# Accepted Manuscript


Stereoselective allylation reactions of acyclic and chiral α-amino-β-hydroxy aldehydes 3: Total synthesis of (+)-1-*epi*-castanospermine

In-Soo Myeong, Won-Hun Ham

PII: S0040-4020(19)30645-3

DOI: https://doi.org/10.1016/j.tet.2019.06.005

Reference: TET 30397

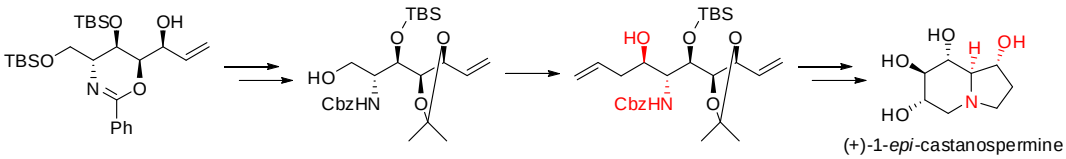
To appear in: *Tetrahedron*

Received Date: 18 April 2019

Revised Date: 28 May 2019

Accepted Date: 3 June 2019

Please cite this article as: Myeong I-S, Ham W-H, Stereoselective allylation reactions of acyclic and chiral α-amino-β-hydroxy aldehydes 3: Total synthesis of (+)-1-*epi*-castanospermine, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.06.005.




(+)-1-*epi*-castanospermine

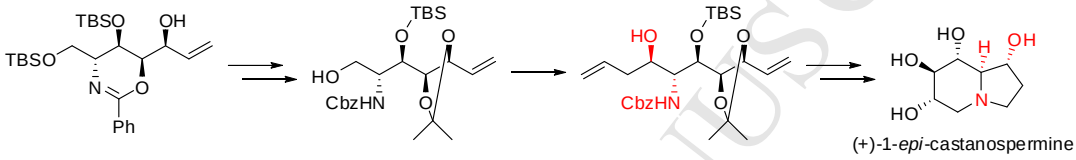
# Stereoselective Allylation Reactions of Acyclic and Chiral α-Amino-β-Hydroxy Aldehydes 3: Total Synthesis of (+)-1-*epi*-Castanospermine

In-Soo Myeong[†] and Won-Hun Ham*[,†,‡]

[†] School of Pharmacy, Sungkyunkwan University, Seobu-ro 2066, Suwon-si, Gyeonggi-do 16419, Republic of Korea; E-mail: whham@skku.edu

[‡] Yonsung Fine Chemicals Co., Ltd., Sujeong-ro 207, Jangan-myeon, Hwaseong-si, Gyeonggi-do 18581, Republic of Korea
*Supporting Information Placeholder*

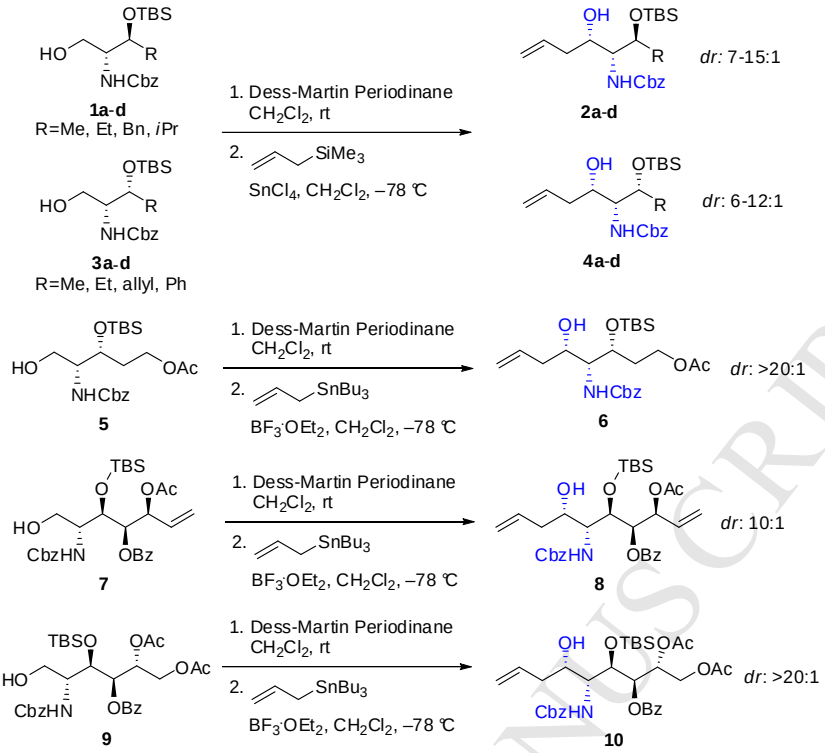
## ABSTRACT




Stereoselective allylation reactions of acyclic, chiral α-amino-β-hydroxy aldehydes containing four contiguous stereocenters were conducted. Allylation mediated by $MgBr_2 \cdot OEt_2$ afforded the *anti*-product. A plausible mechanism of the allylation reaction is also described. The resulting allylation product was used for the total synthesis of (+)-1-*epi*-castanospermine.

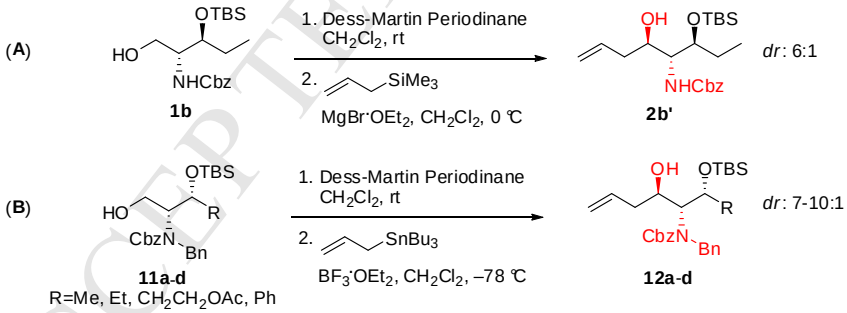
## 1. Introduction

Aminopolyols, whose structures range from simple to complex, are crucial structural motifs in natural products and medicinal agents.[1] Vicinal amino alcohols, a class of amino polyols, have been actively researched because of their structural significance in bioactive natural products.[2] We have previously reported the synthesis of β-amino-α,γ-diols via the stereoselective allylation reaction of α-amino-β-hydroxy aldehydes; the results are summarized in Schemes 1 and 2.[3] The allylation reactions of 2,3-*anti*-α-amino-β-hydroxy substrates **1a-d** mediated by $SnCl_4$ provided the corresponding *syn*-products **2a-d** (Scheme 1).[3a] The allylation reactions of 2,3-*syn*-α-amino-β-hydroxy substrates **3a-d** mediated by $SnCl_4$ furnished *syn*-products **4a-d**.[3a] The allylation of 3,4-*syn*-α-amino-β-hydroxy substrate **5** mediated by $BF_3 \cdot OEt_2$ gave *syn*-product **6**.[3b] The allylation of 5,6-*anti*-α-amino-β-hydroxy substrate **7** mediated by $BF_3 \cdot OEt_2$ provided *syn*-product **8**.[3c] The allylation of 4,5-*anti*-α-amino-β-hydroxy substrate **9** mediated by $BF_3 \cdot OEt_2$ provided *syn*-product **10**.[3c]




