Synthesis of a Key Intermediate for the Synthesis of (+)-Grandisol Utilizing (−)-Quinic Acid

Keizo MATSUO,* Masakatsu MORITA, and Ken-ichi KAWASHIMA

Faculty of Pharmaceutical Sciences, Kinki University, 3–4–1 Kowakae, Higashiosaka, Osaka 577, Japan.
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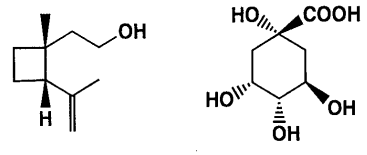
A key intermediate for the synthesis of (+)-grandisol, (4a*R*,6a*R*)-4a-methyl-2-oxabicyclo[4.2.0]octan-1-one, was synthesized starting from (−)-quinic acid as the chiral source.

Key words (+)-grandisol; (−)-quinic acid; chiral synthesis; sex pheromone; conjugate addition

In the course of our synthetic studies on biologically active natural products,[1] we planned to synthesize (+)-grandisol (**1**), which was isolated from *Anthonomaus grandis* BOEHEMAN by Hardee *et al.* and shows biological activity as a sex pheromone.[2] Although many papers on the synthesis of **1** in both racemic and optically active forms[3] have already appeared, we examined the chiral synthesis of (+)-**1** utilizing (−)-quinic acid (**2**) as a chiral source.[4] (−)-Quinic acid (**2**) has four asymmetric centers, of which one is quaternary and the others are secondary. We thought that it might be possible to introduce substituents stereoselectively, by using a bulky protecting group for the 3,4-*cis*-dihydroxyl function of **2**.

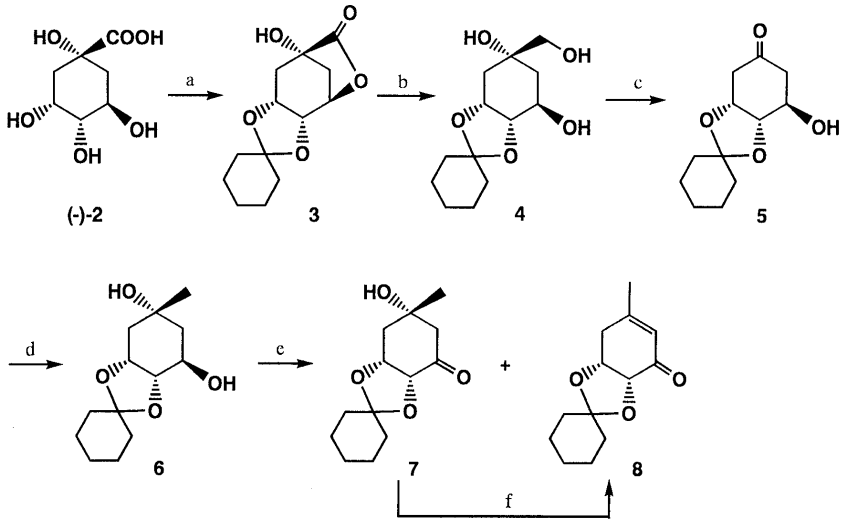
The known compound **5**[5] was synthesized by a modified procedure from (−)-**2** in three steps. Thus, (−)-**2** was treated with cyclohexanone dimethyl acetal in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in a mixture of *N*,*N*-dimethylformamide (DMF) and benzene with continuous removal of the water formed to give a protected hydroxylactone **3** in 72% yield. Sodium borohydride ($NaBH_4$) reduction of **3** in ethanol (EtOH) furnished a triol **4**, which was immediately oxidized with sodium metaperiodate ($NaIO_4$) in phosphate buffer to form the known protected hydroxyketone **5** in 83% yield from **3**. Methylation of **5** was examined with both Grignard and organolithium reagents. When **5** was treated with 4 eq of methylmagnesium bromide in the presence of cerium (III) chloride ($CeCl_3$) in tetrahydrofuran (THF),[6] the starting compound **5** was recovered in 81% yield. On the other hand, treatment of **5** with 3 eq of methyllithium in THF gave the desired addition product **6** in 72% yield.[7] Oxidation of the secondary hydroxyl group of **6** was performed with pyridinium chlorochromate (PCC) in the presence of anhydrous sodium acetate (AcONa) or pyridinium dichromate (PDC), and the results were formation of a mixture of hydroxyketone **7** and enone **8** in both cases. Therefore, each mixture was directly treated with phosphorus oxychloride and pyridine[8] to give the desired enone **8** in 57 or 75% yield from **6**, respectively.

As the enone **8** was in our hands, the photocycloaddition reaction was first examined.[9] Thus, a solution of **8** in acetonitrile (CH_3CN) was irradiated with a 500 W



(+)-Grandisol (1) (-)-Quinic acid (2)

Fig. 1



a) Cyclohexanone dimethyl acetal, *p*-TsOH, in DMF–benzene (72%); b) $NaBH_4$ in EtOH; c) $NaIO_4$ in phosphate buffer (83% from **3**); d) MeLi in THF (72%); e) PDC, molecular sieves in CH_2Cl_2: f) $POCl_3$–pyridine (75% from **6**).

