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Stereoselective Allylation of α-Hydroxy Aldimines and its Application to the Formal Synthesis of (–)-β-Conhydrine

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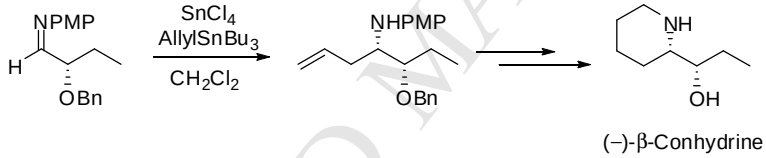
Abstract

Stereoselective allylation of *N*-*p*-methoxyphenyl (PMP)-substituted α-hydroxy aldimines is described. Several Lewis acids ($BF_3 \cdot OEt_2$, $SnCl_4$, $TiCl_4$, $ZnCl_2$, and $MgBr_2 \cdot OEt_2$) were employed to mediate the allylation reactions. The addition of the allyl group generates a new stereocenter and affords the *syn* vicinal amino alcohol. Formal synthesis of (–)-β-conhydrine (**1**) was accomplished via *syn*-selective allyl addition to *N*-PMP-substituted α-hydroxy aldimine.



Introduction

β-Amino alcohols or vicinal amino alcohols, the structures of which range from simple to complex, are crucial structural motifs in natural products and medicinal agents.[1] For example, conhydrines, sphingosines, and docetaxel have β-amino alcohol substructures (Figure 1). Conhydrine was isolated from the seeds and leaves of *Conium maculatum* L., which is a poisonous plant, in 1856, and its structure was confirmed in 1933.[2]

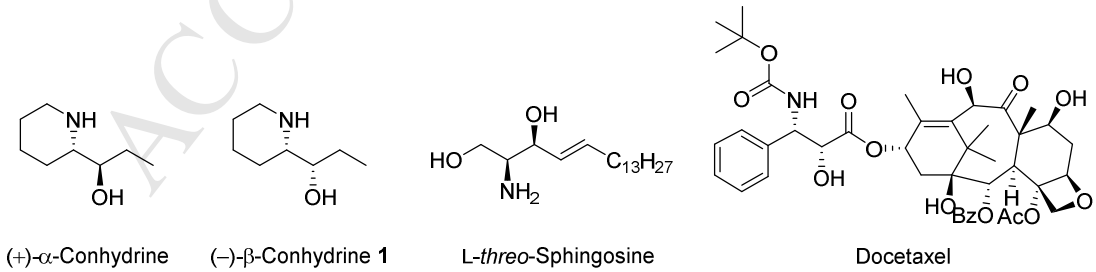


Figure 1. Structures of natural compounds that have β-amino alcohol substructures

The typical synthetic strategies used to access β-amino alcohols are i) addition reactions to α-amino aldehydes;[3] ii) addition reactions to α-hydroxy aldimines;[4] iii) reduction of α-amino ketones;[5] and iv) reduction

of α-hydroxy ketimines (Figure 2).[6] Recently, we have reported stereoselective nucleophilic addition to α-amino β-hydroxy aldehydes to afford various vicinal amino alcohols.[7] In the current study, as a part of our ongoing research, we have focused on addition reactions to α-hydroxy aldimines to afford vicinal amino alcohols.