**Scheme 1**. Previous *syn*-selective allylation reactions of α-amino-β-hydroxy substrates.

The allylation of 2,3-*anti*-α-amino-β-hydroxy substrate **1b** mediated by $MgBr_2 \cdot OEt_2$ provided *anti*-product **2b′** (Scheme 2).[3a] The allylations of 2,3-*syn*-α-amino-β-hydroxy substrates **11a-d** mediated by $BF_3 \cdot OEt_2$ furnished *anti*-products **12a-d**.[3b]




**Scheme 2**. Previous *anti*-selective allylation reactions of α-amino-β-hydroxy substrates.

We have previously synthesized (+)-castanospermine and Neu5Ac methyl ester by *syn*-selective allylation reactions (Fig 1).[3c] In this work, we synthesized (+)-1-*epi*-castanospermine **13** based on the *anti*-selective allylation reaction. (+)-Castanospermine, an indolizidine alkaloid containing five-contiguous stereocenters in its structure, was isolated from *Castanospermum australe* in 1981.[4] (+)-Castanospermine and its epimers, such as (+)-1-*epi*-castanospermine **13**, show anti-viral activity against HIV, HSV, and HCV as well as inhibitory effects against glycosidases.[5] Thus, (+)-1-*epi*-castanospermine **13** has been synthesized by many research groups.[6] In this report, we describe the total synthesis of **13** via an *anti*-selective allylation reaction.

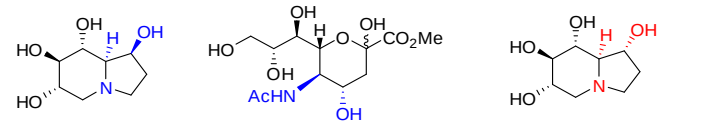
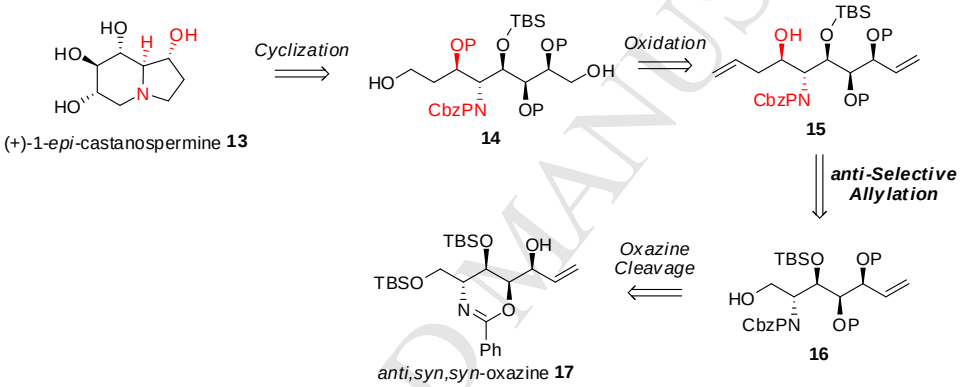



**Figure 1**. Structures of (+)-castanospermine, Neu5Ac methyl ester, and (+)-1-*epi*-castanospermine **13**.

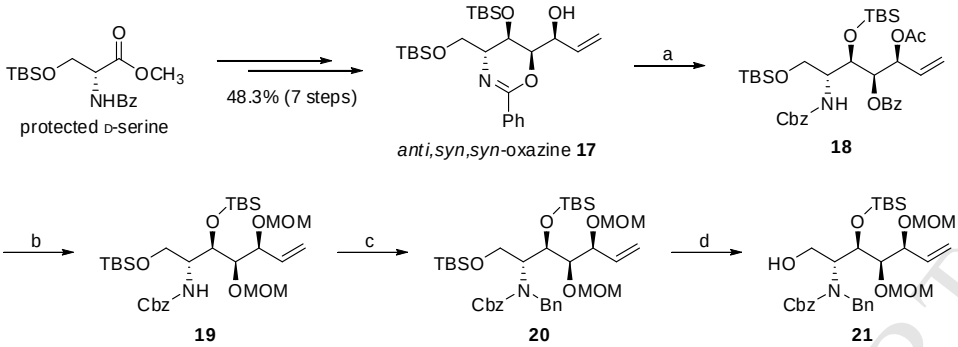
## 2. Results and discussion

Our retrosynthesis shown in Scheme 3 suggests that **13** may be obtained via two consequent cyclization reactions from **14**, which contains a primary diol. Compound **14** may be obtained by the transformation of the terminal olefins in compound **15**, which contains five contiguous stereocenters. Compound **15** may be prepared from primary alcohol **16** via Dess–Martin oxidation and stereoselective allylation. Compound **16** may be prepared from the reported compound *anti*,*syn*,*syn*-oxazine **17**.[7]



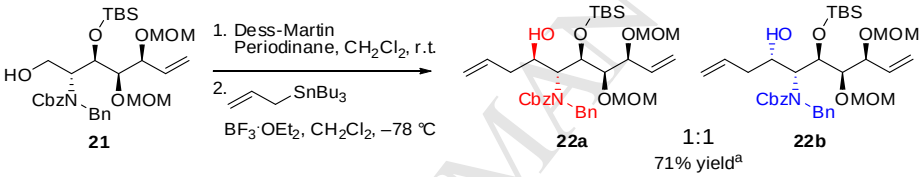

**Scheme 3**. Our retrosynthetic analysis of (+)-1-*epi*-castanospermine **13**.

The synthetic method shown in Scheme 2B was used to prepare *anti*-product **15**. First, we synthesized *N*CbzBn di-protected primary alcohol **21** (Scheme 4). *anti*,*syn*,*syn*-Oxazine **17** was synthesized via our previously reported method from protected D-serine.[7-8]The acetyl group was used to protect the alcohol in **17**. The oxazine ring was cleaved by using CbzCl and aqueous $NaHCO_3$ to generate compound **18**.[9] The acetyl and benzoyl groups in **18** were replaced with MOM groups to produce **19**. Benzylation of **19** afforded *N*CbzBn di-protected **20**. The primary silyl ether in **20** was cleaved in the presence of HF·pyridine in pyridine and tetrahydrofuran (THF) to give primary alcohol **21**.



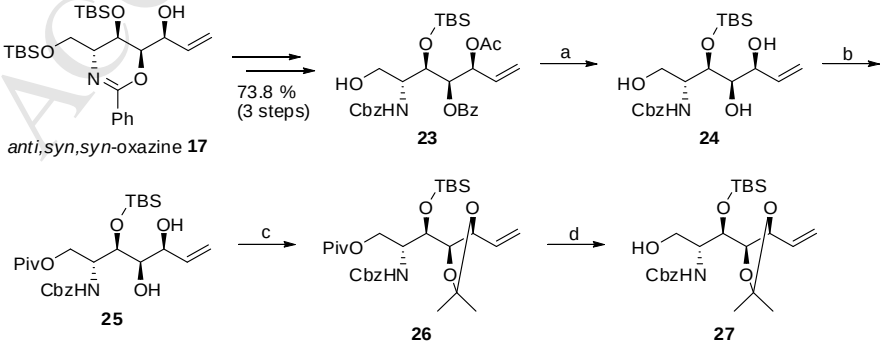

**Scheme 4**. Synthesis of **21**. Reagents and conditions: (a) i. $Ac_2O$, DMAP, pyr., $CH_2Cl_2$, rt, 2 h, 96%; ii. CbzCl, $NaHCO_3$ (aq), $CH_2Cl_2$, 50 °C, 48 h, 85%; (b) i. NaOMe, MeOH, 0 °C, 12 h, 81%; ii. MOMCl, pyridine, DMAP, $CH_2Cl_2$, 40 °C, 12 h, 80%; (c) BnBr, NaH, THF, rt, 12 h, 81%; and (d) HF·pyr., pyr., THF, 0 °C, 12 h, 91%.

