STEREOSELECTIVE SYNTHESIS OF (2S,3R)- and (2S,3S)-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 – (2S,3R)- and (2S,3S)-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 (2S,3R)- and (2S,3S)-ADHP equivalents for the synthesis of ADHP containing natural products. The synthesis is characterized by the stereocontrolled construction of the (2S,3R)- and (2S,3S)-stereocenters starting from Garner’s aldehyde as a common starting material.

INTRODUCTION

(2S,3R)- and (2S,3S)-2-amino-3-(3,4-dihydroxyphenyl)-3-hydroxypropanoic acids (ADHP) 1 are often found in biologically active natural products such as phomopsin B (2), ustiloxin D (3), RA-IV (4), and MPC1001B (5) (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) isolated from Rubia cordifolia and Rubia akane (Rubiaceae) was discovered by a screening program of anticancer natural products. MPC1001B (5) 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), ustiloxin D (3), RA-IV (4), and MPC1001B (5) using ADHP derivatives as a synthetic intermediate.

Stereoselective syntheses of the unusual amino acids of 2–5 are the key to the total synthesis of 2–5. Among them, (2S,3S)- and (2S,3R)-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). The product 7 was transformed to (2S,3S)-8 via the cleavage of the N-Boc hydrazine. Flexible syntheses of (2S,3R)- and (2S,3S)-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). 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 (2S,3S)-ADHP. (2S,3R)-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 (2S,3S)-ADHP derivative 17 via the Sharpless asymmetric dihydroxylation of α,β-unsaturated ester 15 (eq 4). The resulting chiral diol 16 was selectively transformed to mono-nosylate, followed by treatment with NaN₃ to give 17 with high selectivity. The Sharpless asymmetric aminohydroxylation is one of the attractive
methods to provide straightforward access to (2S,3R)-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). 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). In this study, we would like to report the stereoselective synthesis of (2S,3S)-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 which enables flexible access to (2S,3R)- and (2S,3S)-ADHP 25a and 25b.

![Scheme 2](image)

**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 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 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).
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). The stereoselectivity is explained by Felkin–Anh transition state model A. 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.
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). 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). 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, (2S,3R)-35b (dr = 83:17) was transformed to (2S,3R)-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 (2S,3R)- and (2S,3S)-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 (CH₂Cl₂) was distilled from phosphorus pentoxide (P₂O₅). 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 CHCl₃ 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 permangante and butanolic ninhydrin). Single crystals X-ray analysis was performed on a Mercury CCD diffractometer using graphite-monochromated Mo Kα radiation ($\lambda$ = 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 $^{30}$\textsuperscript{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\textsuperscript{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$_4$Cl 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;
**1H NMR** (400 MHz, CDCl$_3$) $\delta$ 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-benzyl-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$_2$Cl$_2$ (40 mL) was added dropwise DMSO (3.6 mL, 50.3 mmol) in CH$_2$Cl$_2$ (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$_2$Cl$_2$ (35 mL) was added dropwise to the mixture. The mixture was stirred for 1 h at −78 °C, then, Et$_3$N (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$_2$Cl$_2$ (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$^{-1}$;

**1H NMR** (300 MHz, CDCl$_3$) $\delta$ 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);

**13C NMR** (75 MHz, CDCl$_3$) $\delta$ 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). 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; [α]$_D^{25}$ −4.8 (c 1.06, CHCl$_3$);

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

$^1$H 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-(benzyl oxy)-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$_2$Cl$_2$ (29 mL) were added Et$_3$N (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$_4$Cl 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;

[α]$_D^{25}$ +10.5 (c 1.37, CHCl$_3$);

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

$^1$H 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 × 3/5 H), 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$_3$) $\delta$ 154.7, 152.7, 152.3, 137.2, 134.8, 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$_7$Si 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$_2$Cl$_2$ (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$_2$SO$_3$ 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$_4$Cl 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$_3$) $\delta$ 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$_3$) $\delta$ 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\textsubscript{30}H\textsubscript{46}NO\textsubscript{6}Si m/z 544.3094 [M+H]\textsuperscript{+}, 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\textsubscript{4}Cl aq. (60 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous MgSO\textsubscript{4}, and filtered. The filtrate was concentrated under reduced pressure. The resulting residue including 31b was subjected to the next reaction without further purification (\textsuperscript{1}H and \textsuperscript{13}C NMR spectra of 31b: Supporting Information). To a solution of the residue in CH\textsubscript{2}Cl\textsubscript{2} (57 mL) were added Et\textsubscript{3}N (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\textsubscript{4}Cl aq. (60 mL) and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine (150 mL), dried over anhydrous MgSO\textsubscript{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; \textsuperscript{1}H 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);
\textsuperscript{13}C NMR for major isomer 35b (dr = 83 : 17) (100 MHz, CDCl\textsubscript{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\textsubscript{34}H\textsubscript{51}NNaO\textsubscript{7}Si m/z 636.3333 [M+Na]\textsuperscript{+}, 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\textsubscript{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\textsubscript{4}, and filtered. The filtrate was concentrated under reduced pressure to give 36b. The aldehyde 36b was dissolved in CH\textsubscript{2}Cl\textsubscript{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 \times 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$_4$Cl aq. (50 mL) and extracted with EtOAc (30 mL \times 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$_3$) $\delta$ 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$_3$) $\delta$ 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$_5$Si 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


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.

