The New Method for Introduction of an Allyl Group into the Angular Position of 2-(TBS-oxymethyl)-2,3,4,6,7,8-hexahydro-1-benzopyran-5-one and Its Application to Chiral Wieland–Miescher Type Compound Synthesis

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The stereoselective introduction of an allyl group into the angular position of 2-(TBS-oxymethyl)-2,3,4,6,7,8-hexahydro-1-benzopyran-5-one was accomplished using Birch reduction and an enolate trapping reaction. It was determined that the allyl group was introduced *via* an unexpected conformation-flipped from the initially formed one. Two diastereomeric Wieland–Miescher type compounds, having the allyl group at the angular position, were synthesized as optically pure forms.

Key words betulin; triterpene; Birch reduction; enolate trapping

Triterpenoid compounds are of interest because they occur widely in nature and have unique biological activities. Recently, Naganuma and his colleagues found that three natural triterpenes, betulin (**1**), uvaol (**2**), and soyasapogenol B (**3**), have reducing effects against the toxicity of cadmium chloride in HepG2 cells (Fig. 1).[1)] They also reported that betulin induced certain proteins, though not metallothionein, which is the representative protein in reducing heavy metal toxicity.[1)]

To clarify the reduction mechanism of cadmium toxicity, we investigated the relationship between expression of activities and structures, with particular focus on the functional groups of betulin, using its analogues. The results showed that both the polar functional group, found at either the C3 or C28 positions, and the isopropenyl group play important roles in reducing cadmium toxicity and the cytotoxicity of betulin (**1**).[2)] However, it is difficult to carry out further investigation into the bioactivities of betulin because the only functional groups of this compound are hydroxyl and isopropenyl, both of which are crucial for its activity. Therefore, we decided to synthesize analogues of betulin, which could not be otherwise derived from natural products. Our synthetic strategy is summarized in Fig. 2, which shows the pentacyclic ring system being divided into two fragments: the AB fragment **4** and the DE fragment **5**. Since our focus was on the angular substituents between the D and E rings, the starting material for **5** needed to be the optically pure bicyclo[4.4.0]decaline derivative **6b**, and the starting material for **4** the Wieland–Miescher ketone **6a**.

The optically active Wieland–Miescher type bicyclic ketone **6a** was effectively synthesized from the prochiral tricarbonyl compound **7a**, using chiral proline as a chiral catalyst (Fig. 3).[3—6)] The optically pure **6a** can be obtained by a single recrystallization, and can be utilized for subsequent syntheses of many natural products.[7—11)] However, the cyclization reaction of compounds with side chains other than a methyl group (*e.g.*, allyl group **7b**) was observed to have serious depreciation of the optical yield.[12)] In addition, proline did not work as a catalyst for this reaction, meaning a stoichiometric amount of proline is required to complete the reaction. If expensive synthetic proline has to be used, this presents a serious economic obstacle. Therefore, before starting the synthesis of the betulin analogues, it was decided to develop an efficient method for synthesizing optically pure bicyclo[4.4.0]decaline derivatives.

Results and Discussion

The essential features of the synthesis reaction are illustrated in Figs. 4 and 5. When the optically active diketone **8** was treated under acidic conditions, a mixture of the two diastereomers **9a** and **9b** resulted. However, by using an acid-catalyzed dehydration reaction, the mixture of **9a** and **9b** was converted to the single enantiomer **10**. Using a dissolving-metal reduction reaction with **10**, it was expected that **11a**

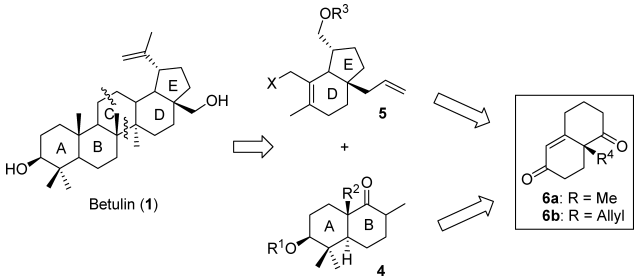

Fig. 2. Retrosynthetic Analysis of Betulin (**1**)

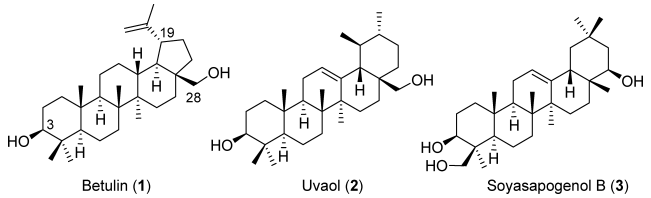

Fig. 1

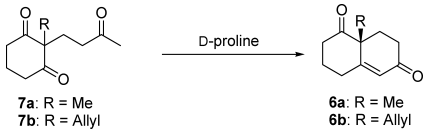

Fig. 3

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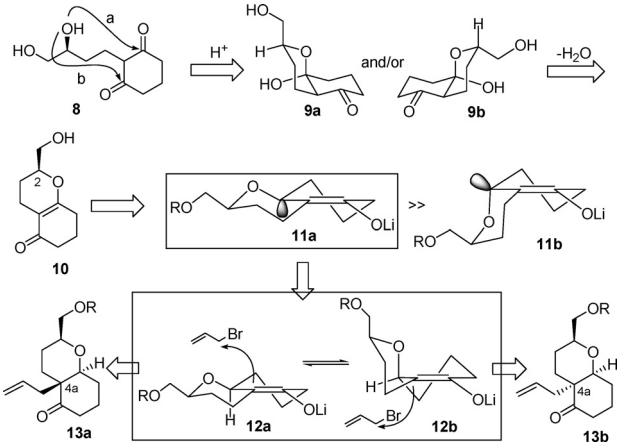


Fig. 4. Synthetic Strategy for Both **13a** and **13b**

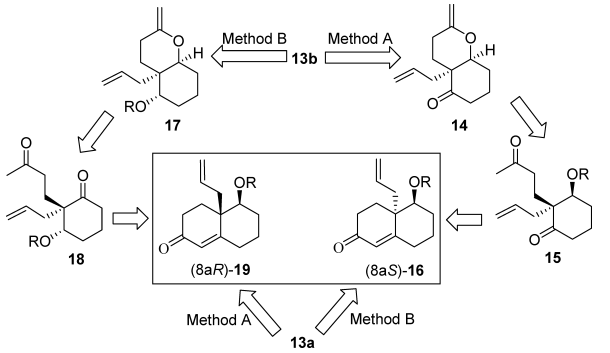


Fig. 5. Synthetic Strategy for Both (8a*S*)-**16** and (8a*R*)-**19**

would be the predominant intermediate product, since the bulky substituent on C2 occupies the equatorial position, whereas it occupies the axial position in intermediate product **11b**. Alkylation of the enolate **11a** at the angular position C4a again gave two conformers, **12a** and **12b**. For both enolate **12a** and **12b**, allyl bromide comes from the axial direction (from the β face for **12a** and the α face for **12b**), according to the stereoelectronic effects. This might be expected to provide (2*S*,4a*S*,8a*S*)-**13a** and (2*S*,4a*R*,8a*S*)-**13b**, respectively. Although the selective reaction favors efficient synthesis, diastereomeric **13a** and **13b** are separable, and it is expected that both could be used as the target molecule. Using the reaction sequence described from **10** to **13a** and **13b**, the chirality at C2 of **10** was transferred to the C4a positions of **13a** and **13b**. This can be considered to be the same as the desymmetrization of the prochiral carbonyl group of the diketone **8** (Fig. 4).

Optically active (8a*S*)-**16** can be synthesized from **13b** *via* the enol ether **14**, followed by hydrolysis and an intramolecular aldol reaction (Method A). Alternately, (8a*R*)-**19** can be synthesized *via* **17** by hydrolysis of the enol ether, oxidation of the secondary alcohol, and an intramolecular aldol reaction (Method B). Similarly, (8a*R*)-**19** and (8a*S*)-**16** can be synthesized from **13a**, using Methods A and B, respectively (Fig. 5).