The result of the allylation reaction of the corresponding aldehyde derived from the Dess–Martin oxidation of compound **21** is shown in Scheme 5. In contrast to our previous strategy (Scheme 2B), which showed *anti*-selectivity, the $BF_3{\cdot}OEt_2$-mediated allylation did not show any stereoselectivity. This result led us to investigate another method.




**Scheme 5**. Allylation of **21**. [a]The yield corresponds to the two-step preparation of the mixed isomers.

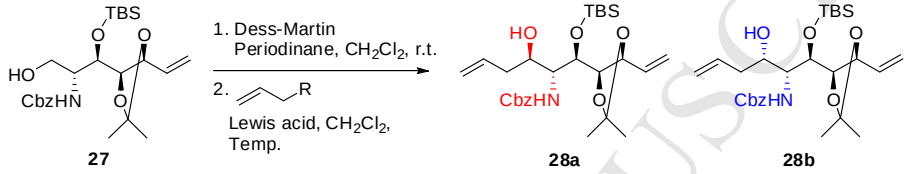
Based on our previous research using *anti*-*N*HCbz-β-*O*TBS substrates, we found that the selectivity of the allylation reaction changed when the substrates were changed.[3] Thus, we altered the substrates to investigate the selectivity of the allylation reaction (Scheme 6). The acetyl and benzoyl protecting groups in **23** were removed by treatment with sodium methoxide, followed by selective pivaloyl (Piv) protection of the primary alcohol.[10] Secondary diol **25** was protected using 2,2-dimethoxypropane at 60 °C in 69% yield. Subsequently, deprotection of the pivaloyl group using diisobutylaluminum hydride (DIBAL) gave primary alcohol **27**.[11]




**Scheme 6**. Synthesis of **27**. Reagents and conditions: (a) NaOMe, MeOH, 0 °C, 12 h, 76%; (b) PivCl, pyridine, $CH_2Cl_2$, 92%; (c) 2,2-dimethoxypropane, PPTS, DMF, 60 °C, 12 h, 69%; and (d) DIBAL, $CH_2Cl_2$, −78 °C, 90%.

The results of the allylations of the corresponding aldehyde obtained by Dess–Martin oxidation of compound **27** are shown in Table 1. The α-amino alcohol was transformed to the aldehyde without epimerization via Dess–Martin oxidation.[12] The allylation reaction with allyltrimethylsilane mediated by $SnCl_4$ led to slight *syn*-selectivity (entry 1). The reaction with allyltrimethylsilane mediated by $TiCl_4$ provided **28a** and **28b** in a 1:3 ratio (entry 2). When $MgBr_2 \cdot OEt_2$ was added as the Lewis acid, *anti*-alcohol **28a** was afforded in a 5:1 diastereoisomeric ratio (entry 3). The $ZnCl_2$-mediated allylation using allyltrimethylsilane did not proceed (entry 4). The reaction with allyltributyltin mediated by $MgBr_2 \cdot OEt_2$ provided the amino alcohols in a 3:1 ratio (entry 5). The $BF_3 \cdot OEt_2$-mediated reaction using allyltributyltin provided *syn*-alcohol **28b** in a 1:5 diastereoisomeric ratio (entry 6).

**Table 1**. Allylation of **27**.

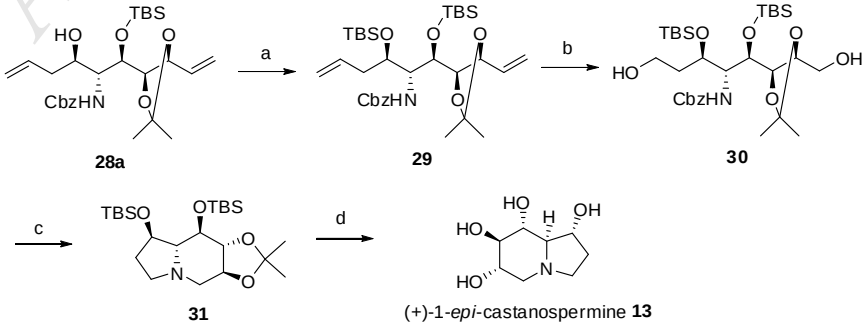



**27** **28a** **28b**

| Entry | R | Lewis acid | Temp. | Time (h) | Ratio (*anti*:*syn*)[a] | **28a** Yield (%)[b] | **28b** Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | $SiMe_3$ | $SnCl_4$ | −78 °C | 1 | 1:3 | 18 | 53 |
| 2 | $SiMe_3$ | $TiCl_4$ | −78 °C | 1 | 1:3 | 12 | 36 |
| 3 | $SiMe_3$ | $MgBr_2 \cdot OEt_2$ | 0 °C | 12 | 5:1 | 53 | 10 |
| 4 | $SiMe_3$ | $ZnCl_2$ | 0 °C | 12 | N.R. | − | |
| 5 | $SnBu_3$ | $MgBr_2 \cdot OEt_2$ | 0 °C | 3 | 3:1 | 51 | 17 |
| 6 | $SnBu_3$ | $BF_3 \cdot OEt_2$ | −78 °C | 1 | 1:5 | 12 | 63 |

[a] The ratio was determined by $^1H$ NMR spectroscopy.
[b] The yield refers to the two-step preparation of the isolated isomer.

A TBS group was used to protect *anti*-alcohol **28a** (Scheme 6). Primary diol **30** was prepared via reductive ozonolysis of **29** and then converted into the corresponding dimesyl derivative. Hydrogenolysis and subsequent treatment of the resulting dimesyl derivative with triethylamine provided protected 1-*epi*-castanospermine **31** in 59% yield. Finally, global deprotection of **31** with 1 N HCl afforded the **13·HCl** salt, which was neutralized by DOWEX-50WX8-100 ion-exchange chromatography to give (+)-1-*epi*-castanospermine **13** in 81% yield. The specific rotation of **13**, $[\alpha]_D^{20}$ +4.5 (*c* 0.1, MeOH), was in good agreement with the reported value, $[\alpha]_D^{25}$ +3.8 (*c* 0.5, MeOH),[6a,6h] which confirmed its absolute configuration. The spectral data for the synthetic (+)-1-*epi*-castanospermine **13** were in good agreement with the reported data.[6h]




**28a** **29** **30**

**31** (+)-1-*epi*-castanospermine **13**

**Scheme 7**. Synthesis of 1-*epi*-castanospermine **13**. Reagents and conditions: (a) TBSCl, imid., DMF, 50 °C, 24

h, 89%; (b) $O_3$, MeOH then $NaBH_4$, 0 °C, 3 h, 56%; (c) i. MsCl, TEA, $CH_2Cl_2$, 0 °C, 1 h; ii. $Pd(OH)_2/C$, $H_2$, rt, 12 h; iii. TEA, MeOH, reflux, 12 h, 59%; and (d) 1 N HCl, MeOH, rt, 12 h, 81%.

