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STEREOSELECTIVE SYNTHESIS OF (2*S*,3*R*)- and (2*S*,3*S*)-2-AMINO-3-(3,4-DIHYDROXYPHENYL)-3-HYDROXYPROPANOIC ACID

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Dedicated to Professor Yasuyuki Kita on cerebration on his 77th birthday

Abstract – (2*S*,3*R*)- and (2*S*,3*S*)-2-amino-3-(3,4-dihydroxyphenyl)-3-hydroxypropanoic acids (ADHP) are often found in an unusual amino acid component of phomopsin B, ustiloxins, RA-IV, and MPC1001B. Herein, we would like to report stereoselective synthesis of (2*S*,3*R*)- and (2*S*,3*S*)-ADHP equivalents for the synthesis of ADHP containing natural products. The synthesis is characterized by the stereocontrolled construction of the (2*S*,3*R*)- and (2*S*,3*S*)-stereocenters starting from Garner's aldehyde as a common starting material.

INTRODUCTION

(2*S*,3*R*)- and (2*S*,3*S*)-2-amino-3-(3,4-dihydroxyphenyl)-3-hydroxypropanoic acids (ADHP) **1** are often found in biologically active natural products such as phomopsin B (**2**),[1] ustiloxin D (**3**),[2] RA-IV (**4**),[3] and MPC1001B (**5**)[4] (Figure 1). Phomopsin B (**2**) was isolated as a toxic principle of lupinosis which is a liver disease in sheep mainly caused by the consumption of lupin stalks colonised by the fungus *Diaporthe toxica*.[1] Ustiloxin D (**3**) is a plant toxin produced by *Ustilaginoidea virens*, a rice plant pathogen.[2] The 13-membered cyclophane ring containing natural products **2** and **3** bind to tubulin and inhibit tubulin polymerization, revealing anticancer activities. RA-IV (**4**)[3] isolated from *Rubia cordifolia* and *Rubia akane* (Rubiaceae) was discovered by a screening program of anticancer natural products. MPC1001B (**5**)[4] isolated from a *Cladorrhinum* sp. KY4922a displayed potent antiproliferative activities against human prostate cancer cell lines. Due to their unique structures and potent biological activities, **2**–**5** have received significant attention as synthetic targets and drug leads. Many efforts have been made for the

total synthesis and synthetic studies of phomopsin B (**2**),[5] ustiloxin D (**3**),[6] RA-IV (**4**),[7] and MPC1001B (**5**)[8] using ADHP derivatives as a synthetic intermediate.

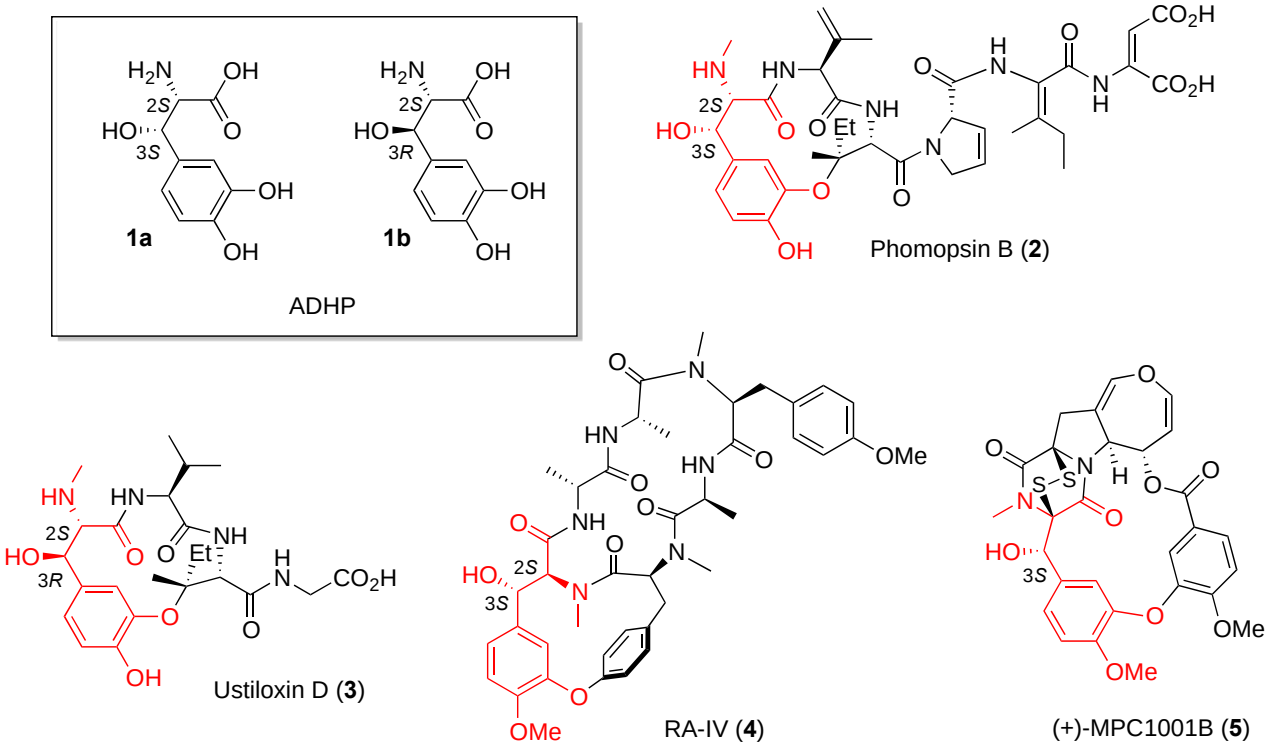
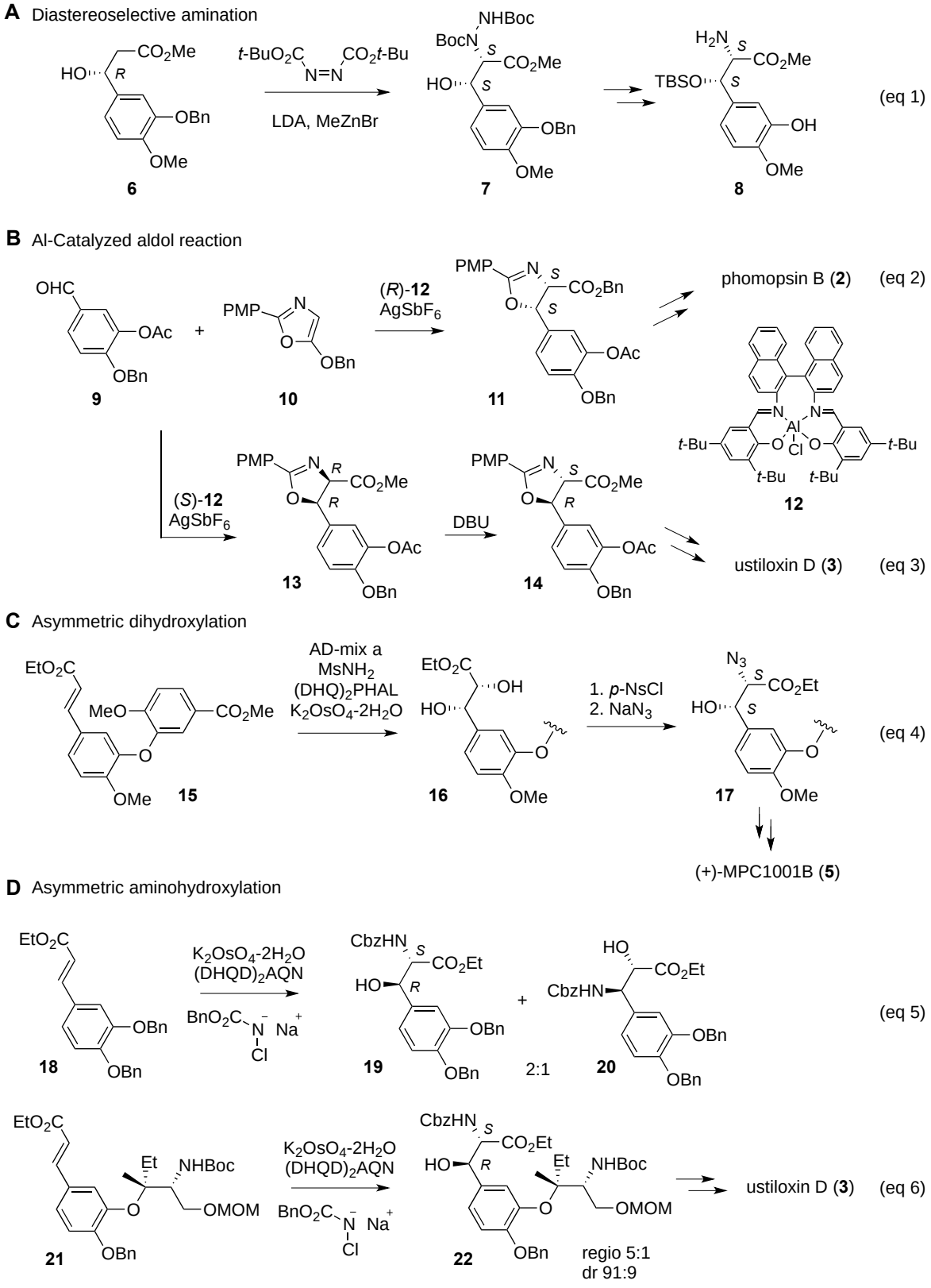