Based on the concept described above, a chiral side chain unit, **24**, synthesized from commercially-available (*S*)-malic acid (**20**), was introduced to 1,3-cyclohexanedione (**25**). The results are summarized in Chart 1. The ester group of **22**,

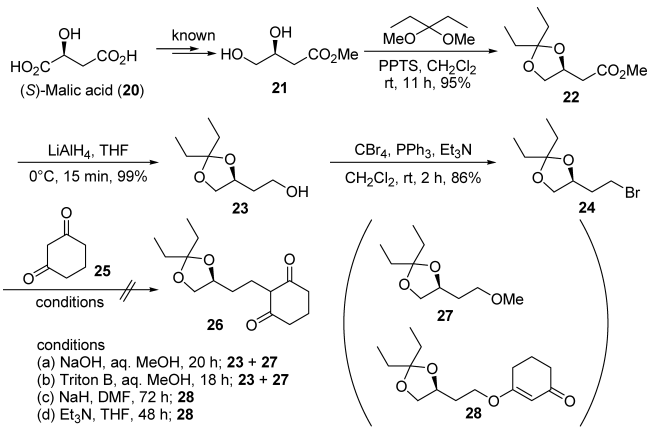


Chart 1

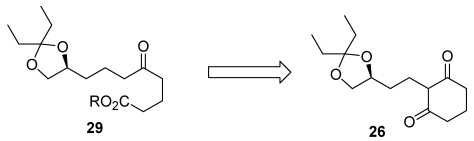


Fig. 6

which was synthesized from the known diol **21**[13] using the usual acetalization process (3,3-dimethoxypentane, PPTS, CH_2Cl_2, rt, 11 h, 95%), was reduced to the alcohol **23** ($LiAlH_4$, THF, 0 °C, 15 min, 99%).[14—19] The resulting hydroxyl group was converted to bromine under standard conditions (CBr_4, PPh_3, Et_3N, CH_2Cl_2, rt, 2 h, 86%), producing **24**. Unfortunately, efforts using the alkylation reactions[20] to produce **26** failed, with the isolable compounds consisting either of a mixture of the alcohol **23** and the methyl ether **27**, or the enol ether **28**. Thus, our focus shifted from synthesizing **26** from the alkylation reaction of 1,3-cyclohexanedione (**25**) to the construction of the substituted 1,3-cyclohexanone-ring system from δ-keto-ester derivative **29** (Fig. 6).

Ethyl acetoacetate (**30**) was regioselectively alkylated with the bromide **24** by the dianion method (NaH, BuLi, THF-HMPA, 0 °C, then **24**, rt, 1 h, 86%),[21] producing a good yield of **31**. This was then alkylated again with ethyl 3-bromopropanoate (**32**) at the C2 position of **31** to provide **33** (NaH, THF, **31**, rt, 2 h, 89%). To remove the ethoxylcarbonyl group, **33** was subjected to alkaline hydrolysis conditions (KOH, ^{t}BuOH–H_2O, reflux, 5 h), acidified with 3 N HCl, followed by both decarboxylation and deacetalization reactions by refluxing the mixture. Finally, the mixture was concentrated under reduced pressure to remove the volatile materials and refluxed in methanolic HCl (AcCl, MeOH) to produce a 74% yield of 5-substituted 6,8-dioxabicyclo[3.2.1]octane derivative **36** as the sole product (Chart 2). The conversion from **33** to **36** can be handled in one flask and can be applied to gram-scale synthesis.

Having established a synthetic route for **36**, which is the synthetic equivalent of **26**, the cyclization reaction of **36** was investigated (Table 1). Lewis acids (entries 1 and 2), a weak Brønsted acid (entry 3), and a carboxylate (entry 4) did not promote any reaction and **36** was completely recovered. However, reaction of **36** with TfOH in CH_2Cl_2 or trifluorotoluene produced the desired bicyclic compound **10**, with yields of 71% or 28%, respectively (entries 5 and 6). The solvent effect of this reaction was remarkable, with the reac-

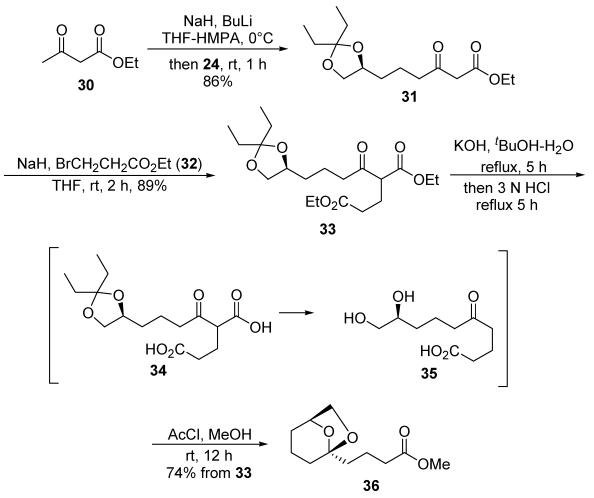
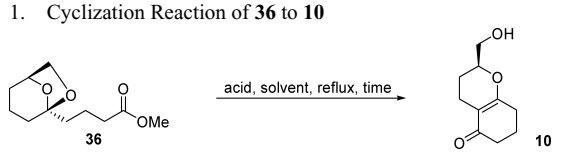


Chart 2

Table 1. Cyclization Reaction of **36** to **10**



Entry	Acid (1 eq)	Solvent	Time (h)	Yield (%)
1	$BF_3 \cdot OEt_2$	CH_2Cl_2	72	No reaction
2	$TiCl_4$	CH_2Cl_2	72	No reaction
3	CSA	CH_2Cl_2	72	No reaction
4	TFA	CH_2Cl_2	72	No reaction
5	TfOH	CH_2Cl_2	24	71
6	TfOH	$PhCF_3$	24	28
7	TfOH	$ClCH_2CH_2Cl$	3	79

tion time shortened and the yield slightly improved by using $ClCH_2CH_2Cl$ (entry 7).

To introduce the angular substituents, the hydroxyl group was protected by a TBS group (TBSCl, imidazole, DMF, rt, 12 h, 100%), followed by reductive alkylation of the α, β-unsaturated ketone moiety of **37**. The TBS ether **37** was reacted under Birch reduction conditions (Li, liq. NH_3, THF $-78\,^{\circ}C$, 1 h), followed by the direct addition of allyl bromide to the mixture to produce the desired ketone **39**, with a 36% yield, together with an unidentified polyallylated compound.[22] The stereochemistry of **39** was determined by ^{1}H-NMR, with the observed n.O.e. shown in the inset of Chart 3. The coupling pattern of the proton in the C8a position showed typical equatorial orientation (a broad singlet) and n.O.e. was observed between the protons in the C2 and C8a positions. Therefore, as expected, protonation at the β position of the carbonyl group (C8a) occurred from the α face to afford an *S* configuration at C8a. Furthermore, the β proton (equatorial) in the C4 position displayed an unexpectedly low field shift in ^{1}H-NMR, the result of the anisotropy effect of the carbonyl group. Using the molecular model, this low field shift in **40** does not seem possible. It is difficult to accept that allyl bromide approached from the α face (equatorial orientation) in **38b**, due to the stereoelectronic effect for a successive alkylation reaction. We speculate that the alkylation occurred after a flipping of conformation from **38b** to **38a**, and then proceeded from the α face. Why **38a** was predominant over

