Stereodivergent Synthesis of (+)- and (-)-isolineatin

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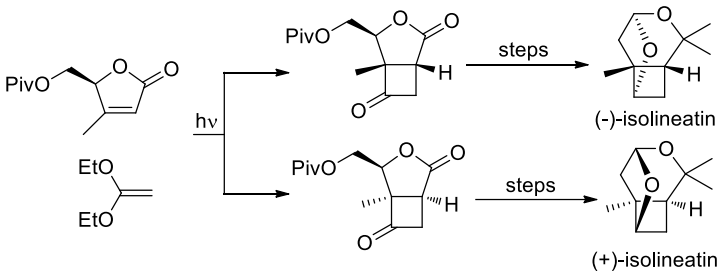


Abstract

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** featuring also a tricyclic acetal**,** has often been described as a by-product 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.

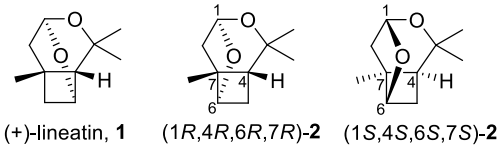
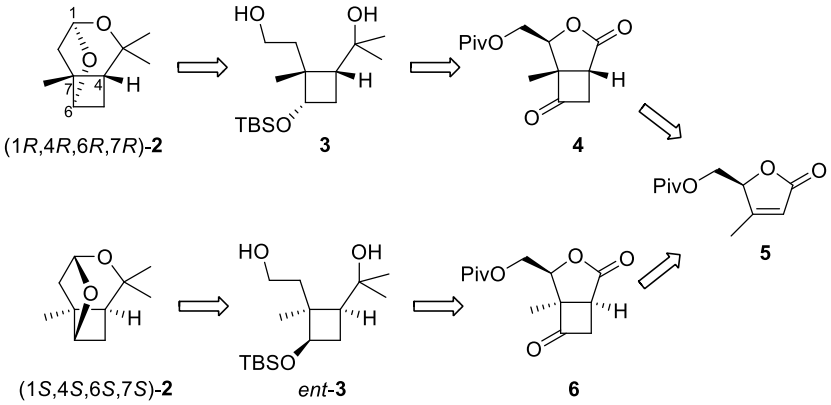


Figure 1. Lineatin, **1**, and isolineatin, **2**

As part of our investigations on 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, which were visualized as potential precursors for isolineatin.[7] Hence, though isolineatin is devoided 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**.

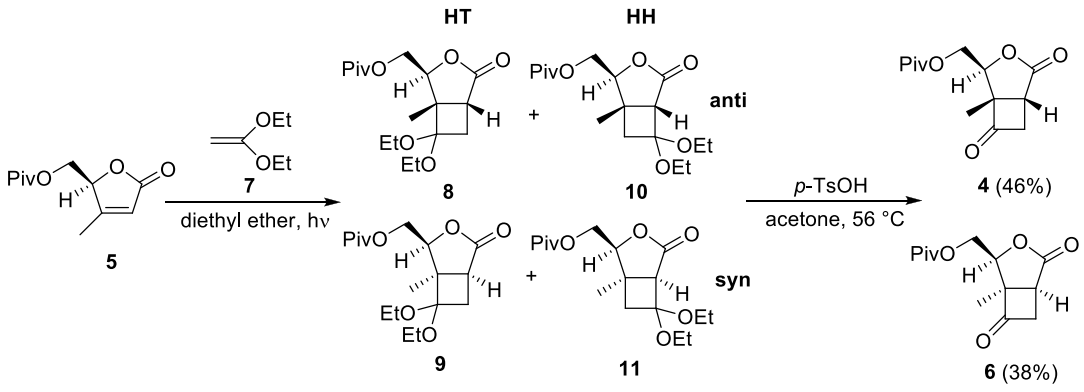
Scheme 1. Retrosynthetic analysis



Results and Discussion

Accordingly, our initial task focused on the preparation of the diastereomeric cyclobutanones **4** and **6** on 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 4 adducts, the head-to-tail (HT) anti and syn isomers and the head-to-head (HH) anti and syn isomers (Scheme 2).[8] It was found that when the reaction of **5** and **7** was performed in diethyl ether the process occurs with excellent regioselectivity giving the HT anti and syn isomers in a similar amount. Taking this into account, our synthesis commenced with 2(5*H*)-furanone **5**, which was obtained in three steps from (*S*)-5-hydroxymethyl-2(*5H*)-furanone, and 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 ether, with a 400W 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 cycloadducts mixture was treated with *p*-TsOH in acetone to 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.