Figure 1. Structures of ADHP **1** and ADHP containing natural products **2**–**5**

Stereoselective syntheses of the unusual amino acids of **2**–**5** are the key to the total synthesis of **2**–**5**. Among them, (2*S*,3*S*)- and (2*S*,3*R*)-ADHP **1** offer synthetic challenges from the viewpoint of stereocontrol of the amino group containing concomitant stereocenters (Scheme 1). In 2001, Greck developed the diastereoselective synthetic route via amination reaction of *R*-ester **6** to give **7** in high stereoselectivity (eq 1).[7] The product **7** was transformed to (2*S*,3*S*)-**8** via the cleavage of the *N*-Boc hydrazine. Flexible syntheses of (2*S*,3*R*)- and (2*S*,3*S*)-ADHP derivatives **11** and **14** via the Evans's aldol type reaction using oxazole **10** were demonstrated in the total synthesis phomopsin B (**2**) and ustiloxin D (**3**) (eq 2 and 3).[5,6,9] Oxazole **10** was treated with benzaldehyde derivative **9** in the presence of chiral aluminum Lewis acid catalyst (*R*)-**12** to provide *cis*-**11** with high enantioselectivity. The resulting **11** was used for the total synthesis of phomopsin B with (2*S*,3*S*)-ADHP. (2*S*,3*R*)-ADHP derivative **14** was also prepared by taking advantage of the aldol reaction using (*S*)-chiral catalyst **12** followed by DBU-mediated isomerization from *cis*-**13** to *trans*-**14**. Tokuyama reported the stereoselective synthesis of (2*S*,3*S*)-ADHP derivative **17** via the Sharpless asymmetric dihydroxylation[100] of α,β-unsaturated ester **15** (eq 4).[8] The resulting chiral diol **16** was selectively transformed to mono-nosylate, followed by treatment with NaN_3 to give **17** with high selectivity. The Sharpless asymmetric aminohydroxylation is one of the attractive

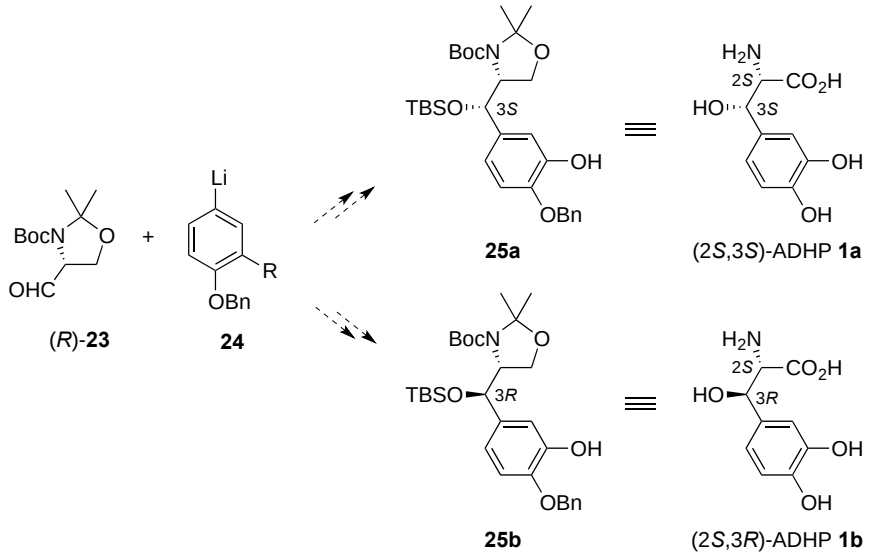
methods to provide straightforward access to (2*S*,3*R*)-ADHP derivatives from dihydroxycinnamic acid derivatives.



Scheme 1. Synthesis of optically active ADHP. A: diastereoselective amination, B: Al-catalyzed aldol type reaction , C: asymmetric dihydroxylation, D: asymmetric aminohydroxylation

However, Miller reported that the aminohydroxylation of **18** resulted in a 2:1 mixture of **19** and **20** in low selectivity (eq 5).[11] On the other hand, Joullié found that the regioselectivity improved when ester **21** bearing bulky side chain on the benzene ring was employed to give **22** with good selectivity (regioisomer ratio 5:1, diastereomeric ratio 91:9, eq 6).[6a,6e]

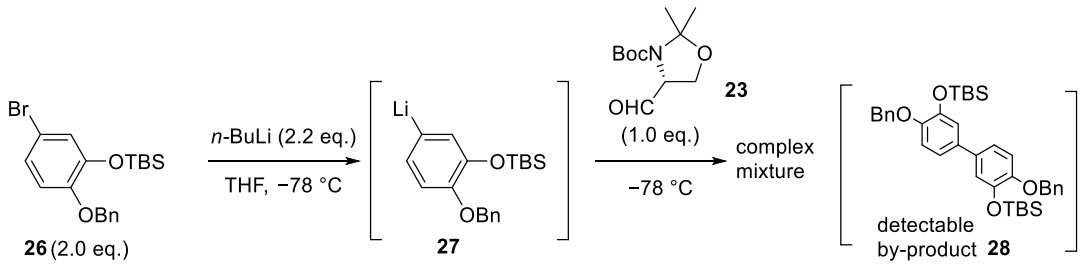
In this study, we would like to report the stereoselective synthesis of (2*S*,3*R*)- and (2*S*,3*S*)-ADHP **25a** and **25b** as equivalents of **1a** and **1b** for the total synthesis of ADHP-containing natural products (Scheme 2). Our new synthesis is characterized by the use of Garner's aldehyde (*R*)-**23** as a common intermediate[12] which enables flexible access to (2*S*,3*R*)- and (2*S*,3*S*)-ADHP **25a** and **25b**.