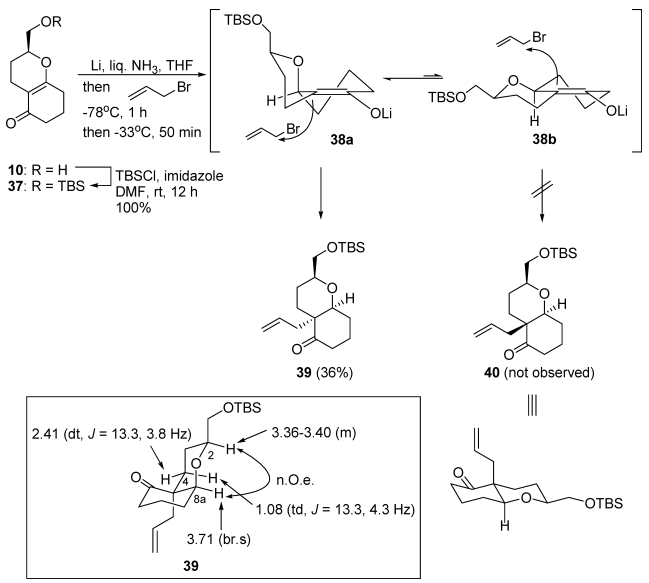


Chart 3

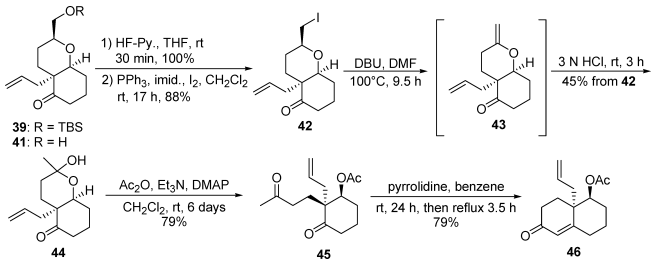


Chart 4

38b is not yet clear. There does not appear to be a large energy difference between the two conformers, but the C–O bond is parallel to the π orbital of the enolate in the conformer **38a**. Therefore, one possible reason for **38a**'s predominance might be the stabilizing effect of the C–O antibonding orbital by ligation of the enolate π orbital (Chart 3). A detailed investigation of this stereochemical outcome is now in progress in our laboratory.

Our next step was conversion of **39** to the target molecules, (8a*S*)-**16** and (8a*R*)-**19**, which are essentially enantiomers. Synthesis of the former was examined first (Chart 4). The TBS group was eliminated using standard conditions (HF pyridine, THF, rt, 30 min, 100%) and the resulting hydroxyl group was converted to iodide, producing **42** with good yield (I_2, PPh_3, imidazole, CH_2Cl_2, rt, 17 h, 88%). E2 elimination of the iodide was carried out with DBU in DMF at 100 °C, and the resulting unstable enol ether, **43**, was hydrolyzed under acidic conditions, without isolation, to provide the acetal **44** (3 N HCl, rt, 3 h, 45% from **42**). Acetylation of **44** (Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 6 d, 79%) resulted in **45**, and was then subjected to an intramolecular aldol reaction using pyrrolidine enamine (pyrrolidine, benzene, rt, 24 h, then reflux, 3.5 h, 79%), to provide the desired **46**, which is equivalent to (8a*S*)-**16** (R = Ac).

The other isomer, **55**, was synthesized according to Charts 5 and 6. The carbonyl group of **39** was reduced by $LiBH_4$ in MeOH–Et_2O at $-30\,^{\circ}C$ to produce a separable mixture of diastereomeric alcohols **48** and **49**. The hydroxyl group of the

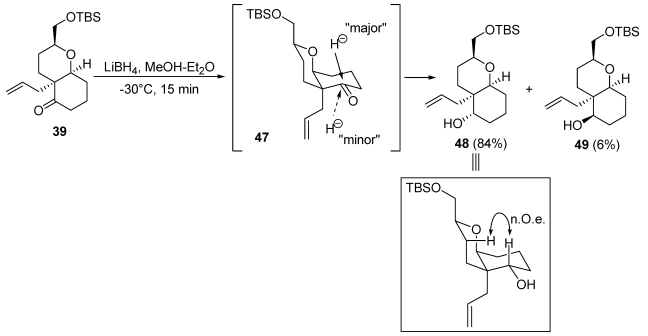


Chart 5

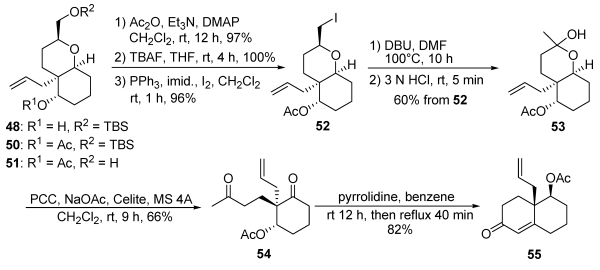


Chart 6

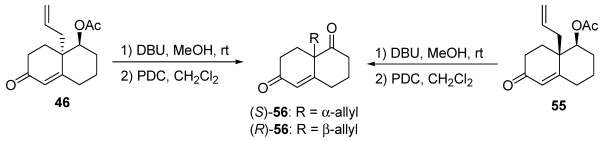


Chart 7

major isomer **48** was expected to have an α configuration, obtained by being reduced from the axial direction. This was confirmed by the observation of n.O.e. between the C3 and C5 protons (Chart 5).

The hydroxyl group of **48** was acetylated (Ac_2O, Et_3N, DMAP, rt, 12 h, 97%) and the TBS group was eliminated by TBAF in THF at rt, to produce **51** in a quantitative yield. Conversion from **51** to the acetal **53** was carried out under essentially the same conditions applied to **41**, giving a 58% overall yield [(1) I_2, PPh_3, imidazole, CH_2Cl_2, rt, 1 h; (2) DBU, DMF, 100 °C, 10 h; (3) 3 N HCl, rt, 5 min]. Finally, **53** was oxidized (PCC, NaOAc, Celite, MS 4A, CH_2Cl_2, rt, 9 h, 66%) and the second ring cyclized (pyrrolidine, benzene, reflux, 1.5 h, 82%), to complete the synthesis of **55**, which is equivalent to (8a*R*)-**19** (R=Ac) (Chart 6).

The absolute configurations of the final products **46** and **55** were confirmed by synthesizing **56**[23,24] from each of these products and comparing the specific rotations of the resultants to that of the known compound (*R*)-**56**[12] (Chart 7). The optical purities of both (*R*)-**56** and (*S*)-**56** were determined by chiral HPLC to be more than 99% ee.

Conclusion

A new stereoselective method for the introduction of an allyl group at the angular position of chiral **10** using Birch reduction and an alkylation reaction was established. Although the synthetic routes for both **46** and **55** are somewhat long, each reaction can be carried out on a large scale and without any loss of the optical purity. Optimization of the synthetic route and the synthesis of betulin and its analogues are currently in progress in our laboratory.

Experimental

General Procedures All melting points were determined with Yazawa Micro Melting Point BY-2 and are uncorrected. ^{1}H-NMR spectra (400 or 600 MHz) and ^{13}C-NMR spectra (100 or 150 MHz) were recorded on JEOL JMN AL-400 or JEOL ECP-600 spectrometers, respectively. Chemical shifts (δ) are given from TMS (0 ppm) as internal standard for ^{1}H-NMR and $^{13}CDCl_3$ (77.0 ppm) for ^{13}C-NMR. Mass spectra and high resolution mass spectra were measured on JEOL JMS-DX303 and MS-AX500 instruments, respectively. IR spectra were recorded on a Shimadzu FTIR-8400. The specific rotations were measured on a JASCO P-1010 polarimeter.

Methyl (4*S*)-2,2-Diethyl-1,3-dioxolane-4-acetate (22) 3,3-Dimethoxypentane (2.2 g, 19.8 mmol) and PPTS (120 mg, 0.46 mmol) were added to a solution of methyl (3*S*)-3,4-dihydroxybutylate (**21**)[15] (2.0 g, 15.2 mmol) in CH_2Cl_2 (40 ml) at room temperature and stirred for 11 h. The solvent and excess reagent were evaporated and the residue was purified by silica gel column chromatography (AcOEt) to afford **22** (2.9 g, 95%) as a colorless oil. $[\alpha]_D^{17}$ +18.7° (c=1.25, $CHCl_3$). IR (neat) cm^{-1}: 1740, 1439, 1202, 1171, 1078. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90 (6H, t, J=7.5 Hz), 1.62 (2H, q, J=7.5 Hz), 1.64 (2H, q, J=7.5 Hz), 2.52 (1H, dd, J=15.7, 6.6 Hz), 2.75 (1H, dd, J=15.7, 6.6 Hz), 3.60 (1H, t, J=7.7 Hz), 3.70 (3H, s), 4.18 (1H, dd, J=8.3, 6.6 Hz), 4.46 (1H, quint, J=6.6 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 7.9, 8.2, 29.6, 29.8, 38.6, 51.8, 69.8, 72.2, 113.0, 170.9. MS *m/z*: 173 ($M^+-CH_2CH_3$, 60), 99 (100). HR-MS *m/z*: 173.0776 (Calcd for $C_8H_{13}O_4$: 173.0814).