The possible transition states by comparing the results in Table 1 (Figure 2A) with the previous allylation data used for the synthesis of (+)-castanospermine (Figure 2B)[3c] are shown in Figure 2. The result obtained when using $SnCl_4$ (entry 1) can be explained by the α-chelation of the nitrogen atom and aldehyde oxygen in comparison with the result depicted in Figure 2B. The result obtained in the presence of $MgBr_2 \cdot OEt_2$ (entry 3) can be explained using the Felkin–Ahn model. It is notable that $MgBr_2 \cdot OEt_2$ is usually considered to be a bidentate Lewis acid, but it acts as a monodentate Lewis acid in the present case. The result obtained in the presence of $BF_3 \cdot OEt_2$ (entry 6) can be explained by the hydrogen bonding between the hydrogen atom of the amine and the aldehyde oxygen. The transition states in Figures 2C and 2D show the results for the α-amino-β-hydroxy aldehydes reported in a previous study.[3a,3b] The results of the allylation reactions in Figures 2A and 2B are similar to those in Figures 2C and 2D, respectively.

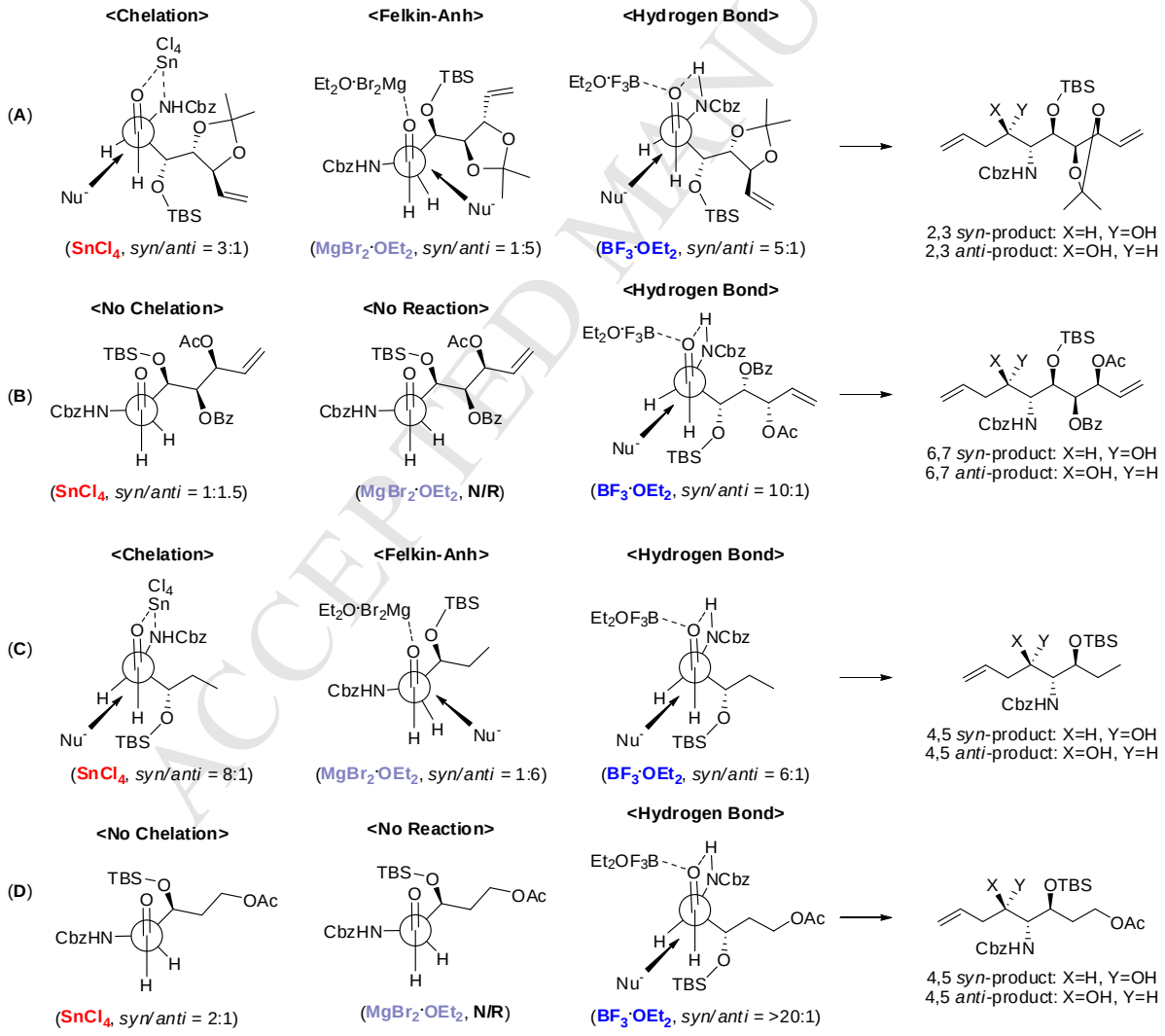



**Figure 2**. Proposed mechanisms of the allylation reaction.

## 3. Conclusions

In summary, the stereoselective allylation of chiral acyclic α-amino-β-hydroxy aldehydes bearing four contiguous stereocenters and its application to the total synthesis of (+)-1-*epi*-castanospermine have been reported. The reaction mediated by $MgBr_2 \cdot OEt_2$ provided the *anti*-product. A study on the mechanism of the allylation reaction was also conducted. The syntheses of more complicated compounds using similar protocols are being investigated, and the results will be reported in due course.

## 4. Experimental

### 4.1. General methods

Commercially available reagents were used without additional purification, unless stated otherwise. All non-aqueous reactions were performed under an argon atmosphere with commercial-grade reagents and solvents, unless stated otherwise. THF was distilled from sodium and benzophenone (indicator). $CH_2Cl_2$ was distilled from calcium hydride. Optical rotations were measured using a Jasco P1020 polarimeter in the solvents specified. Specific rotations are reported in $10^{-1}$ deg $cm^2/g$ and concentrations in g/100 mL. IR spectra were obtained using an FT-IR spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded using an FT-NMR spectrometer at 75, or 300 MHz. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) or deuterated chloroform ($CDCl_3$) as internal standards, and the coupling constants are reported in hertz. High-resolution mass spectroscopy (HRMS) was carried out using an Agilent 6530 Accurate-Mass Q-TOF liquid chromatography (LC)/MS high-resolution mass spectrometer equipped with a magnetic sector–electric sector double-focusing analyzer. Flash chromatography was performed using mixtures of hexanes and ethyl acetate or methanol and chloroform as the eluent.