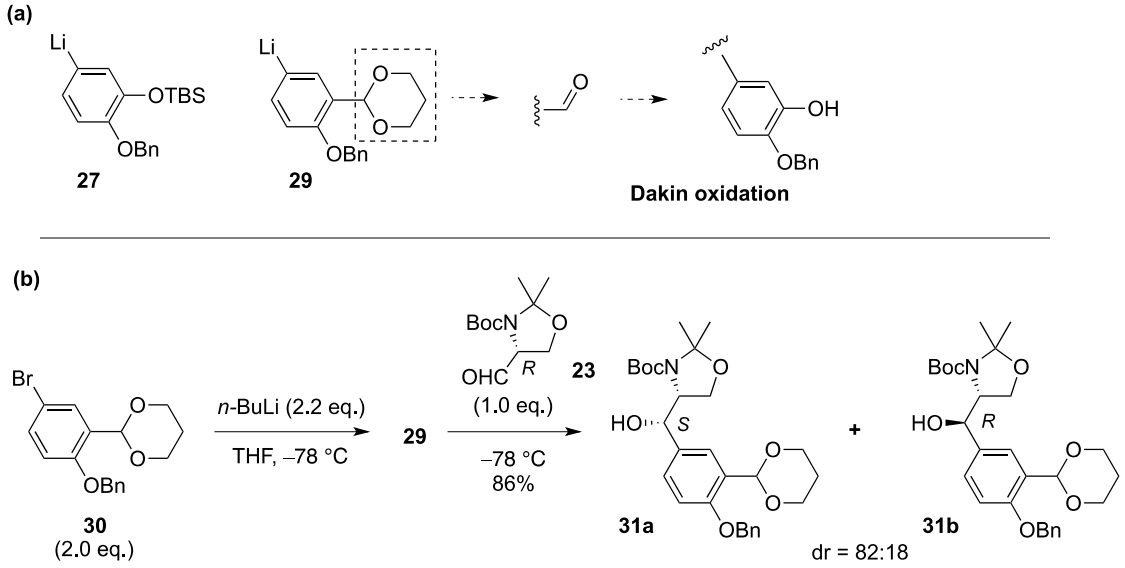
Scheme 2. Diastereoselective synthesis of ADHP equivalents **25a** and **25b** starting from Garner's aldehyde (*R*)-**23**

RESULTS AND DISCUSSION

We initially attempted nucleophilic addition of aryllithium reagent **27** derived from **26**[13] to Garner's aldehyde **23** (Scheme 3). However, the reaction resulted in a complex mixture to give a trace amount of the desired adduct with no reproducibility. The crude NMR analysis suggested the formation of dimer **28**, indicating the unstable propensity of the electron-rich aryllithium **27**. Thus, we turned our attention to acetal **29** as a surrogate of **27**. We expected that decreasing of the electron density of **27** would facilitate the formation of more stable aryllithium **29**. In addition, the putatively masked cyclic acetal group could be transformed to phenol by a series of sequential transformations: acetal hydrolysis and Dakin oxidation. Along this line, bromide **30**[14] was treated with *n*-BuLi in THF at −78 °C to generate the corresponding aryllithium **29** in situ. Then, Garner's aldehyde **23** was added to the solution to furnish a 82:18 mixture of (*S*)-**31a** and (*R*)-**31b** in 86% yield (Scheme 4). The structures of **31a** and **31b** were unambiguously determined by single crystal X-ray analysis of **31a** (Figure 2).[15]

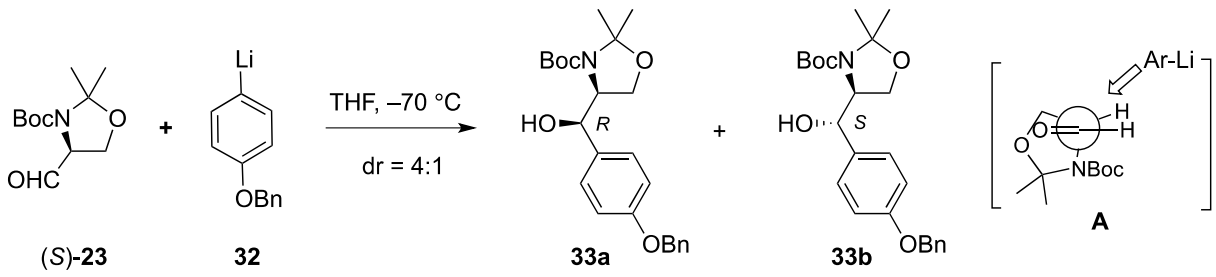


Scheme 3. Initial attempts for addition reaction of **27** to **23**



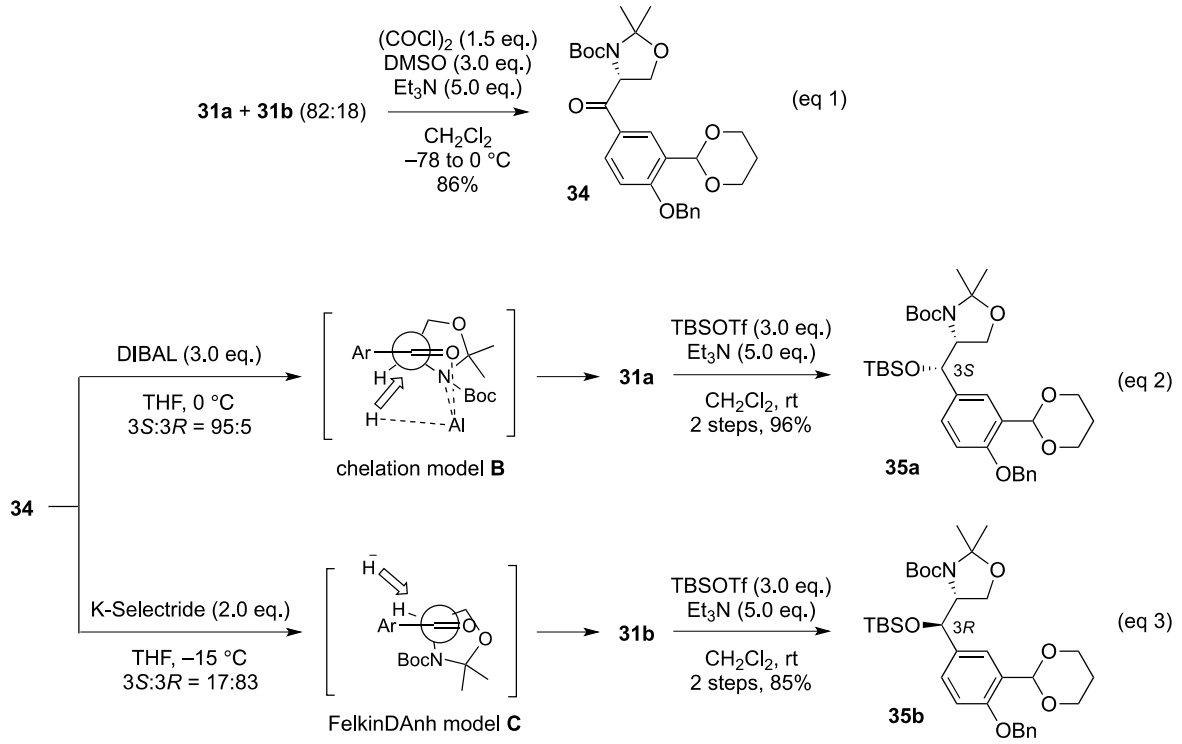
Scheme 4. (a) Structure of acetal surrogate **29** and synthetic plan from acetal to catechol via Dakin oxidation. (b) Addition of **29** to Garner's aldehyde (*R*)-**23**.

