz, $J_{3',4'}$ = 7.3 Hz, $J_{3',2'}$ = 7.3 Hz, 1H, H-3′), 2.12 (ddd, $J_{4',3'}$ = 9.5 Hz, $J_{4',3'}$ = 7.4 Hz, $J_{4',2'}$ = 0.9 Hz, 1H, H-4′), 1.80 (ddd, J_{gem} = 11.8 Hz, $J_{3',4'}$ = 9.5 Hz, $J_{3',2'}$ = 4.4 Hz, 1H, H-3′), 1.08 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 0.83 (s, 9H, $(CH_3)_3C$), 0.02 (s, 3H, CH_3−Si), 0.01 (s, 3H, CH_3−Si); ^{13}C NMR (90 MHz, $CDCl_3$) δ 191.8 (C═S), 85.4 (CH, C-4), 71.3 (C, C-1″), 71.2 (CH_2, C-5), 68.2 (CH, C-2′), 50.7 (CH, C-4′), 49.4 (C, C-1′), 30.1 (CH_2, C-3′), 30.0 (CH_3), 28.8 (CH_3), 25.7 (C, $C(\underline{C}H_3)_3$), 18.0 (C, $\underline{C}(CH_3)_3$), 15.3 (CH_3), −4.9 (CH_3−Si), −5.0 (CH_3−Si); HRMS (ESI-TOF) calcd for $[(C_{17}H_{32}O_4SSi) + Na]^+$ 383.1683, found 383.1676.

2-((1*S*,2*S*,3*S*)-3-*tert*-Butyldimethylsilyloxy-2-methyl-2-vinylcyclobutyl)-2-propanol (26). A solution of **25** (313 mg, 0.87 mmol) in 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine, **18** (494 μL, 2.68 mmol), was stirred at 40 °C for 24 h under an Ar atmosphere. After being cooled, the contents were directly chromatographed (pentane:ether, 7:1). The solvent was removed by distillation at atmospheric pressure to afford **26** (200 mg, 0.80 mmol, 81% yield) as a colorless volatile oil: $[\alpha]_D$ +24.4 (*c* 0.9, $CHCl_3$); IR (ATR) 3570, 2973, 1630, 1550, 1460 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.23 (m, 1H, H-1″), 5.10 (br s, 1H, H-2″), 5.07 (dd, $J_{2'',1''}$ = 6.1 Hz, J_{gem} = 1.5 Hz, 1H, H-2″), 4.26 (m, 1H, H-3′), 2.21 (m, 1H, H-4′), 1.96 (m, 2H, H-4′, H-1′), 1.20 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 0.87 (s, 9H, $(CH_3)_3C$), 0.02 (s, 3H, CH_3−Si), 0.01 (s, 3H, CH_3−Si); ^{13}C NMR (90 MHz, $CDCl_3$) δ 144.4 (CH, C-1″), 112.5 (CH_2, C-2″), 72.2 (C, C-2), 69.7 (CH, C-3′), 51.7 (CH, C-1′), 49.4 (C, C-2′), 30.2 (CH_2, C-4′), 29.1 (CH_3), 28.3 (CH_3), 25.8 (C, $C(\underline{C}H_3)_3$), 21.7 (CH_3), 18.1 (C, $\underline{C}(CH_3)_3$), −4.6 (CH_3−Si), −4.7 (CH_3−Si); HRMS (ESI-TOF) calcd for $[(C_{16}H_{32}O_2Si) + Na]^+$ 307.2064, found 307.2054.

2-[(1*S*,2*S*,3*S*)-3-*tert*-Butyldimethylsilyloxy-2-(2-hydroxyethyl)-2-methylcyclobutyl]-2-propanol (27). To a stirred solution of BH_3−THF (2.0 mL, 1 M in THF, 2.0 mmol) in THF (10 mL) at −15 °C was added dropwise a solution of **26** (200 mg, 0.70 mmol) in THF (4 mL). The mixture was stirred further at −15 °C for 4 h. H_2O (0.7 mL), a 3 M NaOH solution (3.9 mL), and 30% H_2O_2 (2.2 mL) were gradually added, and the mixture was stirred for 1 h at room temperature. The mixture was poured into brine containing 2% hydrochloric acid (5 mL) and extracted with ethyl acetate. The organic

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layer was washed with brine, dried, and evaporated to give a residue that was purified by column chromatography (pentane:ether, 2:1) to give **27** (184 mg, 0.61 mmol, 87% yield) as a colorless oil: $[\alpha]_D$ +33.5 (*c* 1.55, $CHCl_3$); IR (ATR) 3311, 2928, 1462, 1120 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.15 (dd, $J_{3',4'}$ = 7.7 Hz, $J_{3',4'}$ = 7.7 Hz, 1H, H-3′), 3.69 (m, 2H, 2H-2″), 2.39 (br s, 2H, 2OH), 2.09 (m, 1H, H-1″), 2.07 (m, 2H, 2H-4′), 1.75 (m, 2H, H-1′, H-1″), 1.24 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 0.87 (s, 9H, $(CH_3)_3C$), 0.03 (s, 6H, $2CH_3$–Si); ^{13}C NMR (90 MHz, $CDCl_3$) δ 72.1 (C, C-2), 71.3 (CH, C-3′), 59.49 (CH_2, C-2″), 50.0 (CH, C-1′), 45.7 (C, C-2′), 38.9 (CH_2, C-1″), 31.3 (CH_2, C-4′), 29.6 (CH_3), 29.3 (CH_3), 25.7 (C, $C(\underline{C}H_3)_3$), 21.0 (CH_3), 17.9 (C, $\underline{C}(CH_3)_3$), −4.2 (CH_3–Si), −5.0 (CH_3–Si). HRMS (ESI-TOF) calcd for $[(C_{16}H_{34}O_3Si) + Na]^+$ 325.2169, found 325.2168.

