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Total synthesis of actinobolin from D-glucose by way of the stereoselective three-component coupling reaction

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Abstract—The total synthesis of (−)-actinobolin **3**, an antipode of the natural product, starting from D-glucose is described. A three-component coupling reaction of functionalized cyclohexenone (+)-**6** derived from D-glucose by way of Ferrier's carbocyclization reaction, with vinyl cuprate and 2-alkoxypropanal **7** effectively constructed the carbon framework of **3** in a highly stereoselective manner. In an aldol process of the three-component coupling reaction, stereochemical control (chelation and Felkin–Anh conditions) was achieved by the choice of the protecting groups of a hydroxy function in 2-hydroxypropanal and the reaction solvents. The formal synthesis of the natural enantiomer, (+)-actinobolin **1**, starting from D-glucose was also accomplished.

1. Introduction

(+)-Actinobolin **1**, isolated from the culture broth of *Streptomyces griceoviridus* by Haskell and Bartz in 1959, has a broad antibacterial spectrum as well as moderate antitumor activity.[1] The substance is a hydrophilic, amphoteric, water soluble base, and it chelates with iron, aluminum, and other metal ions. It has also been reported that actinobolin, which suppresses antibody production, has a therapeutic effect on autoimmune encephalomyelitis[2] and serves to increase the hardness of human enamel.[3] The structure elucidation study revealed that actinobolin has a highly oxygenated bicyclic γ-lactone (tetrahydroisochromane) framework with five contiguous chiral centers including an L-alanine residue (Fig. 1).[4] Later, in 1979, a structurally related natural product, (−)-bactobolin **2** was discovered in *Pseudomonas* BMG13-A7 and found to show more potent activities than actinobolin.[5] Such interesting and challenging structures with potent biological properties have naturally received considerable attention from the synthetic community, and several reports on total syntheses,[6] synthetic approach,[7] and chemical modification[8] of actinobolin and bactobolin have been described. In 1984, Ohno and co-workers reported the first and elegant total synthesis of (+)-actinobolin **1** starting from L-threonine using an intramolecular Diels–Alder reaction as the key reaction.[6a] Second synthesis was accomplished in 1985 by Weinreb and co-workers.[6b] The features of Weinreb's work were shorter synthetic route than Ohno's synthesis and the preparation of common bicyclic olefinic γ-lactone, which could be utilized for the synthesis of both actinobolin and bactobolin. In 1986, Kozikowski and co-workers also completed the synthesis of actinobolin from L-threonine.[6c,d] Most recently, Ward and co-workers carried out the total synthesis in 1993[6e,f] in which they used the novel diastereoselective 6-*endo-trig* radical cyclization of a thiocarbamate derived from D-glucose. On the other hand, *N*-acetylactinobolin was prepared by two groups.[7] Rahman and Fraser-Raid synthesized it in an optically active form via a [4+2] cycloaddition.[7a] Danishefsky and co-workers achieved a synthesis of racemic *N*-acetylactinobolin utilizing a key siloxy Cope rearrangement.[7b]

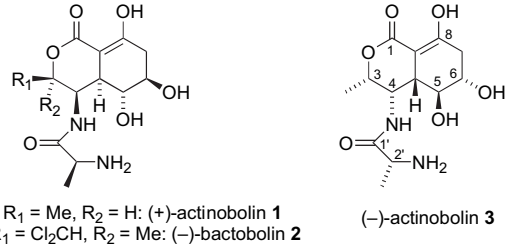

Figure 1. Structures of actinobolin and bactobolin.

We report here the new synthesis of (−)-actinobolin **3**, the antipode of the natural product expected to show some biological activity, starting from D-glucose using stereoselective three-component coupling reactions as the key

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transformation.[9] The formal synthesis of natural enantiomer **1** from D-glucose is also presented.

2. Results and discussion

2.1. Retrosynthesis

Our retrosynthetic analysis for (−)-actinobolin **3** suggested that bicyclic γ-lactone possessing an azide function **4** would be a promising intermediate for the total synthesis (Fig. 2). Lactone **4** was expected to arise from cyclohexanone derivative **5**, which we planned to prepare by way of a one-pot three-component coupling reaction[10] of cyclohexenone (+)-**6**, a vinyl metal species, and 2-hydroxypropanal derivative **7**. The aldol process in the three-component coupling reaction of an enolate generated from (+)-**6** with (*R*)- or (*S*)-**7** was expected to show stereoselectivities, since both partners in the reaction are chiral, therefore, the reaction would proceed under 'double diastereoselection conditions'.[11] The cyclohexenone (+)-**6**, in turn, was envisioned to be synthesized in optically pure form starting from D-glucose utilizing Ferrier's carbocyclization[12] as the key transformation.

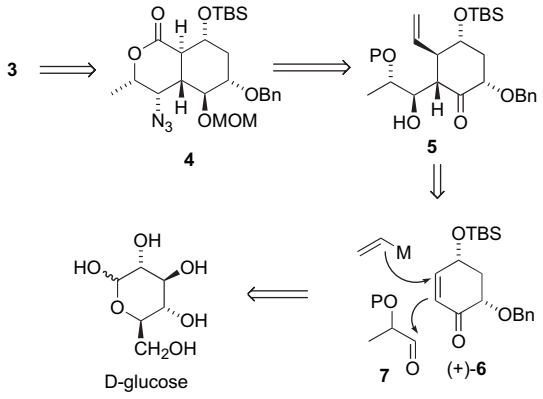
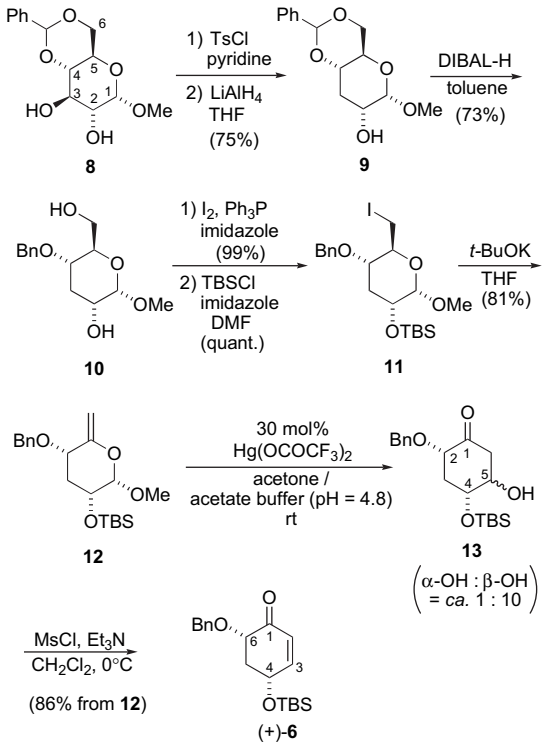


Figure 2. Retrosynthetic analysis of (−)-actinobolin.

2.2. Preparation of subunits

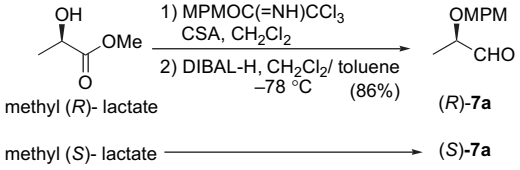
Synthesis of cyclohexenone (+)-**6** commenced from the known 3-deoxy-D-glucose derivative[13] **9** prepared from the commercially available methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **8** in two steps (Scheme 1). Cleavage of a benzylidene acetal in **9** with diisobutylaluminum hydride (DIBAL-H) gave **10**, whose primary hydroxy group was selectively iodinated and the remaining hydroxy function was protected as a TBS ether to afford **11**. Treatment of **11** with *t*-BuOK provided 5-enopyranoside **12**. Catalytic Ferrier's carbocyclization reaction[14] of **12** in acetone–acetate buffer (pH 4.8) gave **13** as a mixture of diastereomer (α-OH/β-OH=ca. 1:10). Use of acetate buffer was effective to suppress the partial hydrolysis of the *O*-TBS group due to the acidity of the catalyst, and greatly improved the cyclization yields. β-Elimination of the hydroxy function cleanly generated cyclohexenone (+)-**6**.

The other requisite subunit, aldehyde **7a**, was synthesized in optically active forms and as a racemate from methyl lactate (Scheme 2). Acid catalyzed *p*-methoxybenzylation of the hydroxy group in methyl (*R*)-lactate,[15] followed by



Scheme 1. Bn=–CH_2Ph, TBS=–$SiMe_2(t\text{-}Bu)$.

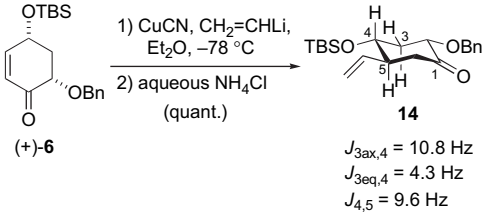
reduction with DIBAL-H afforded (*R*)-**7a** in 86% overall yield. Similar treatment of methyl (*S*)-lactate gave enantiomeric aldehyde (*S*)-**7a**.



Scheme 2. MPM=–$CH_2C_6H_4(p\text{-}OMe)$.

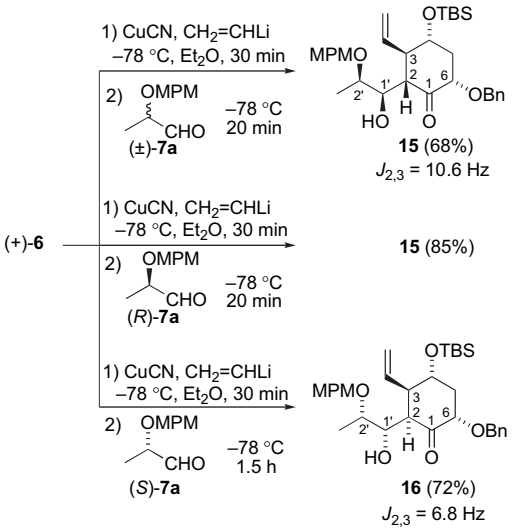
2.3. Three-component coupling reaction

With chiral cyclohexenone (+)-**6** and aldehydes (*R*)-, (*S*)-, and (±)-**7a** in hand, the crucial three-component coupling reaction was investigated using vinyl metal species as the nucleophile (Scheme 3). At first, 1,4-addition of a vinyl group to (+)-**6** was attempted. Treatment of (+)-**6** with higher order vinyl cuprate[16] in Et_2O at −78 °C followed by quenching the reaction with aqueous NH_4Cl, afforded **14** as a single isomer in a quantitative yield. The observed large coupling constants ($J_{3ax,4}$=10.8 Hz, $J_{4,5}$=9.6 Hz) in ^1H NMR spectra of **14** clearly revealed that the vinyl group was introduced from the less crowded β-face.



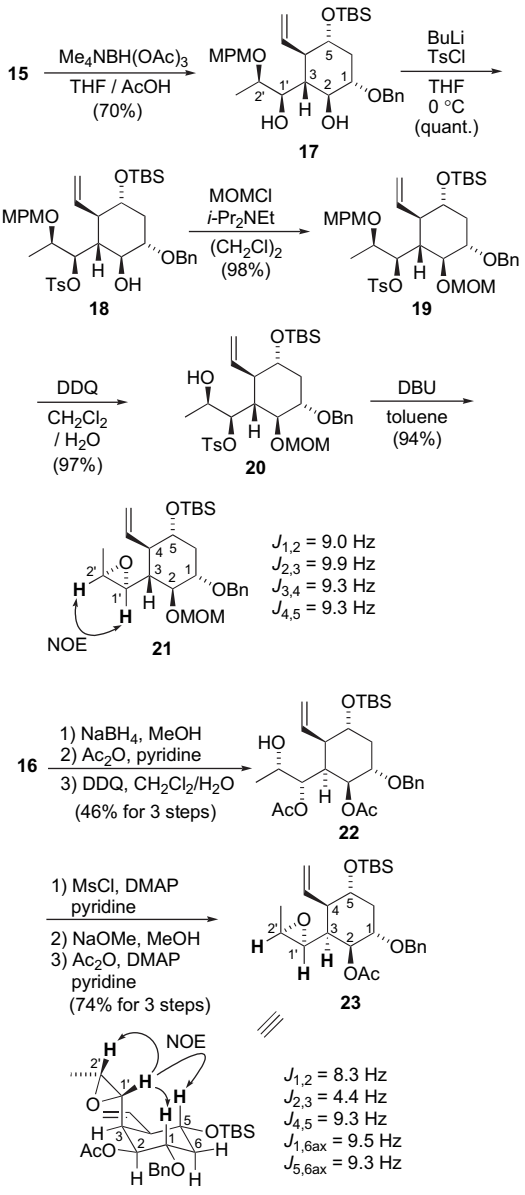
Scheme 3.

Then, the intermediate enolate was trapped with excess amount (6 equiv to (+)-**6**) of racemic aldehyde (±)-**7a** in Et_2O to give **15** as the major isomer in 68% isolated yield after chromatographic separation (Scheme 4). The coupling constant ($J_{2,3}$=10.6 Hz) in ^{1}H NMR spectrum of **15** showed the stereochemical relationship between C-2 and C-3 substituents to be *trans*. The similar reaction employing vinylmagnesium bromide as a nucleophile in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and CuI in THF gave less satisfactory results to afford **15** in 48% yield. When chiral aldehyde (*R*)-**7a** was employed as an electrophile, the same diastereomer **15** was obtained in 85% yield. Interestingly with another chiral aldehyde (*S*)-**7a**, the aldol process was found to proceed much slower than the reaction with (*R*)-**7a**, and a different diastereomer **16**, in which the stereochemistry of substituents at C-2 and C-3 were *cis* ($J_{2,3}$=6.8 Hz), was formed in 72% yield.



Scheme 4.

The stereochemistry at C-1′ of **15** and **16** was determined by NOE experiments of epoxides **21** and **23** derived from **15** and **16**, respectively (Scheme 5). Treatment of **15** with $Me_4NBH(OAc)_3$[17] at room temperature stereoselectively reduced the carbonyl group to give *syn* diol **17** in 70% yield. The hydroxy group at C-2 in **17** was anticipated to show less reactivity than that at C-1′ due to the steric congestion. Indeed, reaction of **17** with BuLi (3 equiv) at 0 °C, followed by treatment with TsCl (2.8 equiv) generated 1′-OTs derivative **18**, quantitatively. The remaining hydroxy function was then masked as a MOM ether to afford **19** in 92% yield. The MPM group in **19** was deprotected by DDQ to afford **20**, which was then converted into epoxide **21** by treatment with DBU. The observed NOE between H-1′ and H-2′ in **21** revealed the relationship of these protons to be cis, showing that the stereochemistry at C-1′ in **15** should be *R*. On the other hand, reduction of **16** with $NaBH_4$ gave β-alcohol, which was converted into diacetate **22** possessing (1′*S*,2*R*) configuration by O-acetylation and deprotection of the *O*-MPM group. Methanesulfonylation of the hydroxy group in **22** followed by treatment with NaOMe provided an epoxide, whose O-acetylation gave **23**. The observed coupling constants and NOE experiments unambiguously supported the whole structure of **23**, indicating the stereochemistry at C-1′ in **16** to be *S*.



Scheme 5. Ts=–$SO_2C_6H_4$(*p*-Me).

The predominant formation of 1′,2′-*syn* isomers (**15** and **16**) in the three-component coupling reactions suggested that the chelation control (chelation between the alkoxy and aldehyde oxygens in (*R*)-**7a** and (*S*)-**7a**) should be an important factor in the aldol process.[11] Reaction of the intermediate enolate with chelated (*R*)-**7a** would proceed in a 'matched pair' manner (route *a* in Fig. 3) to give **15** smoothly, whereas combination of (*S*)-**7a** and the enolate

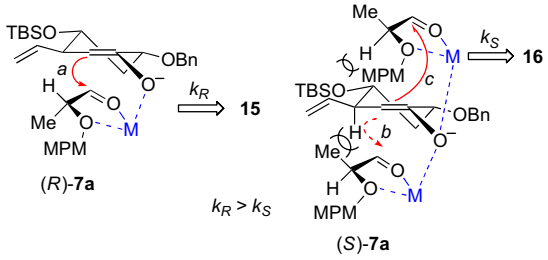


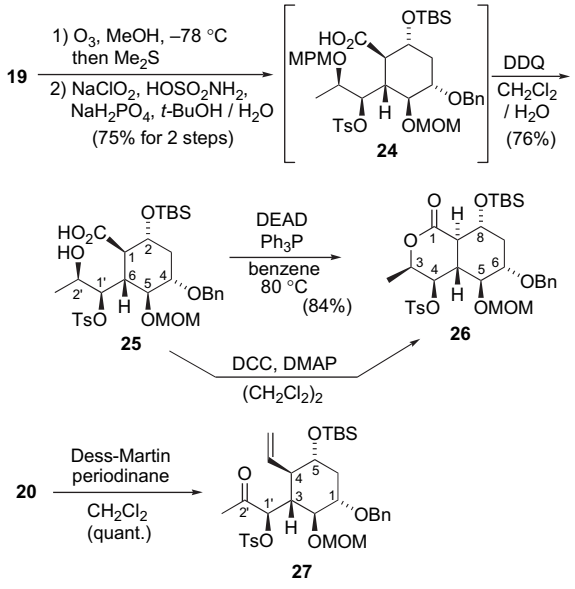
Figure 3.

would be 'mismatched'. The steric repulsion between chelated (*S*)-**7a** and the enolate (routes *b* and *c*) rendered the aldol reaction much sluggish, but gave 2,3-*cis*-adduct **16** stereoselectively via less crowded pathway (route *c*) when (*S*)-**7a** was employed as the electrophile. Apparently, a kinetic resolution had taken place in the aldol process with racemic aldehyde (±)-**7a**, providing **15** as the major product, since the aldol reaction of the intermediate enolate with (*R*)-**7a** was much faster than that with (*S*)-**7a**.