Hamada reported that the addition of aryllithium **32** to (*S*)-**23** gave **33a** as a major isomer (dr = 4:1) (Scheme 5).[16] The stereoselectivity is explained by Felkin–Anh transition state model **A**.[12b,12c] The nucleophile attacks from the least hindered upper face. In this model, the low-lying σ*C–N orbital is aligned parallel with the π- and π*-orbital of the carbonyl group. The orbital interaction would also contribute to the selective addition toward the carbamate nitrogen. Our observation providing **31a** as a major product from (*R*)-**23** in Scheme 4 are similar to that shown in Scheme 5. In this context, stereoselective formation of **31a** would be explained by the transition state model **A**.



Scheme 5. Diastereoselective addition of **32** to (*S*)-**23** and the transition state model **A**[16]

We next attempted stereoselective reduction of ketone **34** which was easily prepared by Swern oxidation of a mixture of **31a** and **31b** (dr = 82:18) (Scheme 6, eq 1). Treatment of **34** with DIBAL gave (*S*)-**31a** in high selectivity (dr = 95:5, eq 2).[17] The stereochemistry of (*S*)-**31a** was unambiguously confirmed by the single crystal X-ray analysis (Figure 2, CCDC 2045769). The stereoselective formation of **31a** was explained by chelation model B in which DIBAL could chelate the carbonyl and nitrogen atom of **34**. In this transition state, an intramolecular hydride shift would take place to create *S* stereochemistry. Switching to the reducing agent to K-Selectride® allowed predominant formation of (*R*)-**31b** (dr = 17:83, eq 3).[16,17] The selective hydride approach would be explained by Felkin–Anh transition state model **C**. These resulting alcohols **31a** and **31b** were converted to TBS ethers **35a** and **35b** in high yields (96% and 85% over 2 steps), respectively.



Scheme 6. Stereoselective reduction of ketone **34**

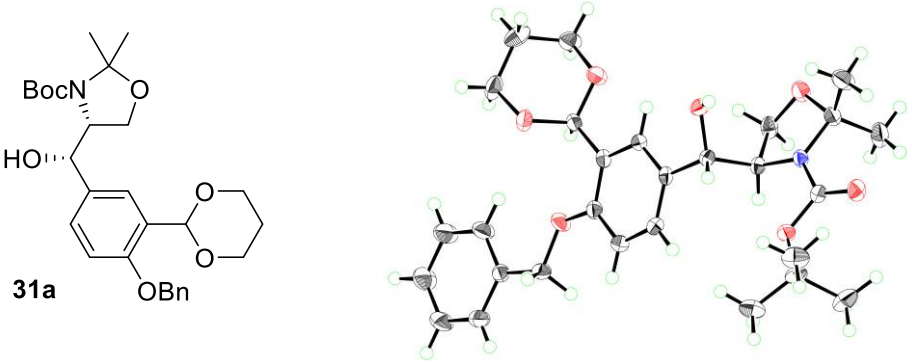
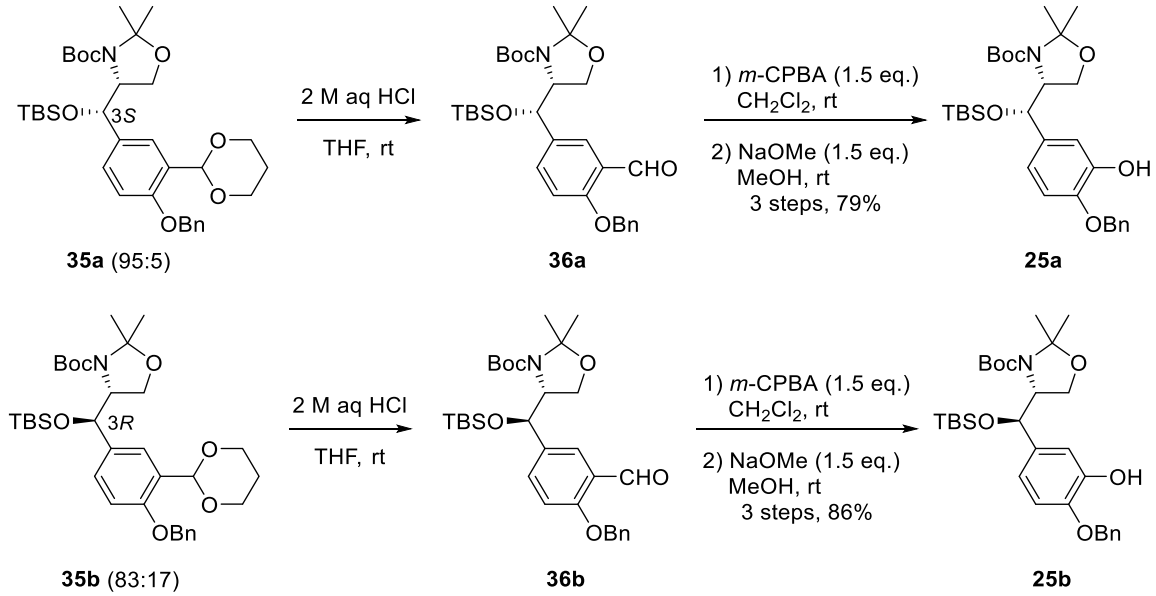


Figure 2. ORTEP view of **31a** referred as CCDC 2045769

(*S*)-Ether **35a** was smoothly transformed to ADHP equivalent (*S*)-**25a**. Removal of the cyclic acetal of **35a** by treatment with 2 M aq HCl in THF gave aldehyde **36a**. Dakin oxidation of **36a** with *m*-chloroperoxybenzoic acid (*m*-CPBA) followed by deformylation using NaOMe in MeOH gave (*S*)-**25a** (3 steps, 79%). In a similar manner, (2*S*,3*R*)-**35b** (dr = 83:17) was transformed to (2*S*,3*R*)-ADHP equivalent **25b** in good overall yield.