Chart 1

* To whom correspondence should be addressed.

mercury lamp under continuous bubbling of ethylene gas, but the desired cyclobutane derivative **9** was not obtained and the starting **8** was recovered.[9] Therefore, we decided to construct the cyclobutane ring in a stepwise mode, and conjugate addition of an allyl group to the enone **8** was examined. The results are summarized in Table 1. When **8** was treated with allylmagnesium bromide in the presence of copper(I) bromide–dimethyl sulfide complex ($CuBr \cdot Me_2S$), the 1,2-addition reaction proceeded to form **10** in 93% yield (run 1).[10] Reaction of **8** with allyltrimethylsilane in the presence of titanium tetrachloride ($TiCl_4$)[11] gave a complex mixture (run 2). But, when **8** was reacted with allyltributyltin in the presence of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf),[12] the desired 1,4-conjugate addition was observed and **11** was obtained in 96% yield (run 3). The stereochemistry of the newly generated chiral center could not be determined at this stage, but it was assumed that the allylation occurred from the β-side owing to the influence of the bulky protecting group. The silyl protecting group of **11** was removed selectively with tetrabutylammonium fluoride (TBAF) to afford **12** in 85% yield. The other protecting group of **12** was removed with dilute AcOH to give a diol **13**,[13] which was oxidized with $NaIO_4$ in MeOH and treated successively with methyl orthoformate in the presence of *p*-TsOH[14] to form an acetal **14**. Compound **14** was reacted with $AcOH–H_2O$ to afford **15** in 58% yield from **12**. $NaBH_4$ reduction of the formyl group and subsequent acidic treatment gave a δ-lactone **16** in 77% yield. When the oxidative cleavage of the side chain of **16** was tried with osmium tetroxide (OsO_4) in the presence of *N*-methylmorpholine-*N*-oxide (NMO) in $CH_3CN–H_2O$ followed by treatment with $NaIO_4$, the aldehyde **17** was obtained in only 14% yield. But, the use of ruthenium(IV) oxide dihydrate ($RuO_2 \cdot 2H_2O$) in the presence of $NaIO_4$ in a mixture of carbon tetrachloride (CCl_4)–H_2O[15] improved the yield to 62%. The formyl group of **17** was then reduced with $NaBH_4$ to form **18** in 55% yield, and this was successively treated with *p*-toluenesulfonyl chloride (*p*-TsCl) and pyridine in dichloromethane (CH_2Cl_2) to give a tosylate **19**. Intramolecular cyclization of **19** was then tried to form a cyclobutane ring. Thus, treatment of **19** with lithium cyclohexylisopropylamide (LCIA) in THF or lithium diisopropylamide (LDA) in the presence of hexamethylphosphoric triamide (HMPA) in THF resulted

Table 1. Addition of Allyl Group to **8**

Run	Reagent	Product	Yield (%)
1	Allylmagnesium bromide, $CuBr \cdot Me_2S$	10	93
2	Allyltrimethylsilane, $TiCl_4$	—	—[a]
3	Allytributyltin, TBDMSOTf	11	96

a) A complex mixture was obtained.

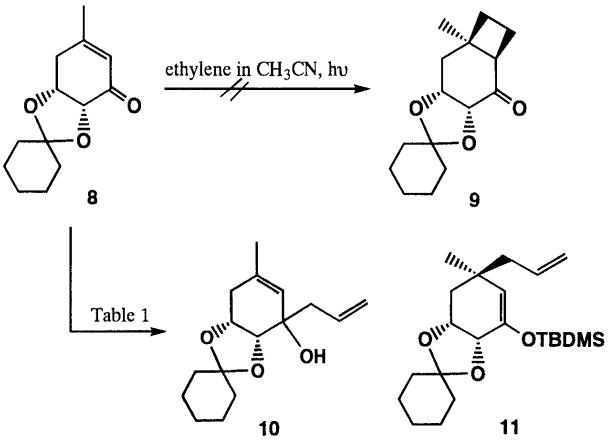
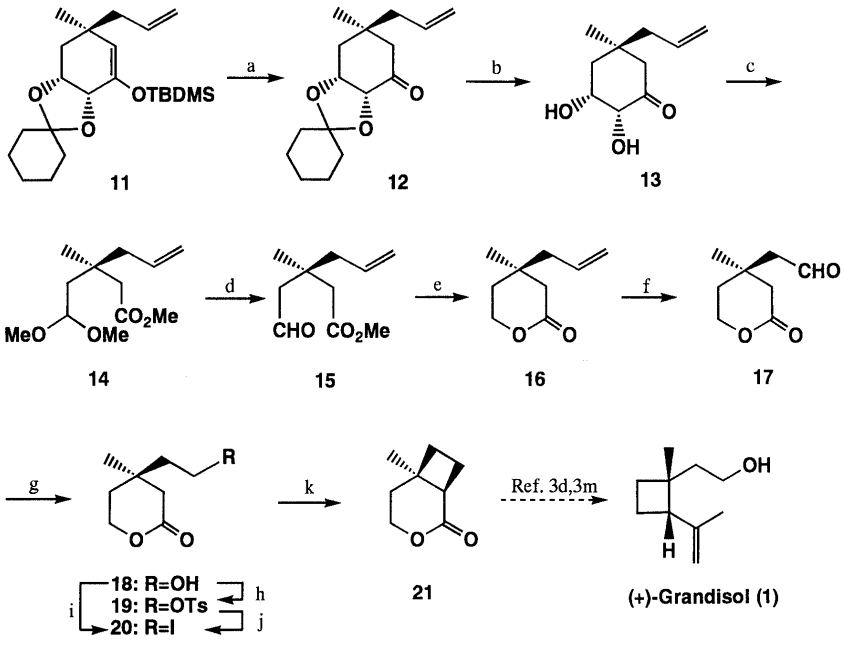