The stereoselective formation of three-component adduct **15** led us to use this compound as the precursor for the synthesis of (−)-actinobolin. Successful conversion of **15** into **19** (Scheme 5) revealed that the required transformations into the desired lactone would be (1) introduction of a nitrogen function at C-1′ via S_N2 fashion and (2) formation of γ-lactone with inversion of the configuration at the C-2′ hydroxy group.

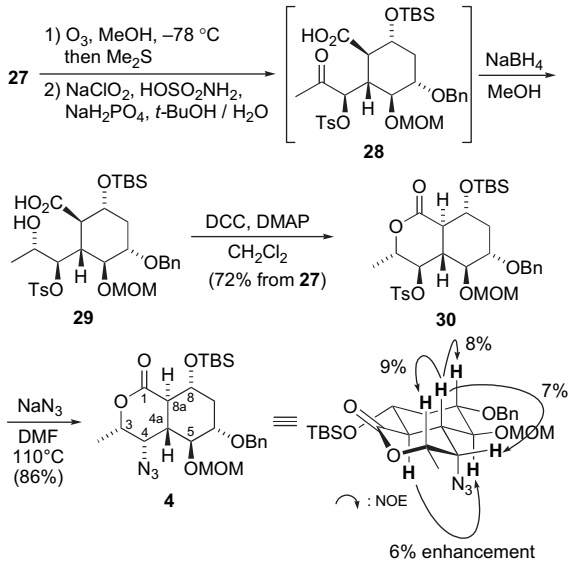
2.4. Total synthesis of (−)-actinobolin

Ozonolysis of a vinyl group in **19** and further oxidation with $NaClO_2$ afforded **24** in 75% yield (Scheme 6). The MPM protecting group in **24** was removed to give hydroxycarboxylic acid **25**. To obtain a γ-lactone with inversion of the hydroxy group, compound **25** was subjected to the intramolecular Mitsunobu reaction[18] (DEAD, PPh_3). However, it was found that the product obtained in 80% yield was γ-lactone **26** with retention of the C-2′ stereochemistry. The structure of **26** was confirmed by the fact that DCC-mediated lactonization of **25** afforded the same lactone **26**. These results revealed that Mitsunobu reagent did not activate the alcohol moiety in **25** probably due to the steric congestion, but activated the carboxylic acid moiety. A similar phenomenon has been documentated,[18b] and mechanistic study on Mitsunobu lactonization of hydroxycarboxylic acid with hindered alcohol system has been reported in detail by DeShong.[19]



Scheme 6. MOM=–CH_2OMe.

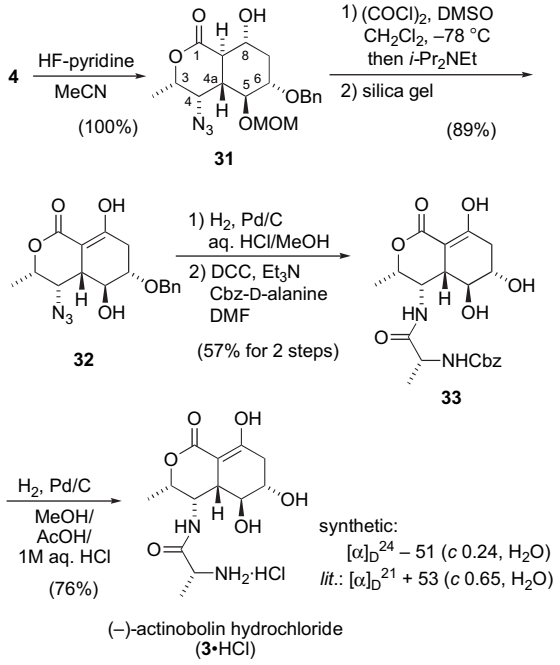
Attempted inversion of a hydroxy function in **20** by intermolecular Mitsunobu reaction proved also fruitless, so we next adopted an oxidation–reduction procedure. Dess–Martin oxidation of **20** provided methyl ketone **27** (Scheme 6). Reduction of **27** with various reducing reagents was carried out, however, the desired inverted alcohol could not be obtained as the major isomer. After several attempts, it was found that the stereoselective reduction successfully proceeded when carboxylic acid **28** was employed as the substrate (Scheme 7). Thus, ozonolysis of **27**, followed by further oxidation gave **28**. Treatment of **28** with $NaBH_4$ provided desired product **29** as the major isomer, and bicyclic compound **30** was obtained in 72% yield from **27** after lactonization followed by separation with silica gel chromatography. Azidolysis of **30** with NaN_3 cleanly provided advanced intermediate **4** in 86% yield, whose structure was confirmed by NOE experiments.



Scheme 7.

With the desired lactone **4** possessing proper functionalities and stereochemistry in hand, the final transformation to **3** was then explored. Deprotection of the *O*-TBS moiety in **4** gave **31**, whose Swern oxidation afforded β-ketoester **32** in 89% yield from **4** (Scheme 8). Interestingly, the methoxymethyl group was unexpectedly removed during the purification process with silica gel chromatography. Hydrogenation of **32** in the presence of Pd catalyst in aqueous HCl reduced the azide function as well as induced removal of the *O*-benzyl group to provide an amine hydrochloride, which, without isolation, was condensed with *N*-benzyloxycarbonyl-D-alanine (Z-D-alanine) by the action of DCC to give protected actinobolin **33** in 57% yield. Finally, removal of the benzyloxycarbonyl group by hydrogenolysis in MeOH–AcOH–aqueous HCl, followed by purification with Sephadex LH-20 (MeOH) furnished (−)-actinobolin hydrochloride (**3**·HCl) in 76% yield. The spectral (^1H and ^{13}C NMR) data of synthetic **3**·HCl were fully identical with those of natural (+)-actinobolin hydrochloride, kindly provided by Dr. Y. Nishimura, and the $[\alpha]_D$ value of the synthetic compound {$[\alpha]_D^{24}$ −51 (*c* 0.24, H_2O): lit.[6c,d] $[\alpha]_D^{21}$ +53 (*c* 0.65, H_2O)} confirmed its unnatural absolute configuration.

Thus, total synthesis of (−)-actinobolin (**3**) starting from D-glucose was accomplished. The high stereoselectivities observed in the three-component coupling reaction under

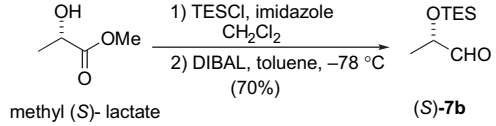


Scheme 8. Cbz=–C(O)OCH$_2$Ph.

the chelation control led us to explore the possibility of the coupling reaction under non-chelation conditions. If a three-component coupling reaction with (*S*)-hydroxypropanal derivative proceeded via Felkin–Anh conditions, the product possessing the proper stereochemistries for the synthesis of actinobolin was anticipated to be obtained as the major isomer, which would bring about the shorter step synthesis of actinobolin.

2.5. Three-component coupling with a TES-aldehyde: a shorter route to (−)-actinobolin

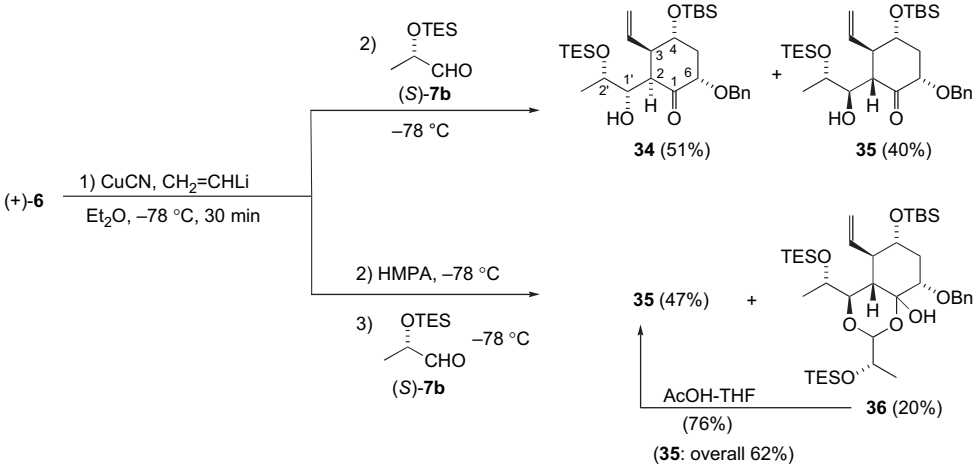
For the aldol reaction under Felkin–Anh conditions, aldehyde **7b** possessing *O*-TES protecting group was employed for three-component coupling reaction. It has been reported that *O*-silyl protecting group does not form chelation between alkoxy and carbonyl oxygens.[20] Aldehyde (*S*)-**7b** was prepared from methyl lactate by protection of the hydroxy group with TESCl, followed by reduction (Scheme 9).[21]



Scheme 9. TES=–SiEt$_3$.

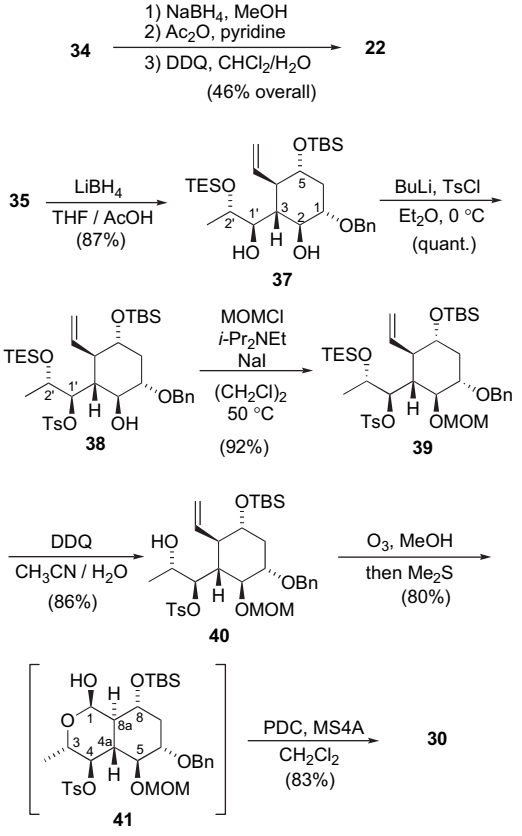
Three-component coupling reaction of (+)-**6**, vinyl cuprate, and aldehyde (*S*)-**7b** at −78 °C resulted in the formation of **34** (chelation product, 51%) and **35** (Felkin–Anh product, 40%) (Scheme 10). Contrary to our expectation, the aldol process provided a 5:4 mixture of chelation and Felkin–Anh products, in spite of using an *O*-TES protecting group. To reduce the degree of the chelation in (*S*)-**7b**, hexamethylphosphoramide (HMPA) was added[22] to the reaction mixture. To our delight, in the presence of HMPA, the three-component coupling reaction with (*S*)-**7b** proceeded stereoselectively to provide Felkin–Anh products **35** and **36** in 47% and 20% isolated yields, respectively, and chelation product **34** could not be isolated in this case. The ketal product **36**, presumably formed by the further reaction of **35** with excess (*S*)-**7b**, was converted into **35** in 76% yield by treatment with acetic acid. Thus, desired compound **35** was obtained in 62% overall yield from (+)-**6** after acetolysis of **36**.

The structure of compound **34** was assigned by comparison of its NMR spectra with those of the structurally related compound **16**, and finally confirmed by its conversion into the known compound **22**, by the similar procedures as described for the preparation of **22** from **16**. On the other hand, the structure of **35** was verified by its transformation into the known synthetic intermediate **30** of actinobolin as shown in Scheme 11. Thus, treatment of **35** with LiBH$_4$, in THF/AcOH at room temperature reduced the carbonyl group stereoselectively to give *syn* diol **37** in 87% yield. Reduction of **35** with NaBH(OAc)$_3$[23] and Me$_4$NBH(OAc)$_3$[17] also gave **37** as a major isomer, but the yields (76% and 25%, respectively) were less satisfactory. Reaction of **37** with BuLi in Et$_2$O at 0 °C, followed by treatment with TsCl generated the 1′-OTs derivative **38**, quantitatively. The remaining



Scheme 10.

hydroxy function was then masked as a MOM ether to afford **39** in 92% yield. The TES protecting group was removed by the action of DDQ[24] to give **40** in 86% yield. Ozonolysis of **40** followed by reductive workup afforded lactol **41** as a single anomer. Oxidation of **41** by PDC provided lactone **30**, which was fully identical with the compound prepared in previous route as shown in Scheme 7. This new synthetic sequence to actinobolin from **35**, which has no necessity to invert the configuration at C-2′ hydroxy group, is three steps shorter than the previous route using *O*-MPM aldehyde (*R*)-**7a**.

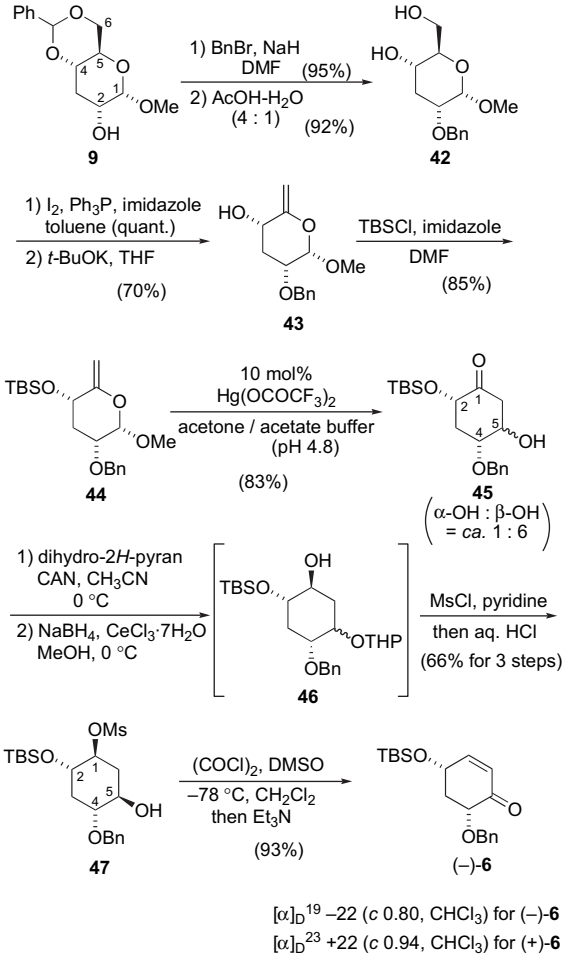


Scheme 11.

2.6. Formal synthesis of (+)-actinobolin

Having established the new synthetic pathways to (−)-actinobolin from D-glucose, we turned our attention to the synthesis of the natural enantiomer **1**, also starting from D-glucose. It is interesting and important issue for synthetic chemistry to prepare both enantiomers from the same starting material. For this purpose, 3-deoxy-D-glucose derivative **9** was again chosen as a building block, and its transformation into the enantiomer of (+)-**6** was investigated.

Benzylation of a hydroxy group in **9**, followed by acetal hydrolysis afforded **42** in 87% overall yield (Scheme 12). Selective iodination of primary alcohol of **42** and subsequent treatment with base gave 5-enopyranoside **43** in 70% yield. Protection of the remaining hydroxy function as a TBS ether afforded **44** in 85% yield. Catalytic Ferrier's carbocyclization of **44** in acetone–acetate buffer generated **45** as a diastereomeric mixture (α:β=ca. 1:6) in 83% yield. Protection of a hydroxy group in **45** as a THP ether and subsequent reduction of the ketone carbonyl gave **46**. Methanesulfonylation of the hydroxy function in **46** followed by acidic workup afforded **47** as the major product in 66% isolated yield. The observed large coupling constants in **47** ($J_{1,2}$=8.8, $J_{4,5}$=9.0 Hz) clearly showed that both OMs and OH groups were in the equatorial positions. Swern oxidation of **47** was accompanied by the β-elimination of the OMs group to furnish (−)-**6** in 93% yield. The spectral data and the absolute value of $[\alpha]_D$ of (−)-**6** {$[\alpha]_D^{19}$ −22 (*c* 0.80, $CHCl_3$)} were fully identical with those of (+)-**6** {$[\alpha]_D^{23}$ +22 (*c* 0.94, $CHCl_3$)}, representing a formal synthesis of (+)-actinobolin.



Scheme 12.

3. Conclusion

In this work, a new synthesis route to both (−)- and (+)-actinobolin starting from D-glucose has been established. This synthesis demonstrated that the methodology involving the three-component coupling reaction on chiral cyclohexenones, derived from D-glucose by way of catalytic Ferrier's carbocyclization, is effective for the chiral and stereoselective synthesis of natural products possessing highly functionalized cyclohexane units. The stereochemical control in three-component coupling reaction by way of the choice of the protecting groups on aldehydes and the reaction

solvents would be an important finding and could be applicable to the stereoselective synthesis of other natural products.

4. Experimental

4.1. General

Melting points were determined on a Mitamura–Riken micro hot stage and were not corrected. Optical rotations were recorded using a sodium lamp (589 nm) with a JASCO DIP-370 instrument with 1 dm tube. Infrared (IR) spectra were measured with a JASCO FT/IR-200 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz on a JEOL Lambda 300 or on a Varian MVX-300 spectrometer. Chemical shifts are reported as δ values in parts per million relative to tetramethylsilane (δ=0) or chloroform (δ=7.26). Coupling constants (J) are reported in Hertz. Abbreviations used are br (broad peak), s (singlet), d (doublet), t (triplet), q (quartet), and m (complex multiplet). ^{13}C NMR spectra were recorded at 75 MHz on the JEOL Lambda 300 spectrometer. Chemical shifts are reported as d values in parts per million relative to chloroform-d (δ=77.00) or methanol-d_4 (δ=49.00) as internal references. Mass spectra are measured by a JEOL GC Mate spectrometer with EI (70 eV) or FAB mode. Organic extracts were dried over solid anhydrous Na_2SO_4 and concentrated below 40 °C under reduced pressure. Column chromatography was carried out with silica gel (Merck Kieselgel 60 F_{254}; 230–400 mesh) or alumina powder (WAKO alumina, activated; 300 mesh) for purification. Preparative TLC (PLC) was performed with Merck PLC plate (Kieselgel 60 F_{254}, 0.5 mm thickness).