### 4.2. *Benzyl (2R,3R,4aR,5S)-3-(tert-butyldimethylsilyloxy)-1,4,5-trihydroxyhept-6-en-2-ylcarbamate* (**24**)

To a solution of **23** (330 mg, 0.58 mmol) in methanol (5.8 mL) was added NaOMe (0.09 mL, 0.29 mmol; 4.4 M solution in methanol) at 0 °C. The reaction mixture was stirred at 0 °C for 12 h, and then, $NH_4Cl$ (aq) was added to quench the reaction. The organic layer was separated, and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. Purification by silica gel column chromatography (hexanes:ethyl acetate = 2:1) gave **24** (190 mg, 0.44 mmol, 76% yield) as a colorless oil. $R_f$ = 0.2 (hexanes:ethyl acetate = 2:1); $[\alpha]_D^{20}$ −10.0 (*c* 0.16, $CHCl_3$); IR (neat) $\nu_{max}$ 3403, 2953, 2929, 2887, 2857, 1700, 1518, 1463, 1408, 1254, 1029, 934, 837, 778, 737, 697; $^1H$ NMR ($CDCl_3$, 300 MHz) δ 7.29–7.38 (m, 5 H), 5.83 (ddd, *J* = 17.3, 10.1, 7.3 Hz, 1 H), 5.61 (d, *J* = 8.3 Hz, 1 H), 5.18–5.40 (m, 2 H), 5.10 (s, 2 H), 4.24 (t, *J* = 7.0 Hz, 1 H), 3.92 (dd, *J* = 11.0, 2.9 Hz, 1 H), 3.66–3.85 (m, 3 H), 3.53 (d, *J* = 6.8 Hz, 1 H), 3.26–3.40 (m, 1 H), 0.91 (s, 9 H), 0.03–0.14 (m, 6 H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 156.8, 137.5, 136.3, 128.5, 128.2, 128.1, 118.1, 75.7, 73.2, 69.8, 67.0, 62.2, 54.8, 29.7, 27.2, 25.8, 18.1, −4.0, −4.9; HRMS (EI+) $[(M+H)^+]$ *m/z* calcd. for $C_{21}H_{36}NO_6Si$ 426.2306; found 426.2305.

4.3. *(2R,3R,4R,5S)-2-(benzyloxycarbonylamino)-3-(tert-butyldimethylsilyloxy)-4,5-Dihydroxyhept-6-enyl pivalate* (**25**)

To a solution of **24** (260 mg, 0.6 mmol) in $CH_2Cl_2$ (5 mL) was added PivCl (0.12 mL, 0.9 mmol) and pyridine (1 mL). The reaction mixture was stirred at 0 °C for 2 h, and then, $NaHCO_3$ (aq) was added to quench the reaction. The organic layer was separated, and the aqueous layer extracted with diethyl ether. The combined organic layers were washed with saturated $CuSO_4$ and brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. Purification by silica gel column chromatography (hexanes:ethyl acetate = 10:1) gave **25** (280 mg, 0.55 mmol, 92% yield) as a colorless oil. $R_f$ = 0.3 (hexanes:ethyl acetate = 4:1); $[\alpha]_D^{20}$ 15.5 (*c* 0.06, $CHCl_3$); IR (neat) $\nu_{max}$ 3439, 2957, 2932, 2858, 1728, 1516, 1461, 1285, 1254, 1161, 934, 838, 778, 697; $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.39 (m, 5 H), 5.80 (ddd, *J* = 17.4, 10.2, 7.2 Hz, 1 H), 5.19–5.40 (m, 3 H), 5.05–5.17 (m, 2 H), 4.34 (dd, *J* = 11.3, 6.1 Hz, 1 H), 4.04–4.28 (m, 3 H), 3.65 (t, *J* = 7.4 Hz, 1 H), 3.51 (dd, *J* = 7.4, 1.6 Hz, 1 H), 3.13 (d, *J* = 2.3 Hz, 1 H), 2.72 (d, *J* = 8.8 Hz, 1 H), 1.15–1.20 (m, 9 H), 0.88–0.94 (m, 9 H), 0.05–0.12 (m, 6 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 178.4, 156.5, 137.5, 136.2, 128.5, 128.3, 118.3, 75.4, 72.9, 68.6, 67.1, 63.5, 53.1, 38.8, 27.1, 25.8, 18.1, −4.0, −4.9; HRMS (EI+) [$(M+H)^+$] *m/z* calcd. for $C_{26}H_{44}NO_7Si$ 510.2882; found 510.2883.

4.4. *(2R,3R)-2-(benzyloxycarbonylamino)-3-(tert-butyldimethylsilyloxy)-3-((4R,5S)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)Propyl pivalate* (**26**)

To a solution of **25** in DMF (5 mL) was added 2,2-dimethoxypropane (0.62 mL, 5 mmol) and PPTS (30 mg, 0.1 mmol) at 60 °C. The reaction mixture was stirred at 60 °C for 12 h, and then, distilled water was added to quench the reaction. The organic layer was separated, and the aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. Purification using silica gel column chromatography (hexanes:ethyl acetate = 30:1) gave **26** (190 mg, 0.35 mmol, 69% yield) as a colorless oil. $R_f$ = 0.6 (hexanes:ethyl acetate = 4:1); $[\alpha]_D^{20}$ 43.7 (*c* 0.05, $CHCl_3$); IR (neat) $\nu_{max}$ 3351, 2957, 2932, 2858, 1732, 1512, 1462, 1370, 1253, 1151, 1061, 929, 837, 776, 697; $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.29–7.39 (m, 5 H), 5.89 (ddd, *J*=17.0, 10.7, 5.9 Hz, 1 H), 5.19–5.30 (m, 2 H), 4.98–5.16 (m, 3 H), 4.18–4.35 (m, 3 H), 4.06–4.17 (m, 1 H), 3.97–4.05 (m, 2 H), 1.34–1.42 (m, 6 H), 1.13–1.22 (m, 9 H), 0.83–0.94 (m, 9 H), 0.02–0.14 (m, 6 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 178.3, 155.8, 136.9, 136.3, 128.5, 128.3, 128.2, 117.0, 109.8, 81.5, 76.3, 73.7, 66.9, 63.1, 52.5, 38.8, 27.3, 27.1, 27.0, 25.9, 25.8, 18.3, −4.5, −4.8; HRMS (EI+) [$(M+H)^+$] *m/z* calcd. for $C_{29}H_{48}NO_7Si$ 550.3195; found 550.3194.

4.5. *Benzyl (1R,2R)-1-(tert-butyldimethylsilyloxy)-1-((4R,5S)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-hydroxypropan-2-ylcarbamate* (**27**)

To a solution of **26** (200 mg, 0.37 mmol) in $CH_2Cl_2$ (3.7 mL) was added DIBAL (1.1 mL, 1.1 mmol; 1.0 M solution in hexanes) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, and then, 2 M potassium sodium tartrate was added to quench the reaction. The organic layer was separated, and the aqueous layer extracted with diethyl ether. The combined organic layers were washed with brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. Purification using silica gel column chromatography (hexanes:ethyl acetate = 4:1) gave **27** (160 mg, 0.33 mmol, 90% yield) as a colorless oil. $R_f$ = 0.2 (hexanes:ethyl acetate = 4:1); $[\alpha]_D^{20}$ 0.7 (*c* 0.2, $CHCl_3$); IR (neat) $\nu_{max}$ 3438, 2954, 2931,

2887, 2857, 1720, 1514, 1471, 1371, 1253, 1128, 1060, 930, 837, 776, 697; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.23–7.34 (m, 5 H), 5.86 (ddd, *J* = 15.9, 10.0, 5.7 Hz, 1 H), 5.48 (d, *J* = 4.9 Hz, 1 H), 5.12–5.31 (m, 2 H), 5.05 (s, 2 H), 4.22 (t, *J* = 4.9 Hz, 1 H), 3.99–4.11 (m, 2 H), 3.65–3.95 (m, 4 H), 1.27–1.39 (m, 6 H), 0.83 (s, 9 H), −0.05 to 0.07 (m, 6 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 156.3, 136.6, 136.2, 128.5, 128.3, 128.2, 117.1, 109.5, 81.8, 77.7, 73.6, 67.0, 62.3, 60.4, 53.9, 27.4, 26.9, 25.9, 21.0, 18.3, 14.2, −4.6, −4.9; HRMS (EI+) [$(M+H)^+$] *m/z* calcd. for $C_{24}H_{40}NO_6Si$ 466.2619; found 466.2621.