Chart 2



a) TBAF in THF (85%); b) $AcOH–H_2O$; c) 1) $NaIO_4$ in MeOH; 2) $CH(OMe)_3$, *p*-TsOH in CH_2Cl_2; d) $AcOH–H_2O$ (58% from **12**); e) $NaBH_4$ in EtOH (77%); f) $RuO_2 \cdot 2H_2O$, $NaIO_4$ in $CCl_4–H_2O$ (62%); g) $NaBH_4$ in EtOH (55%); h) *p*-TsCl, pyridine, DMAP in CH_2Cl_2 (62%); i) Ph_3P, I_2, imidazole (49%); j) NaI in acetone (73%); k) LCIA, HMPA in THF (46%).

Chart 3

in the recovery of **19** or the formation of a complex mixture, respectively. Therefore, we decided to change the leaving group. Thus, **18** was treated with triphenylphosphine (Ph_3P) and iodine in the presence of imidazole[16] to form an iodide **20** in 49% yield. Compound **20** was also obtained in 73% yield by the reaction of **19** and sodium iodide (NaI). Intramolecular cyclization of **20** was performed successfully with 2.3 eq of LDA or 2.6 eq of LCIA in THF in the presence of HMPA to furnish the known key synthetic intermediate **21** in 41 or 46% yield, respectively. IR, ^{1}H-NMR and MS data for the synthesized **21** were identical with those reported. The specific optical rotation of the synthesized **21** is $[\alpha]_D^{20}$ $-42.8°$ ($c=0.28$, $CHCl_3$) and the reported value is $[\alpha]_D^{25}$ $-43.1°$ ($c=0.4$, $CHCl_3$).[3d] These results show that the allylation of **8** occurred in a highly stereoselective manner from the β-side of the molecule, as expected. HPLC analysis using a chiral column showed that (−)-**21** was optically pure. The synthesis of (+)-grandisol (**1**) from **21** has been reported,[3d,m] so the present synthesis of (−)-**21** represents an alternative formal synthesis of (+)-**1**.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus, model MP-S3, and are uncorrected. IR spectra were measured with a Hitachi 260-30 infrared spectrometer, and ^{1}H-NMR spectra were recorded on a JEOL JNM-GSX270 (270 MHz) spectrometer using tetramethylsilane as an internal standard. High-resolution mass spectra (HRMS) were taken with a JEOL LMS-HX100 instrument at 70 eV. Optical rotations were recorded on a JASCO DIP-370 polarimeter.

(1*S*,3*S*,4*R*,5*R*)-3,4-*O*-Cyclohexylidene-1,3,4-trihydroxy-6-oxabicyclo-[3.2.1]octan-7-one (3) *p*-TsOH (0.183 g, 0.96 mmol) and cyclohexanone dimethylacetal (64.5 ml, 429.36 mmol) were added to a solution of (−)-quinic acid (40.0 g, 208.15 mmol) in a mixture of benzene (160 ml) and DMF (168 ml) and the whole was refluxed for 30 h. During the reaction, water formed was removed with the Dean-Stark apparatus. After addition of AcOEt, the mixture was washed with a saturated Na_2CO_3 solution, H_2O and brine, successively. The combined washings were extracted with AcOEt and the organic solution was added to the above organic layer. The combined organic layers were washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue, which was crystallized from benzene to yield **3** (38.108 g, 72%) as colorless needles, mp 142—146 °C. IR (Nujol) cm^{-1}: 3400, 1760. ^{1}H-NMR ($CDCl_3$) δ: 1.5—1.78 (10H, m, cyclohexylidene), 2.185 (1H, dd, $J=15$, 3 Hz, C(2)-H), 2.37 (1H, ddd, $J=15$, 7.5, 2.5 Hz, C(2)-H), 2.30 (1H, ddt, $J=12$, 6, 2.5 Hz, C(8)-H), 2.66 (1H, d, $J=12$ Hz, C(8)-H), 3.03 (1H, s, OH), 4.30 (1H, ddd, $J=6.5$, 2.5, 1 Hz, C(4)-H), 4.48 (1H, ddd, $J=7.5$, 6.5, 3 Hz, C(3)-H), 4.74 (1H, dd, $J=6.5$, 3 Hz, C(5)-H). $[\alpha]_D^{21}$ $-25.4°$ ($c=1.046$, $CHCl_3$).