4.2. Total synthesis of (−)-actinobolin

4.2.1. Methyl 4-*O*-benzyl-3-deoxy-α-D-*ribo*-hexopyranoside (10). To a solution of methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*ribo*-hexopyranoside[13] **9** (1.57 g, 5.90 mmol) in toluene (10 mL) under Ar at 0 °C was slowly added 1.01 mol/L solution of DIBAL-H in toluene (23.4 mL, 23.6 mmol). After being stirred at room temperature for 6 h, the reaction mixture was quenched with water, and the products were extracted with EtOAc. The organic layer was washed successively with 1 mol/L aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was recrystallized from EtOAc/hexane (2:5, 28 mL), to afford **10** (1.15 g, 73%) as colorless crystals: R_f 0.12 (EtOAc/toluene=1:1); mp 130.0–130.5 °C; $[\alpha]_D^{20}$ +184 (c 0.95, $CHCl_3$); IR (KBr disk) 3240, 2900, 1120, 1095, 1075, 1055, 1030, 1000, 715 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.40–7.24 (5H, m), 4.65 (1H, d, J=11.6 Hz), 4.64 (1H, d, J=3.5 Hz), 4.47 (1H, d, J=11.6 Hz), 3.83 (1H, dd, J=3.3, 11.5 Hz), 3.73 (1H, dd, J=4.4, 11.5 Hz), 3.63 (1H, ddd, J=3.5, 4.3, 11.7 Hz), 3.59 (1H, ddd, J=3.3, 4.4, 9.8 Hz), 3.45 (1H, ddd, J=4.6, 9.8, 11.3 Hz), 3.44 (3H, s), 2.38 (1H, ddd, J=4.3, 4.6, 11.5 Hz), 1.68 (1H, ddd, J=11.3, 11.5, 11.7 Hz); ^{13}C NMR (75 MHz) δ 137.8, 128.5, 127.8, 127.7, 98.4, 71.9, 70.9, 70.7, 67.3, 62.2, 55.0, 33.3; LRMS (EI) m/z 268 (M$^+$, 14.5%), 236 (53), 146 (100); HRMS (EI) m/z calcd for $C_{14}H_{20}O_5$ (M$^+$) 268.1311, found 268.1310. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.47; H, 7.21.

4.2.2. Methyl 4-*O*-benzyl-2-*O*-(*tert*-butyldimethylsilyl)-3,6-dideoxy-6-iodo-α-D-*ribo*-hexopyranoside (11). To a solution of **10** (1.04 g, 3.88 mmol) in toluene (25 mL) were added PPh_3 (1.63 g, 6.22 mmol), imidazole (0.840 g, 12.3 mmol), and iodine (1.97 g, 7.76 mmol), and the reaction mixture was stirred at room temperature for 28 h. The reaction mixture was diluted with EtOAc, and washed successively with 10% aqueous $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 60 g, EtOAc/toluene=1:5) to give methyl 4-*O*-benzyl-3,6-dideoxy-6-iodo-α-D-*ribo*-hexopyranoside (1.16 g, 99%) as a colorless syrup: R_f 0.55 (EtOAc/toluene=1:1); $[\alpha]_D^{22}$ +124 (c 0.85, $CHCl_3$); IR (neat) 3440, 2940, 1600, 1455, 1030 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.40–7.27 (5H, m), 4.67 (1H, s), 4.65 and 4.47 (each 1H, 2d, J=11.2 Hz), 3.68 (1H, ddd, J=4.9, 10.5, 11.5 Hz), 3.56 (1H, dd, J=2.0, 10.5 Hz), 3.49 (3H, s), 3.41 (1H, ddd, J=2.0, 6.8, 9.4 Hz), 3.30 (1H, dd, J=6.8, 10.5 Hz), 3.29 (1H, ddd, J=4.4, 9.4, 11.2 Hz), 2.38 (1H, ddd, J=4.4, 4.9, 11.5 Hz), 1.95 (1H, br d, J=10.5 Hz), 1.68 (1H, ddd, J=11.2, 11.5, 11.5 Hz); ^{13}C NMR (75 MHz) δ 137.7, 128.5, 127.94, 127.88, 98.6, 75.5, 70.8, 70.1, 67.3, 55.3, 33.1, 7.6; LRMS (EI) m/z 378 (M$^+$, 0.8%), 346 (1.4), 219 (37.6), 201 (41.9) 175 (84.6), 117 (100); HRMS (EI) m/z calcd for $C_{14}H_{19}O_4I$, (M$^+$) 378.0328, found 378.0328. Anal. Calcd for $C_{14}H_{19}IO_4$: C, 44.46; H, 5.06. Found: C, 44.65; H, 5.05.

To a solution of the 6-iodide derivative (10.3 g, 27.2 mmol) in DMF (200 mL) were added imidazole (11.1 g, 163 mmol) and TBSCl (6.20 g, 41.1 mmol), and the reaction mixture was stirred at room temperature for 8.5 h. The reaction mixture was diluted with EtOAc, washed with H_2O, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 300 g, EtOAc/toluene=1:20) to give 2-*O*-silyl ether **11** (13.4 g, 100%) as a colorless syrup: R_f 0.81 (EtOAc/toluene=1:8); $[\alpha]_D^{25}$ +89.4 (c 0.93, $CHCl_3$); IR (neat) 2960, 2930, 2860, 1100, 1030, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.27 (5H, m), 4.66 (1H, d, J=11.3 Hz), 4.55 (1H, d, J=3.4 Hz), 4.47 (1H, d, J=11.3 Hz), 3.73 (1H, ddd, J=3.4, 4.1, 11.6 Hz), 3.55 (1H, dd, J=2.1, 10.2 Hz), 3.47 (3H, s), 3.43 (1H, ddd, J=2.1, 6.6, 9.1 Hz), 3.31 (1H, dd, J=6.6, 10.2 Hz), 3.29 (1H, ddd, J=4.6, 9.1, 11.6 Hz), 2.15 (1H, ddd, J=4.1, 4.6, 11.5 Hz), 1.88 (1H, ddd, J=11.5, 11.6, 11.6 Hz), 0.89 (9H, s), 0.08 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 128.5, 128.2, 127.9, 127.8, 127.7, 99.4, 75.9, 70.7, 69.6, 68.5, 55.3, 32.6, 25.8, 18.2, 8.1, −4.6; LRMS (EI) m/z 461 (M$^+$−OMe, 2.7%), 435 (34.3), 329 (22.8), 313 (33.6), 201 (96.9), 91 (100); HRMS (EI) m/z calcd for $C_{19}H_{30}IO_3Si$, (M$^+$−OMe) 461.1009, found 461.1007.

4.2.3. Methyl 4-*O*-benzyl-2-*O*-(*tert*-butyldimethylsilyl)-3,6-dideoxy-α-D-*erythro*-hex-5-enopyranoside (12). To a solution of **11** (13.4 g, 27.2 mmol) in THF (260 mL) was added *t*-BuOK (12.3 g, 81.6 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with EtOAc, washed successively with H_2O and brine, and then dried over Na_2CO_3. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 200 g, EtOAc/hexane=1:30 containing 1 vol % Et_3N) to give **12** (8.0 g, 81%) as a colorless

syrup: R_f 0.68 (EtOAc/hexane=1:5); $[\alpha]_D^{24}$ +42.0 (*c* 0.61, $CHCl_3$); IR (neat) 2960, 2930, 2855, 1660, 1260, 1100, 1030, 840 cm^{-1}; ^1H NMR (300 MHz) δ 7.42–7.24 (5H, m), 4.83 (1H, br s), 4.69 and 4.64 (each 1H, 2d, *J*=12.3 Hz), 4.60 and 4.59 (each 1H, 2br s), 3.94–3.82 (2H, m), 3.47 (3H, s), 2.15–2.05 (1H, m), 2.01 (1H, m), 0.89 (9H, s), 0.08 (6H, s); ^{13}C NMR (75 MHz) δ 154.9, 138.2, 128.4, 127.7, 127.4, 100.8, 95.1, 72.4, 71.2, 68.4, 55.4, 34.2, 25.8, 18.2, −4.6; HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{20}H_{32}O_4Si$, $(M+H)^+$ 365.2152, found 365.2148.

4.2.4. A mixture of (2*S*,4*R*,5*R*)-2-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-5-hydroxy-cyclohexen-1-one and its (5*S*)-isomer (13). To a solution of **12** (4.46 g, 12.2 mmol) in acetone (300 mL) and acetate buffer (0.1 mol/L solution, prepared from 0.2 mol/L aqueous sodium acetate and acetic acid, pH 4.8, 150 mL) was added $Hg(OCOCF_3)_2$ (1.56 g, 3.66 mmol), and the mixture was stirred at room temperature for 14 h. The reaction mixture was partially concentrated and then extracted with EtOAc. The organic layer was washed successively with 10% aqueous KI solution and 20% aqueous $Na_2S_2O_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 90 g, EtOAc/hexane=1:5) to give **13** as a diastereomeric mixture (5*S*:5*R*=ca. 1:10, 3.97 g, 93%) as a colorless syrup: R_f 0.51 (EtOAc/hexane=1:5); ^1H NMR (300 MHz, for the major isomer) δ 7.40–7.28 (5H, m), 4.87 and 4.49 (each 1H, 2d, *J*=11.6 Hz), 3.98 (1H, dd, *J*=6.1, 12.7 Hz), 3.75 (1H, ddd, *J*=4.1, 8.3, 10.6 Hz), 3.60 (1H, ddd, *J*=5.1, 8.3, 12.1 Hz), 2.76 (1H, dd, *J*=5.1, 13.8 Hz), 2.51 (1H, br s), 2.39 (1H, dd, *J*=12.1, 13.8 Hz), 2.35 (1H, ddd, *J*=4.1, 6.1, 12.1 Hz), 1.69 (1H, ddd, *J*=10.6, 12.1, 12.7 Hz), 0.90 (9H, s), 0.13 and 0.11 (each 3H, 2s); ^{13}C NMR (75 MHz, for the major isomer) δ 204.9, 137.5, 128.5, 128.0, 127.9, 78.6, 73.8, 73.4, 72.2, 43.8, 36.5, 25.7, 17.9, −4.3, −4.6; HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{19}H_{30}O_4Si$, $(M+H)^+$ 351.1992, found 351.2002.

4.2.5. (4*R*,6*S*)-6-Benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-cyclohexenone [(+)-6]. To a solution of **13** (3.97 g, 11.3 mmol) in CH_2Cl_2 (80 mL) were added MsCl (3.50 mL, 25.2 mmol) and Et_3N (12.6 mL, 90.4 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 2.5 h. The reaction mixture was diluted with EtOAc, and washed successively with 1 mol/L aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 70 g, EtOAc/hexane=1:6) to give (+)-**6** (3.50 g, 86% from **12**) as a white solid: R_f 0.57 (EtOAc/hexane=1:4); mp 46.5–47.5 °C; $[\alpha]_D^{23}$ +22.0 (*c* 0.94, $CHCl_3$); IR (KBr disk) 2955, 2930, 2860, 1700, 1255, 1100, 1070, 965, 940 cm^{-1}; ^1H NMR (300 MHz) δ 7.45–7.28 (5H, m), 6.77 (1H, ddd, *J*=1.9, 2.1, 10.2 Hz), 5.96 (1H, dd, *J*=2.4, 10.2 Hz), 4.99 and 4.66 (each 1H, 2d, *J*=11.7 Hz), 4.58 (1H, dddd, *J*=2.1, 2.4, 5.1, 10.0 Hz), 3.91 (1H, dd, *J*=4.9, 13.7 Hz), 2.51 (1H, dddd, *J*=1.9, 4.9, 5.1, 11.9 Hz), 2.09 (1H, ddd, *J*=10.0, 11.9, 13.7 Hz), 0.90 (9H, s), 0.12 and 0.11 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 198.2, 153.8, 137.8, 128.4, 127.9, 127.8, 127.3, 76.6, 72.4, 67.7, 40.8, 25.7, 18.0, −4.6, −4.8; HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{19}H_{28}O_3Si$, $(M+H)^+$ 333.1886, found 333.1883. Anal. Calcd for $C_{19}H_{28}O_3Si$: C, 68.63; H, 8.49. Found: C, 68.46; H, 8.52.

4.2.6. (2*R*)-2-(4-Methoxybenzyloxy)propanal [(*R*)-7a] and its enantiomer [(*S*)-7a]. To a solution of methyl (*R*)-lactate (1.14 g, 11.0 mmol) in CH_2Cl_2 (20 mL) were added (4-methoxybenzyl)trichloroacetimidate (6.17 g, 21.8 mmol) and CSA (0.50 g, 2.15 mmol) at room temperature, and the reaction mixture was stirred for 15 h. The reaction mixture was quenched with MeOH and the products were extracted with EtOAc. The organic layer was washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (EtOAc/hexane=1:20) to give methyl (*R*)-lactate *p*-methoxybenzyl ether (2.40 g) as a colorless syrup: ^1H NMR (300 MHz) δ 7.29 and 6.88 (each 2H, 2d, *J*=8.6 Hz), 4.62 and 4.39 (each 1H, 2d, *J*=11.4 Hz), 4.05 (1H, q, *J*=6.9 Hz), 3.80 and 3.75 (each 3H, 2s), 1.42 (3H, d, *J*=6.9 Hz); ^{13}C NMR (75 MHz) δ 173.7, 159.3, 129.58, 129.48, 113.7, 73.5, 71.6, 55.2, 51.8, 18.7.

To a solution of methyl (*R*)-lactate *p*-methoxybenzyl ether (2.40 g, 10.7 mmol) in CH_2Cl_2 (50 mL) was added 1.01 mol/L solution of DIBAL-H in toluene (13.7 mL, 13.9 mmol) at −78 °C, and the reaction mixture was stirred for 20 min at −78 °C. The reaction mixture was quenched with water, and the products were extracted with EtOAc. The organic layer was washed successively with 1 mol/L aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (EtOAc/hexane=1:15) to give (*R*)-**7a** (1.82 g, 86% for two steps) as a colorless liquid: $[\alpha]_D^{20}$ +26.0 (*c* 0.93, $CHCl_3$); IR (neat) 2940, 2840, 2480, 1730, 1615, 1515, 1250, 1035 cm^{-1}; ^1H NMR (300 MHz) δ 9.63 (1H, d, *J*=1.7 Hz), 7.29 and 6.89 (each 2H, 2d, *J*=8.6 Hz), 4.58 and 4.53 (each 1H, 2d, *J*=11.5 Hz), 3.87 (1H, qd, *J*=6.8, 1.7 Hz), 3.81 (3H, s), 1.31 (3H, d, *J*=6.8 Hz); ^{13}C NMR (75 MHz,) δ 203.5, 159.5, 129.6, 129.3, 113.9, 79.1, 71.7, 55.2, 15.3; HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{11}H_{14}O_3$, $(M+H)^+$ 195.1040, found 195.1021.

The similar treatment of methyl (*S*)-lactate (1.14 g, 11.0 mmol) as described for the preparation of (*R*)-**7a** afforded (2*S*)-2-(4-methoxybenzyloxy)propanal [(*S*)-**7a**] (1.26 g, 60% for two steps) as a colorless liquid: $[\alpha]_D^{20}$ −25.0 (*c* 0.95, $CHCl_3$).

4.2.7. (3*R*,4*R*,6*S*)-6-Benzyloxy-4-(*tert*-butyldimethylsilyloxy)-3-vinylcyclohexan-1-one (14). To a suspension of copper(I) cyanide (CuCN, 18.0 mg, 0.20 mmol) in ether (0.6 mL) at −78 °C was added dropwise vinyllithium (freshly prepared from tetravinyltin and PhLi, according to the procedure reported by Seyferth and Weiner,[16] 1.0 mol/L solution in ether, 0.45 mL, 0.45 mmol) under Ar. After being stirred at −78 °C for 3 min, the mixture was allowed to warm to 0 °C and further stirred at 0 °C for 1 min. The resulting clear solution was cooled to −78 °C, and to this solution was added slowly a solution of enone (+)-**6** (50.0 mg, 0.15 mmol) in ether (0.6 mL) via a cannula. After being stirred at −78 °C for 15 min, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the

products were extracted with EtOAc. The organic layer was washed successively with saturated aqueous $NaHCO_3$, brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 1 g, EtOAc/hexane=1:10) to give **14** (54.1 mg, 100%) as a colorless syrup: $[\alpha]_D^{23}$ −93.1 (*c* 1.00, $CHCl_3$); IR (KBr disk) 2960, 2930, 2860, 1730, 1260, 1100, 860, 840, 780, 700 cm^{-1}; ^1H NMR (300 MHz) δ 7.42–7.28 (5H, m), 5.77 (1H, ddd, *J*=6.9, 10.5, 17.4 Hz), 5.08 (1H, dd, *J*=0.9, 10.5 Hz), 5.20 (1H, dd, *J*=0.9, 17.4 Hz), 4.87 and 4.49 (each 1H, 2d, *J*=11.9 Hz), 3.98 (1H, dd, *J*=6.3, 12.9 Hz), 3.74 (1H, ddd, *J*=4.3, 9.6, 10.8 Hz), 2.50–2.36 (3H, m), 2.25 (1H, m), 1.85 (1H, ddd, *J*=10.8, 12.3, 12.9 Hz), 0.87 (9H, s), 0.06 and 0.05 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 207.5, 138.8, 137.8, 128.6, 116.1, 78.3, 72.1, 71.7, 50.0, 41.9, 41.6, 25.9, 18.2, −4.2, −4.4; HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{21}H_{33}O_3Si$, $(M+H)^+$ 361.2199, found 361.2197.