Scheme 7. Synthesis of ADHP equivalents **25a** and **25b** from **35a** and **35b**

In summary, we have developed stereoselective synthesis of (2*S*,3*R*)- and (2*S*,3*S*)-ADHP equivalents from Garner's aldehyde as a common starting material. The present method is scalable to prepared **25a** and **25b** on multi gram scale. Total synthesis of phomopsin B (**2**) and ustiloxin D (**3**) using **25a** and **25b** and further improvement of the diastereoselectivity are ongoing in our laboratory.

EXPERIMENTAL

General: All reagents and solvents were purchased from either Aldrich Chemical Company, Inc., Kanto Kagaku Co., Inc., Merck & Co., Inc., Nacalai Tesque Company, Ltd., Peptide Institute, Tokyo Chemical Industry Co., Ltd., or FUJIFILM Wako Pure Chemical Corporation, and used without further purification unless otherwise indicated. Dichloromethane (CH_2Cl_2) was distilled from phosphorus pentoxide (P_2O_5). Dimethyl sulfoxide (DMSO) was dried with MS4A, then fractionally distilled under reduced pressure. Methanol (MeOH) and tetrahydrofuran (THF) of anhydrous grade were used. Optical rotations were taken on a JASCO P-1030 or P-1010 polarimeter with a sodium lamp (D line) using $CHCl_3$ of a spectrochemical analysis grade. Melting points were determined with a Yanaco MP-21 melting point apparatus and were uncorrected. FTIR spectra were measured on a JASCO FT/IR-6200 or FT/IR-4100

infrared spectrophotometer. ^{1}H NMR spectra were recorded on Bruker AVANCE 300 (300 MHz), JEOL JNM-LA 400 (400 MHz), Bruker AVANCE 400 (400 MHz), JEOL JNM-ECS 400 (400 MHz), or JEOL JNM-ECA 600 (600 MHz) spectrometer. Chemical shifts of ^{1}H NMR were reported in parts per million (ppm, δ) relative to $CHCl_3$ (δ = 7.26) in $CDCl_3$. ^{13}C NMR spectra were recorded on Bruker AVANCE 300 (75 MHz), JEOL JNM-LA 400 (100 MHz), Bruker AVANCE 400 (100 MHz), or JEOL JNM-ECA 600 (150 MHz) spectrometer. Chemical shifts of ^{13}C NMR were reported in ppm (δ) relative to $CDCl_3$ (δ = 77.0) in $CDCl_3$. Low resolution mass spectra (LRMS) and high resolution mass spectra (HRMS) were obtained on JEOL JMS-AX500 for fast atom bombardment ionization (FAB) or JEOL JMS-T100LP for electrospray ionization (ESI). All reactions were monitored by thin layer chromatography (TLC), which was performed with precoated plates (silica gel 60 F-254, 0.25 mm thickness, manufactured by Merck). TLC visualization was accompanied using UV lamp (254 nm) or a charring solution (ethanoic phosphomolybdic acid, aqueous potassium permanganate and butanolic ninhydrin). Single crystals X-ray analysis was performed on a Mercury CCD diffractometer using graphite-monochromated Mo Kα radiation (λ = 0.71070 Å). The crystals were mounted on a CryoLoop with Paratone oil and placed in N2 stream at 200(2) K. Determination of the cell parameters and collection of the reflection intensities were performed using the CrystalClear software package. The structures were solved by direct methods using the program SIR97 and refined against F with full-matrix least squares techniques using the program SHELXL-97. All calculations were performed using the Yadokari-XG software package.

Addition reaction of aryllithium 29 to (*R*)-23

To a solution of **30**[14] (13.6 g, 38.8 mmol) in THF (190 mL) was slowly added *n*-BuLi (16 mL, 42.7 mmol, 2.65 M solution in hexane) at −78 °C to generate **29** in situ. After 30 min at −78 °C with stirring, a solution of (*R*)-**23**[18] (4.45 g, 19.4 mmol) in THF (39 mL) was added dropwise. The mixture was stirred for 1.5 h, quenched with sat. NH_4Cl aq. (250 mL), and extracted with EtOAc (200 mL × 3). The combined organic layers were washed with brine (600 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 15 : 1 to 1 : 1) to give a 82 : 18 mixture of **31a** and **31b** (8.38 g, 86%, dr = 82 : 18) as a white solid. ^{1}H and ^{13}C NMR spectra resulted in multiple signals because of the mixture of diastereomers and rotamers in $CDCl_3$ (Supporting Information). NMR data of the major isomer **31a** is shown in the experimental section of the improved synthesis of **31a** (95 : 5, next page). To estimate the diastereomeric ratio, assignable proton signals; a doublet of doublets proton at 4.70 ppm for the secondary benzyl alcohol proton of **31b** and aromatic doublet protons at 6.89 ppm for **31a** and **31b** were selected. The dr was calculated by the following equation: (integrated value B at 6.89 ppm – A) / integrated value A at 4.70 ppm;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2.4 Hz, 1 H), 7.45–7.30 (m, 6 H), 6.90 (d, *J* = 8.4 Hz, 1 H), 5.91 (s, 1 H), 5.13–5.10 (m, 2 H + 1 × 82/100 H), 4.70 (dd, *J* = 9.4, 3.8 Hz, 1 × 18/100 H), 4.26–3.62 and 2.39–1.31 (m, 25 H);

tert-Butyl (*R*)-4-(4-(benzyloxy)-3-(1,3-dioxan-2-yl)benzoyl)-2,2-dimethyloxazolidine-3-carboxylate (34)

To a solution of $(COCl)_2$ (2.2 mL, 25.2 mmol) in CH_2Cl_2 (40 mL) was added dropwise DMSO (3.6 mL, 50.3 mmol) in CH_2Cl_2 (9 mL) at −78 °C under argon. After the mixture was stirred at −78 °C for 30 min, a 82:18 mixture of **31a** and **31b** (8.38 g, 16.8 mmol) in CH_2Cl_2 (35 mL) was added dropwise to the mixture. The mixture was stirred for 1 h at −78 °C, then, Et_3N (12 mL, 83.9 mmol) was added to the mixture. The mixture was stirred for 15 min at −78 °C and for 20 min at 0 °C, quenched with sat. $NaHCO_3$ aq. (100 mL), and extracted with CH_2Cl_2 (60 mL × 3). The combined organic layers were washed with brine (200 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5 : 1 to 2 : 1) to give ketone **34** (7.21 g, 86%, a 3 : 2 mixture of rotamers) as a white solid;

mp 154–157 °C;

$[\alpha]_D^{25}$ +13.1 (*c* 1.55, $CHCl_3$);