(4*S*)-4-(2-Hydroxyethyl)-2,2-diethyl-1,3-dioxolane (23)[14—19] A solution of **22** (5.0 g, 24.7 mmol) in THF (30 ml) was added to a suspension of $LiAlH_4$ (1.4 g, 37.1 mmol) in THF (150 ml) at 0 °C and the mixture was stirred for 15 min at the same temperature. Et_2O was added to the mixture and 28% aqueous ammonia solution was added to the mixture. The resulting inorganic precipitate was filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (AcOEt) to provide **23** (4.3 g, 99%) as a colorless oil. $[\alpha]_D^{17}$ +2.2° (c=1.27, $CHCl_3$) [lit. for *S*-enantiomer[16]: $[\alpha]_D$ +1.5 (c=1.0, CH_2Cl_2), for *R* enantiomer[19]: $[\alpha]_D^{25}$ −2.6° (c=0.935, $CHCl_3$)]. IR (neat) cm^{-1}: 3414, 1464, 1173, 1082, 1057, 918. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.90 (3H, t, J=7.3 Hz), 0.91 (3H, t, J=7.3 Hz), 1.63 (2H, q, J=7.3 Hz), 1.65 (2H, q, J=7.3 Hz), 1.80—1.85 (2H, m), 2.38 (1H, br), 3.54 (1H, t, J=7.9 Hz), 3.80 (2H, br), 4.10 (1H, dd, J=7.9, 6.4 Hz), 4.24 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 8.0, 8.3, 29.6, 29.9, 35.5, 60.6, 70.1, 75.4, 112.9. MS *m/z*: 145 ($M^+-CH_2CH_3$, 79), 71 (100). HR-MS *m/z*: 145.0845 (Calcd for $C_7H_{13}O_3$: 145.0865).

(4*S*)-4-(2-Bromoethyl)-2,2-diethyl-1,3-dioxolane (24) CBr_4 (23.8 g, 71.7 mmol), Et_3N (9.7 g, 95.6 mmol), and **23** (8.3 g, 47.8 mmol) were successively added to a solution of PPh_3 (41.4 g, 0.16 mol) in CH_2Cl_2 (200 ml) at 0 °C and the mixture was stirred for 2 h at room temperature. Et_2O was added to the mixture and filtered through a Celite pad. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel chromatography [AcOEt–hexane (1 : 5)] to give **24** (9.8 g, 86%) as a colorless oil. $[\alpha]_D^{16}$ −24.3° (c=1.25, $CHCl_3$). IR (neat) cm^{-1}: 2972, 2939, 2882, 1464, 1173, 1078, 1059, 920. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (6H, t, J=7.3 Hz), 1.62 (2H, q, J=7.3 Hz), 1.64 (2H, q, J=7.3 Hz), 2.04 (1H, dtd, J=14.4, 7.5, 4.4 Hz), 2.15 (1H, ddt, J=14.4, 7.5, 4.4 Hz), 3.48—3.56 (3H, m), 4.11 (1H, dd, J=7.9, 6.2 Hz), 4.24 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 8.0, 8.3, 29.5, 29.6, 29.9, 37.0, 69.5, 74.2, 112.9. MS *m/z*: 209, 207 ($M^+-CH_2CH_3$, 99, 100), 135, 133 (30, 31), 57 (98). HR-MS *m/z*: 208.9985 (Calcd for $C_7H_{12}O_2{}^{81}$Br: 209.0001), 207.0007 (Calcd for $C_7H_{12}O_2{}^{79}$Br: 207.0021).

[(4*S*)-2,2-Diethyl-1,3-dioxolan-4-yl]-3-oxo-hexanoic Acid Ethyl Ester (31) Ethyl acetoacetate (**30**) (10 g, 76.9 mmol) was added to a suspension of NaH (oil free, 3.8 g, 94.2 mmol) in THF (200 ml) and HMPA (20 ml) at 0 °C. After being stirred for 10 min at the same temperature, BuLi (1.32 M solution in hexane, 64.1 ml, 84.6 mmol) was added and the stirring was continued for another 10 min. **24** (9.1 g, 38.5 mmol) was added to the mixture and stirred for 1 h at room temperature. The mixture was neutralized with 3 N HCl and the aqueous solution was extracted with Et_2O. The combined organic solution was washed with aqueous saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography [AcOEt–hexane (1 : 6)] to afford **31** (9.5 g, 86%) as a colorless oil. $[\alpha]_D^{18}$ +13.1° (c=1.27, $CHCl_3$). IR (neat) cm^{-1}:

1744, 1717, 1080, 1031, 920. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (3H, t, J=7.3 Hz), 0.89 (3H, t, J=7.4 Hz), 1.28 (3H, t, J=7.2 Hz), 1.54—1.72 (8H, m), 2.61 (2H, t, J=7.0 Hz), 3.43 (2H, s), 3.46 (1H, t, J=9.9 Hz), 4.04 (2H, m), 4.19 (2H, q, J=7.2 Hz). MS m/z: 286 (M^+, 2), 257 (100). HR-MS m/z: 286.1772 (Calcd for $C_{15}H_{26}O_5$: 286.1780).

Ethyl 7-[(4*S*)-(2,2-Diethyl-1,3-dioxolan-4-yl)]-3-ethoxycarbonyl-4-oxoheptanoate (33) Compound **31** (7.3 g, 25.5 mmol) was added to a suspension of NaH (oil free, 1.5 g, 38.3 mmol) in THF (200 ml) at 0 °C. After being stirred for 30 min at the same temperature, ethyl-3-bromopropionate (**32**) (5.5 g, 30.6 mmol) was added and the stirring was continued for 2 h at room temperature. The mixture was extracted with Et_2O and the combined organic solution was washed with saturated aqueous NaCl solution. The organic solution was dried over anhydrous $MgSO_4$ and concentrated to afford the oil, which was purified by silica gel column chromatography [AcOEt–hexane (1 : 5)] to provide **33** (8.8 g, 89%, an inseparable diastereomeric mixture) as a colorless oil. IR (neat) cm^{-1}: 1735, 1716, 1375, 1182, 1080, 1024, 920. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (3H, t, J=7.3 Hz), 0.89 (3H, t, J=7.3 Hz), 1.26 (3H, t, J=7.3 Hz), 1.27 (3H, t, J=7.3 Hz), 1.52—1.70 (4H, m), 1.60 (2H, q, J=7.5 Hz), 1.62 (2H, q, J=7.5 Hz), 2.15 (2H, t, J=7.2 Hz), 2.34 (2H, td, J=7.2, 2.0 Hz), 2.52—2.69 (2H, m), 3.46 (1H, m), 3.56 (1H, t, J=7.2 Hz), 4.02—4.07 (2H, m), 4.13 (2H, q, J=7.1 Hz), 4.19 (2H, q, J=7.1 Hz). MS m/z: 357 ($M^+-CH_2CH_3$, 6), 311 (100). HR-MS m/z: 357.1923 (Calcd for $C_{18}H_{29}O_7$: 357.1913).

4-[(1*S*,5*S*)-6,8-Dioxabicyclo[3.2.1]oct-5-yl]-butyric Acid Methyl Ester (36) KOH (1.1 g, 19.4 mmol) was added to a solution of **33** (3.4 g, 8.8 mmol) in ^{t}BuOH (50 ml) and H_2O (12 ml) and refluxed for 5 h. After being cooled to room temperature, the mixture was acidified by 3 N HCl and was refluxed for 5 h. The solvent was evaporated at the reduced pressure and the residue was dissolved into MeOH. AcCl (6.9 g, 88.2 mmol) was added to the solution at 0 °C and stirred at room temperature for 12 h. The mixture was neutralized with saturated aqueous $NaHCO_3$ solution and the aqueous phase was extracted with AcOEt. The organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was purified by silica gel column chromatography [AcOEt–hexane (1 : 5)] to provide **36** (1.4 g, 74% from **33**) as a colorless oil. $[\alpha]_D^{18}$ −42.1° (c=1.02, $CHCl_3$). IR (neat) cm^{-1}: 1736, 1437, 1259, 1175, 1109, 1016, 907. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.48 (1H, m), 1.61—1.85 (9H, m), 2.35 (2H, t, J=7.2 Hz), 3.66 (3H, s), 3.81 (1H, t, J=6.2 Hz), 3.91 (1H, d, J=6.2 Hz), 4.51 (1H, br). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 16.9, 18.7, 28.4, 34.08, 34.13, 36.7, 51.5, 69.0, 74.8, 108.4, 173.9. MS m/z: 214 (M^+, 2), 129 (100). HR-MS m/z: 214.1189 (Calcd for $C_{11}H_{18}O_4$: 214.1205).