4.2.8. Three-component coupling reaction with (±)-7a. To a suspension of copper(I) cyanide (CuCN, 112 mg, 1.25 mmol) in ether (3.0 mL) at −78 °C was added dropwise vinyllithium (freshly prepared from tetravinyltin and PhLi, 1.0 mol/L solution in ether, 2.51 mL, 2.51 mmol) under Ar. After being stirred at −78 °C for 10 min, the mixture was allowed to warm to 0 °C and further stirred at 0 °C for 2 min. The resulting clear solution was cooled to −78 °C, and to this solution was added slowly a solution of enone (+)-**6** (209 mg, 0.627 mmol) in ether (1.0 mL) via a cannula. After being stirred at −78 °C for 30 min, a solution of aldehyde (±)-**7a** (740 mg, 3.76 mmol) in ether (1.0 mL) was added to the mixture dropwise via a cannula, and the mixture was stirred for 20 min at −78 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the products were extracted with EtOAc. The organic layer was washed successively with saturated aqueous $NaHCO_3$, brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 35 g, EtOAc/hexane=1:8) to give (2*S*,3*R*,4*R*,6*S*)-6-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-[(1′*R*,2′*R*)-1′-hydroxy-2′-(4-methoxybenzyloxy)propyl]-3-vinylcyclohexan-1-one (**15**) (228.9 mg, 68%) as a colorless syrup: R_f 0.59 (EtOAc/hexane=1:3); $[\alpha]_D^{23}$ −69.0 (*c* 0.56, $CHCl_3$); IR (neat) 3420, 2960, 2930, 2860, 2360, 1715, 1615 cm^{-1}; ^1H NMR (300 MHz) δ 7.36–7.26 (7H, m), 6.84 (2H, d, *J*=8.8 Hz), 5.40 (1H, ddd, *J*=11.7, 15.0, 17.2 Hz), 5.21 (1H, dd, *J*=1.6, 11.7 Hz), 5.20 (1H, dd, *J*=1.6, 17.2 Hz), 4.67 (1H, d, *J*=11.5 Hz), 4.57 (1H, d, *J*=11.2 Hz), 4.43 (1H, d, *J*=11.5 Hz), 4.31 (1H, d, *J*=11.2 Hz), 3.95 (1H, dd, *J*=6.3, 12.7 Hz), 3.90–3.75 (1H, m), 3.85–3.70 (2H, m), 3.81 (3H, s), 2.68 (1H, ddd, *J*=10.6, 12.4, 15.0 Hz), 2.44 (1H, ddd, *J*=4.6, 6.1, 10.8 Hz), 2.28 (1H, d, *J*=10.6 Hz), 1.85 (1H, ddd, *J*=10.8, 12.6, 12.7 Hz), 1.18 (3H, d, *J*=6.1 Hz), 0.84 (9H, s), 0.03 (6H, s); ^{13}C NMR (75 MHz) δ 210.9, 159.1, 137.5, 130.6, 129.4, 128.5, 127.8, 119.9, 113.7, 113.6, 78.2, 77.3, 73.9, 71.7, 71.1, 70.3, 55.1, 54.6, 48.3, 42.0, 25.7, 17.9, 16.1, −4.4; HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{32}H_{47}O_6Si$, $(M+H)^+$ 555.3142, found 555.3151. Anal. Calcd for $C_{32}H_{46}O_6Si$: C, 69.28; H, 8.36. Found: C, 69.36; H, 8.42.

4.2.9. Three-component coupling reaction with (*R*)-7a. The similar treatment of (+)-**6** (600 mg, 1.81 mmol) with copper(I) cyanide (CuCN, 259 mg, 2.89 mmol), vinyllithium (5.80 mmol), and aldehyde (*R*)-**7a** (1.09 g, 5.61 mmol) afforded **15** (855.1 mg, 85%).

4.2.10. Three-component coupling reaction with (*S*)-7a. The similar treatment of (+)-**6** (78.7 mg, 0.237 mmol) with copper(I) cyanide (CuCN, 42.4 mg, 0.474 mmol) and vinyllithium (1.0 mol/L solution in ether, 0.95 mL, 0.95 mmol) as described for the preparation of **15** afforded 1,4-addition intermediate. To an ethereal solution of the enolate (5 mL) at −78 °C was added a solution of aldehyde (*S*)-**7a** (184 mg, 0.948 mmol) in ether (1.0 mL) dropwise via a cannula. After being stirred at −78 °C for 1.5 h, the reaction mixture was quenched and processed similarly as described for the preparation of **15**. Purification by column chromatography (silica gel: 18 g, EtOAc/hexane=1:10) gave (2*R*,3*R*,4*R*,6*S*)-6-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-[(1′*S*,2′*S*)-1′-hydroxy-2′-(4-methoxybenzyloxy)propyl]-3-vinylcyclohexan-1-one (**16**) (91.9 mg, 72%) as a white solid: R_f 0.69 (EtOAc/hexane=1:2); mp 118–119 °C; $[\alpha]_D^{19}$ −15.0 (*c* 0.66, $CHCl_3$); IR (neat) 3420, 2930, 2860, 1700, 1255, 1140, 1090, 860, 840 cm^{-1}; ^1H NMR (300 MHz) δ 7.40–7.24 (5H, m), 7.21 and 6.84 (each 2H, 2d, *J*=8.8 Hz), 5.80 (1H, ddd, *J*=9.3, 10.0, 16.7 Hz), 5.13 (1H, dd, *J*=1.7, 10.0 Hz), 5.09 (1H, dd, *J*=1.7, 16.7 Hz), 4.62 and 4.56 (each 1H, 2d, *J*=11.3 Hz), 4.41 (1H, ddd, *J*=4.6, 9.3, 10.1 Hz), 4.29 (1H, dd, *J*=6.1, 12.3 Hz), 4.24 and 4.23 (each 1H, 2d, *J*=11.4 Hz), 3.72–3.68 (1H, m), 3.71 (3H, s), 3.19 (1H, qd, *J*=6.1, 7.6 Hz), 3.00 (1H, br s), 2.69 (1H, dd, *J*=3.2, 6.8 Hz), 2.57 (1H, ddd, *J*=6.8, 9.3, 9.3 Hz), 2.33 (1H, ddd, *J*=4.6, 6.1, 12.4 Hz), 1.74 (1H, ddd, *J*=10.1, 12.3, 12.4 Hz), 1.20 (3H, d, *J*=6.1 Hz), 0.83 (9H, s), 0.04 and 0.02 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 210.0, 159.4, 138.1, 136.9, 129.8, 129.6, 128.3, 127.9, 127.7, 118.6, 113.9, 80.3, 75.8, 72.1, 72.1, 70.3, 68.8, 55.2, 54.6, 53.9, 42.9, 25.8, 18.1, 15.1, −4.2, −4.4; HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{32}H_{47}O_6Si$, $(M+H)^+$ 555.3142, found 555.3139.

4.2.11. (1*S*,2*S*,3*S*,4*R*,5*R*)-1-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-3-[(1′*R*,2′*R*)-1′-hydroxy-2′-(4-methoxybenzyloxy)propyl]-4-vinylcyclohexan-2-ol (17). To a solution of **15** (164 mg, 0.296 mmol) in AcOH/THF (2:1, 3.3 mL) was added $Me_4NBH(OAc)_3$ (479 mg, 1.82 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was quenched with saturated aqueous Rochelle salt solution, and the products were extracted with EtOAc. The organic layer was washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 6 g, EtOAc/hexane=1:8) to give **17** (114 mg, 70%) as a white solid: R_f 0.59 (EtOAc/hexane=1:2); $[\alpha]_D^{21}$ −15.0 (*c* 0.91, $CHCl_3$); mp 81–84 °C; IR (neat) 3500, 2960, 2930, 2860, 2360, 1615 cm^{-1}; ^1H NMR (300 MHz) δ 7.36–7.32 (5H, m), 7.26 and 6.86 (each 2H, 2d, *J*=8.7 Hz), 5.28 (1H, ddd, *J*=9.9, 10.3, 16.6 Hz), 5.11 (1H, dd, *J*=2.2, 9.9 Hz), 5.08 (1H, dd, *J*=2.2, 16.6 Hz), 4.68 and 4.53 (each 1H, 2d, *J* =11.7 Hz), 4.58 and 4.35 (each 1H, 2d, *J*=11.0 Hz), 4.00 (1H, qd, *J*=6.1, 8.2 Hz), 3.82–3.76 (1H, m), 3.79 (3H, s), 3.63 (1H, dd, *J*=2.1, 8.2 Hz), 3.32 (1H, ddd, *J*=3.9, 9.8, 10.7 Hz), 3.24 (1H, ddd, *J*=3.9, 9.0, 12.9 Hz), 2.83 (1H, d, *J*=2.0 Hz), 2.73 (1H, d, *J*=2.1 Hz), 2.25 (1H,

ddd, J=9.8, 10.3, 10.7 Hz), 2.19 (1H, ddd, J=3.9, 3.9, 11.8 Hz), 1.39 (1H, ddd, J=10.7, 11.8, 12.9 Hz), 1.32 (1H, m), 1.13 (3H, d, J=6.1 Hz), 0.83 (9H, s), −0.04 (6H, s); ^{13}C NMR (75 MHz) δ 159.2, 139.0, 138.4, 130.6, 129.6, 128.4, 127.7, 119.2, 113.8, 80.0, 78.4, 74.6, 71.6, 71.1, 71.0, 70.7, 55.2, 51.9, 43.0, 37.5, 25.8, 18.0, 15.3, −4.3, −4.4; HRMS (FAB$^+$, NBA matrix) m/z calcd for $C_{32}H_{49}O_6Si$, $(M+H)^+$ 557.3298, found 557.3304. Anal. Calcd for $C_{32}H_{48}O_6Si$: C, 69.03; H, 8.69. Found: C, 69.20; H, 8.63.

4.2.12. (1*S*,2*S*,3*S*,4*R*,5*R*)-1-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-3-[(1′*R*,2′*R*)-2′-(4-methoxybenzyloxy)-1′-(*p*-toluenesulfonyloxy)propyl]-4-vinylcyclohexan-2-ol (18). To a solution of **17** (413 mg, 0.742 mmol) in THF (8.3 mL) were added 1.59 mol/L solution of BuLi in hexane (1.40 mL, 2.23 mmol) and TsCl (293 mg, 2.08 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 20 min. The mixture was diluted with EtOAc, and washed successively with saturated aqueous NH_4Cl solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 11 g, EtOAc/hexane=1:7) to give **18** (534 mg, 100%) as a colorless oil: R_f 0.59 (EtOAc/hexane=1:2); $[\alpha]_D^{22}$ +3.0 (c 1.05, $CHCl_3$); IR (neat) 3560, 2960, 2930, 2860, 1615 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.78 (2H, d, J=8.4 Hz), 7.39–7.27 (5H, m), 7.19 and 7.12 (each 2H, 2d, J=8.6 Hz), 6.79 (2H, d, J=8.4 Hz), 5.30–5.20 (3H, m), 4.86 (1H, d, J=7.5 Hz), 4.67 and 4.52 (each 1H, 2d, J=11.6 Hz), 4.30 and 4.16 (each 1H, 2d, J=11.8 Hz), 3.90 (1H, qd, J=6.1, 7.5 Hz), 3.78 (3H, s), 3.67 (1H, ddd, J=1.5, 8.5, 10.2 Hz), 3.29 (1H, ddd, J=4.4, 12.0, 12.2, Hz), 3.19 (1H, ddd, J=4.4, 8.5, 12.2 Hz), 2.95 (1H, d, J=1.5 Hz), 2.37 (3H, s), 2.12 (1H, m), 2.08–2.00 (1H, m), 1.46 (1H, dd, J=10.2, 11.9 Hz), 1.26 (1H, m), 1.06 (3H, d, J=6.1 Hz), 0.83 (9H, s), −0.03 and −0.05 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 159.0, 143.9, 138.3, 135.1, 130.5, 129.4, 128.5, 127.8, 120.6, 113.5, 86.1, 79.5, 75.6, 72.1, 71.3, 71.1, 70.9, 55.2, 51.1, 43.5, 37.4, 25.7, 21.6, 18.0, 16.7, −4.3, −4.4; HRMS (FAB$^+$, NBA matrix) m/z calcd for $C_{39}H_{54}NaO_8SSi$, $(M+Na)^+$ 733.3207, found 733.3207.

4.2.13. (1*S*,2*S*,3*S*,4*R*,5*R*)-1-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-3-[(1′*R*,2′*R*)-2′-(4-methoxybenzyloxy)-1′-(*p*-toluenesulfonyloxy)propyl]-2-methoxymethyloxy-4-vinylcyclohexane (19). To a solution of **18** (536 mg, 0.754 mmol) in $(CH_2Cl)_2$ (11 mL) were added i-Pr_2NEt (1.30 mL, 7.54 mmol) and MOMCl (0.570 mL, 7.54 mmol) at 0 °C, and the reaction mixture was stirred at 50 °C for 3.5 h. The reaction mixture was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 20 g, EtOAc/hexane=1:10) to give **19** (557 mg, 98%) as a colorless oil: R_f 0.67 (EtOAc/hexane=1:2); $[\alpha]_D^{23}$ +16.0 (c 1.0, $CHCl_3$); IR (neat) 2980, 2930, 2860, 1615 1515 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.76 (2H, d, J=8.0 Hz), 7.36–7.27 (5H, m), 7.16 (2H, d, J=8.0 Hz), 7.08 and 6.79 (each 2H, 2d, J=8.7 Hz), 5.30–5.26 (3H, m), 4.90 (1H, d, J=8.7 Hz), 4.87 and 4.75 (each 1H, 2d, J=5.3 Hz), 4.59 and 4.53 (each 1H, 2d, J=11.6 Hz), 4.25 and 4.13 (each 1H, 2d, J=11.6 Hz), 4.00 (1H, qd, J=6.3, 8.7 Hz), 3.77 (3H, s), 3.58 (1H, dd, J=10.4, 10.5 Hz), 3.37–3.28 (1H, m), 3.32 (3H, s), 3.22 (1H, ddd, J=3.9, 10.4, 11.6 Hz), 2.36 (3H, s), 2.20–2.10 (1H, m), 2.11 (1H, ddd, J=3.9, 3.9, 12.4 Hz), 1.62 (1H, dd, J=10.5, 10.5 Hz), 1.29 (1H, ddd, J=11.6, 11.6, 12.4 Hz), 1.05 (3H, d, J=6.3 Hz), 0.81 (9H, s), −0.04 and −0.05 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 158.2, 143.8, 138.3, 138.2, 135.1, 130.7, 129.2, 129.1, 128.3, 127.7, 127.6, 113.4, 98.9, 86.2, 80.0, 78.5, 75.2, 71.5, 70.8, 70.7, 57.0, 55.1, 51.3, 43.0, 38.3, 25.7, 21.5, 17.9, 16.8, −4.3, −4.5; HRMS (FAB$^+$, NBA matrix) m/z calcd for $C_{41}H_{58}O_9SSiK$, $(M+K)^+$ 793.3208, found 793.3197.

4.2.14. (1*S*,2*S*,3*S*,4*R*,5*R*)-1-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-3-[(1′*R*,2′*R*)-2′-hydroxy-1′-(*p*-toluenesulfonyloxy)propyl]-2-methoxymethyloxy-4-vinylcyclohexane (20). To a solution of **19** (674 mg, 0.89 mmol) in CH_2Cl_2/H_2O (10:1, 11 mL) was added DDQ (405 mg, 1.78 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc and washed successively with 10% aqueous $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 18 g, EtOAc/hexane=1:4) to give **20** (549 mg, 97%) as a colorless oil: R_f 0.34 (EtOAc/hexane=1:2); $[\alpha]_D^{22}$ −9.0 (c 1.1, $CHCl_3$); IR (neat) 3500, 2960, 2930, 2860, 2360 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.83 (2H, d, J=8.0 Hz), 7.36–7.27 (7H, m), 5.32–5.25 (3H, m), 4.89 and 4.78 (each 1H, 2d, J=5.1 Hz), 4.83 (1H, d, J=4.6 Hz), 4.59 and 4.54 (each 1H, 2d, J=11.6 Hz), 3.93 (1H, qd, J=4.6, 5.8 Hz), 3.64 (1H, br s), 3.51 (1H, dd, J=10.3, 10.9 Hz), 3.37 (1H, ddd, J=4.0, 11.9, 11.9 Hz), 3.32 (3H, s), 3.25 (1H, ddd, J=4.0, 10.9, 12.8 Hz), 2.44 (3H, s), 2.22 (1H, ddd, J=11.5, 11.9 Hz), 2.14 (1H, ddd, J=4.0, 4.1, 12.2 Hz), 1.72 (1H, dd, J=10.3, 11.5 Hz), 1.33 (1H, ddd, J=11.9, 12.2, 12.8 Hz), 1.04 (3H, d, J=4.6 Hz), 0.81 (9H, s), −0.04 and −0.05 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 144.9, 138.3, 138.1, 133.7, 129.7, 128.4, 127.8, 127.7, 120.6, 99.0, 85.9, 79.9, 78.0, 71.6, 70.5, 69.1, 57.3, 52.2, 44.2, 38.3, 25.7, 21.6, 19.7, 17.9, −4.4, −4.5; HRMS (FAB$^+$, NBA matrix) m/z calcd for $C_{33}H_{51}O_8SSi$, $(M+H)^+$ 635.3074, found 635.3084.