(3*S*,4*S*,5*R*)-3,4-*O*-Cyclohexylidene-3,4,5-trihydroxycyclohexanone (5) $NaBH_4$ (3.9 g, 93.09 mmol) was added portionwise to a solution of **3** (22.108 g, 86.94 mmol) in EtOH (425 ml) under ice-cooling. The mixture was stirred at room temperature for 2 h. After removal of the EtOH under reduced pressure, the residue was dissolved in H_2O under cooling and the solution was salted out. The mixture was extracted with $CHCl_3$ and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave crude **4** as an oil, which was dissolved in phosphate buffer solution (pH 7, 460 ml). $NaIO_4$ (29.299 g, 136.98 mmol) was added portionwise to the above solution under ice-cooling. The mixture was stirred at room temperature for 3 h and the precipitates formed were removed by filtration and washed with $CHCl_3$. The filtrate was extracted with $CHCl_3$ and the organic extracts were combined with the washings. The combined organic layers were washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue, which was crystallized from AcOEt–acetone to afford **5** (18.028 g, 83% from **3**) as colorless needles, mp 98 °C. IR (Nujol) cm^{-1}: 3450, 1710. ^{1}H-NMR ($CDCl_3$) δ: 1.34—1.70 (10H, m, cyclohexylidene), 2.16 (1H, br s, OH), 2.45 (1H, ddd, $J=18$, 3.5, 2.5 Hz, C(6)-H), 2.70 (2H, dt, $J=18$, 3.5 Hz, C(2)-H), 2.81 (1H, dd, $J=18$, 3.5 Hz, C(6)-H), 4.23—4.28 (1H, m, C(4)-H), 4.31 (1H, dt, $J=7$, 2.5 Hz, C(3)-H), 4.71 (1H, ddd, $J=7$, 3, 2.5 Hz, C(5)-H).

(1*R*,2*S*,3*R*,5*R*)-1,2-*O*-Cyclohexylidene-1,2,3,5-tetrahydroxy-5-methylcyclohexane (6) A solution of **5** (2.154 g, 9.52 mmol) in dry THF (18 ml) was added dropwise to a solution of MeLi (20.4 ml, 1.6 M THF solution, 28.56 mmol) in dry THF (100 ml) at −78 °C under an N_2 atmosphere and the whole was stirred at the same temperature for 30 min and at −30 °C for 2.5 h. After addition of H_2O (90 ml) and salting out, the mixture was extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue, which was purified by SiO_2 column chromatography (AcOEt : benzene = 1 : 1) to afford **6** (1.661 g, 72%) as a colorless oil. IR (neat) cm^{-1}: 3400. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, s, CCH_3), 1.52—1.78 (10H, m, cyclohexylidene), 1.81 (1H, dd, $J=8$, 4 Hz, C(4)-H), 2.0 (2H, ddd, $J=12$, 5, 3 Hz, C(6)-H), 2.24 (1H, m, C(4)-H), 2.38 (1H, br s, C(3)-OH), 3.26 (1H, br s, C(5)-OH), 3.88 (1H, dd, $J=8$, 5 Hz, C(1)-H), 4.12 (1H, dd, $J=15$, 8 Hz, C(2)-H), 4.45 (1H, ddd, $J=8$, 6, 5 Hz, C(3)-H). $[\alpha]_D^{20}$ $-45.5°$ ($c=0.908$, $CHCl_3$). HRMS *m/z*: Calcd for $C_{13}H_{22}O_4$: 242.1567. Found: 242.1543.

(5*R*,6*S*)-5,6-*O*-Cyclohexylidene-5,6-dihydroxy-3-methyl-2-cyclohexenone (8) A mixture of **6** (7.939 g, 32.76 mmol), PDC (18.54 g, 49.28 mmol) and powdered molecular sieves (19 g) was stirred at room temperature for 16 h. After addition of ether, the mixture was filtered with the aid of Celite. The filtrate was concentrated under reduced pressure to give a residue, which was purified by SiO_2 column chromatography (ether) to afford a mixture of **7** and **8** (5.960 g). A part of the mixture was chromatographed again to obtain pure **7** as a colorless oil. IR (neat) cm^{-1}: 3450, 1720. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, s, CCH_3), 1.40—1.70 (10H, m, cyclohexylidene), 2.09 (1H, dd, $J=15.5$, 3.5 Hz, C(4)-H), 2.44 (1H, dt, $J=15.5$, 3 Hz, C(4)-H), 2.46 (1H, d, $J=14$ Hz, C(6)-H), 2.63 (1H, dd, $J=14$, 3 Hz, C(6)-H), 3.48 (1H, s, OH), 4.29 (1H, d, $J=6$ Hz, C(2)-H), 4.62 (1H, ddd, $J=6$, 3.5, 2.5 Hz, C(3)-H). $[\alpha]_D^{19}$ $-45.0°$ ($c=0.986$, $CHCl_3$). *Anal.* Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.65; H, 8.25.