(2*S*)-2-Hydroxymethyl-2,3,4,6,7,8-hexahydro-1-benzopyran-5-one (10) (Table 1, Entry 7) A mixture of **36** (1.0 g, 4.7 mmol) and TfOH (0.70 g, 4.7 mmol) in $ClCH_2CH_2Cl$ (60 ml) was refluxed for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel chromatography [$CHCl_3$–MeOH (20 : 1)] to afford **10** (0.67 g, 79%) as colorless solid. The analytical sample was recrystallized from AcOEt to provide colorless needles (mp 88—89 °C). $[\alpha]_D^{17}$ +211.0° (c=1.21, MeOH). IR (neat) cm^{-1}: 3422, 1589, 1404, 1254, 1186, 1036, 638. ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.50—1.62 (1H, m), 1.85—1.94 (3H, m), 1.92—2.07 (1H, m), 2.26—2.29 (3H, m), 2.36—2.39 (2H, m), 3.59 (1H, dd, J=12.1, 5.7 Hz), 3.64 (1H, dd, J=12.1, 4.3 Hz), 3.92—3.97 (1H, m). ^{13}C-NMR (100 MHz, CD_3OD) δ: 18.4, 22.0, 23.9, 29.6, 37.4, 64.8, 79.6, 112.1, 174.5, 200.8. MS m/z: 182 (M^+, 56). HR-MS m/z: 182.0936 (Calcd for $C_{10}H_{14}O_3$: 182.0943).

(2*S*)-2-(*tert*-Butyldimethylsilanyloxymethyl)-2,3,4,6,7,8-hexahydro-1-benzopyran-5-one (37) Imidazole (190 mg, 2.9 mmol) and TBSCl (320 mg, 2.2 mmol) were added successively to a solution of **10** (260 mg, 1.4 mmol) in anhydrous DMF (20 ml) at 0 °C and the mixture was allowed to stir at room temperature for 12 h. The mixture was extracted with Et_2O and the combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was purified by silica gel column chromatography [AcOEt–hexane (1 : 3)] to afford **37** (420 mg, 100%) as a colorless oil. $[\alpha]_D^{16}$ +125.5° (c=1.24, $CHCl_3$). IR (neat) cm^{-1}: 1626, 1396, 1250, 1182, 837. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.08 (6H, s), 0.90 (9H, s), 1.62 (1H, m), 1.89—1.97 (3H, m), 2.08—2.17 (1H, m), 2.34—2.43 (5H, m), 3.71 (2H, dd, J=10.9, 5.1 Hz), 3.78 (2H, dd, J=10.9, 5.1 Hz), 3.98 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: −5.22, −5.18, 17.2, 20.9, 23.1, 25.7, 25.9, 28.7, 36.7, 65.0, 77.7, 111.4, 171.1, 198.0. MS m/z: 296 (M^+, 0.2), 281 (40), 239 (100). HR-MS m/z: 296.1790 (Calcd for $C_{16}H_{28}O_3Si$: 296.1808).

(2*S*,4a*S*,8a*S*)-4a-Allyl-2-(*tert*-butyldimethylsilanyloxymethyl)-octahydro-1-benzopyran-5-one (39) Lithium metal (38 mg, 5.5 mmol) was added to liquid NH_3 (distilled over sodium metal, 5 ml) at −78 °C. After being stirred for 10 min, a solution of **37** (740 mg, 2.5 mmol) in anhydrous THF (4 ml) was added and the mixture was stirred for 50 min at the same temperature. Allyl bromide (1.5 g, 12.5 mmol) was added to the mixture and stirred at −78 °C for 1 h and at −33 °C for 50 min. The reaction was quenched with ^{t}BuOH and stirred at room temperature to evaporate liquid NH_3. The mixture was extracted with Et_2O and the combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography [AcOEt–hexane (1 : 50)] to give **39** (300 mg, 36%) as a colorless oil. $[\alpha]_D^{17}$ −55.9° (c=1.13, $CHCl_3$). IR (neat) cm^{-1}: 1709, 1458, 1256, 1128, 1094, 1065, 837, 777. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.03 (6H, s), 0.72 (9H, s), 1.09 (1H, td, J=13.4, 4.5 Hz), 1.26—1.33 (1H, m), 1.50 (1H, m), 1.81—1.88 (2H, m), 2.09—2.16 (3H, m), 2.30 (1H, br d, J=15.1 Hz), 2.41 (1H, dt, J=13.4, 3.3 Hz), 2.44—2.51 (2H, m), 3.36—3.40 (1H, m), 3.44 (1H, dd, J=10.5, 5.5 Hz), 3.58 (1H, dd, J=10.5, 5.5 Hz), 3.71 (1H, br s), 5.01—5.07 (2H, m), 5.58 (1H, ddt, J=17.7, 9.9, 7.2 Hz). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: −5.3, −5.1, 18.4, 21.0, 25.2, 25.9, 26.4, 28.8, 38.3, 41.5, 51.8, 66.8, 78.7, 81.7, 118.3, 131.9, 212.9. MS m/z: 338 (M^+, 0.3), 281 (59), 197 (69), 105 (60), 75 (100). HR-MS m/z: 338.2231 (Calcd for $C_{19}H_{34}O_3Si$: 338.2277).

(2*S*,4a*S*,8a*S*)-4a-Allyl-2-(hydroxymethyl)-octahydro-1-benzopyran-5-one (41) HF-pyridine solution (0.5 ml) was added to a solution of **39** (160 mg, 0.48 mmol) in THF (5 ml) at 0 °C and the mixture was stirred for 30 min at room temperature. The mixture was extracted with Et_2O and the combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was chromatographed on silica gel [AcOEt–hexane (1 : 1)] to afford **41** (110 mg, 100%) as a colorless oil. $[\alpha]_D^{15}$ −63.9° (c=1.24, $CHCl_3$). IR (neat) cm^{-1}: 3435, 1705, 1447, 1130, 1072, 1042, 995, 918. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.12 (1H, ddd, J=13.4, 10.0, 7.8 Hz), 1.25 (1H, br s), 1.35—1.40 (2H, m), 1.84—1.89 (2H, m), 2.09—2.17 (3H, m), 2.29—2.33 (1H, m), 2.42 (1H, dt, J=13.4, 3.4 Hz), 2.49 (2H, dd, J=13.9, 7.0 Hz), 3.42—3.48 (2H, m), 3.48—3.55 (1H, m), 3.76 (1H, br s), 5.04—5.08 (2H, m), 5.57 (1H, ddt, J=16.6, 10.2, 7.1 Hz). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 21.0, 24.4, 26.3, 28.5, 38.3, 41.4, 51.8, 66.1, 78.4, 81.8, 118.5, 131.6, 212.6. MS m/z: 224 (M^+, 9), 193 (100). HR-MS m/z: 224.1392 (Calcd for $C_{13}H_{20}O_3$: 224.1412).