4.2.15. (1*S*,2*S*,3*S*,4*R*,5*R*)-1-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-2-methoxymethyloxy-3-[(1′*S*,2′*R*)-2′-methyloxiranyl]-4-vinylcyclohexane (21). To a solution of **20** (78.5 mg, 0.124 mmol) in toluene (1.6 mL) was added DBU (0.15 mL, 0.99 mmol) at 0 °C, and the reaction mixture was stirred at 50 °C for 20 h. The reaction mixture was diluted with EtOAc, and washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 1 g, EtOAc/hexane=1:6) to give **21** (49.7 mg, 94%) as a colorless syrup; $[\alpha]_D^{24}$ −14.0 (c 0.53, $CHCl_3$); IR (neat) 2960, 2920, 2860, 1260, 1080, 1020 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.36–7.27 (5H, m), 5.80 (1H, ddd, J=9.3, 10.5, 15.9 Hz), 5.26 (1H, dd, J=1.8, 10.5 Hz), 5.10 (1H, dd, J=1.8, 15.9 Hz), 4.97 and 4.69 (each 1H, 2d, J=6.3 Hz), 4.61 and 4.59 (each 1H, 2d, J=11.4 Hz), 3.48 (1H, dd, J=9.0, 9.9 Hz), 3.29–3.45 (2H, m), 3.36 (3H, s), 3.01 (1H, qd, J=4.2, 5.7 Hz), 2.78 (1H, dd, J=4.2, 9.3 Hz), 2.26 (1H, ddd, J=4.2, 4.2, 11.1 Hz), 2.14 (1H, ddd, J=9.3, 9.3, 9.3 Hz), 1.47 (1H, ddd, J=11.1,

11.1, 11.1 Hz), 1.28–1.40 (1H, m), 1.30 (3H, d, J=5.7 Hz), 0.84 (9H, s), −0.01 and −0.02 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 138.72, 138.40, 128.38, 127.65, 117.01, 98.24, 79.87, 79.58, 71.78, 70.24, 59.39, 56.48, 55.10, 52.62, 42.21, 39.35, 25.83, 18.09, 14.75, −4.37; HRMS (FAB$^+$, NBA matrix) m/z calcd for $C_{26}H_{43}O_5Si$, $(M+H)^+$ 463.2880, found 463.2875.

4.2.16. (1*S*,2*S*,3*R*,4*R*,5*R*)-2-Acetoxy-1-benzyloxy-5-(*tert*-butyldimethylsilyloxy)-3-[(1′*S*,2′*S*)-1′-acetoxy-2′-hydroxypropyl]-4-vinylcyclohexane (22). To a solution of **16** (32.8 mg, 0.0591 mmol) in MeOH (1.2 mL) was added $NaBH_4$ (22.4 mg, 0.592 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 35 min. The reaction mixture was diluted with EtOAc, and washed successively with 1 mol/L aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 1 g, EtOAc/hexane=1:5) to give an alcohol (21.7 mg, 66%) as a colorless syrup.

To a solution of the alcohol (21.7 mg, 0.0390 mmol) in pyridine (1 mL) were added Ac_2O (0.5 mL) and DMAP (1.0 mg) at 0 °C, and the reaction mixture was stirred at 50 °C for 4 h. The reaction mixture was diluted with EtOAc, and washed successively with 1 mol/L aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was dissolved in CH_2Cl_2/H_2O (10:1, 1.0 mL). To this solution was added DDQ (42.0 mg, 0.185 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc and washed successively with 20% aqueous $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 0.5 g, EtOAc/hexane=1:5) to give **22** (14.3 mg, 46% from **16**) as a colorless syrup: $[\alpha]_D^{26}$ +3.7 (c 0.57, $CHCl_3$); IR (neat) 3500, 2970, 2860, 1740, 1250 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.24–7.38 (5H, m), 6.10 (1H, ddd, J=10.2, 10.5, 16.5 Hz), 5.13–5.07 (2H, m), 5.08 (1H, dd, J=1.5, 9.0 Hz), 4.93 (1H, dd, J=1.5, 11.1 Hz), 4.66 and 4.59 (each 1H, 2d, J=12.6 Hz), 3.99 (1H, qd, J=1.5, 6.6 Hz), 3.81 (1H, ddd, J=3.0, 3.0, 4.2 Hz), 3.55 (1H, ddd, J=3.0, 3.0, 9.0 Hz), 2.98 (1H, ddd, J=3.3, 3.9, 11.1 Hz), 2.56 (1H, ddd, J=3.0, 3.9, 10.2 Hz), 2.06 and 2.01 (each 3H, 2s), 1.90 (1H, ddd, J=2.7, 2.7, 15.3 Hz), 1.72 (1H, ddd, J=3.0, 4.2, 15.3 Hz), 1.10 (3H, d, J=6.6 Hz), 0.87 (9H, s), 0.07 and 0.06 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 170.74, 170.40, 138.89, 137.87, 128.10, 127.38, 127.18, 118.24, 74.35, 73.74, 71.29, 70.75, 69.14, 65.15, 48.43, 32.17, 28.52, 25.72, 21.28, 20.80, 20.32, 17.99, −4.73, −4.99; HRMS (FAB$^+$, NBA matrix) m/z calcd for $C_{28}H_{44}O_7SiNa$, $(M+Na)^+$ 543.2754, found 543.2757.

4.2.17. (1*S*,2*S*,3*R*,4*R*,5*R*)-2-Acetoxy-1-benzyloxy-5-(*tert*-butyldimethylsilyloxy)-3-[(1′*S*,2′*R*)-2′-methyloxiranyl]-4-vinylcyclohexane (23). To a solution of **22** (16.8 mg, 0.0323 mmol) in pyridine (1 mL) at 0 °C were added MsCl (0.025 mL, 0.32 mmol) and DMAP (1.0 mg), and the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with EtOAc, and washed successively with 1 mol/L aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was roughly purified by column chromatography (silica gel: 1 g, EtOAc/hexane=1:5) to give mesylate (17.9 mg, 93%) as a colorless syrup.

To a solution of the mesylate (17.9 mg, 0.0300 mmol) in MeOH (1 mL) was added NaOMe (5.1 mg, 0.15 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was neutralized with acidic resin (Amberlite 120B, H^+ form) and filtered. Removal of the solvent gave a residue, which was dissolved in pyridine (1 mL). To this solution were added Ac_2O (0.5 mL) and DMAP (1.0 mg) at room temperature, and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with EtOAc, and washed successively with 1 mol/L aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 0.5 g, EtOAc/hexane=1:15) to give **23** (11.0 mg, 74% from **22**) as a colorless syrup: $[\alpha]_D^{24}$ −2.5 (c 0.22, $CHCl_3$); IR (neat) 2960, 2940, 2860, 1820 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.39–7.24 (5H, m), 5.69 (1H, ddd, J=9.8, 9.8, 16.8 Hz), 5.10 (1H, dd, J=1.5, 16.8 Hz), 5.07 (1H, dd, J=1.5, 9.8 Hz), 4.95 (1H, dd, J=4.4, 8.3 Hz), 4.72 and 4.64 (each 1H, 2d, J =11.9 Hz), 3.85 (1H, ddd, J=4.6, 8.3, 9.5 Hz), 3.74 (1H, ddd, J=4.1, 9.3, 9.3 Hz), 2.96 (1H, qd, J=3.9, 5.6 Hz), 2.86 (1H, dd, J=3.9, 5.6 Hz), 2.41–2.26 (2H, m), 2.20 (1H, ddd, J=4.1, 4.6, 13.1 Hz), 2.08 (3H, s), 1.62 (1H, ddd, J=9.3, 9.5, 13.1 Hz), 1.18 (3H, d, J=5.6 Hz), 0.83 (9H, s), 0.02 and 0.00 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 170.76, 138.67, 137.50, 128.30, 127.50, 127.45, 118.09, 76.31, 73.74, 72.23, 68.39, 53.86, 51.20, 50.93, 37.68, 36.70, 25.71, 21.28, 18.00, 13.76, −4.29, −4.61; HRMS (FAB$^+$, NBA matrix) m/z calcd for $C_{26}H_{40}O_5SiNa$, $(M+Na)^+$ 483.2543, found 483.2543.

4.2.18. (4*S*,5*S*,6*S*,1*R*,2*R*)-4-Benzyloxy-2-(*tert*-butyldimethylsilyloxy)-6-[(1′*R*,2′*R*)-2′-hydroxy-1′-(*p*-toluenesulfonyloxy)propyl]-5-methoxymethyloxy-cyclohexancarboxylic acid (25). Ozone was introduced to a solution of **19** (7.9 mg, 0.010 mmol) in MeOH (1 mL) at −78 °C for 5 min. To the reaction mixture was added Me_2S (0.070 mL, 0.95 mmol) at −78 °C. After being stirred at room temperature for 12 h, the reaction mixture was diluted with Et_2O. The organic layer was washed with brine, and then dried. Removal of the solvent gave a crude aldehyde, which was used for the next reaction without purification.

To a solution of the crude aldehyde in t-BuOH/H_2O (1:1, 0.2 mL) were added $NaH_2PO_4\cdot H_2O$ (16 mg, 0.10 mmol), $HOSO_2NH_2$ (9.7 mg, 0.10 mmol), and $NaClO_2$ (9.1 mg, 0.10 mmol) at room temperature, and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with EtOAc, and washed successively with 1 mol/L aqueous HCl solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 1 g, EtOAc/hexane=1:1) to give carboxylic acid **24** (6.1 mg, 75% for two steps) as a colorless syrup.

To a solution of carboxylic acid **24** (6.1 mg, 0.0081 mmol) in CH_2Cl_2/H_2O (10:1, 0.5 mL) was added DDQ (3.7 mg,

0.016 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 20 min. The reaction mixture was diluted with EtOAc and washed successively with 10% aqueous $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 0.5 g, EtOAc/hexane=1:2) to give **25** (3.9 mg, 76% from **19**) as a colorless syrup: R_f 0.34 (EtOAc/hexane=1:1); IR (neat) 3480, 2955, 2930, 1730, 1715, 1255, 1180, 1100, 850 cm^{-1}; ^1H NMR (300 MHz) δ 7.86 (2H, d, J=8.3 Hz), 7.39–7.25 (7H, m), 4.91 and 4.76 (each 1H, 2d, J=6.1 Hz), 4.72 (1H, br), 4.56 (2H, s), 4.17 (1H, qd, J=6.4, 3.4 Hz), 3.71 (1H, ddd, J=4.0, 10.0, 11.7 Hz), 3.47–3.27 (2H, m), 3.36 (3H, s), 2.85 (1H, dd, J=10.0, 10.5 Hz), 2.42 (3H, s), 2.23 (1H, ddd, J=2.2, 10.5, 10.5, Hz), 2.11 (1H, ddd, J=4.0, 4.0, 12.7 Hz), 1.34 (1H, ddd, J=11.7, 11.7, 12.7 Hz), 1.26 (1H, s), 1.06 (3H, d, J=6.4 Hz), 0.82 (9H, s), −0.02 (6H, s); HRMS (FAB^+, NBA matrix) m/z calcd for $C_{32}H_{48}O_{10}SSiNa$, $(M+Na)^+$ 675.2636, found 675.2627.

4.2.19. (3*R*,4*R*,4a*S*,5*S*,6*S*,8*R*,8a*R*)-6-Benzyloxy-8-(*tert*-butyldimethylsilyloxy)-5-methoxymethyloxy-3-methyl-4-(*p*-toluenesulfonyloxy)-perhydroisochroman-1-one (26). *By Mitsunobu reaction*: To a solution of **25** (3.2 mg, 0.0049 mmol) in benzene (1 mL) were added Ph_3P (3.2 mg, 0.012 mmol) and DEAD (0.0022 mL, 0.012 mmol) at 0 °C, and the reaction mixture was stirred at 80 °C for 30 h. The reaction mixture was diluted with Et_2O and washed successively with brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 0.5 g, EtOAc/hexane=1:4) to give **26** (2.6 mg, 84%) as a colorless oil: R_f 0.16 (EtOAc/hexane=1:5); $[\alpha]_D^{23}$ +22.6 (c 0.69, $CHCl_3$); IR (neat) 2960, 2930, 2860, 1760, 1360, 1180, 1015, 940, 850 cm^{-1}; ^1H NMR (300 MHz) δ 7.81 (2H, d, J=8.4 Hz), 7.40–7.22 (7H, m), 5.29 (1H, s), 5.12 and 4.71 (each 1H, 2d, J=6.3 Hz), 4.59 and 4.54 (each 1H, 2d, J=11.4 Hz), 4.53 (1H, q, J=6.3 Hz), 3.84 (1H, ddd, J=4.7, 9.3, 9.3 Hz), 3.54 (3H, s), 3.48 (1H, dd, J=8.4, 11.4 Hz), 3.31 (1H, ddd, J=4.2, 8.4, 11.4 Hz), 2.44 (3H, s), 2.32–2.18 (2H, m), 1.78 (1H, dd, J=11.4, 12.9 Hz), 1.44 (3H, d, J=6.3 Hz), 1.50–1.33 (1H, m), 0.82 (9H, s), 0.09 and 0.08 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 169.7, 144.6, 138.1, 134.8, 129.5, 128.5, 127.8, 127.7, 127.6, 98.3, 80.0, 79.3, 78.9, 73.9, 72.0, 66.1, 57.1, 47.3, 44.6, 39.2, 29.7, 25.8, 21.7, 18.0, 16.4, −4.7, −4.8; HRMS (FAB^+, NBA matrix) m/z calcd for $C_{32}H_{46}O_9SSiNa$, $(M+Na)^+$ 657.2529, found 657.2521.

By DCC-mediated lactonization: To a solution of **25** (1.9 mg, 0.0029 mmol) in $(CH_2Cl)_2$ (0.3 mL) were added DCC (2.0 mg, 0.0096 mmol) and DMAP (1 mg) at 0 °C, and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with EtOAc, and successively washed with 1 mol/L aqueous HCl solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 0.5 g, EtOAc/hexane=1:4) to give **26** (1.1 mg, 60%).

4.2.20. (1*S*,2*S*,3*S*,4*R*,5*R*)-1-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-2-methoxymethyloxy-3-[(*R*)-1′-(*p*-toluenesulfonyloxy)-2′-oxopropyl]-4-vinylcyclohexane (27). To a solution of **20** (131 mg, 0.206 mmol) in CH_2Cl_2 (2.6 mL) was added Dess–Martin periodinane (874 mg, 2.06 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 23 h. The reaction mixture was diluted with EtOAc and washed successively with 10% aqueous $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 2 g, EtOAc/hexane=1:9) to give **27** (130 mg, 100%) as a colorless oil: R_f 0.65 (EtOAc/hexane=1:2); $[\alpha]_D^{19}$ −6.0 (c 0.56, $CHCl_3$); IR (neat) 2960, 2930, 2860, 1720, 1600 cm^{-1}; ^1H NMR (300 MHz) δ 7.85 (2H, d, J=8.0 Hz), 7.36–7.30 (7H, m), 5.41 (1H, ddd, J=8.8, 10.3, 17.1 Hz), 5.26 (1H, dd, J=2.0, 10.3 Hz), 5.15 (1H, dd, J=2.0, 17.1 Hz), 4.69 and 4.57 (each 1H, 2d, J=5.1 Hz), 4.56 and 4.20 (each 1H, 2d, J=11.5 Hz), 3.47 (1H, dd, J=9.0, 10.8 Hz), 3.36 (1H, ddd, J=4.1, 9.0, 11.6 Hz), 3.30 (1H, ddd, J=4.4, 8.8, 11.6 Hz), 3.23 and 2.45 (each 3H, 2s), 2.23 (1H, dd, J=10.8, 11.2 Hz), 2.18 (3H, s), 2.15 (1H, ddd, J=4.1, 4.4, 12.4 Hz), 2.01 (1H, ddd, J=8.8, 8.8, 11.2 Hz), 1.32 (1H, ddd, J=8.8, 11.6, 12.4 Hz), 0.82 (9H, s), −0.04 and −0.05 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 204.4, 145.0, 138.1, 137.7, 133.9, 129.7, 128.4, 127.9, 127.8, 127.7, 120.8, 98.1, 82.8, 79.4, 76.9, 71.5, 71.0, 56.8, 50.3, 45.8, 38.5, 26.5, 25.7, 21.6, 17.9, −4.3, −4.5; HRMS (FAB^+, NBA matrix) m/z calcd for $C_{33}H_{48}O_8SSiNa$, $(M+Na)^+$ 655.2737, found 655.2740.

4.2.21. (3*S*,4*R*,4a*S*,5*S*,6*S*,8*R*,8a*R*)-6-Benzyloxy-8-(*tert*-butyldimethylsilyloxy)-5-methoxymethyloxy-3-methyl-4-(*p*-toluenesulfonyloxy)-perhydroisochroman-1-one (30). Ozone was introduced to a solution of **27** (300 mg, 0.473 mmol) in MeOH (30 mL) at −78 °C for 10 min. To the reaction mixture was added Me_2S (3.00 mL, 40.8 mmol) at −78 °C, and the reaction mixture was stirred at room temperature for 3 h. The products were extracted with Et_2O, and the organic layer was washed with brine, and then dried. Removal of the solvent gave a crude aldehyde (311 mg), which was used for the next reaction without purification.

To a solution of the crude aldehyde (311 mg) in t-BuOH/H_2O (1:1, 6 mL) were added $NaH_2PO_4 \cdot H_2O$ (382 mg, 2.45 mmol), $HOSO_2NH_2$ (238 mg, 2.45 mmol), and $NaClO_2$ (222 mg, 2.45 mmol) at room temperature, and the reaction mixture was stirred at room temperature for 10 h. The reaction mixture was diluted with EtOAc, and washed successively with 1 mol/L aqueous HCl solution and brine, and then dried. Removal of the solvent gave a residue, which was roughly purified by column chromatography (silica gel: 7 g, EtOAc/hexane=1:4, containing 1 vol % AcOH) to give carboxylic acid **28** (308 mg) as a colorless syrup. This was used for the next reaction without further purification.