A solution of the mixture of **7** and **8** (4.924 g, 20.49 mmol) in pyridine (56 ml) was treated dropwise with $POCl_3$ (5.1 ml, 137.69 mmol) under ice-cooling and the reaction mixture was stirred at room temperature for 38 h. After addition of a saturated NH_4Cl solution under ice-cooling, the mixture was extracted with AcOEt. The combined extracts were washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue, which was purified by SiO_2 column chromatography (AcOEt : benzene = 1 : 3) to afford **8** (3.416 g, 75% from **6**) as a colorless oil. IR (neat) cm^{-1}: 1660, 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.28—1.62 (10H, m, cyclohexylidene), 1.97 (3H, d, $J=1$ Hz, CCH_3), 2.66—2.73 (2H, m, C(4)-H), 4.17 (1H, d, $J=5$ Hz, C(6)-H), 4.53 (1H, ddd, $J=5$, 4, 2 Hz, C(5)-H), 4.62 (1H, dd, $J=3$, 1 Hz, C(2)-H). $[\alpha]_D^{22}$ $-50.5°$ ($c=1.026$, EtOH). *Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 70.73; H, 8.13.

(4*R*,5*S*)-3-Allyl-4,5-*O*-cyclohexylidene-3,4,5-trihydroxy-1-methyl-1-cyclohexene (10) Allymagnesium bromide (1 M diethyl ether solution, 2.7 ml, 2.7 mmol) was added dropwise to a solution of $CuBr \cdot Me_2S$ (20 mg, 0.093 mmol) in dry THF (9 ml) at −40 °C under an N_2 atmosphere. A solution of **8** (0.2 g, 0.90 mmol) in dry THF (9 ml) was added to the above solution and the whole was stirred at 40 °C for 50 min. After addition of a saturated NH_4Cl solution, the mixture was extracted with ether and the combined organic layers were washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue, which was purified by SiO_2 PTLC (AcOEt : benzene = 1 : 7) to give **10** (0.221 g, 93%) as a colorless oil. IR (neat) cm^{-1}: 3500, 1660, 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.50—1.66 (10H, m, cyclohexylidene), 1.75 (3H, d, $J=1.5$ Hz, CCH_3), 2.32—2.40 (4H, m, C(6)-H, $C\underline{H}_2CH=$), 2.88 (1H, s, OH), 4.08 (1H, dd, $J=7.5$, 1.5 Hz, C(4)-H), 4.45 (1H, ddd, $J=7.5$, 6, 5.5 Hz, C(5)-H), 5.06—5.15 (2H, m, $CH=C\underline{H}_2$), 5.47 (1H, dd, $J=2$, 1.5 Hz, C(2)-H), 5.815 (1H, ddt, $J=18$, 9, 7.5 Hz, $C\underline{H}=CH_2$). HRMS *m/z*: Calcd for $C_{16}H_{24}O_3$: 264.1725. Found: 264.1702.

(1*R*,2*R*,5*R*)-5-Allyl-3-*tert*-butyldimethylsilyloxy-1,2-*O*-cyclohexylidene-1,2-dihydroxy-5-methyl-3-cyclohexene (11) Allyltributyltin (0.18 ml, 0.54 mmol) was added to a solution of **8** (100 mg, 0.54 mmol) in dry CH_2Cl_2 (5 ml) at −78 °C under an N_2 atmosphere. TBDMSOTf (0.13 ml, 0.54 mmol) was added to the above solution and the whole was stirred at −78 °C for 1.5 h. After addition of a saturated Na_2CO_3 solution, the mixture was warmed to room temperature and extracted

with AcOEt. The combined organic layers were washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue, which was purified by SiO_2 PTLC (AcOEt : *n*-hexane = 1 : 125) to afford **11** (0.164 g, 96%) as a yellow oil. IR (neat) cm^{-1}: 1640. ^1H-NMR ($CDCl_3$) δ: 0.155 (3H, s, $SiCH_3$), 0.185 (3H, s, $SiCH_3$), 0.945 (12H, s, CCH_3, $SiC(CH_3)_3$), 1.20—1.60 (10H, m, cyclohexylidene), 1.60—1.70 (2H, m, C(4)-H), 2.09 (1H, dd, J = 12.5, 7 Hz, $C\underline{H}_2CH=$), 2.15 (1H, dd, J = 12.5, 7 Hz, $C\underline{H}_2CH=$), 4.29 (1H, d, J = 7 Hz, C(2)-H), 4.39 (1H, dt, J = 9.5, 7 Hz, C(3)-H), 4.89 (1H, s, C(6)-H), 4.98—5.068 (2H, m, $CH=C\underline{H}_2$), 5.78 (1H, ddt, J = 17, 9.5, 7 Hz, $C\underline{H}=CH_2$). HRMS *m/z*: Calcd for $C_{22}H_{38}O_3Si$: 378.2569. Found: 378.2580.