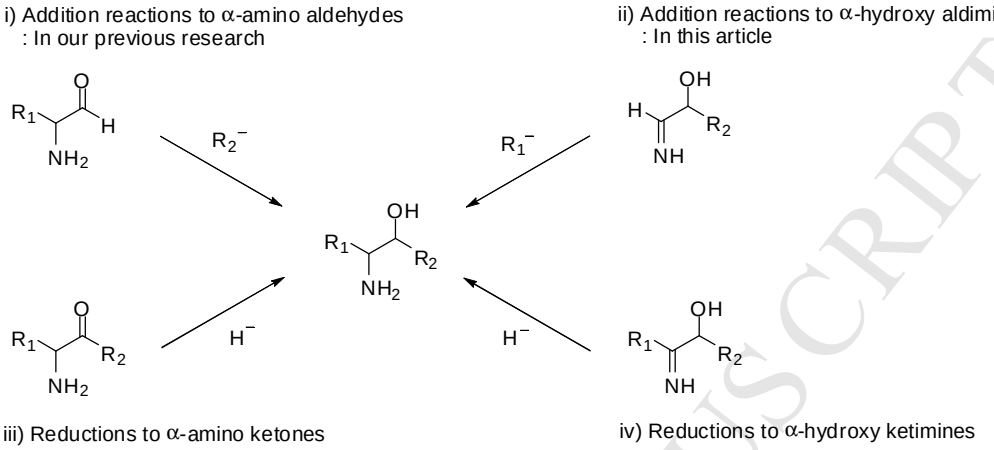


Figure 2. Typical strategies for the synthesis of vicinal amino alcohols

Nucleophilic addition to aldimines requires particular conditions because of their lower reactivity than that of carbonyl compounds.[8,9a] One of the strategies used to increase the electrophilicity of the azomethine carbon and thus increase the reactivity of the aldimine is the use of an electron-withdrawing group (EWG) to protect the imino nitrogen.[9a] In addition, the coordination of a Lewis acid with the imino nitrogen has an activating effect, increasing the electrophilicity of the azomethine carbon.[8,9b] Conversely, protecting the imino nitrogen using an electron-donating group such as an aryl moiety results in a less reactive aldimine.[9b]

In case of less reactive aldimines, the electron-donating group can strengthen the coordination between the Lewis acid and the imino nitrogen.[10] Diastereoselective nucleophilic additions to aldimines are stereocontrolled according to the Felkin-Anh model and chelation[1c,11] mediated by Lewis acids.[12] Thus, using a Lewis acid can both increase the reactivity of the aldimine and promote diastereoselective nucleophilic addition to it. To verify this, we explored Lewis-acid-mediated nucleophilic addition reactions to less reactive aldimines. *N*-*p*-methoxyphenyl (PMP) aldimine was selected as the less reactive aldimine because of its facile deprotection.[13a]

Although nucleophilic addition to other *N*-protected α-hydroxy aldimines has been investigated by several researchers, for example, Fadnavis,[14] Das,[15] Akiba,[16] Saksena,[17] Cainelli,[18] Evans,[19] Yamamoto,[4a] and Claremon,[4b] nucleophilic addition to *N*-PMP α-hydroxy aldimines remains relatively unexplored, and Lewis-acid-promoted addition to α-hydroxy aldimines is also relatively novel.

We established the formation method for *N*-PMP aldimines based on the ketimine formation method reported by Menche et al.[20] The allyl group was selected as a nucleophile because of the versatility afforded by its possible subsequent transformations, which include ozonolysis, olefin metathesis, hydrogenation, and dihydroxylation.[11e]

We herein present a method for stereoselective nucleophilic allyl addition to *N*-PMP α-hydroxy aldimines and its application to the formal synthesis of (–)-β-conhydrine (**1**).

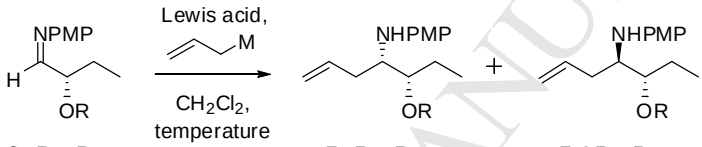
Results and Discussion

Allylation of *O*-protected α-hydroxy aldimines

The enantiomerically pure *O*-benzyl-protected α-hydroxy aldehyde was prepared by a previously reported method.[14b] *O*-*t*-Butyldimethylsilyl (TBS)-protected α-hydroxy aldehyde was afforded by a similar method.[21] The details of the experimental methods are described in the Experimental Section. The aldehydes are easily converted to the corresponding *N*-PMP-protected α-hydroxy aldimines using *p*-anisidine and $Ti(OiPr)_4$.[20]

Each aldimine was subjected to allyl addition reactions with different Lewis acids and allyl reagents. The results of the allylations of the *O*-protected α-hydroxy aldimines are shown in Table 1.