To a solution of **28** (308 mg, 0.473 mmol) in MeOH (6.5 mL) was added $NaBH_4$ (35.8 mg, 0.946 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with EtOAc, and successively washed with 1 mol/L aqueous HCl solution and brine, and then dried. Removal of the solvent gave a residue, which was roughly purified by column chromatography (silica gel: 7 g, EtOAc/hexane=1:4, containing 1 vol % AcOH) to give a colorless syrup, which was dissolved in CH_2Cl_2 (6 mL).

To this solution were added DCC (231 mg, 1.12 mmol) and DMAP (9.1 mg, 0.074 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc, and washed successively with 1 mol/L aqueous HCl solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 6 g, EtOAc/hexane=1:5) to give lactone **30** (216 mg, 72% from **27**) as a colorless syrup: R_f 0.54 (EtOAc/toluene=1:6); $[\alpha]_D^{19}$ +3.0 (*c* 0.91, $CHCl_3$); IR (neat) 2960, 2930, 2860, 1760, 1600 cm^{-1}; ^1H NMR (300 MHz) δ 7.78 (2H, d, *J*=8.3 Hz), 7.36–7.28 (7H, m), 5.15 (1H, d, *J*=3.2 Hz), 4.99 (1H, d, *J*=6.4 Hz), 4.82 (1H, q, *J*=6.9 Hz), 4.62–4.52 (3H, m), 3.85 (1H, ddd, *J*=4.9, 9.5, 10.4 Hz), 3.53 (1H, dd, *J*=8.4, 10.5 Hz), 3.46 (3H, s), 3.35 (1H, ddd, *J*=4.7, 8.4, 10.7 Hz), 2.44 (3H, s), 2.39 (1H, dd, *J*=9.5, 13.7 Hz), 2.26 (1H, ddd, *J*=4.7, 4.9, 13.4 Hz), 1.90 (1H, ddd, *J*=3.2, 10.5, 13.7 Hz), 1.53 (3H, d, *J*=6.9 Hz), 1.44 (1H, ddd, *J*=10.4, 10.7, 13.4 Hz), 0.84 (9H, s), 0.11 and 0.09 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 169.1, 144.8, 138.0, 134.4, 129.7, 128.4, 127.7, 127.6, 127.5, 97.8, 80.0, 79.5, 79.2, 77.7, 71.9, 66.5, 56.6, 45.6, 43.2, 38.9, 25.9, 21.6, 18.7, 18.0, −4.7, −5.0; HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{32}H_{46}NaO_9SSi$, $(M+Na)^+$ 657.2529, found 657.2522. Anal. Calcd for $C_{32}H_{46}O_9SSi$: C, 60.54; H, 7.30. Found: C, 60.61; H, 7.39.

4.2.22. (3*S*,4*S*,5*S*,6*S*,8*R*,9*R*,10*S*)-4-Azido-6-benzyloxy-8-(*tert*-butyldimethylsilyloxy)-5-methoxymethyloxy-3-methyl-perhydroisochroman-1-one (4). To a solution of lactone **30** (25.0 mg, 0.0394 mmol) in DMF (1 mL) was added NaN_3 (25.0 mg, 0.385 mmol) at room temperature, and the reaction mixture was stirred at 110 °C for 4 h. The reaction mixture was diluted with EtOAc and washed with brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 0.5 g, EtOAc/toluene=1:7) to give **4** (17.2 mg, 86%) as a colorless oil: R_f 0.33 (EtOAc/toluene=1:6); $[\alpha]_D^{21}$ −96.0 (*c* 0.70, $CHCl_3$); IR (neat) 2960, 2930, 2860, 2110, 1745 cm^{-1}; ^1H NMR (300 MHz) δ 7.40–7.19 (5H, m), 4.97 and 4.76 (each 1H, 2d, *J*=5.9 Hz), 4.63 and 4.56 (each 1H, 2d, *J*=11.7 Hz), 4.47 (1H, qd, *J*=2.4, 6.6 Hz), 4.11 (1H, dd, *J*=1.9, 2.4 Hz), 3.80 (1H, ddd, *J*=4.6, 9.6, 11.2 Hz), 3.59 (1H, dd, *J*=8.9, 10.2 Hz), 3.41 (3H, s), 3.30 (1H, ddd, *J*=3.9, 8.9, 12.9 Hz), 2.50 (1H, dd, *J*=9.6, 13.5 Hz), 2.25 (1H, ddd, *J*=3.9, 4.6, 12.5 Hz), 1.79 (1H, ddd, *J*=1.9, 10.2, 13.5 Hz), 1.50 (3H, d, *J*=6.6 Hz), 1.40 (1H, ddd, *J*=11.2, 12.5, 12.5 Hz), 0.85 (9H, s), 0.12 and 0.06 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 168.8, 138.2, 128.4, 127.8, 127.5, 98.7, 79.3, 78.8, 78.6, 71.8, 67.0, 59.4, 56.0, 43.8, 42.7, 39.0, 25.9, 18.2, 18.1, −4.6, −4.8; HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{25}H_{39}N_3O_6SiCs$, $(M+Cs)^+$ 638.1659, found 638.1633.

4.2.23. (3*S*,4*S*,5*S*,6*S*,10*S*)-4-Azido-6-benzyloxy-5,8-dihydroxy-3-methyl-5,6,7,4a-tetrahydroisochroman-1-one (32). To a solution of azide **4** (41.3 mg, 0.0817 mmol) in CH_3CN (3 mL) in a polyethylene vial was added HF/pyridine (ca. 0.1 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 10 min. The reaction mixture was diluted with EtOAc and neutralized with saturated aqueous $NaHCO_3$ solution. The organic layer was washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave crude alcohol **31** (33.4 mg) as a white solid. A solution of $(COCl)_2$ (2.0 mol/L solution in CH_2Cl_2, 1.28 mL, 2.56 mmol) and DMSO (0.400 mL, 5.17 mmol) in CH_2Cl_2 (1 mL) was stirred at −78 °C for 10 min under Ar. To this mixture was added a solution of the crude alcohol **31** (33.4 mg) in CH_2Cl_2 (1 mL) at −78 °C. After stirring at −78 °C for 2 h, to the reaction mixture was added *i*-Pr_2NEt (1.32 mL, 7.66 mmol) at −78 °C. The resulting mixture was further stirred at room temperature for 2 h and then diluted with Et_2O. The mixture was washed with brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 1 g, EtOAc/hexane=1:4) to give **32** (25.2 mg, 89% from **4**) as a colorless syrup: R_f 0.47 (EtOAc/hexane=1:1); $[\alpha]_D^{23}$ −16.0 (*c* 0.92, $CHCl_3$); IR (neat) 3460, 3030, 2900, 2120, 1650 cm^{-1}; ^1H NMR (300 MHz) δ 13.04 (1H, s), 7.44–7.30 (5H, m), 4.73 and 4.54 (each 1H, 2d, *J*=11.4 Hz), 4.49 (1H, qd, *J*=1.5, 6.6 Hz), 4.04 (1H, dd, *J*=1.5, 2.9 Hz), 3.74 (1H, dd, *J*=9.3, 9.5 Hz), 3.62 (1H, ddd, *J*=6.4, 9.5, 9.5 Hz), 2.93 (1H, ddd, *J*=1.1, 6.4, 18.3 Hz), 2.88 (1H, s), 2.72 (1H, dddd, *J*=1.1, 2.5, 2.9, 9.3 Hz), 2.45 (1H, ddd, *J*=2.5, 9.5, 18.3 Hz), 1.52 (3H, d, *J*=6.6 Hz); ^{13}C NMR (75 MHz) δ 172.6, 169.7, 137.2, 128.7, 128.3, 128.0, 90.0, 77.3, 76.3, 71.7, 70.1, 58.3, 42.2, 34.6, 18.4; LRMS (EI) *m/z* 345 (M^+, 1.3%), 239 (9.0), 191 (5.6), 91 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{19}N_3O_5$, (M^+) 345.1325, found 345.1326.

4.2.24. *N*-Benzyloxycarbonyl-(−)-actinobolin (33). To a solution of **32** (6.5 mg, 0.019 mmol) in MeOH (1 mL) were added 10% Pd/C (2.0 mg) and 4 mol/L HCl in dioxane (0.0095 mL, 0.038 mmol). The reaction mixture was stirred under an atmospheric pressure of H_2 at room temperature for 18 h. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated to give a residue, which was dissolved in DMF (0.5 mL). To this solution were added DCC (19.4 mg, 0.0940 mmol), *N*-benzyloxycarbonyl-D-alanine (12.6 mg, 0.0564 mmol), and Et_3N (0.100 mL, 0.717 mmol). The mixture was stirred at room temperature for 14 h, and then concentrated to give a residue, which was purified by preparative TLC (acetone/toluene=1:2) to give **33** (4.7 mg, 57% from **32**) as a colorless oil: R_f 0.34 (acetone/toluene=1:1); $[\alpha]_D^{24}$ +34.0 (*c* 0.17, $CHCl_3$); IR (neat) 3330, 2980, 2930, 1650, 1540, 1230, 1050 cm^{-1}; ^1H NMR (300 MHz) δ 13.05 (1H, s), 7.40–7.30 (5H, m), 6.78 (1H, br d, *J*=8.9 Hz), 5.19 (1H, br d, *J*=6.9 Hz), 5.11 and 5.04 (each 1H, 2d, *J*=11.7 Hz), 4.70–4.60 (1H, br s), 4.61 (1H, qd, *J*=1.5, 6.6 Hz), 4.33 (1H, ddd, *J*=1.5, 1.8, 8.9 Hz), 4.27 (1H, qd, *J*=6.9, 7.2 Hz), 3.89 (1H, ddd, *J*=6.9, 9.6, 9.9 Hz), 3.14 (1H, dd, *J*=9.6, 9.6 Hz), 3.05 (1H, br s), 2.93 (1H, dd, *J*=6.9, 18.9 Hz), 2.65 (1H, dd, *J*=1.8, 9.6 Hz), 2.47 (1H, dd, *J*=9.9, 18.9 Hz), 1.41 (3H, d, *J*=7.2 Hz), 1.34 (3H, d, *J*=6.6 Hz); ^{13}C NMR (75 MHz) δ 175.9, 175.6, 170.4, 156.0, 135.6, 128.6, 128.4, 128.3, 89.8, 76.8, 71.6, 68.0, 67.5, 50.9, 46.3, 43.4, 36.4, 17.9, 17.6; LRMS (EI) *m/z* 434 (M^+, 9.1%), 416 (6.8), 325 (3.8), 223 (100); HRMS (EI) *m/z* calcd for $C_{21}H_{26}N_2O_8$, (M^+) 434.1689, found 434.1696.

4.2.25. (−)-Actinobolin hydrochloride (3·HCl). To a solution of **33** (3.4 mg, 0.0078 mmol) in MeOH (0.6 mL) and AcOH (0.5 mL) were added 10% Pd/C (3 mg) and 1 mol/L aqueous HCl solution (0.023 mL, 0.023 mmol). The reaction mixture was stirred under an atmospheric pressure of

H_2 at room temperature for 30 min. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated. The residue was purified by column chromatography (Sephadex LH-20, MeOH as an eluent) to give **3**·HCl (2.0 mg, 76%) as an amorphous solid: $[\alpha]_D^{24}$ −51.2 (*c* 0.24, H_2O), {lit.[6c,d] for (+)-actinobolin hydrochloride: $[\alpha]_D^{21}$ +53 (*c* 0.65, H_2O)}; ^{1}H NMR (300 MHz, MeOH-d_4) δ 4.70 (1H, qd, *J*=1.8, 6.6 Hz), 4.56 (1H, dd, *J*=1.8, 3.5 Hz), 4.01 (1H, q, *J*=6.9 Hz), 3.78 (1H, ddd, *J*=6.6, 9.6, 9.8 Hz), 3.13 (1H, dd, *J*=9.6, 9.6 Hz), 2.82–2.74 (1H, m), 2.81 (1H, dd, *J*=6.6, 18.9 Hz), 2.35 (1H, ddd, *J*=2.7, 9.6, 18.9 Hz), 1.50 (3H, d, *J*=6.9 Hz), 1.33 (3H, d, *J*=6.6 Hz); ^{13}C NMR (75 MHz, MeOH-d_4) δ 175.1, 172.7, 172.1, 91.8, 79.3, 72.8, 70.1, 50.2, 47.0, 43.3, 38.0, 18.5, 18.1; HRMS (FAB$^+$, NBA matrix) *m*/*z* calcd for $C_{13}H_{21}N_2O_6$, (M+H)$^+$ 301.1400, found 301.1400. The ^{1}H and ^{13}C NMR spectra of the synthetic compound were fully identical with those of natural (+)-actinobolin hydrochloride.

4.3. An improved route to (−)-actinobolin

4.3.1. (2*S*)-2-(Triethylsilyloxy)propanal [(*S*)-7b]. To a solution of methyl (*S*)-lactate (335 mg, 3.22 mmol) in CH_2Cl_2 (7 mL) were added TESCl (0.620 mL, 3.69 mmol) and imidazole (285 mg, 4.19 mmol) at 0 °C, and the mixture was stirred at room temperature for 10 min. The reaction mixture was diluted with EtOAc, and washed successively with 1 mol/L aqueous HCl solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (EtOAc/hexane=1:20) to give methyl (*S*)-lactate triethylsilyl ether (702 mg, 100%) as a colorless syrup: R_f 0.77 (EtOAc/hexane=1:3); $[\alpha]_D^{22}$ −26.9 (*c* 1.06, $CHCl_3$); IR (neat) 2955, 2880, 1760, 1740, 1145, 1005, 745 cm^{-1}; ^{1}H NMR (300 MHz) δ 4.34 (1H, q, *J*=6.6 Hz), 3.73 (3H, s), 1.41 (3H, d, *J*=6.6 Hz), 0.96 (9H, t, *J*=7.8 Hz), 0.62 (6H, q, *J*=7.8 Hz); ^{13}C NMR (75 MHz) δ 174.5, 68.0, 51.8, 21.5, 6.6, 4.5.

To a solution of methyl (*S*)-lactate triethylsilyl ether (702 mg, 3.21 mmol) in toluene (10 mL) was added 1.01 mol/L solution of DIBAL-H in toluene (3.76 mL, 3.80 mmol) at −78 °C, and the mixture was stirred at −78 °C for 2 h. The reaction mixture was quenched with water, and the products were extracted with EtOAc. The organic layer was washed successively with 1 mol/L aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (EtOAc/hexane=1:50) to give (*S*)-**7b** (426 mg, 70%) as a colorless syrup: R_f 0.77 (EtOAc/hexane=1:3); $[\alpha]_D^{23}$ −6.5 (*c* 1.1, $CHCl_3$); IR (neat) 2960, 2880, 1740, 1140, 1010 cm^{-1}; ^{1}H NMR (300 MHz) δ 9.62 (1H, s), 4.08 (1H, q, *J*=6.8 Hz), 1.29 (3H, d, *J*=6.8 Hz), 0.97 (9H, t, *J*=7.8 Hz), 0.64 (6H, q, *J*=7.8 Hz); ^{13}C NMR (75 MHz,) δ 204.2, 73.5, 18.6, 6.6, 4.7; HRMS (FAB$^+$, NBA matrix) *m*/*z* calcd for $C_{11}H_{14}O_3$, (M+H)$^+$ 189.1325, found 189.1311.