(2*S*,3*R*,5*S*)-5-Allyl-2,3-*O*-cyclohexylidene-2,3-dihydroxy-5-methylcyclohexanone (12) TBAF (25.32 ml, 1 M THF solution, 25.32 mmol) was added to a solution of **11** (4.793 g, 12.66 mmol) in dry THF (96 ml) under ice-cooling and an N_2 atmosphere and the whole was stirred for 1.5 h. After addition of a saturated NH_4Cl solution, the mixture was extracted with AcOEt and the combined organic layers were washed with H_2O and brine, respectively, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue, which was purified by SiO_2 column chromatography (AcOEt : *n*-hexane = 1 : 4) to afford **12** (2.874 g, 85%) as a colorless oil. IR (neat) cm^{-1}: 1720, 1710, 1640. ^1H-NMR ($CDCl_3$) δ: 1.28—1.75 (10H, m, cyclohexylidene), 1.81 (2H, dd, J = 15, 5 Hz, C(4)-H), 2.07 (1H, dd, J = 15, 7.5 Hz, C(6)-H), 2.17 (1H, d, J = 13 Hz, $C\underline{H}_2CH=$), 2.26 (1H, d, J = 13 Hz, $C\underline{H}_2CH=$), 2.37 (1H, dd, J = 15, 3 Hz, C(6)-H), 4.31 (1H, d, J = 6 Hz, C(2)-H), 4.61 (1H, ddd, J = 6, 5, 3 Hz, C(3)-H), 5.02—5.14 (2H, m, $CH=C\underline{H}_2$), 5.78 (1H, ddt, J = 18, 10, 7 Hz, $C\underline{H}=CH_2$). HRMS *m/z*: Calcd for $C_{16}H_{24}O_3$: 264.1725. Found: 264.1718.

(3*R*)-Methyl 3-(Formylmethyl)-3-methyl-5-hexenoate (15) A solution of **12** (2.517 g, 9.53 mmol) in 80% AcOH (120 ml) was stirred at room temperature for 40 h. Concentration of the mixture under reduced pressure gave crude **13** (1.991 g), which was dissolved in MeOH–H_2O (2 : 1). $NaIO_4$ (5.108 g, 23.88 mmol) was added portionwise to the above mixture and the whole was stirred at room temperature for 14 h. After addition of H_2O, the mixture was extracted with AcOEt and the combined organic layers were washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue, which was dissolved in MeOH (33 ml). Trimethyl orthoformate (7.23 ml, 66.05 mmol) and *p*-TsOH (55 mg, 0.032 mmol) were added to the above solution and the whole was refluxed for 3 h. After cooling to room temperature, the mixture was diluted with ether and the whole was washed with a saturated $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave crude **14** (2.103 g). A part of the crude **14** was purified by SiO_2 PTLC. IR (neat) cm^{-1}: 1720, 1640. ^1H-NMR ($CDCl_3$) δ: 1.04 (3H, s, CCH_3), 1.65 (1H, dd, J = 15, 5 Hz, $C\underline{H}_2CH=$), 1.75 (1H, dd, J = 15, 5 Hz, $C\underline{H}_2CH=$), 2.16 (2H, ddd, J = 7, 2, 1 Hz, C(4)-H), 2.29 (2H, s, C(2)-H), 3.30 (6H, s, $2\times OCH_3$), 3.645 (3H, s, $COOCH_3$), 4.51 (1H, t, J = 5 Hz, C(5)-H), 5.01—5.12 (2H, m, $CH=C\underline{H}_2$), 5.82 (1H, ddt, J = 17, 10, 7.5 Hz, $C\underline{H}=CH_2$). $[\alpha]_D^{20}$ −2.3° (c = 1.0, MeOH). The crude **14** (2.053 g) was dissolved in 70% AcOH (50 ml) and the solution was stirred at 60 °C for 6 h. After cooling, the solution was concentrated under reduced pressure to give a residue, which was purified by SiO_2 column chromatography ($CHCl_3$) to afford **15** (1.014 g, 58% from **12**) as a pale yellow oil. IR (neat) cm^{-1}: 1710, 1630. ^1H-NMR ($CDCl_3$) δ: 1.14 (3H, s, CCH_3), 2.22 (2H, d, J = 7 Hz, $C\underline{H}_2CH=$), 2.43 (2H, d, J = 5 Hz, C(2)-H), 2.53 (dd, J = 4, 2 Hz, C(4)-H), 3.66 (3H, s, $COOCH_3$), 5.03—5.17 (2H, m, $CH=C\underline{H}_2$), 5.78 (1H, ddt, J = 17, 10, 7 Hz, $C\underline{H}=CH_2$), 9.84 (1H, t, J = 2 Hz, CHO). HRMS *m/z*: Calcd for $C_9H_{13}O_3$ ($M^+ - CH_3$): 169.0864. Found: 169.0884.