Table 1. Lewis-acid-mediated nucleophilic allyl addition reactions of *O*-protected α-hydroxy aldimines



2a R = Bn
2b R = TBS

7a R = Bn
7b R = TBS

7a' R = Bn
7b' R = TBS

Entry	Aldimine	Lewis acid	Allyl reagent	Temp (°C)	Ratio (7a:7a')[a]	Yield (%)[b]
1	2a	$SnCl_4$	$AllylSnBu_3$	-78	8:1	72%
2	2a	$TiCl_4$	$AllylSnBu_3$	-78	Trace	Trace
3	2a	$MgBr_2{\cdot}OEt_2$	$AllylSnBu_3$	0	2:1	45%
4	2a	$BF_3{\cdot}OEt_2$	$AllylSnBu_3$	-78	5:1	48%
5	2a	N/A	AllylMgBr	0	1.3:1	72%
6	2a	$ZnCl_2$	AllylMgBr	0	4.5:1	67%
7	2a	$SnCl_4$	$AllylSiMe_3$	-78	N.R.	N.R.
8[c]	2a	$SnCl_4$	$AllylSnBu_3$	-78	N.R.	N.R.
9	2b	$SnCl_4$	$AllylSnBu_3$	-78	6:1	45%
10	2b	$TiCl_4$	$AllylSnBu_3$	-78	4:1	65%
11	2b	$MgBr_2{\cdot}OEt_2$	$AllylSnBu_3$	0	4:1	60%
12	2b	$BF_3{\cdot}OEt_2$	$AllylSnBu_3$	-78	4:1	61%
13	2b	N/A	AllylMgBr	0	1.2:1	85%
14	2b	$ZnCl_2$	AllylMgBr	0	8:1	62%

[a] Ratio determined by the method described below.
[b] Yields refer to three-step yields of mixed isomers.
[c] THF was used as the solvent instead of CH_2Cl_2.

The reactions of *O*-benzyl α-hydroxy aldimine **2a** with the Lewis acids $TiCl_4$, $MgBr_2{\cdot}OEt_2$, and $ZnCl_2$ did not give satisfactory results (entries 2, 3, and 6). The Grignard reaction in the absence of Lewis acid did not afford the stereocontrolled product (entry 5). When $BF_3{\cdot}OEt_2$ was used as the Lewis acid, the reaction afforded a

moderately *syn*-selective product (entry 4), and the reaction mediated by $SnCl_4$ afforded a *syn*-selective product (entry 1). In our previous study, $AllylSiMe_3$ was used as the nucleophile and gave several satisfactory results.[7] However, it did not work well in this case (entry 7). When tetrahydrofuran (THF) was used as the solvent, the reaction did not progress (entry 8), so dichloromethane (CH_2Cl_2) was adopted as the solvent to allow the Lewis acids to work sufficiently.

In order to investigate the influence of the α-hydroxy protecting group, reactions with *O*-TBS α-hydroxy aldimine **2b** were conducted. The Grignard reaction without a Lewis acid was not stereoselective, and reactions with the Lewis acids $SnCl_4$, $TiCl_4$, $MgBr_2 \cdot OEt_2$, and $BF_3 \cdot OEt_2$ did not give satisfactory results (entries 9–12). The Grignard reaction in the absence of a Lewis acid did not afford the stereocontrolled product (entry 13). When $ZnCl_2$ was used as the Lewis acid, the reaction afforded a *syn*-selective product (entry 14). In the case of **7a** and **7a'**, the *syn*/*anti* adducts were separated by silica column chromatography and the *syn*/*anti* ratios were determined by NMR. However, in the case of silyl protection, **7b** and **7b'** were inseparable by TLC. In order to determine the *syn*/*anti* ratios, the TBS group was removed, benzylation was conducted, and the diastereomers were separated by silica column chromatography. The reaction conditions are decribed in the Experimental Section. By the formal synthesis of (–)-β-conhydrine (**1**) the *syn*-configuration of the amino alcohol **7a** was confirmed.