4.3.2. Three-component coupling reaction with (*S*)-7b. To a suspension of copper(I) cyanide (CuCN, 43.3 mg, 0.483 mmol) in ether (1.0 mL) at −78 °C was added dropwise vinyllithium (1.0 mol/L solution in ether, 0.75 mL, 0.75 mmol) under Ar. After being stirred at −78 °C for 10 min, the mixture was allowed to warm to 0 °C and further stirred at 0 °C for 1 min. The resulting clear solution was cooled to −78 °C, and to this solution was added slowly a solution of enone (+)-**6** (100 mg, 0.302 mmol) in ether (1.0 mL) via a cannula. After being stirred at −78 °C for 30 min, a solution of aldehyde (*S*)-**7b** (265 mg, 1.40 mmol) in ether (1.5 mL) was added to the mixture dropwise via a cannula, and the mixture was stirred for 2 h at −78 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the products were extracted with EtOAc. The organic layer was washed successively with saturated aqueous $NaHCO_3$, brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 7 g, EtOAc/hexane=1:40) to give (2*R*,3*R*,4*R*,6*S*)-6-benzyloxy-4-(*tert*-butyldimethylsilyloxy)-2-[(1′*S*,2′*S*)-1′-hydroxy-2′-(triethylsilyloxy)propyl]-3-vinylcyclohexan-1-one (**34**) (84.8 mg, 51%) and its (1′*R*)-isomer (**35**) (66.7 mg, 40%) as a colorless syrup. Data for **34**: R_f 0.62 (EtOAc/hexane=1:6); mp 82.5–83.0 °C; $[\alpha]_D^{23}$ −35.5 (*c* 1.02, $CHCl_3$); IR (KBr disk) 3500, 2960, 2880, 1710, 1260, 1090, 1020 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.44–7.25 (5H, m), 5.83 (1H, ddd, *J*=9.0, 9.0, 16.8 Hz), 5.15 (1H, dd, *J*=1.4, 9.0 Hz), 5.11 (1H, dd, *J*=1.4, 16.8 Hz), 4.82 (1H, d, *J*=11.4 Hz), 4.49–4.36 (2H, m), 4.40 (1H, d, *J*=11.4 Hz), 3.60 (1H, dd, *J*=1.5, 6.4 Hz), 3.52 (1H, qd, *J*=5.9, 6.4 Hz), 3.00 (1H, s), 2.68 (1H, dd, *J*=1.5, 9.0 Hz), 2.58 (1H, ddd, *J*=9.0, 9.0, 9.2 Hz), 2.39 (1H, ddd, *J*=4.6, 6.4, 12.4 Hz), 1.76 (1H, ddd, *J*=10.5, 10.5, 12.4 Hz), 1.16 (3H, d, *J*=5.9 Hz), 0.95 (9H, t, *J*=7.8 Hz), 0.85 (9H, s), 0.60 (6H, q, *J*=7.8 Hz), 0.06 and 0.05 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 210.0, 138.1, 137.0, 128.3, 127.8, 127.7, 118.4, 80.5, 73.0, 72.2, 70.5, 68.7, 54.2, 53.8, 41.0, 25.8, 19.7, 18.0, 6.8, 5.0, −4.3, −4.4; HRMS (FAB$^+$, NBA matrix) *m*/*z* calcd for $C_{30}H_{53}O_5Si_2$, (M+H)$^+$ 549.3432, found 549.3435. Anal. Calcd for $C_{30}H_{52}O_5Si_2$: C, 65.64; H, 9.55. Found: C, 65.36; H, 9.36. Data for **35**: R_f 0.52 (EtOAc/hexane=1:6); $[\alpha]_D^{23}$ −64.3 (*c* 0.71, $CHCl_3$); IR (neat) 3540, 2960, 2930, 1715, 1090, 835, 775 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.42–7.25 (5H, m), 5.44 (1H, ddd, *J*=8.0, 10.7, 16.0 Hz), 5.22 (1H, dd, *J*=1.7, 8.0 Hz), 5.21 (1H, dd, *J*=1.7, 16.0 Hz), 4.81 and 4.39 (each 1H, 2d, *J*=11.4 Hz), 4.05–3.96 (2H, m), 3.82 (1H, ddd, *J*=4.4, 8.4, 11.2 Hz), 3.28 (1H, dd, *J*=8.8, 12.2 Hz), 3.10 (1H, d, *J*=12.2 Hz), 2.76–2.60 (2H, m), 2.47 (1H, ddd, *J*=4.4, 6.1, 12.7 Hz), 1.85 (1H, ddd, *J*=11.2, 12.7, 12.7 Hz), 1.27 (3H, d, *J*=6.1 Hz), 0.93 (9H, t, *J*=7.9 Hz), 0.85 (9H, s), 0.63–0.47 (6H, m), 0.06 and 0.03 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 212.5, 138.6, 137.6, 128.5, 127.9, 127.8, 119.7, 78.6, 75.7, 72.0, 70.6, 69.9, 54.2, 47.0, 42.3, 25.7, 21.6, 18.0, 7.0, 5.1, −4.3, −4.4; HRMS (FAB$^+$, NBA matrix) *m*/*z* calcd for $C_{30}H_{53}O_5Si_2$, (M+H)$^+$ 549.3432, found 549.3423. Anal. Calcd for $C_{30}H_{52}O_5Si_2$: C, 65.64; H, 9.55. Found: C, 65.42; H, 9.56.

4.3.3. Three-component coupling reaction with (*S*)-7b in the presence of HMPA. The similar treatment of (+)-**6** (96.8 mg, 0.291 mmol) with copper(I) cyanide (CuCN, 36.5 mg, 0.408 mmol) and vinyllithium (1.0 mol/L solution in ether, 0.65 mL, 0.65 mmol) as described for the preparation of **34** afforded 1,4-addition intermediate. To an ethereal solution of the enolate (4 mL) at −78 °C was added HMPA (0.345 mL, 1.98 mmol) and, after 5 min, a solution of

aldehyde (*S*)-**7b** (232 mg, 1.23 mmol) in ether (1.2 mL) was added to the mixture dropwise over 60 min via a cannula. After being stirred at −78 °C for 2 h, the reaction mixture was quenched and processed similarly as described for the preparation of **34**. Purification by column chromatography (silica gel: 3 g, EtOAc/hexane=1:40) gave **35** (75.2 mg, 47%) and bicyclic ketal (**36**) (42.2 mg, 20%) as a colorless syrup. Data for **36**: R_f 0.65 (EtOAc/hexane=1:6); $[\alpha]_D^{24}$ −49.1 (*c* 1.21, $CHCl_3$); IR (neat) 3440, 2955, 2880, 1100, 1075, 1000 cm^{-1}; ^1H NMR (300 MHz) δ 7.38–7.25 (5H, m), 5.34 (1H, ddd, *J*=9.6, 9.6, 17.4 Hz), 5.13–5.00 (3H, m), 4.95 and 4.65 (each 1H, 2d, *J*=11.6 Hz), 4.52 (1H, q, *J*=6.0 Hz), 4.03 (1H, d, *J*=10.2 Hz), 3.86 (1H, qd, *J*=3.9, 6.0 Hz), 3.39 (1H, dd, *J*=4.8, 11.7 Hz), 3.24 (1H, s), 3.22 (1H, ddd, *J*=4.8, 9.9, 11.4 Hz), 2.19 (1H, ddd, *J*=9.6, 9.9, 11.4 Hz), 2.02 (1H, ddd, *J*=4.8, 4.8, 12.6 Hz), 1.72 (1H, ddd, *J*=11.4, 11.7, 12.6 Hz), 1.39 (1H, dd, *J*=10.2, 11.4 Hz), 1.16 and 1.06 (each 3H, 2d, *J*=6.0 Hz), 0.94 and 0.89 (each 9H, 2t, *J*=7.8 Hz), 0.81 (9H, s), 0.60 and 0.53 (each 6H, 2q, *J*=7.8 Hz), −0.02 and −0.07 (each 3H, 2s); HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{39}H_{72}O_7Si_3Na$, $(M+Na)^+$ 759.4484, found 759.4493.

4.3.4. Conversion of 36 to 35. A solution of **36** (20.8 mg, 0.0282 mmol) in THF (1.5 mL) and AcOH (1.5 mL) was stirred at room temperature for 3 days. The reaction mixture was diluted with EtOAc, and washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 0.5 g, EtOAc/hexane=1:6) to give **35** (11.8 mg, 76%).

4.3.5. Conversion of 34 to 22. To a solution of **34** (52.1 mg, 0.0949 mmol) in MeOH (1 mL) was added $NaBH_4$ (16.0 mg, 0.423 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 10 min. The mixture was diluted with EtOAc, and washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried over Na_2SO_4. Removal of the solvent gave a residue, which was roughly purified by column chromatography (EtOAc/hexane=1:15) to give diol (34.5 mg, 66%). To a solution of the diol (34.5 mg, 0.0626 mmol) in pyridine (1 mL) were added Ac_2O (0.5 mL) and DMAP (1.0 mg) at 0 °C, and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with EtOAc, and washed successively with 1 mol/L aqueous HCl solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was dissolved in CH_2Cl_2/H_2O (10:1, 1.0 mL). To this solution was added DDQ (15.3 mg, 0.0673 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc and washed successively with 10% aqueous $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 1 g, EtOAc/hexane=1:7) to give **22** (22.7 mg, 46% from **34**).

4.3.6. (1*S*,2*S*,3*S*,4*R*,5*R*)-1-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-3-[(1′*R*,2′*S*)-1′-hydroxy-2′-(triethylsilyloxy)propyl]-4-vinylcyclohexan-2-ol (37). To a solution of **35** (22.0 mg, 0.0401 mmol) in AcOH/THF [1:5 (v/v), 1 mL] was added $LiBH_4$ (12.0 mg, 0.551 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 10 min. The mixture was diluted with EtOAc and washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried over Na_2CO_3. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 1 g, EtOAc/hexane=1:7) to give **37** (19.2 mg, 87%) as a colorless syrup: R_f 0.40 (EtOAc/toluene=1:6); $[\alpha]_D^{21}$ +6.5 (*c* 0.895, $CHCl_3$); IR (neat) 3420, 2955, 2930, 2880, 1255, 1090, 1070, 840 cm^{-1}; ^1H NMR (300 MHz) δ 7.44–7.20 (5H, m), 5.30 (1H, ddd, *J*=9.3, 10.2, 16.8 Hz), 5.14 (1H, dd, *J*=2.4, 10.2 Hz), 5.10 (1H, dd, *J*=2.4, 16.8 Hz), 4.78 and 4.68 (each 1H, 2d, *J* =12.3 Hz), 4.28 (1H, d, *J*=1.8 Hz), 4.03 (1H, qd, *J*=5.1, 6.3 Hz), 3.74–3.61 (2H, m), 3.40–3.26 (2H, m), 2.32 (1H, d, *J*=9.0 Hz), 2.18 (1H, ddd, *J*=4.2, 4.2, 12.0 Hz), 2.10 (1H, ddd, *J*=9.3, 9.6, 11.4 Hz), 1.56 (1H, dd, *J*=9.6, 9.9 Hz), 1.46 (1H, ddd, *J*=11.4, 11.4, 12.0 Hz), 1.15 (3H, d, *J*=6.3 Hz), 0.97 (9H, t, *J*=7.8 Hz), 0.83 (9H, s), 0.63 (6H, q, *J*=7.8 Hz), −0.01 and −0.04 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 139.4, 139.0, 128.3, 127.7, 127.5, 119.1, 79.3, 75.2, 72.5, 72.0, 71.5, 71.1, 53.2, 42.9, 38.8, 25.8, 19.3, 18.0, 6.7, 4.8, −4.3, −4.4; HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{30}H_{55}O_5Si_2$, $(M+H)^+$ 551.3588, found 551.3590. Anal. Calcd for $C_{30}H_{54}O_5Si_2$: C, 65.40; H, 9.88. Found: C, 65.48; H, 10.02.

4.3.7. (1*S*,2*S*,3*S*,4*R*,5*R*)-1-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-3-[(1′*R*,2′*S*)-1′-(*p*-toluenesulfonyloxy)-2′-(triethylsilyloxy)propyl]-4-vinylcyclohexan-2-ol (38). To a solution of **37** (39.0 mg, 0.0708 mmol) in THF (2 mL) were added 1.59 mol/L solution of BuLi in hexane (0.140 mL, 0.223 mmol) and TsCl (81 mg, 0.42 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 10 min. The mixture was diluted with EtOAc, and washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 10 g, EtOAc/hexane=1:10) to give **38** (50.0 mg, 100%) as a white solid: R_f 0.71 (EtOAc/toluene=1:6); $[\alpha]_D^{26}$ +7.7 (*c* 0.79, $CHCl_3$); IR (KBr disk) 3410, 2960, 1360, 1175, 1090, 1070, 925 cm^{-1}; ^1H NMR (300 MHz) δ 7.81 (2H, d, *J*=8.4 Hz), 7.39–7.27 (7H, m), 5.32–5.15 (2H, m), 5.06 (1H, dd, *J*=3.6, 15.6 Hz), 4.74 (1H, d, *J*=12.0 Hz), 4.68 (1H, d, *J*=5.7 Hz), 4.66 (1H, d, *J*=12.0 Hz), 4.30 (1H, qd, *J*=5.7, 6.3 Hz), 4.15 (1H, s), 3.62 (1H, dd, *J*=8.7, 8.7 Hz), 3.29–3.16 (2H, m), 2.43 (3H, s), 2.06 (1H, ddd, *J*=3.9, 3.9, 12.0 Hz), 1.81–1.74 (2H, m), 1.22 (1H, ddd, *J*=11.4, 11.4, 12.0 Hz), 1.05 (3H, d, *J*=6.3 Hz), 0.94 (9H, t, *J*=7.8 Hz), 0.81 (9H, s), 0.61 (6H, q, *J*=7.8 Hz), −0.05 and −0.08 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 144.7, 138.9, 134.2, 129.7, 128.3, 127.9, 127.8, 127.5, 120.1, 84.4, 79.4, 71.9, 71.6, 71.0, 69.9, 51.6, 42.4, 38.3, 25.7, 21.6, 20.5, 17.9, 6.7, 4.7, −4.3, −4.5; HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{37}H_{61}O_7SSi_2$, $(M+H)^+$ 705.3677, found 705.3684.

4.3.8. (1*S*,2*S*,3*S*,4*R*,5*R*)-1-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-3-[(1′*R*,2′*S*)-1′-(*p*-toluenesulfonyloxy)-2′-(triethylsilyloxy)propyl]-2-methoxymethyloxy-4-vinylcyclohexane (39). To a solution of **38** (33.6 mg, 0.0477 mmol) in $(CH_2Cl)_2$ (1 mL) were added *i*-Pr_2NEt (0.088 mL, 0.51 mmol) and MOMCl (0.039 mL, 0.52 mmol) at 0 °C, and the reaction mixture was stirred at 50 °C for 3.5 h. The mixture was diluted with EtOAc and washed successively

with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 1 g, EtOAc/hexane=1:10) to give **39** (35.8 mg, 92%) as a pale yellow syrup: R_f 0.71 (EtOAc/toluene=1:6); $[\alpha]_D^{22}$ −10.5 (*c* 0.92, $CHCl_3$); IR (neat) 2955, 2930, 1360, 1180, 1100, 1075, 1000, 925, 840 cm^{-1}; ^1H NMR (300 MHz) δ 7.80 (2H, d, *J*=7.8 Hz), 7.40–7.22 (7H, m), 5.38–5.10 (3H, m), 4.85 and 4.74 (each 1H, 2d, *J*=5.0 Hz), 4.66–4.52 (1H, m), 4.58 (2H, s), 4.26 (1H, qd, *J*=6.0, 9.0 Hz), 3.52 (1H, dd, *J*=9.3, 9.3 Hz), 3.30 (3H, s), 3.36–3.20 (1H, m), 3.15 (1H, ddd, *J*=3.9, 11.7, 12.0 Hz), 2.43 (3H, s), 2.11 (1H, ddd, *J*=3.9, 4.3, 12.3 Hz), 2.16–1.92 (2H, m), 1.27 (1H, ddd, *J*=12.0, 12.0, 12.3 Hz), 1.02 (3H, d, *J*=6.0 Hz), 0.95 (9H, t, *J*=7.8 Hz), 0.83 (9H, s), 0.60 (6H, q, *J*=7.8 Hz), −0.05 and −0.06 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 144.5, 138.7, 138.5, 134.5, 129.6, 128.3, 127.8, 127.7, 127.5, 119.7, 98.7, 85.0, 80.3, 78.9, 71.6, 70.8, 69.0, 57.0, 52.0, 38.8, 25.8, 21.6, 21.2, 18.0, 6.8, 5.1, −4.3, −4.4; HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{39}H_{64}O_8SSi_2Na$, $(M+Na)^+$ 771.3758, found 771.3767.

4.3.9. (1*S*,2*S*,3*S*,4*R*,5*R*)-1-Benzyloxy-5-(*tert*-butyldimethylsilyloxy)-3-[(1′*R*,2′*S*)-2′-hydroxy-1′-(*p*-toluenesulfonyloxy)propyl]-2-methoxymethyloxy-4-vinylcyclohexane (40). To a solution of **39** (31.7 mg, 0.0423 mmol) in CH_3CN/H_2O (10:1, 3 mL) was added DDQ (10.6 mg, 0.0467 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with EtOAc and washed successively with 20% aqueous $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 1 g, EtOAc/hexane=1:4) to give **40** (23.1 mg, 86%) as a white solid: R_f 0.40 (EtOAc/hexane=1:2); mp 107.8–108.5 °C; $[\alpha]_D^{26}$ −31.7 (*c* 0.89, $CHCl_3$); IR (neat) 3420, 2930, 2860, 1360, 1180, 1100, 1075, 840 cm^{-1}; ^1H NMR (300 MHz) δ 7.79 (2H, d, *J*=8.0 Hz), 7.37–7.28 (7H, m), 5.30 (1H, ddd, *J*=9.6, 10.2, 16.6 Hz), 5.17 (1H, dd, *J*=2.3, 10.2 Hz), 5.13 (1H, dd, *J*=2.3, 16.6 Hz), 4.88 (2H, s), 4.85 (1H, d, *J*=5.4 Hz), 4.60 and 4.55 (each 1H, 2d, *J*=11.8 Hz), 3.94 (1H, qd, *J*=6.3, 5.4 Hz), 3.63 (1H, dd, *J*=9.8, 10.4 Hz), 3.41 (3H, s), 3.31 (1H, ddd, *J*=4.0, 9.8, 11.7 Hz), 3.21 (1H, ddd, *J*=4.0, 11.2, 11.7 Hz), 2.44 (3H, s), 2.16 (1H, ddd, *J*=9.6, 11.2, 11.4 Hz), 2.16 (1H, ddd, *J*=4.0, 4.0, 11.9 Hz), 1.89 (1H, dd, *J*=10.4, 11.7 Hz), 1.36 (1H, ddd, *J*=11.7, 11.7, 11.9 Hz), 1.03 (3H, d, *J*=6.3 Hz), 0.82 (9H, s), −0.04 and −0.06 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 144.7, 138.6, 138.2, 134.3, 129.7, 128.4, 127.8, 127.7, 119.6, 99.5, 84.3, 79.7, 77.2, 71.7, 70.4, 68.2, 57.1, 51.6, 38.7, 25.7, 21.6, 21.4, 18.0, −4.3, −4.4; HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{33}H_{50}O_8SSiNa$, $(M+Na)^+$ 657.2894, found 657.2893.