(3*R*)-3-Allyl-3-methyl-5-pentanolide (16) $NaBH_4$ (0.123 g, 2.93 mmol) was added to a solution of **15** (1.014 g, 5.50 mmol) in MeOH (165 ml) under ice-cooling and the whole was stirred at room temperature for 2.5 h. After addition of a saturated NH_4Cl solution, the mixture was acidified with dilute HCl (pH 2) and extracted with $CHCl_3$. The combined organic layers were washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue, which was purified by SiO_2 column chromatography (AcOEt : *n*-hexane = 1 : 2) to afford **16** (0.652, 77%) as a colorless oil. IR (neat) cm^{-1}: 1720, 1640. ^1H-NMR ($CDCl_3$) δ: 1.07 (3H, s, CCH_3), 1.62 (2H, dt, J = 15, 6.5 Hz, C(4)-H), 2.1 (2H, d, J = 7 Hz, $C\underline{H}_2CH=$), 2.26 (1H, dd, J = 17, 1 Hz, C(2)-H), 2.4 (1H, d, J = 17 Hz, C(2)-H), 4.34 (2H, t, J = 6.5 Hz, C(5)-H), 5.06—5.19 (2H, m, $CH=C\underline{H}_2$), 5.77 (1H, ddt, J = 17, 10, 7 Hz, $C\underline{H}=CH_2$). $[\alpha]_D^{20}$ −2.0° (c = 0.97, MeOH).

(3*R*)-3-(2-Formylmethyl)-3-methyl-5-pentanolide (17) A solution of **16** (0.312 g, 2.02 mmol) in CCl_4 (18 ml) and $RuO_2\cdot 2H_2O$ (37 mg, 0.25 mmol) were added to a solution of $NaIO_4$ (1.799 mg, 8.41 mmol) in H_2O (18 ml) under ice-cooling. The mixture was stirred for 10 min, then 2-propanol (0.7 ml) was added to it. After salting out, the whole was extracted with AcOEt and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue, which was purified by SiO_2 column chromatography (AcOEt : benzene = 1 : 1) to afford **17** (0.195 g, 62%) as a colorless oil. IR (neat) cm^{-1}: 1750, 1720. ^1H-NMR ($CDCl_3$) δ: 1.25 (3H, s, CCH_3), 1.81 (1H, ddt, J = 14.5, 6, 2 Hz, C(4)-H), 1.97 (1H, dt, J = 14.5, 6 Hz, C(4)-H), 2.41 (1H, dd, J = 15.5, 2 Hz, C(2)-H), 2.53 (2H, t, J = 2 Hz, $CC\underline{H}_2CHO$), 2.57 (1H, d, J = 15.5 Hz, C(2)-H), 4.40 (2H, dd, J = 7.5, 6 Hz, C(5)-H), 9.82 (1H, t, J = 2 Hz, $CH_2C\underline{H}O$). $[\alpha]_D^{22}$ −13.1° (c = 1.025, $CHCl_3$). HRMS *m/z*: Calcd for $C_8H_{12}O_3$: 156.0731. Found: 156.0759.

(3*R*)-3-(2-Hydroxyethyl)-3-methyl-5-pentanolide (18) $NaBH_4$ (17 mg, 0.41 mmol) was added to a solution of **17** (140 mg, 0.90 mmol) in EtOH (20 ml) under ice-cooling and the mixture was stirred at room temperature for 30 min. It was concentrated under reduced pressure to give a residue, which was taken up in a saturated NH_4Cl solution under ice-cooling and salted out. The whole was extracted with $CHCl_3$ and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue, which was purified by SiO_2 PTLC (AcOEt : benzene = 2 : 1) to give **18** (78 mg, 55%) as a colorless oil. IR (neat) cm^{-1}: 3400, 1750. ^1H-NMR ($CDCl_3$) δ: 1.13 (3H, s, CCH_3), 1.69 (2H, dt, J = 14.5, 7 Hz, $CC\underline{H}_2CH_2OH$), 1.87 (2H, ddd, J = 14.5, 7, 5 Hz, C(4)-H), 2.33 (1H, dd, J = 16.5, 1.5 Hz, C(2)-H), 2.49 (1H, d, J = 16.5 Hz, C(2)-H), 3.77 (2H, t, J = 7 Hz, $CH_2C\underline{H}_2OH$), 4.37 (2H, t, J = 7 Hz, C(5)-H). $[\alpha]_D^{22}$ +5.3° (c = 1.025, MeOH).