FTIR (neat) 3376, 2977, 2935, 2865, 1698, 1605, 1501, 1389, 1365, 1254, 1173, 1093, 1006 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (m, 1 H), 7.95 (m, 1 H), 7.42–7.31 (m, 6 H), 7.00 (d, *J* = 8.7 Hz, 1 × 2/3H), 6.96 (d, *J* = 8.7 Hz, 1 × 1/3H), 5.89 (s, 1 × 2/3H), 5.87 (s, 1 × 1/3H), 5.49 (dd, *J* = 7.7, 3.8 Hz, 1 × 1/3H), 5.38 (dd, *J* = 7.7, 3.8 Hz, 1 × 2/3H), 5.19 (s, 2 × 2/3H), 5.17 (s, 2 × 1/3H), 4.34–4.21 (m, 3 H), 4.04–3.88 (m, 3 H), 2.25 (m, 1 H), 1.75 (s, 3 × 2/3H), 1.72 (s, 3 × 1/3H), 1.60–1.49 (m, 7 H), 1.28 (s, 6 H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2, 193.5, 159.6, 159.5, 152.0, 151.3, 136.1, 130.8, 128.54, 128.51, 128.2, 128.02, 127.95, 127.85, 127.7, 127.5, 127.4, 126.9, 112.04, 111.99, 96.3, 95.0, 94.4, 80.4, 80.0, 70.22, 70.16, 67.5, 67.41, 67.37, 66.2, 65.8, 61.5, 61.2, 28.3, 28.2, 25.73, 25.65, 25.3, 24.7, 24.6;

HRMS (FAB) calcd for $C_{28}H_{36}NO_7$ *m*/*z* 498.2492 $[M+H]^+$, found 498.2479, and $C_{28}H_{34}NO_7$ *m*/*z* 496.2335 $[M-H]^+$, found 496.2326.

DIBAL reduction of 34

To a solution of **34** (3.04 g, 6.11 mmol) in THF (31 mL) was slowly added DIBAL (18 mL, 18.3 mmol, 1.02 M solution in hexane) at 0 °C under argon. The mixture was stirred for 1 h and quenched with sat.

potassium sodium tartrate aq. (40 mL) with vigorous stirring. The mixture was stirred for additional 1 h at room temperature and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (90 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 5 : 1 to 1 : 1) to give **31a** (2.95 g, 96%, dr = 95 : 5) as a white solid. X-Ray crystallographic analysis of **31a** recrystallized from EtOAc confirmed the relative and absolute structure (CCDC 2045769).[15] To estimate the diastereomeric ratio, assignable proton signals; a doublet of doublets proton at 4.70 ppm for the secondary benzyl alcohol proton of **31b** and aromatic doublet protons at 6.89 ppm for **31a** and **31b** were selected. The dr was calculated by the following equation: (integrated value B at 6.89 ppm – A) / integrated value A at 4.70 ppm;

mp 140–141 °C;

$[\alpha]_D^{25}$ −4.8 (*c* 1.06, $CHCl_3$);

FTIR (neat) 3469, 2978, 2934, 2862, 1690, 1391, 1367, 1254, 1220, 1149, 1095 cm^{-1};

^1H NMR for major isomer **31a** (dr = 95 : 5) (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 2.0 Hz, 1 H), 7.44–7.29 (m, 6 H), 6.89 (d, *J* = 8.8 Hz, 1 H), 5.90 (s, 1 H), 5.09 (m, 3 H), 4.24–3.63 and 2.51–1.36 (m, 25 H);

^{13}C NMR spectra of **31a** resulted in multiple signals (Supporting Information);

HRMS (FAB) calcd for $C_{28}H_{38}NO_7$ *m*/*z* 500.2648 $[M+H]^+$, found 500.2658, and $C_{28}H_{36}NO_7$ *m*/*z* 498.2492 $[M-H]^+$, found 498.2493.

tert-Butyl (_R_)-4-((_S_)-(4-(benzyloxy)-3-(1,3-dioxan-2-yl)phenyl)((_tert_-butyldimethylsilyl)oxy)-methyl)-2,2-dimethyloxazolidine-3-carboxylate (35a)

To a solution of **31a** (2.95 g, 5.90 mmol, dr = 95 : 5) in CH_2Cl_2 (29 mL) were added Et_3N (4.1 mL, 29.5 mmol) and TBSOTf (4.1 mL, 17.7 mmol) at 0 °C. The mixture was stirred for 1 h at room temperature and quenched with sat. NH_4Cl aq. (40 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (30 mL × 2). The combined organic layers were washed with brine (90 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20 : 1 to 5 : 1) to give **35a** (3.66 g, quant., a 3 : 2 mixture of rotamers) as a colorless sticky oil;

$[\alpha]_D^{25}$ +10.5 (*c* 1.37, $CHCl_3$);

FTIR (neat) 2957, 2930, 2857, 1690, 1392, 1365, 1253, 1094, 1005 cm^{-1};

^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1 × 3/5 H), 7.62 (s, 1 × 2/5 H), 7.46–7.28 (m, 6 H), 6.88 (d, *J* = 8.4 Hz, 1 H), 5.88 (s, 1 H), 5.45 (s, 1 × 3/5 H), 5.11 (s, 1 × 2/5 H), 5.09 (s, 2 × 2/5 H), 5.07 (s, 2 × 3/5 H), 4.25-4.08 (m, 3 H), 4.00–3.89 (m, 3 H), 3.66 (t, *J* = 8.1 Hz, 1 × 2/5 H), 3.59 (t, *J* = 8.1 Hz, 1 × 3/5 H),

2.20 (m, 1 H), 1.68 (s, 3 × 2/5 H), 1.59 (s, 3 × 3/5H), 1.51–1.46 (m, 13 H), 0.93 (s, 9 H), 0.05 (s, 3 H), −0.17 (s, 3 H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 152.7, 152.3, 137.2, 134.8, 134.6, 128.3, 127.6, 127.3, 127.04, 126.95, 125.3, 118.3, 111.7, 96.9, 94.7, 94.3, 79.8, 79.7, 72.8, 70.5, 70.2, 63.7, 62.7, 62.1, 28.4, 26.3, 26.2, 26.0, 25.9, 25.7, 25.4, 23.1, 18.1, −4.9;

HRMS (FAB) calcd for $C_{34}H_{50}NO_7Si$ *m*/*z* 612.3357 $[M-H]^+$, found 612.3357.

tert-Butyl (_R_)-4-((_S_)-(4-(benzyloxy)-3-hydroxyphenyl)((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (25a)

To a solution of **35a** (3.62 g, 5.90 mmol, dr = 95 : 5) in THF (20 mL) was added 2 M aq. HCl (20 mL) at 0 °C and the solution was stirred for 3 h at room temperature. The mixture was quenched with sat. $NaHCO_3$ aq. (70 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give **36a**. The aldehyde **36a** was dissolved in CH_2Cl_2 (29 mL). *m*-CPBA (2.03 g, 8.84 mmol, contained with 25% water) was added to the solution at 0 °C under argon. The mixture was stirred for 15 h at room temperature and quenched with sat. Na_2SO_3 aq. (25 mL), and extracted with EtOAc (25 mL × 3). The combined organic layers were washed with sat. $NaHCO_3$ aq. (75 mL) then brine (75 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The resulting residue was subjected the next reaction without further purification. To a solution of residue in MeOH (29 mL) was added NaOMe (0.50 g, 8.84 mmol) at 0 °C under argon. The mixture was stirred for 3 h at room temperature and quenched with sat. NH_4Cl aq. (30 mL), and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (90 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20 : 1 to 10 : 1) to give **25a** (2.53 g, 79% over 3 steps, a 5 : 4 mixture of rotamers) as a colorless amorphous solid;