4.6. *Benzyl (1R,2R,3R)-1-(tert-butyldimethylsilyloxy)-1-((4R,5S)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-hydroxyhex-5-en-2-ylcarbamate* (**28a**)

To a solution of **27** (26 mg, 0.05 mmol) in anhydrous dichloromethane (0.5 mL) was added Dess–Martin periodinane (68 mg, 0.15 mmol) at room temperature. The reaction mixture was stirred at ambient temperature for 2 h. The mixture was diluted with $Et_2O$, and then, saturated $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq) were added. The resulting heterogeneous mixture was stirred at room temperature until the organic layer was clear. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude aldehyde. To a solution of the crude aldehyde in anhydrous $CH_2Cl_2$ (0.5 mL) was added $MgBr_2 \cdot OEt_2$ (52 mg, 0.075 mmol) at 0 °C, and the resulting solution was stirred for 5 min at 0 °C. Allyltrimethylsilane (0.02 mL, 0.1 mmol) was added to this reaction mixture at 0 °C, and the mixture was stirred at 0 °C until the reaction was complete, as indicated by TLC monitoring. The reaction mixture was diluted with ethyl acetate and quenched with aqueous saturated $NaHCO_3$ (aq). The organic phase was washed with saturated brine, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexanes:ethyl acetate = 10:1) gave **28a** (14 mg, 0.027 mmol, 53% yield) as a colorless oil. $R_f$ = 0.4 (hexanes:ethyl acetate = 4:1); $[\alpha]_D^{20}$ −7.1 (*c* 0.1, $CHCl_3$); IR (neat) $\nu_{max}$ 3439, 3071, 2955, 2932, 2896, 2858, 1707, 1642, 1513, 1462, 1380, 1253, 1215, 1126, 1072, 1026, 927, 837, 776, 697; $^{1}$H NMR ($CDCl_3$, 300 MHz) δ 7.30–7.40 (m, 5 H), 5.80–5.99 (m, 2 H), 5.06–5.30 (m, 7 H), 4.25–4.34 (m, 1 H), 4.04–4.13 (m, 2 H), 3.83–3.97 (m, 2 H), 3.16–3.27 (m, 1 H), 2.19–2.45 (m, 2 H), 1.38–1.43 (m, 6 H), 0.87–0.91 (m, 9 H), 0.03–0.08 (m, 6 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 156.7, 136.8, 136.1, 135.0, 128.5, 128.4, 128.3, 117.6, 117.1, 109.9, 81.9, 73.8, 72.3, 67.2, 57.7, 37.9, 27.3, 27.1, 26.0, 18.4, 17.5, −4.5, −4.8; HRMS (EI+) [$(M+H)^+$] *m/z* calcd. for $C_{27}H_{44}NO_6Si$ 506.2932; found 506.2927.

4.7. *Benzyl (1R,2R,3S)-1-(tert-butyldimethylsilyloxy)-1-((4R,5S)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3-hydroxyhex-5-en-2-ylcarbamate* (**28b**)

To a solution of **27** (32 mg, 0.06 mmol) in anhydrous dichloromethane (0.6 mL) was added Dess–Martin periodinane (82 mg, 0.18 mmol) at room temperature. The reaction mixture was stirred at ambient temperature for 2 h. The mixture was diluted with $Et_2O$, and then, saturated $NaHCO_3$ (aq) and $Na_2S_2O_3$ (aq) were added. The resulting heterogeneous mixture was stirred at room temperature until the organic layer was clear. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude aldehyde. To a solution of the crude aldehyde in anhydrous $CH_2Cl_2$ (0.6 mL) was added $TiCl_4$ or $SnCl_4$ or $BF_3 \cdot OEt_2$ (0.09 mmol) at −78 °C, and the resulting solution was stirred for 5 min at −78 °C. Allyltrimethylsilane or allyltributyltin (0.12 mmol) was added to this reaction mixture at −78 °C, and the mixture was stirred at −78 °C until reaction completion, as indicated by TLC monitoring. The reaction mixture was diluted with ethyl acetate and quenched with aqueous

saturated $NaHCO_3$ (aq). The organic phase was washed with saturated brine, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel column chromatography (hexanes:ethyl acetate = 10:1) gave **28b** (20 mg, 0.038 mmol, 63%) as a colorless oil. $R_f$ = 0.3 (hexanes:ethyl acetate = 4:1); $[\alpha]_D^{20}$ −3.2 (*c* 0.15, $CHCl_3$); IR (neat) $\nu_{max}$ 3439, 2928, 2856, 1725, 1506, 1462, 1379, 1252, 1214, 1074, 925, 837, 776, 697; $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.29–7.43 (m, 5 H), 5.68–6.02 (m, 2 H), 5.41 (d, *J* = 9.4 Hz, 1 H), 5.02–5.32 (m, 6 H), 4.14–4.26 (m, 2 H), 4.09 (t, *J* = 6.4 Hz, 1 H), 3.90 (dd, *J* = 7.7, 4.4 Hz, 1 H), 3.84 (dd, *J* = 9.4, 5.1 Hz, 1 H), 2.71–2.81 (m, 1 H), 2.12–2.37 (m, 2 H), 1.37–1.44 (m, 6 H), 0.88–0.93 (m, 9 H), 0.02–0.09 (m, 6 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 156.2, 137.2, 136.4, 134.1, 128.5, 128.2, 128.1, 118.2, 116.8, 109.5, 82.1, 78.7, 74.1, 69.0, 66.9, 54.6, 38.3, 26.9, 26.8, 25.9, 18.3, 17.5, −4.5, −4.8; HRMS (EI+) [$(M+H)^+$] *m/z* calcd. for $C_{27}H_{44}NO_6Si$ 506.2932; found 506.2934.

4.8. *Benzyl (5R,6R,7R)-5-allyl-7-((4R,5S)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ylcarbamate* (**29**)

To a solution of **28a** (100 mg, 0.2 mmol) in DMF (2 mL) were added TBSCl (94 mg, 0.6 mmol) and imidazole (52 mg, 0.6 mmol) at 40 °C. After 12 h, the reaction mixture was washed with $H_2O$, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel chromatography (hexanes:ethyl acetate = 30:1) gave **29** (110 mg, 0.18 mmol, 89% yield) as a colorless oil. $R_f$ = 0.4 (hexanes:ethyl acetate = 6:1); $[\alpha]_D^{20}$ −1.4 (*c* 0.35, $CHCl_3$); IR (neat) $\nu_{max}$ 3439, 2955, 2930, 2895, 2857, 1728, 1507, 1472, 1379, 1254, 1213, 1070, 926, 837, 776, 697; $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.30–7.39 (m, 5 H), 5.77–5.99 (m, 2 H), 5.03–5.29 (m, 7 H), 4.23 (dd, *J* = 5.6, 3.8 Hz, 1 H), 4.17 (dd, *J* = 9.1, 6.1 Hz, 1 H), 4.00–4.12 (m, 2 H), 3.91 (td, *J* = 8.9, 1.8 Hz, 1 H), 2.49 (dt, *J* = 14.0, 7.0 Hz, 1 H), 2.28 (dt, *J* = 14.0, 7.0 Hz, 1 H), 1.41 (s, 6 H), 0.81–0.97 (m, 18 H), −0.01 to 0.16 (m, 12 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 156.1, 137.3, 136.5, 135.2, 128.4, 128.4, 128.1, 117.4, 116.8, 109.7, 82.4, 74.6, 74.1, 72.6, 66.8, 57.5, 38.0, 27.2, 27.2, 26.1, 25.9, 18.4, 18.1, −4.4, −4.7; HRMS (EI+) [$(M+H)^+$] *m/z* calcd. for $C_{33}H_{58}NO_6Si_2$ 620.3797; found 620.3792.