4.3.10. Lactone (30) from 40. Ozone was introduced to a solution of **40** (45.2 mg, 0.0712 mmol) in MeOH (4.5 mL) at −78 °C for 6 min. To the reaction mixture was added Me_2S (0.5 mL) at −78 °C, and the reaction mixture was stirred at room temperature for 3 h and then diluted with Et_2O. The organic layer was washed with brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 1 g, EtOAc/hexane=1:6) to give lactol **41** (36.2 mg, 80%) as a colorless syrup: R_f 0.56 (EtOAc/hexane=1:2); IR (neat) 3420, 2960, 2930, 2860, 1720, 1600 cm^{-1}; ^1H NMR (300 MHz) δ 7.81 (2H, d, *J*=8.3 Hz), 7.50–7.20 (7H, m), 5.23 (1H, d, *J*=2.5 Hz), 4.75 (1H, d, *J*=6.7 Hz), 4.67–4.53 (3H, m), 4.33 (1H, dd, *J*=9.5, 10.0 Hz), 4.08 (1H, qd, *J*=6.7, 9.5 Hz), 3.83 (1H, dd, *J*=7.4, 7.6 Hz), 3.72 (1H, ddd, *J*=5.4, 9.3, 9.8 Hz), 3.59 (1H, ddd, *J*=4.6, 7.6, 8.4 Hz), 3.28 (3H, s), 2.43 (3H, s), 2.42–2.33 (1H, m), 2.20 (1H, ddd, *J*=4.6, 5.4, 13.4 Hz), 1.85 (1H, ddd, *J*=2.5, 9.8, 10.2 Hz), 1.47 (1H, ddd, *J*=8.4, 9.3, 13.4 Hz), 0.87 (3H, d, *J*=6.7 Hz), 0.82 (9H, s), 0.02 (6H, s); ^{13}C NMR (75 MHz) δ 144.4, 138.8, 135.3, 129.5, 128.3, 127.8, 127.7, 127.4, 96.2, 90.1, 86.0, 79.1, 77.9, 71.2, 67.1, 66.7, 55.9, 48.1, 38.7, 37.4, 25.7, 21.6, 18.3, 17.6, −4.2, −5.0.

To a solution of lactol **41** (15.1 mg, 0.0237 mmol) in CH_2Cl_2 (1 mL) were added PDC (178 mg, 0.473 mmol) and MS4A (300 mg) at 0 °C, and the reaction mixture was stirred at room temperature for 12 h. The insoluble material was removed by filtration through a pad of Celite, and the filtrate was diluted with EtOAc. The organic layer was washed with 10% aqueous $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 1 g, EtOAc/toluene=1:19) to give **30** (12.5 mg, 83%).

4.4. Formal synthesis of (+)-actinobolin

4.4.1. Methyl 2-*O*-benzyl-3-deoxy-α-D-glucopyranoside (42). To a suspension of NaH (18.0 mg, 0.450 mmol) in DMF (0.5 mL) at 0 °C was added a solution of **9** (20.0 mg, 0.0751 mmol) in DMF (0.5 mL). After being stirred for 10 min, to the mixture was added BnBr (0.0180 mL, 0.151 mmol) at 0 °C, and the mixture was stirred at room temperature for 10 min. The reaction mixture was diluted with EtOAc, and washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 0.5 g, EtOAc/hexane=1:6) to give methyl 4,6-*O*-benzylidene-2-*O*-benzyl-3-deoxy-α-D-*ribo*-hexopyranoside (25.4 mg, 95%) as a white solid: R_f 0.55 (EtOAc/hexane =1:2); mp 102.0–102.5 °C; $[\alpha]_D^{20}$ +21.4 (*c* 0.99, $CHCl_3$); IR (KBr disk) 2940, 2900, 2860, 1500, 1100, 1050, 990 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.27 (5H, m), 5.49 (1H, s), 4.68 (1H, d, *J*=3.3 Hz), 4.67 and 4.58 (each 1H, 2d, *J*=12.6 Hz), 4.25 (1H, dd, *J*=4.5, 10.2 Hz), 3.77 (1H, ddd, *J*=4.5, 9.6, 10.2 Hz), 3.66 (1H, dd, *J*=10.2, 10.6 Hz), 3.60 (1H, ddd, *J*=3.3, 4.2, 11.7 Hz), 3.49 (1H, ddd, *J*=4.5, 9.6, 11.7 Hz), 3.45 (3H, s), 2.27 (1H, ddd, *J*=4.2, 4.5, 11.4 Hz), 2.05 (ddd, *J*=11.4, 11.7, 11.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 137.4, 129.1, 128.5, 128.3, 127.91, 127.86, 126.2, 101.8, 98.0, 76.7, 73.8, 71.0, 69.4, 63.9, 55.1, 30.1; LRMS (EI) *m/z* 356 (M^+, 1.7%), 265 (4.5), 233 (3.4), 218 (81.6), 162 (61.9), 105 (100), 91 (100); HRMS (EI) *m/z* calcd for $C_{19}H_{30}IO_3Si$ 356.1624, found 356.1629. Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.56; H, 6.93.

A solution of methyl 4,6-*O*-benzylidene-2-*O*-benzyl-3-deoxy-α-D-*ribo*-hexopyranoside (25.4 mg, 0.0713 mmol) in 80% AcOH (1 mL) was stirred at 80 °C for 1 h. The reaction

mixture was concentrated to give a residue, which was purified by column chromatography (silica gel: 0.6 g, EtOAc/toluene=1:1) to afford **42** (17.5 mg, 92%) as a white solid: R_f 0.1 (EtOAc/toluene=1:1); mp 101.0–102.0 °C; $[\alpha]_D^{20}$ +65.1 (*c* 0.71, $CHCl_3$); IR (KBr disk) 3320, 2900, 2880, 1105, 1050, 1030, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.28 (5H, m), 4.64 (1H, d, *J*=4.2 Hz), 4.64 and 4.56 (each 1H, 2d, *J*=12.3 Hz), 3.85 (1H, dd, *J*=3.7, 11.5 Hz), 3.75 (1H, dd, *J*=3.6, 11.5 Hz), 3.62 (1H, ddd, *J*=4.8, 10.0, 11.2 Hz), 3.56–3.45 (2H, m), 3.42 (3H, s), 2.11 (1H, ddd, *J*=4.7, 4.8, 11.4 Hz), 1.87 (1H, ddd, *J*=11.2, 11.4, 11.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 128.5, 127.90, 127.85, 97.1, 73.5, 71.9, 71.9, 66.1, 62.6, 55.0, 33.1; HRMS (FAB$^+$, NBA matrix) *m/z* (M+H)$^+$ calcd for $C_{14}H_{21}O_5$ 269.1389, found 269.1384. Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.79; H, 7.50.

4.4.2. Methyl 2-*O*-benzyl-3,6-dideoxy-α-D-*xylo*-hex-5-enopyranoside (43). To a solution of **42** (997 mg, 3.72 mmol) in toluene (20 mL) were added PPh_3 (1.56 g, 5.95 mmol), imidazole (1.01 g, 14.8 mmol), and iodine (1.51 g, 5.95 mmol), and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with EtOAc, and washed successively with 10% aqueous $Na_2S_2O_3$ solution, saturated aqueous $NaHCO_3$ and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 30 g, EtOAc/hexane=1:2) to give methyl 2-*O*-benzyl-3,6-dideoxy-6-iodo-α-D-glucopyranoside (1.40 g, 100%) as a colorless syrup: R_f 0.55 (EtOAc/hexane=1:1); $[\alpha]_D^{22}$ +64.2 (*c* 1.3, $CHCl_3$); IR (neat) 3430, 2940, 2900, 1090, 1060, 980 cm^{-1}; ^1H NMR (300 MHz) δ 7.38–7.27 (5H, m), 4.69 (1H, d, *J*=3.4 Hz), 4.63 and 4.56 (each 1H, 2d, *J*=12.4 Hz), 3.62–3.23 (6H, m), 3.48 (3H, s), 2.19 (1H, ddd, *J*=4.6, 4.6, 11.5 Hz), 1.89 (1H, ddd, *J*=11.5, 11.5, 11.5 Hz); ^{13}C NMR (75 MHz) δ 137.9, 128.5, 127.9, 127.8, 97.3, 73.7, 71.5, 71.2, 69.5, 55.3, 33.4, 7.3; LRMS (EI) *m/z* 378 (M$^+$, 0.9%), 347 (1.1), 272 (13.9), 240 (100), 135 (89.5), 91 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{19}IO_4$, (M$^+$) 378.0328, found 378.0335.

To a solution of the iodide (2.40 g, 9.59 mmol) in THF (45 mL) was added *t*-BuOK (2.14 g, 28.8 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc, and successively washed with H_2O and brine, and then dried over Na_2CO_3. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 40 g, EtOAc/hexane=1:10 contain 1 vol % Et_3N) to give enopyranoside **43** (1.10 g, 70%) as a colorless syrup: R_f 0.54 (EtOAc/hexane=1:1); $[\alpha]_D^{20}$ +62.3 (*c* 0.23, $CHCl_3$); IR (neat) 3440, 2940, 1680, 1085, 1055, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.22 (5H, m), 4.72 (1H, d, *J*=3.3 Hz), 4.70 (1H, br s), 4.67 (1H, d, *J*=12.6 Hz), 4.65 (1H, br s), 4.61 (1H, d, *J*=12.6 Hz), 4.09 (1H, m), 3.67 (1H, ddd, *J*=3.3, 4.7, 11.1 Hz), 3.49 (3H, s), 2.25 (1H, ddd, *J*=4.7, 5.7, 11.3 Hz), 2.04 (1H, d, *J*=8.7 Hz), 1.94 (1H, ddd, *J*=11.3, 11.1, 10.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 137.8, 128.5, 128.0, 127.9, 99.3, 94.6, 73.1, 71.5, 66.0, 55.5, 34.0; HRMS (FAB$^+$, glycerol matrix) *m/z* (M+H)$^+$ calcd for $C_{14}H_{19}O_4$: 251.1283, found 251.1289.

4.4.3. Methyl 2-*O*-benzyl-4-*O*-(*tert*-butyldimethylsilyl)-3,6-dideoxy-α-D-*xylo*-hex-5-enopyranoside (44). To a solution of enopyranoside **43** (26.7 mg, 0.107 mmol) in DMF (1 mL) were added imidazole (21.8 mg, 0.320 mmol) and TBSCl (24.1 mg, 0.160 mmol), and the mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with EtOAc, washed with H_2O, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel; 4 g, EtOAc/hexane=1:50 containing 1 vol % Et_3N) to give **44** (33.1 mg, 85%) as a white solid: R_f 0.70 (EtOAc/hexane =1:20); mp 78–79 °C; $[\alpha]_D^{23}$ +41.0 (*c* 1.1, $CHCl_3$); IR (KBr disk) 2955, 2860, 1665, 1115, 1060, 1000, 855, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.24 (5H, m), 4.77 (1H, d, *J*=2.4 Hz), 4.74 and 4.72 (each 1H, 2br s), 4.65 and 4.58 (each 1H, 2d, *J*=12.6 Hz), 3.68 (1H, ddd, *J*=2.4, 6.9, 9.6 Hz), 3.56–3.30 (1H, m), 3.42 (3H, s), 2.23–1.90 (2H, m), 0.92 (9H, s), 0.10 and 0.08 (each 3H, 2s); HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{20}H_{33}O_4Si$, (M+H)$^+$ 365.2148, found 365.2149.

4.4.4. A mixture of (2*S*,4*R*,5*R*)-4-benzyloxy-2-(*tert*-butyldimethylsilyloxy)-5-hydroxy-cyclohexan-1-one and its (5*S*)-isomer (45). To a solution of **44** (2.30 g, 6.31 mmol) in acetone (120 mL) and acetate buffer (0.1 mol/L solution, pH 4.8, 120 mL) was added $Hg(OCOCF_3)_2$ (0.81 g, 1.9 mmol), and the mixture was stirred at room temperature for 48 h. The reaction mixture was partially concentrated and the products were extracted with EtOAc. The organic layer was washed successively with 10% aqueous KI solution, 20% $Na_2S_2O_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 45 g, EtOAc/hexane=1:5) to give **45** (1.84 g, 83%) as a diastereomeric mixture (5*S*:5*R*=ca. 1:6): R_f 0.41 (EtOAc/hexane=1:2); IR (neat) 3450, 2930, 2860, 1740, 1250, 1150, 1075, 840 cm^{-1}; ^1H NMR (300 MHz, for the major isomer) δ 7.42–7.28 (5H, m), 4.77 and 4.58 (each 1H, 2d, *J*=11.5 Hz), 4.15 (1H, dd, *J*=6.6, 12.5 Hz), 3.76 (1H, ddd, *J*=5.4, 8.8, 12.2 Hz), 3.62 (1H, ddd, *J*=4.0, 8.8, 11.6 Hz), 2.76 (1H, dd, *J*=5.4, 13.9 Hz), 2.46 (1H, ddd, *J*=4.0, 6.6, 12.5 Hz), 2.37 (1H, dd, *J*=12.2, 13.9 Hz), 1.62 (1H, ddd, *J*=11.6, 12.5, 12.5 Hz), 0.90 (9H, s), 0.13 and 0.02 (each 3H, 2s); ^{13}C NMR (75 MHz, for the major isomer) δ 204.6, 137.6, 128.6, 128.1, 127.9, 79.4, 74.1, 72.1, 71.8, 43.5, 35.2, 25.7, 18.4, −4.6, −5.5; HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{19}H_{31}O_4Si$, (M+H)$^+$ 351.1992, found 351.1992.

4.4.5. (1*S*,2*S*,4*R*,5*R*)-4-benzyloxy-2-(*tert*-butyldimethylsilyloxy)-5-hydroxy-1-methanesulfonyloxy-cyclohexane (47). To a solution of **45** (207 mg, 0.591 mmol) in acetonitrile (4 mL) were added CAN (64.8 mg, 0.118 mmol) and dihydro-2*H*-pyran (0.11 mL, 1.2 mmol), and the reaction mixture was stirred at 0 °C for 50 min. The reaction mixture was diluted with EtOAc, and washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 6 g, EtOAc/hexane=1:15) to give *O*-THP ether (227 mg, 89%) as a diastereomer mixture. To a solution of the THP ether (227 mg, 0.522 mmol) in MeOH (5 mL) in the presence of $CeCl_3 \cdot 7H_2O$ (389 mg, 1.04 mmol) was added $NaBH_4$ (29.6 mg, 0.782 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. The reaction mixture was diluted with

EtOAc, and washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a crude **46**, which was dissolved in pyridine (4 mL). To this solution were added MsCl (0.067 mL, 0.86 mmol) and DMAP (15 mg, 0.12 mmol) at 0 °C, and the reaction mixture was stirred at 80 °C for 13 h. The reaction mixture was diluted with 1 mol/L aqueous HCl solution and stirred at room temperature for 1 h. The products were extracted with EtOAc, and the organic layer was washed successively with saturated aqueous $NaHCO_3$ solution and brine, and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 4 g, EtOAc/hexane=1:3) to give **47** (167 mg, 66% from **45**) as a colorless syrup: R_f 0.50 (EtOAc/hexane=1:1); $[\alpha]_D^{22}$ ~0 (*c* 0.92, $CHCl_3$); IR (neat) 3450, 2960, 2930, 2890, 2860, 1255, 1180, 1080, 955, 920, 840 cm^{-1}; ^1H NMR (300 MHz) δ 7.42–7.27 (5H, m), 4.65 and 4.55 (each 1H, 2d, *J*=11.5 Hz), 4.31 (1H, ddd, *J*=4.4, 8.8, 11.7 Hz), 3.68–3.52 (2H, m), 3.22 (1H, ddd, *J*=4.4, 9.0, 11.7 Hz), 3.00 (3H, s), 2.63 (1H, s), 2.52 (1H, ddd, *J*=4.7, 4.9, 12.6 Hz), 2.20 (1H, ddd, *J*=4.4, 4.7, 12.9 Hz), 1.60 (1H, ddd, *J*=11.7, 12.0, 12.6 Hz), 1.35 (1H, ddd, *J*=11.7, 11.7, 12.9 Hz), 0.88 (9H, s), 0.08 and 0.06 (each 3H, 2s); ^{13}C NMR (75 MHz) δ 137.8, 128.6, 128.1, 127.9, 82.2, 71.9, 70.7, 70.6, 38.4, 35.4, 35.0, 25.7, 17.9, −4.4, −4.9; HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{20}H_{35}O_6SSi$, $(M+H)^+$ 431.1924, found 431.1919.

4.4.6. Preparation of enantiomeric cyclohexenone [(−)-6]. A solution of $(COCl)_2$ (2.0 mol/L solution in CH_2Cl_2, 0.11 mL, 0.22 mmol) and DMSO (0.030 mL, 0.423 mmol) in CH_2Cl_2 (0.5 mL) was stirred at −78 °C for 10 min under Ar. To this mixture was added a solution of **47** (15.4 mg, 0.0358 mmol) in CH_2Cl_2 (0.5 mL) at −78 °C. After being stirred at −78 °C for 2 h, the reaction mixture was quenched by addition of Et_3N (0.040 mL, 0.29 mmol) at −78 °C. The resulting suspension was further stirred at 0 °C for 1 h, and then diluted with Et_2O. The organic layer was washed with brine and then dried. Removal of the solvent gave a residue, which was purified by column chromatography (silica gel: 1 g, EtOAc/hexane=1:7) to give (−)-**6** (11.1 mg, 93%) as a white solid: mp 46–47 °C; $[\alpha]_D^{19}$ −22.0 (*c* 0.80, $CHCl_3$); HRMS (FAB$^+$, NBA matrix) *m/z* calcd for $C_{19}H_{29}O_3Si$, $(M+H)^+$ 333.1886, found 333.1889. Anal. Calcd for $C_{21}H_{24}O_5$: C, 68.63; H, 8.49. Found: C, 68.49; H, 8.39. The ^1H and ^{13}C NMR spectra were fully identical with those of (+)-**6**.

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