(3*R*)-3-Methyl-3-(2-tosyloxyethyl)-5-pentanolide (19) Dry pyridine (0.02 ml), *p*-TsCl (44 mg, 0.23 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP) were added to a solution of **18** (30 mg, 0.19 mmol) in dry CH_2Cl_2 under ice-cooling. The mixture was stirred at room temperature for 14 h, then washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue, which was purified by SiO_2 PTLC (AcOEt : benzene = 1 : 3) to afford **19** (37 mg, 62%) as a colorless oil. IR (neat) cm^{-1}: 1725, 1600. ^1H-NMR ($CDCl_3$) δ: 1.07 (3H, s, CCH_3), 1.72 (2H, dt, J = 10, 6.5 Hz, $CC\underline{H}_2CH_2OTs$), 1.80 (2H, ddd, J = 14.5, 6.5, 2 Hz, C(4)-H), 2.27 (1H, dd, J = 16.5, 1.5 Hz, C(2)-H), 2.39 (1H, d, J = 16.5 Hz, C(2)-H), 2.47 (3H, s, $ArCH_3$), 4.13 (2H, dt, J = 6.5, 3.5 Hz, $CH_2C\underline{H}_2OTs$), 4.32 (2H, dd, J = 6.5, 5 Hz, C(5)-H), 7.34—7.40 (2H, m, ArH), 7.76—7.82 (2H, m, ArH). $[\alpha]_D^{22}$ +4.3° (c = 1.015, $CHCl_3$). HRMS *m/z*: Calcd for $C_{15}H_{20}O_5S$: 312.1031. Found: 312.1054.

(3*R*)-3-(2-Iodoethyl)-3-methyl-5-pentanolide (20) Method A: A solution of **18** (30 mg, 0.19 mmol) in dry CH_2Cl_2 (1 ml) was added to a mixture of Ph_3P (76 mg, 0.29 mmol), imidazole (20 mg, 0.29 mmol) and I_2 (73 mg, 0.29 mmol) in dry CH_2Cl_2 (4 ml) under an N_2 atmosphere and the whole was stirred at room temperature for 30 min. The mixture was concentrated under reduced pressure to give a residue, which was purified by SiO_2 PTLC (AcOEt : benzene = 2 : 1) to give **20** (25 mg, 49%) as a pale yellow oil.

Method B: A mixture of **19** (127 mg, 0.41 mmol) and NaI (80 mg, 0.53 mmol) in dry acetone (10 ml) was refluxed for 7 h and stirred at room temperature for 15 h. After addition of H_2O, the mixture was extracted with ether and the combined organic layers were washed with 1% $Na_2S_2O_3$ aqueous solution and brine. The organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue, which was purified by SiO_2 PTLC (AcOEt : benzene = 2 : 1) to afford **20** (79 mg, 73%) as a yellow oil. IR (neat) cm^{-1}: 1720. ^1H-NMR ($CDCl_3$) δ: 1.09 (3H, s, CCH_3), 1.67 (1H, ddt, J = 14, 6, 1 Hz, $CC\underline{H}_2CH_2I$), 1.80 (1H, dt, J = 14, 6 Hz, CCH_2CH_2I), 2.05 (2H, ddd, J = 9, 6, 2 Hz, C(4)-H, 2.31 (1H, dd, J = 17, 1 Hz, C(2)-H), 2.39 (1H, d, J = 17 Hz, C(2)-H), 3.13 (2H, ddd, J = 9, 6, 2 Hz, $CH_2C\underline{H}_2I$), 4.35 (2H, dd, J = 6, 5 Hz, C(5)-H).

(1*R*,6*R*)-6-Methyl-3-oxabicyclo[4.2.0]octan-2-one (21) *n*-BuLi (1.6 M *n*-hexane solution, 0.298 ml, 0.48 mmol) was added dropwise to a solution of *N*-isopropylcyclohexylamine (0.08 ml, 0.48 mmol) in dry THF (7 ml) at −78 °C and the whole was stirred for 1.5 h. A solution of **20** (49 mg, 0.19 mmol) in dry THF was added dropwise to the above mixture and the whole was stirred at room temperature for 4 h. After addition

of a saturated NH_4Cl solution, the mixture was extracted with ether and the combined organic layers were washed with H_2O and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure gave a residue, which was purified by SiO_2 PTLC (AcOEt : *n*-hexane = 10 : 1) to afford **21** (12 mg, 46%) as a pale yellow oil. HPLC analysis using Daicel Chiralcel OB-H (0.46 × 25 cm, *n*-hexane : 2-propanol = 50 : 1) indicated that **21** was optically pure. IR (neat) cm^{-1}: 1730. ^1H-NMR ($CDCl_3$) δ: 1.25 (3H, s, CCH_3), 1.66 (2H, ddd, J = 14.5, 9, 4 Hz, C(5)-H), 1.84 (1H, ddd, J = 13, 6, 3 Hz, C(7)-H), 1.98 (1H, d, J = 7 Hz, C(8)-H), 2.1 (1H, ddd, J = 18, 11, 7 Hz, C(7)-H), 2.37—2.54 (1H, m, C(1)-H), 2.87 (1H, dd, J = 11, 7 Hz, C(8)-H), 4.39 (1H, ddd, J = 11, 6, 4 Hz, C(4)-H), 4.56 (1H, ddd, J = 11, 9, 3 Hz, C(4)-H). $[\alpha]_D^{20}$ −42.8° (c = 0.28, $CHCl_3$). (lit.,[3d] $[\alpha]_D^{25}$ −43.1° (c = 0.4, $CHCl_3$). HRMS m/z: Calcd for $C_8H_{12}O_2$: 140.0838. Found: 140.0855.

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