4.9. *Benzyl (5R,6R,7R)-5-(2-hydroxyethyl)-7-((4R,5S)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ylcarbamate* (**30**)

Compound **29** (100 mg, 0.17 mmol) was dissolved in dry methanol (1.7 mL) and cooled to −78 °C. Ozone was then passed through the solution until the reaction was complete. The reaction mixture was quenched with $NaBH_4$ (64 mg, 1.7 mmol) and allowed to warm to rt for 3 h. Distilled water was added to quench the reaction, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*. Purification by silica gel column chromatography (hexanes:ethyl acetate = 4:1) gave **30** (60 mg, 0.095 mmol, 56% yield) as a colorless oil. $R_f$ = 0.3 (hexanes:ethyl acetate = 2:1); $[\alpha]_D^{20}$ −16.7 (*c* 0.1, $CHCl_3$); IR (neat) $\nu_{max}$ 3440, 2953, 2931, 2887, 2857, 1704, 1529, 1472, 1380, 1254, 1060, 837, 776, 697; $^1$H NMR ($CDCl_3$, 300 MHz) δ 7.29–7.39 (m, 5 H), 5.58 (d, *J* = 7.5 Hz, 1 H), 5.14 (d, *J* = 12.2 Hz, 1 H), 5.01 (d, *J* = 12.2 Hz, 1 H), 4.15–4.32 (m, 2 H), 3.92–4.05 (m, 2 H), 3.85 (ddd, *J* = 10.7, 7.1, 4.5 Hz, 1 H), 3.71 (dt, *J* = 10.4, 5.3 Hz, 1 H), 3.53–3.64 (m, 3 H), 2.20–2.50 (m, 2 H), 1.65–1.94 (m, 2 H), 1.34–1.45 (m, 6 H), 0.82–0.95 (m, 18 H), 0.02–0.15 (m, 12 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 156.8, 136.6, 128.5, 128.4, 128.2,

109.6, 82.5, 75.6, 71.9, 69.6, 66.8, 65.0, 59.0, 58.1, 33.8, 27.3, 26.9, 25.9, 25.8, 18.2, 17.9, −4.3, −4.6, −4.7, −5.0; HRMS (EI+) [$(M+H)^+$] *m/z* calcd. for $C_{31}H_{58}NO_8Si_2$ 628.3695; found 628.3693.

### 4.10. *(3aS,8R,8aR,9R,9aR)-8,9-Bis(tert-butyldimethylsilyloxy)-2,2-dimethyloctahydro-[1,3]dioxolo[4,5-f]indolizine* (**31**)

To a solution of **30** (50 mg, 0.08 mmol) in $CH_2Cl_2$ (0.8 mL) were added MsCl (0.02 mL, 0.24 mmol) and TEA (0.04 ml, 0.24 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and then, $NaHCO_3$ was added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried with $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo*, and the resulting residue was used immediately without any further purification. The resulting substance was dissolved in dry methanol and hydrogenated overnight in the presence of 20% $Pd(OH)_2/C$ (50 mg) at room temperature. The catalyst was removed via filtration through Celite, and the filtrate was concentrated *in vacuo*. TEA was added to a solution of the resulting residue in MeOH at rt, and the mixture was heated at reflux for 12 h. Then, the reaction mixture was concentrated *in vacuo*. Purification by silica gel column chromatography (hexanes:ethyl acetate = 20:1) gave **31** (22 mg, 0.047 mmol, 59% yield) as a colorless oil. $R_f$ = 0.3 (hexanes:ethyl acetate = 6:1); $[\alpha]_D^{20}$ −14.5 (*c* 0.05, $CHCl_3$); IR (neat) $\nu_{max}$ 2953, 2930, 2898, 2857, 2802, 1711, 1472, 1371, 1254, 1231, 1159, 1104, 837, 779; $^1$H NMR ($CDCl_3$, 300 MHz) δ 4.11 (ddd, *J* = 8.8, 6.3, 5.1 Hz, 1 H), 3.88 (td, *J* = 9.2, 5.1 Hz, 1 H), 3.26 (t, *J* = 9.1 Hz, 1 H), 3.14 (t, *J* = 9.0 Hz, 1 H), 3.00 (dd, *J* = 11.2, 5.1 Hz, 1 H), 2.91 (td, *J* = 8.8, 3.2 Hz, 1 H), 2.64 (td, *J* = 9.0, 7.7 Hz, 1 H), 2.13–2.32 (m, 3 H), 1.60–1.73 (m, 2 H), 1.38 (s, 6 H), 0.87–0.94 (m, 18 H), 0.06–0.13 (m, 12 H); $^{13}$C NMR ($CDCl_3$, 75 MHz) δ 110.2, 84.6, 77.7, 74.9, 70.6, 69.6, 56.8, 50.6, 33.9, 26.8, 26.7, 25.8, 18.3, 18.3, −4.6, −4.9, −5.0, −5.1; HRMS (EI+) [$(M+H)^+$] *m/z* calcd. for $C_{23}H_{48}NO_4Si_2$ 458.3116; found 458.3115.

### 4.11. *(1R,6S,7R,8R,8aR)-Octahydroindolizine-1,6,7,8-tetraol, 1-epi-castanospermine* (**13**)

1 N HCl was added to a solution of **31** (20 mg, 0.04 mmol) in MeOH (0.6 mL). After stirring for 24 h, the reaction mixture was concentrated *in vacuo*, furnishing **13·HCl** as a white solid. Further purification upon treating **13·HCl** with ion-exchange resin (DOWEX-50WX8-100) afforded (+)-1-*epi*-castanospermine **13** (5 mg, 0.033 mmol, 81%) as a white solid; $[\alpha]_D^{20}$ 4.5 (*c* 0.1, MeOH); IR (neat) $\nu_{max}$ 3347, 2923, 2831, 1604, 1448, 1118, 1090, 1065, 1030, 641; $^1$H NMR ($D_2O$, 300 MHz) δ 4.17 (ddd, *J* = 9.0, 6.0, 3.4 Hz, 1 H), 3.54 (ddd, *J* = 10.3, 8.7, 5.3 Hz, 1 H), 3.20–3.35 (m, 2 H), 3.10 (dd, *J* = 11.1, 5.2 Hz, 1 H), 2.90 (td, *J* = 9.0, 1.7 Hz, 1 H), 2.58 (q, *J* = 9.2 Hz, 1 H), 2.18–2.31 (m, 1 H), 2.23 (t, *J* = 10.8 Hz, 1 H), 2.14 (dd, *J* = 8.1, 6.7 Hz, 1 H), 1.63 (dddd, *J* = 13.9, 9.0, 3.5, 1.8 Hz, 1 H); $^{13}$C NMR ($D_2O$, 75 MHz) δ 78.4, 73.5, 72.8, 72.6, 69.5, 54.4, 50.8, 32.2; HRMS (EI+) [$(M+H)^+$] *m/z* calcd. for $C_8H_{16}NO_4$ 190.1074; found 190.1076.