(2*S*,4a*S*,8a*S*)-4a-Allyl-2-(iodomethyl)-octahydro-1-benzopyran-5-one (42) PPh_3 (326 mg, 1.2 mmol), imidazole (90 mg, 1.3 mmol), and I_2 (314 mg, 1.2 mmol) were successively added to a solution of **41** (93 mg, 0.41 mmol) in anhydrous CH_2Cl_2 (4 ml) at room temperature and stirred for 17 h. The solvent was evaporated and Et_2O was added to the residue. The organic solution was washed with washed with saturated aqueous $Na_2S_2O_3$ solution and the aqueous solution was extracted with Et_2O. The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was purified by silica gel chromatography [AcOEt–hexane (1 : 2)] to afford **42** (121 mg, 88%) as a colorless oil. $[\alpha]_D^{15}$ −16.3° (c=1.36, $CHCl_3$). IR (neat) cm^{-1}: 1705, 1445, 1124, 1067, 920. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.13 (1H, td, J=13.3, 4.4 Hz), 1.39 (1H, dtd, J=16.0, 12.3, 4.1 Hz), 1.69 (1H, ddt, J=16.0, 4.4, 2.4 Hz), 1.84—1.92 (2H, m), 2.10—2.20 (3H, m), 2.28—2.35 (1H, m), 2.41 (1H, dt, J=12.7, 3.4 Hz), 2.44—2.54 (2H, m), 3.10 (1H, dd, J=10.2, 6.2 Hz), 3.13 (1H, dd, J=10.2, 5.1 Hz), 3.32 (1H, dddd, J=12.0, 6.2, 5.1, 2.4 Hz), 3.76 (1H, s), 5.00—5.17 (2H, m), 5.57 (1H, ddt, J=16.3, 9.5, 7.3 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 9.7, 21.1, 26.4, 28.5, 28.8, 38.3, 41.2, 51.3, 77.0, 82.0, 118.5, 131.5, 212.2. MS m/z: 334 (M^+, 37), 292 (100), 193 (46), 165 (43). HR-MS m/z: 334.0410 (Calcd for $C_{13}H_{19}IO_2$: 334.0430).

(4a*S*,8a*S*)-4a-Allyl-2-hydroxy-2-methyl-octahydro-1-benzopyran-5-one (44) DBU (580 mg, 3.8 mmol) was added to a solution of **42** (430 mg, 1.3 mmol) in anhydrous DMF (7.0 ml) at room temperature and stirred at 100 °C for 9.5 h. The reaction mixture was acidified (*ca.* pH 4) using 3 N HCl solution and stirred at room temperature for 3 h. The mixture was extracted with Et_2O and the combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was chromatographed on silica gel [AcOEt–hexane (1 : 2)] to afford **44** (130 mg, 45% from **42**) as a colorless oil. $[\alpha]_D^{17}$ −123.9° (c=1.02, $CHCl_3$). IR (neat) cm^{-1}: 3412, 1701, 1119, 1067, 1009, 920. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.57 (3H, s), 1.57—1.63 (2H, m), 1.68—1.73 (1H, m), 1.85 (2H, br), 2.08—2.22 (4H, m), 2.27—2.32 (1H, m), 2.49 (2H, m), 4.28 (1H, br), 5.00—5.10 (2H, m), 5.59 (1H, ddt, J=16.8, 9.5, 7.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.4, 24.5, 26.2, 29.8, 31.7, 38.6, 41.5,

50.9, 74.2, 95.7, 118.3, 131.6, 212.7. MS *m/z*: 224 (M^+, 12), 206 (54), 123 (51), 43 (100). HR-MS *m/z*: 224.1405 (Calcd for $C_{13}H_{20}O_3$: 224.1412).

(2*S*,3*S*)-3-Acetoxy-2-allyl-2-(3-oxobutyl)cyclohexanone (45) Et_3N (13 mg, 0.13 mmol), Ac_2O (6.5 mg, 0.064 mmol), and a catalytic amount of DMAP were added to a solution of **44** (9.5 mg, 0.042 mmol) in anhydrous CH_2Cl_2 (1 ml) at room temperature and stirred for 6 d. The solvent and excess reagents were evaporated at reduced pressure and the residue was extracted with Et_2O. The organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography [AcOEt–hexane (1 : 2)] to afford **45** (8.9 mg, 79%) as a colorless oil. $[\alpha]_D^{17}$ +5.4° (*c*=1.40, $CHCl_3$). IR (neat) cm^{-1}: 1738, 1713, 1373, 1236, 1169, 1030, 920. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.61 (1H, br), 1.68—1.74 (1H, m), 1.83—1.97 (3H, m), 2.05 (3H, s), 2.05—2.13 (1H, m), 2.13 (3H, s), 2.19—2.30 (2H, m), 2.33 (1H, dd, *J*=11.0, 5.5 Hz), 2.37—2.42 (2H, m), 2.49 (1H, dd, *J*=14.2, 6.6 Hz), 4.98—5.08 (3H, m), 5.60 (1H, dddd, *J*=16.9, 9.1, 7.9, 6.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.2, 21.1, 23.8, 25.4, 30.1, 36.2, 37.2, 38.0, 55.1, 75.4, 118.6, 132.6, 169.7, 207.5, 210.8. MS *m/z*: 266 (M^+, 1), 206 (32), 136 (37), 43 (100). HR-MS *m/z*: 266.1508 (Calcd for $C_{15}H_{22}O_4$: 266.1518).

(1*S*,8a*S*)-1-Acetoxy-8a-allyl-1,2,3,4,8,8a-hexahydro-6(7*H*)-naphthalenone (46) Pyrrolidine (39 mg, 0.55 mmol) was added to a solution of **45** (150 mg, 0.55 mmol) in benzene (5 ml) at room temperature and stirred for 24 h at the same temperature, followed by being refluxed for 3.5 h. The mixture was extracted with AcOEt and the combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was chromatographed on silica gel [AcOEt–hexane (1 : 2)] to afford **46** (110 mg, 79%) as a colorless solid. The analytical sample was recrystallized from hexane to provide colorless needles (mp 75—76 °C). $[\alpha]_D^{22}$ −37.8° (*c*=1.22, $CHCl_3$). IR (neat) cm^{-1}: 1732, 1672, 1373, 1238, 1161, 1018, 962, 920. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.73—1.89 (4H, m), 1.93—2.10 (2H, m), 2.05 (3H, s), 2.31—2.41 (2H, m), 2.44—2.54 (4H, m), 5.00 (1H, br s), 5.18 (1H, d, *J*=17.2 Hz), 5.19 (1H, d, *J*=10.0 Hz), 5.79 (1H, ddt, *J*=17.2, 10.0, 7.2 Hz), 5.89 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 20.4, 21.3, 25.5, 26.9, 31.7, 34.0, 38.4, 42.6, 74.8, 119.5, 126.9, 131.9, 165.7, 170.0, 198.5. MS *m/z*: 248 (M^+, 5), 206 (100), 188 (70), 165 (89), 147 (76), 123 (52), 43 (60). HR-MS *m/z*: 248.1387 (Calcd for $C_{15}H_{20}O_3$: 248.1412).

(2*S*,4a*S*,5*S*,8a*S*)-4a-Allyl-2-(*tert*-butyldimethylsilanyloxymethyl)-5-hydroxy-octahydro-1-benzopyran-5-one (48) and (2*S*,4a*S*,5*R*,8a*S*)-4a-Allyl-2-(*tert*-butyldimethylsilanyloxymethyl)-5-hydroxy-octahydro-1-benzopyran-5-one (49) MeOH (35 mg, 1.1 mmol) and $LiBH_4$ (2.4 mg, 0.092 mmol) were successively added to a solution of **40** (31 mg, 0.092 mmol) in Et_2O (5 ml) at −30 °C and stirred for 15 min at the same temperature. The mixture was extracted with Et_2O and the combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was chromatographed on silica gel [AcOEt–hexane (1 : 19)] to afford **49** (2 mg, 6%) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.06 (6H, s), 0.89 (9H, s), 1.34—1.68 (5H, m), 1.68—1.93 (5H, m), 2.02—2.21 (2H, m), 3.20 (1H, br), 3.32 (1H, br d, *J*=1.7 Hz), 3.39—3.49 (1H, m), 3.52—3.68 (3H, m), 4.92—5.08 (2H, m), 5.62—5.79 (1H, m). From the later fraction, **48** (26 mg, 84%) was obtained as a colorless oil. $[\alpha]_D^{16}$ −4.4° (*c*=1.32, $CHCl_3$). IR (neat) cm^{-1}: 3412, 1450, 1254, 1084, 837, 717. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.05 (3H, s), 0.06 (3H, s), 0.89 (9H, s), 1.25 (1H, br s), 1.43 (1H, td, *J*=13.2, 5.4 Hz), 1.52—1.66 (6H, m), 1.71 (1H, tt, *J*=8.0, 2.8 Hz), 1.75—1.80 (1H, m), 2.05 (1H, dt, *J*=13.2, 3.1 Hz), 2.11 (1H, dd, *J*=14.0, 7.4 Hz), 2.25 (1H, dd, *J*=14.0, 7.4 Hz), 3.33—3.38 (1H, m), 3.40 (1H, br s), 3.51 (1H, dd, *J*=10.5, 5.4 Hz), 3.65 (1H, dd, *J*=10.5, 5.6 Hz), 4.12 (1H, dd, *J*=11.2, 4.4 Hz), 5.05—5.11 (2H, m), 5.91 (1H, ddt, *J*=17.3, 9.6, 7.4 Hz). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: −5.3, −5.2, 18.4, 19.8, 23.9, 25.9, 26.5, 28.1, 30.2, 36.2, 39.8, 66.8, 69.0, 78.5, 79.3, 117.5, 135.0. FAB-MS *m/z*: 341 (M^++1).