(1*S*,6*S*,7*S*)-7-*tert*-Butyldimethylsilyloxy-2,2,6-trimethyl-3-oxabicyclo[4.2.0]oct-4-ene (28). To a solution of diol **27** (200 mg, 0.66 mmol) in anhydrous CH_2Cl_2 (17 mL) was added dropwise a solution of Dess–Martin periodinane 15 wt % in CH_2Cl_2 (2.80 mL, 1.32 mmol) under an Ar atmosphere. The reaction mixture was stirred at room temperature for 4 h and then diluted with CH_2Cl_2 (10 mL). The organic layer was washed successively with a solution of $Na_2S_2O_3$ (2.6 g) in saturated aqueous $NaHCO_3$ (8 mL), a saturated $NaHCO_3$ solution, and brine. The organic layer was dried, filtered, and concentrated under atmospheric pressure. The crude residue was purified by column chromatography (pentane:ether, 12:1). The solvent was removed by distillation at atmospheric pressure to give **28** (150 mg, 0.53 mmol, 80% yield) as a colorless volatile oil: ^1H NMR (360 MHz, $CDCl_3$) δ 6.26 (d, $J_{4,5}$ = 6.3 Hz, 1H, H-4), 4.53 (dd, $J_{5,4}$ = 6.3 Hz, $J_{5,1}$ = 1.5 Hz, 1H, H-5), 3.70 (d, $J_{7,8}$ = 5.8 Hz, 1H, H-7), 2.28 (m, 1H, H-1), 2.02 (ddd, J_{gem} = 12.2 Hz, $J_{8,1}$ = 9.6 Hz, $J_{8,7}$ = 5.8 Hz, 1H, H-8), 1.61 (dd, J_{gem} = 12.2 Hz, $J_{8,1}$ = 8.9 Hz, 1H, H-8), 1.13 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.89 (s, 9H, $(CH_3)_3C$), 0.02 (s, 3H, CH_3–Si), 0.01 (s, 3H, CH_3–Si); ^{13}C NMR (90 MHz, $CDCl_3$) δ 141.0 (CH, C-4), 107.6 (CH, C-5), 73.9 (C, C-2), 73.4 (CH, C-7), 46.0 (CH, C-1), 39.8 (C, C-6), 29.0 (CH_2, C-8), 25.9 (CH_3), 25.8 (C, $C(\underline{C}H_3)_3$), 23.2 (CH_3), 20.8 (CH_3), 18.3 (C, $\underline{C}(CH_3)_3$), −4.9 (CH_3–Si), −4.9 (CH_3–Si); HRMS (ESI-TOF) calcd for $[(C_{16}H_{30}O_2Si) + Na]^+$ 305.1907, found 305.1903.

(1*S*,4*S*,6*R*,7*S*)-3,3,7-Trimethyl-2,9-dioxatricyclo[4.2.1.0^{4,7}]-nonane, (+)-Isolineatin. To a solution of **28** (150 mg, 0.53 mmol) in THF (10 mL) was added a 1.0 M solution of TBAF in THF (2.1 mL, 2.1 mmol), and the resulting solution was stirred for 4 h at room temperature. The reaction mixture was washed with brine and dried, and the solvent was removed at atmospheric pressure to give a crude which was used in the next reaction without further purification. To a solution of this crude in anhydrous CH_2Cl_2 (8 mL) was added dropwise a solution of Dess–Martin periodinane 15 wt % in CH_2Cl_2 (1.50 mL, 0.72 mmol) under an Ar atmosphere. The reaction mixture was stirred at room temperature for 3 h and then diluted with CH_2Cl_2 (7 mL). The organic layer was washed successively with a solution of $Na_2S_2O_3$ (2.6 g) in saturated aqueous $NaHCO_3$ (8 mL), a saturated $NaHCO_3$ solution, and brine. The organic layer was dried, filtered, and concentrated under atmospheric pressure. The crude residue was dissolved in anhydrous ether (4 mL) and cooled to −78 °C. A solution of DIBAL-H 1 M in hexane (1.0 mL, 1.0 mmol) was added, dropwise, under an Ar atmosphere. The mixture was stirred at −78 °C for 30 min and at 0 °C for 1.5 h. Then the mixture was poured into ice-cold 10% aqueous tartaric acid (5 mL) and stirred for 20 min. *p*-TsOH (100 mg, 0.51 mmol) was added, and the mixture was stirred further for 5 h at room temperature. CH_2Cl_2 (3 mL) was added, and the organic layer was washed successively with a saturated aqueous $NaHCO_3$ solution and brine and dried. The solvent was removed by distillation at atmospheric pressure. The crude residue was purified by column chromatography (pentane:ether, 6:1). The solvent was removed by distillation through a Vigreux column under atmospheric pressure to give isolineatin, (+)-**2** (29 mg, 0.17 mmol, 32% yield), as a colorless oil: $[\alpha]_D$ +21.0 (*c* 0.7, $CDCl_3$). The spectroscopic data were identical to those of (−)-**2**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental procedures, ^1H and ^{13}C NMR spectra of all new compounds, and 2-D NMR spectra for compounds **8**, **9**, **12**, **16**, **20**, and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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