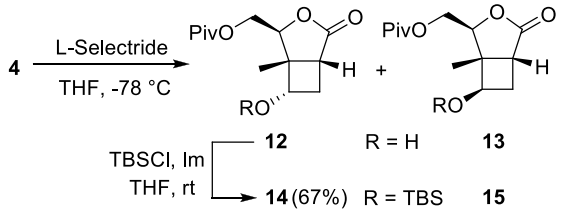
Scheme 2. Synthesis of cyclobutanones **4** and **6**



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

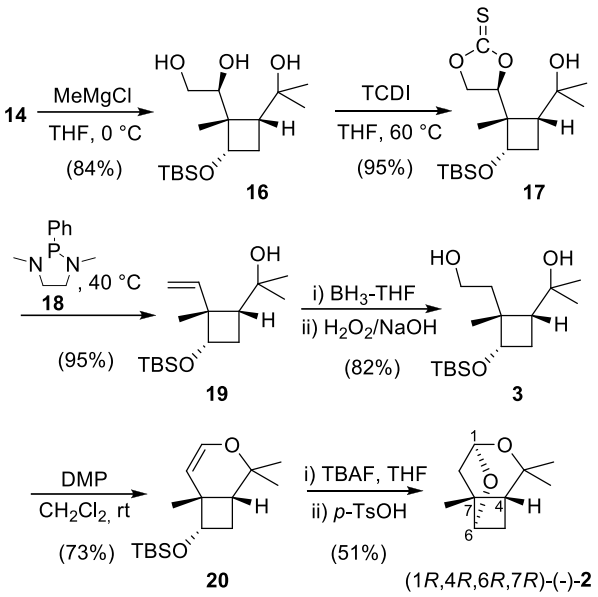
12 and **13** in 97% overall yield. The unfavorable proportion of the necessary endo alcohol **12** prompted us to investigate other reducing agents. Satisfyingly, when the reaction was performed with L-Selectride in THF at -78 °C, the stereoselectivity was reversed affording a 9:1 mixture of **12** and **13** in 88% yield. Other attempts, using NB-Enantride or $LiAl(^tBuO)_3H$ did neither improve 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 diethylether 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 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 work-up, to provide the desired diol **3** in 82% yield for the two steps.

Scheme 4. Synthesis of (-)-isolineatin



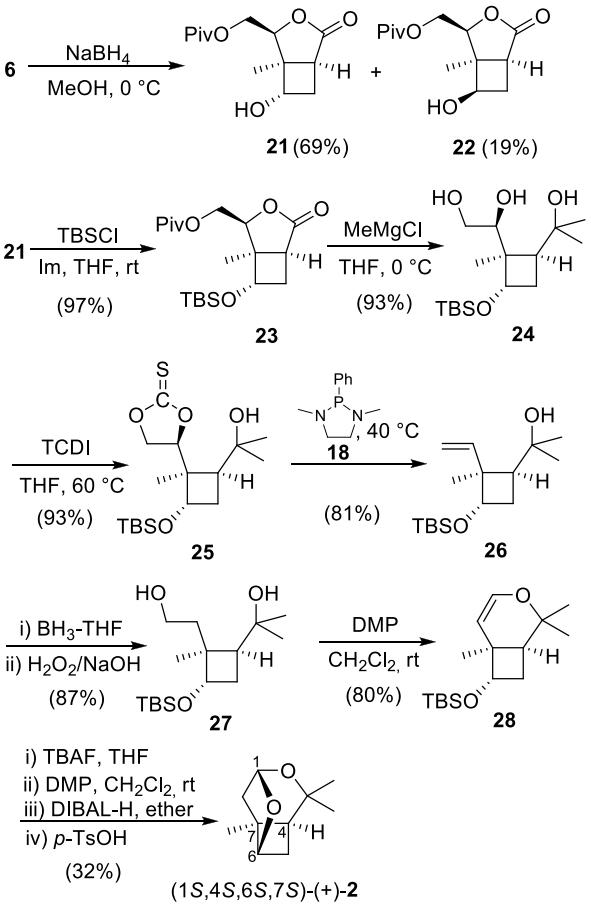
From diol **3**, the envisioned final steps of our approach were oxidation of the primary alcohol to the corresponding aldehyde and then desilylation with simultaneous ketal formation. Accordingly, for the oxidation of the primary alcohol, compound **3** was treated with Dess-Martin periodinane.[13] 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 and, 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] Since any 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 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 overall 88% yield and 3.6:1 ratio. Since these isomeric alcohols were readily separated, we continued the synthesis with the major exo isomer **21** and we planned to invert the configuration of this center later on, through an oxidation-reduction sequence.

Thus, starting from alcohol **21,** and following the same step sequence as above**,** the dihydropyran **28** was synthesized in 47% overall yield. The bicyclic compound **28** was desilylated and the free alcohol 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, $CDCl_3$).