(2*S*,4a*S*,5*S*,8a*S*)-5-Acetoxy-4a-allyl-2-(*tert*-butyldimethylsilanyloxymethyl)-octahydro-1-benzopyran-5-one (50) Et_3N (140 mg, 1.4 mmol), Ac_2O (280 mg, 2.8 mmol), and a catalytic amount of DMAP were successively added to a solution of **48** (310 mg, 0.92 mmol) in anhydrous CH_2Cl_2 (6 ml) at room temperature and stirred for 12 h. The solvent and excess reagents were evaporated at reduced pressure and the residue was extracted with Et_2O. The combined organic solution was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography [AcOEt–hexane (1 : 5)] to afford **50** (340 mg, 97%) as a colorless oil. $[\alpha]_D^{15}$ +9.3° (*c*=1.27, $CHCl_3$). IR (neat) cm^{-1}: 1736, 1364, 1242, 1086, 1028, 837, 777. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.05 (3H, s), 0.06 (3H, s), 0.88 (9H, s), 1.43—1.67 (9H, m), 1.78—1.79 (1H, m), 2.04 (3H, s), 2.18 (1H, dd, *J*=14.3, 8.1 Hz), 2.27 (1H, dd, *J*=14.3, 7.1 Hz), 3.32—3.36 (1H, m), 3.44 (1H, br s), 3.50 (1H, dd, *J*=10.5, 5.4 Hz), 3.66 (1H, dd, *J*=10.5, 6.1 Hz), 5.05 (1H, d, *J*=16.1 Hz), 5.06 (1H, d, *J*=10.5 Hz), 5.38 (1H, dd, *J*=11.4, 4.5 Hz), 5.82 (1H, ddt, *J*=16.1, 10.5, 7.7 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: −5.2, −5.0, 18.4, 19.3, 21.3, 24.2, 26.0, 26.3, 26.5, 28.3, 36.5, 38.8, 66.8, 71.6, 78.7, 78.8, 117.6, 134.0, 170.5. FAB-MS *m/z*: 383 (M^++1), 325, 265, 173.

(2*S*,4a*S*,5*S*,8a*S*)-5-Acetoxy-4a-allyl-2-hydroxy-octahydro-1-benzopyran-5-one (51) TBAF (1.0 M solution in THF, 1.5 ml, 1.50 mmol) was added to a solution of **50** (478 mg, 1.25 mmol) in THF (5 ml) at 0 °C and stirred for 4 h at room temperature. The mixture was extracted with AcOEt and the combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was chromatographed on silica gel [AcOEt–hexane (1 : 2)] to afford **51** (337 mg, 100%) as a colorless oil. $[\alpha]_D^{15}$ +22.9° (*c*=1.16, $CHCl_3$). IR (neat) cm^{-1}: 3435, 1732, 1448, 1375, 1244, 1088, 1028, 914, 880. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.23—1.29 (1H, m), 1.33 (1H, br d, *J*=16.8 Hz), 1.43—1.79 (8H, m), 2.04 (3H, s), 2.14 (1H, br), 2.19 (1H, dd, *J*=14.4, 7.0 Hz), 2.28 (1H, dd, *J*=14.4, 8.1 Hz), 3.40—3.44 (1H, m), 3.48 (1H, s), 3.55 (2H, br s), 5.06 (1H, d, *J*=16.9 Hz), 5.07 (1H, d, *J*=10.3 Hz), 5.36 (1H, dd, *J*=11.1, 4.3 Hz), 5.82 (1H, ddt, *J*=16.9, 10.3, 8.1 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 19.2, 21.2, 23.3, 26.3, 26.5, 28.1, 36.5, 38.8, 66.2, 71.3, 78.3, 78.8, 117.8, 133.7, 170.4. FAB-MS *m/z*: 269 (M^++1), 209.

(2*S*,4a*S*,5*S*,8a*S*)-5-Acetoxy-4a-allyl-2-(iodomethyl)-octahydro-1-benzopyran-5-one (52) PPh_3 (560 mg, 2.2 mmol), imidazole (160 mg, 2.3 mmol), and I_2 (540 mg, 2.2 mmol) were successively added to a solution of **51** (190 mg, 0.71 mmol) in anhydrous CH_2Cl_2 (5 ml) at room temperature and stirred for 1 h. The solvent was evaporated and the residue was extracted with AcOEt. The organic solution was washed with washed with saturated aqueous $Na_2S_2O_3$ solution and the aqueous phase was extracted with AcOEt. The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was purified by silica gel chromatography [AcOEt–hexane (1 : 5)] to afford the iodide **52** (260 mg, 96%) as a colorless oil; $[\alpha]_D^{17}$ +35.3° (*c*=1.25, $CHCl_3$). IR (neat) cm^{-1}: 1734, 1373, 1242, 1032, 999, 914, 669. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.40—1.69 (9H, m), 1.75—1.83 (1H, m), 2.04 (3H, s), 2.19 (1H, dd, *J*=14.4, 6.8 Hz), 2.28 (1H, dd, *J*=14.4, 7.8 Hz), 3.20 (2H, d, *J*=5.4 Hz), 3.23—3.30 (1H, m), 3.49 (1H, br s), 5.055 (1H, d, *J*=16.7 Hz), 5.065 (1H, d, *J*=10.1 Hz), 5.39 (1H, dd, *J*=11.4, 4.8 Hz), 5.80 (1H, dddt, *J*=16.7, 10.1, 7.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 10.0, 19.3, 21.3, 26.3, 26.5, 27.4, 28.3, 36.2, 38.5, 71.4, 77.0, 79.3, 117.8, 133.7, 170.4. MS *m/z*: 378 (M^+, 0.2), 336 (11), 276 (100), 237 (24), 149 (55), 148 (43). HR-MS *m/z*: 378.0682 (Calcd for $C_{15}H_{23}IO_3$: 378.0692).

(4a*S*,5*S*,8a*S*)-5-Acetoxy-4a-allyl-2-hydroxy-2-methyl-octahydro-1-benzopyran-5-one (53) DBU (25 mg, 0.16 mmol) was added to a solution of **52** (20 mg, 0.054 mmol) in anhydrous DMF (0.5 ml) at room temperature and stirred at 100 °C for 10 h. The reaction mixture was acidified (*ca.* pH 3) using 3 N HCl solution and stirred at room temperature for 5 min. The mixture was extracted with Et_2O and the organic solution was washed with saturated aqueous $NaHCO_3$ solution. The aqueous solution was extracted with AcOEt and the combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was chromatographed on silica gel [AcOEt–hexane (1 : 2)] to afford the acetal **53** (8.7 mg, 60% from **53**) as a colorless oil. $[\alpha]_D^{22}$ −23.4° (*c*=1.06, $CHCl_3$). IR (neat) cm^{-1}: 3433, 1734, 1719, 1375, 1244, 1217, 1028, 914. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.26—1.49 (3H, m), 1.42 (3H, s), 1.58—1.87 (7H, m), 2.04 (3H, s), 2.15—2.35 (2H, m), 4.02 (2H, br s), 5.00—5.10 (2H, m), 5.34 (1H, dd, *J*=11.4, 4.3 Hz), 5.87 (1H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 19.2, 21.2, 24.2, 25.9, 26.5, 30.3, 30.5, 36.5, 37.8, 70.7, 70.9, 95.4, 117.5, 133.9, 170.5. MS *m/z*: 251 (M^+−OH, 13), 250 (M^+−H_2O, 10), 166 (45), 132 (49), 107 (49), 43 (100). HR-MS *m/z*: 250.1549 (Calcd for $C_{15}H_{22}O_3$: 250.1569).