## 5. Acknowledgment

This work was supported by Yonsung Fine Chemicals Co., Ltd. We thank the Yonsung R&D Center analysis research department for the HRMS measurements.

## 6. References


1. For selected reviews, see: (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989,** *89*, 149-164; (b) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1991,** *30*, 1531-1546; (c) Marshall, J. A. *Chem. Rev.* **1996,** *96*, 31-48; (d) Reetz, M. T. *Chem. Rev.* **1999,** *99*, 1121-1162; (e) Bergmeier, S. C. *Tetrahedron* **2000,** *17*, 2561-2576; (f) Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136-2157; (g) Hili, R.; Baktharaman, S.; Yudin, A. K. *Eur. J. Org. Chem.* **2008,** *2008*, 5201-5213; (h) Karjalainen, O. K.; Koskinen, A. M. *Org. Biomol. Chem.* **2012,** *10*, 4311-4326; (i) Passiniemi, M.; Koskinen, A. M. *Beilstein J. Org. Chem.* **2013,** *9*, 2641-2659.
2. For selected research of amino alcohol syntheses, see: (a) Kang, T.; Kim, H.; Kim, J. G.; Chang, S. *Chem. Commun.* **2014,** *50*, 12073-12075; (b) Hu, Y.; Wu, W.; Dong, X.-Q.; Zhang, X. *Org. Chem. Front.* **2017,** *4*, 1499-1502; (c) Jin, L.; Zeng, X.; Li, S.; Hong, X.; Qiu, G.; Liu, P. *Chem. Commun.* **2017,** *53*, 3986-3989; (d) Hua, Y.-G.; Yang, Q.-Q.; Yang, Y.; Wang, M.-J.; Chu, W.-C.; Bai, P.-Y.; Cui, D.-Y.; Zhang, E.; Liu, H.-M. *Tetrahedron Lett.* **2018,** *59*, 2748-2751; (e) Lim, J. J.; Leitch, D. C. *Org. Process Res. Dev.* **2018,** *22*, 641-649; (f) Mou, X.-Q.; Chen, X.-Y.; Chen, G.; He, G. *Chem. Commun.* **2018,** *54*, 515-518; (g) Gryko, D.; Jurczak, J. *Helv. Chim. Acta* **2000,** *83*, 2705-2711; (h) Gryko, D.; Prokopowicz, P.; Jurczak, J. *Tetrahedron: Asymmetry* **2002,** *13*, 1103-1113.
3. (a) Myeong, I.-S.; Lee, Y.-T.; Lee, S.-H.; Jung, C.; Kim, J.-S.; Park, S.-H.; Kang, J.; Lee, S.-J.; Ye, I.-H.; Ham, W.-H. *Tetrahedron: Asymmetry* **2017,** *28*, 1053-1060; (b) Myeong, I.-S.; Lee, S.-H.; Ham, W.-H. *Tetrahedron* **2018,** *74*, 3888-3896; (c) Myeong, I.-S.; Lee, Y.-T.; Kang, J.; Ham, W.-H. *J. Org. Chem.* **2019,** *84*, 4211-4220.
4. Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981,** *20*, 811-814.
5. (a) Whitby, K.; Taylor, D.; Patel, D.; Ahmed, P.; Tyms, A. S. *Antivir. Chem. Chemother.* **2004,** *15*, 141-151; (b) Whitby, K.; Pierson, T. C.; Geiss, B.; Lane, K.; Engle, M.; Zhou, Y.; Doms, R. W.; Diamond, M. S. *J. Virol.* **2005,** *79*, 8698-8706; (c) de Melo, E. B.; da Silveira Gomes, A.; Carvalho, I. *Tetrahedron* **2006,** *62*, 10277-10302.
6. (a) Ina, H.; Kibayashi, C. *J. Org. Chem.* **1993,** *58*, 52-61; (b) Graßberger, V.; Berger, A.; Dax, K.; Fechter, M.; Gradnig, G.; Stütz, A. E. *Liebigs Ann. Chem.* **1993,** *1993*, 379-390; (c) Cronin, L.; Murphy, P. V. *Org. Lett.* **2005,** *7*, 2691-2693; (d) Karanjule, N. S.; Markad, S. D.; Shinde, V. S.; Dhavale, D. D. *J. Org. Chem.* **2006,** *71*, 4667-4670; (e) Wu, T.-J.; Huang, P.-Q. *Tetrahedron Lett.* **2008,** *49*, 383-386; (f) Izquierdo, I.; Tamayo, J. A.; Rodríguez, M.; Franco, F.; Re, D. L. *Tetrahedron* **2008,** *64*, 7910-7913; (g) Ritthiwigrom, T.; Nash, R. J.; Pyne, S. G. *Tetrahedron* **2010,** *66*, 9340-9347; (h) Liu, G.; Wu, T. J.; Ruan, Y. P.; Huang, P. Q. *Chem. Eur. J.* **2010,** *16*, 5755-5768; (i) Bowen, E. G.; Wardrop, D. J. *Org. Lett.* **2010,** *12*, 5330-5333; (j) Kalamkar, N. B.; Puranik, V. G.; Dhavale, D. D. *Tetrahedron* **2011,** *67*, 2773-2778.
7. (a) Kim, J.-S.; Kang, J.-C.; Yoo, G.-H.; Jin, X.; Myeong, I.-S.; Oh, C.-Y.; Ham, W.-H. *Tetrahedron* **2015,** *71*, 2772-2776; (b) Park, S.-H.; Jin, X.; Kang, J.-C.; Jung, C.; Kim, S.-S.; Kim, S.-S.; Lee, K.-Y.; Ham, W.-H. *Org. Biomol. Chem.* **2015,** *13*, 4539-4550; (c) Myeong, I. S.; Ham, W. H. *Eur. J. Org. Chem.* **2019,** *2019*, 1077-1082.
8. (a) Mu, Y.; Jin, T.; Kim, G. W.; Kim, J. S.; Kim, S. S.; Tian, Y. S.; Oh, C. Y.; Ham, W. H. *Eur. J. Org. Chem.* **2012,** *2012*, 2614-2620; (b) Kim, J.-Y.; Mu, Y.; Jin, X.; Park, S.-H.; Pham, V.-T.; Song, D.-K.; Lee, K.-Y.; Ham, W.-H. *Tetrahedron* **2011,** *67*, 9426-

9432.
9. Myeong, I.-S.; Kim, J.-S.; Lee, Y.-T.; Kang, J.-C.; Park, S.-H.; Jung, C.; Ham, W.-H. *Tetrahedron: Asymmetry* **2016,** *27*, 823-828.
10. (a) Boschelli, D.; Takemasa, T.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett.* **1985,** *26*, 5239-5242; (b) Nicolaou, K.; Webber, S. *Synthesis* **1986,** *1986*, 453-461.
11. Carreira, E. M.; Du Bois, J. *J. Am. Chem. Soc.* **1995,** *117*, 8106-8125.
12. Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000,** *41*, 1359-1362.