Scheme 5. Synthesis of (+)-isolineatin



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 nitrogen atmosphere. Flash column chromatography was performed using silica gel (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz or 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 ppm (δ) ($CDCl_3$, δ 7.26 or acetone-d_6, δ 2.05). Carbon chemical shifts are reported in ppm (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 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 ºC and a stream of MeOH at -15 ºC 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 400W 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 hexane-EtOAc, 10:1 to hexane-EtOAc, 5:1) 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 ºC, a 1.0 M solution of L-Selectride® in THF (1.65 mL, 1.65 mmol) was added dropwise. After 3h of stirring at -78 ºC, the reaction was quenched by the slow addition of saturated NH_4Cl solution and 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), imidazole (54 mg, 0.79 mmol) and *tert*-butyldimethylsilyl chloride (121 mg, 0.78 mmol) were added. The mixture was allowed to stir 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 ºC (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, 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 MeMgCl 3 M in ether (1.8 mL, 5.4 mmol) dropwise 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 (2x15 mL) and EtOAc (2x15 mL). The organic extracts were washed with brine, dried, and the solvents 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}; ^1H 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 ºC for 5 h under Ar atmosphere. After cooling, 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}; ^1H 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 ºC for 24 h under Ar atmosphere. After cooling, 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}; ^1H 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, a solution of **19** (150 mg, 0.53 mmol) in THF (4 mL) was added dropwise. The mixture was stirred further at -15 °C for 4 h. Then, H_2O (0.4 mL), a 3M 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 which 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}; ^1H 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), a solution of Dess-Martin periodinane 15% wt in CH_2Cl_2 (1.90 mL, 0.90 mmol) was added dropwise under argon 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*,4R,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), a 1.0 M solution of TBAF in THF (210 μL, 0.21 mmol) was added and the resulting solution was allowed to stir 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 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), 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), $NaBH_4$ (25 mg, 0.63 mmol) was slowly added. After 1 h of stirring at 0 ºC, the reaction was quenched by the slow addition of saturated NH_4Cl solution and 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 ºC (from pentane-EtOAc); $[\alpha]_D$ +86.7 (*c* 0.3, $CHCl_3$); MS (ESI+, MeOH) 279.0 ($[M+Na]^+$, 100); IR (ATR) ν 3404, 2957, 1728, 1127, 935 cm^{-1}; ^{1}H 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 ºC (from pentane-EtOAc); $[\alpha]_D$ +65.2 (*c* 1.35, $CHCl_3$); IR (ATR) 3386, 2972, 1726, 1280, 1145, 1043, 970 cm^{-1}; ^{1}H 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), imidazole (54 mg, 0.79 mmol) and *tert*-butyldimethylsilyl chloride (121 mg, 0.78 mmol) were added. The mixture was allowed to stir 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 ºC (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-hydroxy1-methylethyl)-1-methylcyclobutyl]-1,2-ethanediol (24). To an ice-cooled solution of **23** (100 mg, 0.27 mmol) in anhydrous THF (10 mL), MeMgCl 3 M in ether (0.8 mL, 2.4 mmol) was added dropwise 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 (2x5 mL) and EtOAc (2x5 mL). The organic extracts were washed with brine, dried, and the solvents 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 ºC (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, ($C\underline{H}_3$)$_3$C) 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 ºC for 4 h under 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}; ^{1}H NMR (500 MHz, d_6-acetone) 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)$_3$C), 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 ºC for 24 h under Ar atmosphere. After cooling, 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, a solution of **26** (200 mg, 0.70 mmol) in THF (4 mL) was added dropwise. The mixture was stirred further at -15 °C for 4 h. Then, 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 layer was washed with brine, dried, and evaporated to give a residue which 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), a solution of Dess-Martin periodinane 15% wt in CH_2Cl_2 (2.80 mL, 1.32 mmol) was added dropwise under argon 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: ^{1}H 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), a 1.0 M solution of TBAF in THF (2.1 mL, 2.1 mmol) was added and the resulting solution was allowed to stir for 4 h at room temperature. Then, reaction mixture was washed with brine**,** 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 above crude in anhydrous CH_2Cl_2 (8 mL), a solution of Dess-Martin periodinane 15% wt in CH_2Cl_2 (1.50 mL, 0.72 mmol) was added, dropwise, under 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), cooled at -78 °C and a solution of DIBAL-H 1 M in hexane (1.0 mL, 1.0 mmol) was added, dropwise, under 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 allowed to stir for 20 min**.** Then, *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**.

Acknowledgment. We acknowledge financial support from DGES (projects CTQ2007-60613/BQU and CTQ2010-15380/BQU) and grant from the Generalitat de Catalunya to (L.P.).

Supporting Information Available: General experiments procedures and, ^1H and ^{13}C NMR spectra of all new compounds and 2D 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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