$[\alpha]_D^{25}$ +14.2 (*c* 1.43, $CHCl_3$);

FTIR (neat) 3421, 2954, 2929, 2885, 2857, 1687, 1508, 1456, 1377, 1364, 1275, 1254, 1173, 1120, 1094, 1070, 1009 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42–7.35 (m, 5 H), 6.97–6.72 (m, 3 H), 5.64 (brs, 1 × 4/9 H), 5.59 (brs, 1 × 5/9 H), 5.27 (d, *J* = 3.0 Hz, 1 × 5/9 H), 5.13–5.01 (m, 1 + 1 × 4/9 + 1 × 5/9 H), 4.86 (d, *J* = 4.8 Hz, 1 × 4/9 H), 4.15 (m, 1 H), 3.96 (m, 1 × 5/9 H), 3.87 (m, 1 × 4/9 H), 3.74 (dd, *J* = 8.8, 6.8 Hz, 1 × 4/9 H), 3.66 (dd, *J* = 8.8, 6.8 Hz, 1 × 5/9 H), 1.67 (s, 3 × 4/9 H), 1.59 (s, 3 × 5/9 H), 1.49–1.46 (m, 3 + 9 × 5/9 H), 1.36 (s, 9 × 4/9 H), 0.91 (s, 9 × 5/9 H), 0.90 (s, 9 × 4/9 H), 0.05 (s, 3 H), −0.15 (s, 3 × 5/9 H), −0.17 (s, 3 × 4/9 H);^{13}C NMR (150 MHz, $CDCl_3$) δ 152.8, 152.3, 145.5, 145.0, 144.8, 136.4, 136.3, 136.2, 128.70, 128.67,

128.40, 128.35, 127.9, 127.8, 118.1, 117.7, 113.0, 112.6, 111.7, 111.6, 94.7, 94.3, 80.0, 79.6, 73.2, 71.1, 71.0, 63.9, 63.7, 63.5, 62.4, 28.4, 28.3, 26.7, 26.6, 26.1, 26.0, 25.8, 25.4, 23.3, 18.2, −4.9;
HRMS (FAB) calcd for $C_{30}H_{46}NO_6Si$ *m*/*z* 544.3094 $[M+H]^+$, found 544.3091.

Reduction of 34 with K-Selectride®

To a solution of **34** (5.94 g, 11.9 mmol) in THF (60 mL) was added K-Selectride® (23.8 mL, 23.8 mmol, 1.0 M solution in THF) at −15 °C and the solution was stirred for 1 h at −15 to −10 °C. The mixture was quenched with sat. NH_4Cl aq. (60 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The resulting residue including **31b** was subjected to the next reaction without further purification (^1H and ^{13}C NMR spectra of **31b**: Supporting Information). To a solution of the residue in CH_2Cl_2 (57 mL) were added Et_3N (7.92 mL, 56.9 mmol) and TBSOTf (7.84 mL, 34.1 mmol) at 0 °C and the solution was stirred for 30 min at room temperature. The mixture was quenched with sat. NH_4Cl aq. (60 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 40 : 1 to 1 : 1) to give **35b** (5.96 g, 85% over 2 steps, dr = 83 : 17, a 1 : 1 mixture of rotamers) as a colorless amorphous solid; The dr was calculated after the conversion of **35b** to **25b**;
^1H NMR for major isomer **35b** (dr = 83 : 17) δ 7.49–7.30 (m, 7 H), 6.90 (m, 1 H), 5.87 (m, 1 H), 5.24 (d, *J* = 5.7 Hz, 1 × 1/2 H), 5.15 (d, *J* = 5.7 Hz, 1 × 1/2 H), 5.08 (s, 2 H), 4.27–3.84 (m, 7 H), 2.17 (m, 1 H), 1.60–1.51 (m, 13 H), 1.36 (s, 3 × 1/2 H), 1.33 (s, 3 × 1/2 H), 0.89 (s, 9 × 1/2 H), 0.88 (s, 9 × 1/2 H), 0.07 (s, 3 × 1/2 H), 0.04 (s, 3 × 1/2 H), −0.08 (s, 3 × 1/2 H), −0.11 (s, 3 × 1/2 H);
^{13}C NMR for major isomer **35b** (dr = 83 : 17) (100 MHz, $CDCl_3$) δ 155.1, 152.8, 152.0, 137.4, 134.3, 133.4, 132.8, 128.4, 127.6, 127.12, 127.08, 111.9, 111.8, 97.2, 97.0, 94.8, 94.2, 79.89, 79.83, 71.8, 71.3, 70.5, 70.4, 67.5, 67.3, 62.3, 62.6, 62.2, 61.9, 28.7, 28.5, 26.1, 25.94, 25.87, 25.8, 24.7, 23.2, 18.1, −4.7, −5.0; HRMS (ESI) calcd for $C_{34}H_{51}NNaO_7Si$ *m*/*z* 636.3333 $[M+Na]^+$, found 636.3333.

***tert*-Butyl (*R*)-4-((*R*)-(4-(benzyloxy)-3-hydroxyphenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (25b)**

To a solution of **35b** (5.96 g, 9.70 mmol, dr = 83 : 17) in THF (32 mL) was added 2 M aq. HCl (32 mL) at 0 °C and the solution was stirred for 3 h at room temperature. The mixture was quenched with sat. $NaHCO_3$ aq. (70 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (90 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give **36b**. The aldehyde **36b** was dissolved in CH_2Cl_2 (49 mL). *m*-CPBA (3.87 g, 14.6

mmol) was added to the solution at 0 °C. and the solution was stirred for 20 h at room temperature. The mixture was quenched with sat. $NaHCO_3$ aq. (50 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (90 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The resulting residue was subjected to the next reaction without further purification. To a solution of the residue in MeOH (49 mL) was added NaOMe (828 mg, 14.6 mmol) at 0 °C and the solution was stirred for 19 h at room temperature. The mixture was quenched with sat. NH_4Cl aq. (50 mL) and extracted with EtOAc (30 mL × 3). The combined organic layers were washed with brine (90 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc = 20 : 1 to 10 : 1) to give **25b** (5.01 g, 86% over 3 steps, dr = 83 : 17, a 1 : 1 mixture of rotamers) as a colorless amorphous solid;