(2*R*,3*S*)-3-Acetoxy-2-allyl-2-(3-oxobutyl)-cyclohexanone (54) Celite, powdered molecular sieves 4 Å, and a solution of **53** (78 mg, 0.29 mmol) in anhydrous CH_2Cl_2 (1.5 ml) were added to a suspension of PCC (190 mg, 0.87 mmol) and NaOAc (24 mg, 0.29 mmol) in anhydrous CH_2Cl_2 (1.5 ml) at room temperature. After being stirred for 9 h, Florisil was added and stirred for several minutes. The mixture was filtered through a Celite pad and the filtrate was concentrated at reduced pressure. The residue was purified by silica gel column chromatography [AcOEt–hexane (1 : 2)] to afford **54** (51 mg, 66%) as a colorless oil. $[\alpha]_D^{24}$ −17.5° (*c*=1.11, $CHCl_3$). IR (neat) cm^{-1}: 1738, 1711, 1373, 1232. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.79—1.88

(2H, m), 1.91—1.97 (3H, m), 2.05 (3H, s), 2.12 (3H, s), 2.06—2.22 (2H, m), 2.28—2.37 (2H, m), 2.43—2.52 (3H, m), 5.02—5.12 (3H, m), 5.60 (1H, ddt, J=11.6, 6.6, 4.9 Hz); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 20.5, 21.0, 25.0, 25.3, 30.1, 33.7, 37.5, 38.1, 54.5, 75.7, 118.9, 132.4, 169.8, 207.3, 211.9. MS *m/z*: 266 (M^+, 1), 206 (32), 163 (34), 148 (46), 136 (52), 43 (100). HR-MS *m/z*: 266.1503 (Calcd for $C_{15}H_{22}O_4$: 266.1518).

(1*S*,8a*R*)-1-Acetoxy-8a-allyl-1,2,3,4,8,8a-hexahydro-6(7*H*)-naphthalenone (55) Pyrrolidine (2.5 mg, 0.036 mmol) was added to a solution of **54** (9.5 mg, 0.036 mmol) in benzene (0.5 ml) at room temperature and stirred for 12 h at the same temperature, followed by being refluxed for 40 min. The mixture was extracted with AcOEt and the combined organic solution was dried over anhydrous $MgSO_4$, and concentrated. The residue was chromatographed on silica gel [AcOEt–hexane (1 : 2)] to afford **55** (7.3 mg, 82%) as a colorless oil. $[\alpha]_D^{16}$ +46.4° (c=1.03, $CHCl_3$). IR (neat) cm^{-1}: 1732, 1674, 1373, 1238, 1036, 916. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.49 (1H, qt, J=13.2, 4.5 Hz), 1.76—1.84 (2H, m), 1.91—1.99 (2H, m), 2.10 (3H, s), 2.10—2.17 (1H, m), 2.20—2.24 (1H, m), 2.32—2.39 (2H, m), 2.42—2.51 (2H, m), 2.65 (1H, dd, J=14.5, 6.8 Hz), 4.80 (1H, dd, J=11.5, 4.6 Hz), 5.07 (1H, d, J=10.1 Hz), 5.14 (1H, dd, J=17.0, 1.3 Hz), 5.78 (1H, m), 5.91 (1H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.2, 23.8, 26.8, 30.8, 32.2, 34.0, 36.9, 43.7, 78.4, 118.2, 127.1, 133.9, 164.5, 170.1, 198.9. MS *m/z*: 248 (M^+, 0.1), 220 (10), 188 (19), 165 (23), 139 (25), 105 (100), 77 (25). HR-MS *m/z*: 248.1389 (Calcd for $C_{15}H_{20}O_3$: 248.1412).

(*S*)-8a-Allyl-3,4,8,8a-tetarahydro-1,6(2*H*,7*H*)-naphthalenedione [(*S*)-56] DBU (34.2 mg, 0.225 mmol) was added to a solution of **46** (46.5 mg, 0.187 mmol) in methanol (1.0 ml) at room temperature and the mixture was stirred for 3.5 h at the same temperature. The mixture was concentrated at the reduced pressure. 3% HCl and H_2O were added to the residue and extracted with Et_2O. The combined organic solution was successively washed with saturated aqueous $NaHCO_3$ and NaCl solution, dried over anhydrous $MgSO_4$. The solvent was evaporated to provide the crude alcohol (36.6 mg), which was used to the next reaction without further purification.

PDC (0.211 g, 0.561 mmol) was added to a solution of the crude alcohol (36.6 mg) in anhydrous CH_2Cl_2 (1.5 ml) and stirred for 18 h at room temperature. Florisil and Et_2O was added to the mixture and filtered through a Celite pad. The filtrate was concentrated and the residue was purified by silica gel column chromatography [AcOEt–hexane (1 : 2)] to afford **(*S*)-56** (29.6 mg, 77% from **46**) as colorless oil. $[\alpha]_D^{22}$ −80.4° (c=0.55, $CHCl_3$) [lit.[12]) for *R*-enantiomer: $[\alpha]_D^{25}$ +90° (c=1.1, $CHCl_3$)]. IR (neat) cm^{-1}: 1710, 1670. ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.72 (1H, qt, J=13.4, 4.3 Hz), 2.03—2.11 (1H, m), 2.14—2.20 (1H, m), 2.23 (1H, dt, J=14.8, 4.5 Hz), 2.42 (1H, d, J=4.5 Hz), 2.42—2.44 (1H, m), 2.49—2.51 (1H, m), 2.52—2.54 (1H, m), 2.56 (1H, dd, J=14.6, 7.7 Hz), 2.64—2.70 (2H, m), 2.79 (1H, td, J=13.5, 5.4 Hz), 5.12—5.16 (2H, m), 5.56—5.64 (1H, m), 5.90 (1H, d, J= 1.4 Hz). ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 23.2, 26.0, 31.8, 33.2, 38.2, 39.6, 54.5, 119.2, 126.3, 131.5, 164.8, 197.9, 209.1. MS *m/z*: 204 (M^+, 33.1), 43 (100). HR-MS *m/z*: 204.1158 (Calcd for $C_{13}H_{16}O_2$: 204.1150). *Anal.* Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.28; H, 7.99.

(*R*)-8a-Allyl-3,4,8,8a-tetarahydro-1,6(2*H*,7*H*)-naphthalenedione [(*R*)-56] DBU (31.3 mg, 0.205 mmol) was added to a solution of **55** (42.5 mg, 0.171 mmol) in methanol (1.0 ml) at room temperature and the mixture was stirred for 6 h at the same temperature. The mixture was concentrated at the reduced pressure. 3% HCl and H_2O were added to the residue and extracted with Et_2O. The combined organic solution was successively washed with saturated aqueous $NaHCO_3$ and NaCl solution, dried over anhydrous $MgSO_4$. The solvent was evaporated to provide the crude alcohol (31.9 mg), which was used to the next reaction without further purification.

PDC (0.258 g, 0.685 mmol) was added to a solution of the crude alcohol (31.9 mg) in anhydrous CH_2Cl_2 (1.5 ml) and stirred for 18 h at room temperature. Florisil and Et_2O was added to the mixture and filtered through a Celite pad. The filtrate was concentrated and the residue was purified by silica gel column chromatography [AcOEt–hexane (1 : 2)] to afford **(*R*)-56** (17.9 mg, 51% from **56**) as colorless oil; $[\alpha]_D^{21}$ +72.8° (c=0.28, $CHCl_3$) [lit.[12]) $[\alpha]_D^{25}$+90° (c=1.1, $CHCl_3$)]. The other spectral data were identified with those of **(*S*)-56**.

HPLC Conditions for (*S*)-56 and (*R*)-56 HPLC column: DICEL CHIRALCEL OD-H. Solvent: ^{i}PrOH–hexane (2.5 : 97.5). Flow rate: 0.5 ml/min. Retention time: (*S*)-**57**; 44.5 min, (*R*)-**57**; 43.1 min.

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