^{1}H NMR for major isomer **25b** (dr = 83 : 17) (400 MHz, $CDCl_3$) δ 7.42–7.32 (m, 5 H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.79 (dd, *J* = 8.2, 2.0 Hz, 1 × 1/2 H), 6.73 (dd, *J* = 8.2, 2.0 Hz, 1 × 1/2 H), 5.58 (s, 1 × 1/2 H), 5.55 (s, 1 × 1/2 H), 5.17 (d, *J* = 5.6 Hz, 1 × 1/2 H), 5.08 (s, 2 H), 5.04 (d, *J* = 5.6 Hz, 1 × 1/2 H), 4.26 (brd, *J* = 9.4 Hz, 1 × 1/2 H), 4.21 (brd, *J* = 9.4 Hz, 1 × 1/2 H), 4.14 (m, 1 × 1/2 H), 4.00 (m, 1 × 1/2 H), 3.87 (t, *J* = 9.4, 7.0 Hz, 1 H), 1.59–1.46 (m, 12 H), 1.36 (s, 3 × 1/2 H), 1.34 (s, 3 × 1/2 H), 0.89 (s, 9 H), 0.07 (s, 3 × 1/2 H), 0.04 (s, 3 × 1/2 H), −0.06 (s, 3 × 1/2 H), −0.08 (s, 3 × 1/2 H);

^{13}C NMR for major isomer **25b** (dr = 83 : 17) (100 MHz, $CDCl_3$) δ 152.8, 152.1, 145.3, 145.23, 145.15, 145.0, 136.5, 136.4, 134.7, 134.3, 128.7, 128.4, 128.3, 127.8, 118.8, 114.1, 113.8, 111.4, 94.7, 94.1, 79.9, 71.8, 71.3, 71.2, 62.7, 62.6, 62.2, 62.0, 28.8, 28.5, 25.8, 24.8, 24.7, 23.1, 18.1, −4.7, −4.8, −5.0;

HRMS (ESI) calcd for $C_{30}H_{45}NNaO_6Si$ *m*/*z* 566.2914 $[M+Na]^+$, found 566.2914; ^{1}H NMR signals, −0.15 ppm for **25a** and, −0.08 and −0.06 ppm for **25b**, are selected to calculate the dr (83 : 17).

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REFERENCES AND NOTES

1. (a) C. C. J. Culvenor, P. A. Cockrum, J. A. Edgar, J. L. Frahn, C. P. Gorst-Allman, A. J. Jones, W. F. O. Marasas, K. E. Murray, L. W. Smith, P. S. Steyn, R. Vleggaar, and P. L. Wessels, *J. Chem. Soc., Chem. Commun.*, 1983, 1259; (b) M. F. Mackay, A. Van Donkelaar, and C. C. J. Culvenor, *J. Chem. Soc., Chem. Commun.*, 1986, 1219; (c) C. C. J. Culvenor, J. A. Edgar, M. F. Mackay, C. P.

Gorst-Allman, W. F. O. Marasas, P. S. Steyn, R. Vleggaar, and P. L. Wessels, *Tetrahedron*, 1989, **45**, 2351.

2. (a) Y. Koiso, M. Natori, S. Iwasaki, S. Sato, R. Sonoda, Y. Fujita, H. Yaegashi, and Z. Sato, *Tetrahedron Lett.*, 1992, **33**, 4157; (b) Y. Koiso, Y. Li, S. Iwasaki, K. Hanaoka, T. Kobayashi, R. Sonoda, Y. Fujita, H. Yaegashi, and Z. Sato, *J. Antibiot.*, 1994, **47**, 765.
3. (a) H. Itokawa, K. Takeya, N. Mori, T. Hamanaka, T. Sonobe, and K. Mihara, *Chem. Pharm. Bull.*, 1984, **32**, 284; (b) H. Itokawa and K. Takeya, *Heterocycles*, 1993, **35**, 1467; (c) H. Itokawa, K. Takeya, Y. Hitotsuyanagi, and H. Morita, In *The Alkaloids*; ed. by G. A. Cordell, Academic Press: New York, 1997; Vol. 49, pp. 301–387.
4. (a) N. Tsumagari, R. Nakai, H. Onodera, A. Hasegawa, E. S. Rahayu, K. Ando, and Y. Yamashita, *J. Antibiot.*, 2004, **57**, 532; (b) H. Onodera, A. Hasegawa, N. Tsumagari, R. Nakai, T. Ogawa, and Y. Kanda, *Org. Lett.*, 2004, **6**, 4101.
5. J. S. Grimley, A. M. Sawayama, H. Tanaka, M. M. Stohlmeyer, T. F. Woiwode, and T. J. Wandless, *Angew. Chem. Int. Ed.*, 2007, **46**, 8157.
6. (a) B. Cao, H. Park, and M. M. Joullié, *J. Am. Chem. Soc.*, 2002, **124**, 520; (b) H. Tanaka, A. M. Sawayama, and T. J. Wandless, *J. Am. Chem. Soc.*, 2003, **125**, 6864; (c) A. M. Sawayama, H. Tanaka, and T. J. Wandless, *J. Org. Chem.*, 2004, **69**, 8810; (d) P. Li, C. D. Evans, and M. M. Joullié, *Org. Lett.*, 2005, **7**, 5325; (e) P. Li, C. D. Evans, Y. Wu, B. Cao, E. Hamel, and M. M. Joullié, *J. Am. Chem. Soc.*, 2008, **130**, 2351; (f) A. L. Brown, Q. I. Churches, and C. A. Hutton, *J. Org. Chem.*, 2015, **80**, 9831.
7. O. Poupardin, F. Ferreira, J. P. Genet, and C. Greck, *Tetrahedron Lett.*, 2001, **42**, 1523.
8. T. Kurogi, S. Okaya, H. Fujiwara, K. Okano, and H. Tokuyama, *Angew. Chem. Int. Ed.*, 2016, **55**, 283.
9. D. A. Evans, J. M. Janey, N. Magomedov, and J. S. Tedrow, *Angew. Chem. Int. Ed.*, 2001, **40**, 1884.
10. P. R. Fleming and K. B. Sharpless, *J. Org. Chem.*, 1991, **56**, 2869.
11. L. Dong and M. J. Miller, *J. Org. Chem.*, 2002, **67**, 4759.
12. (a) P. Garner and J. M. Park, *Org. Synth.*, 1992, **70**, 18; (b) M. Passiniemi and A. M. P. Koskinen, *Beilstein J. Org. Chem.*, 2013, **9**, 2641; (c) X. Liang, J. Anderscha, and M. Bols, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2136.
13. K. Kawada, A. Arimura, T. Tsuri, M. Fuji, T. Komurasaki, S. Yonezawa, A. Kugimiya, N. Haga, S. Mitsumori, M. Inagaki, T. Nakatani, Y. Tamura, S. Takechi, T. Taishi, J. Kishino, and M. Ohtani, *Angew. Chem. Int. Ed.*, 1998, **37**, 973.
14. M. Berwe, W. Jöntgen, J. Krüger, Y. Cancho-Grande, T. Lampe, M. Michels, H. Paulsen, S. Raddatz, and S. Weigand, *Org. Process Res. Dev.*, 2011, **15**, 1348.

15. CCDC 2045769 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.
16. N. Okamoto, O. Hara, K. Makino, and Y. Hamada, *J. Org. Chem.*, 2002, **67**, 9210.
17. A. Nishida, H. Sorimachi, M. Iwaida, M. Matsumizu, T. Kawade, and M. Nakagawa, *Synlett*, 1998, 389.
18. A. D. Campbell, T. M. Raynham, and R. J. K. Taylor, *Synthesis*, 1998, 1707.