The possible transition states for nucleophilic addition are summarized in Figure 3. The preference for the *E*-aldimine configuration has been reported,[22] which is in accordance with our suggested conformation. The observed *syn*-selectivity for allyl addition to *O*-benzyl α-hydroxy aldimine **2a** can be explained by α-chelation (via a five-membered cyclic transition state) between the hydroxy group and the aldimine nitrogen (transition state A) (entries 1, 6). The unexpected *syn*-selectivity reported in entry 4 seems to be due to the steric repulsion between the Lewis acid and ethyl group in the transition state B and C. Consequently, reaction would proceed through the more favored transition state C as shown in Figure 3. Similarly, the addition of the allyl reagent to *O*-TBS α-hydroxy aldimine **2b** proceeded according to the anti-Felkin-Anh model (transition state C) (entries 9−12, and 14).

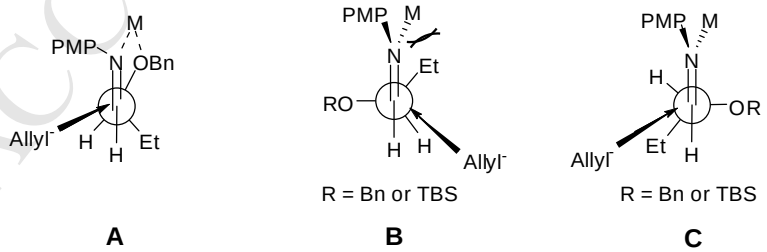
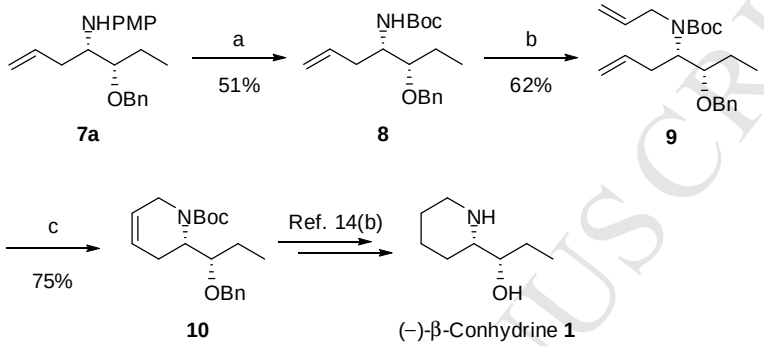


Figure 3. Proposed mechanisms of allylation reactions of *O*-protected α-hydroxy aldimines

Formal synthesis of (–)-β-conhydrine (1)

These results allowed the formal synthesis of (–)-β-conhydrine **1** (Scheme 1). The *N*-PMP-protected β-amino alcohol **7a** was subjected to PMP deprotection in the presence of ammonium cerium(IV) nitrate. The

PMP group was removed and the addition of Boc_2O to afford the *N*-Boc-protected β-amino alcohol **8** was accomplished. Various *N*-protection groups were tested for the next steps. Unfortunately, the *N*-PMP-protected and *N*-Cbz-protected dienes gave unsatisfactory results. The installation of the allyl group onto nitrogen was accomplished to afford diene **9**. The ring-closing metathesis of **9** with Grubbs' 2nd generation catalyst produced compound **10**. The spectra and specific rotation of compound **10** were in good agreement with reported data.[14b] Compound **10** has previously been transformed into (–)-β-conhydrine (**1**), thus completing the formal synthesis.[14b]



Reagents and conditions : (a) (i) CAN, ACN/H_2O = 2:1, 0 °C to r.t.; (ii) Boc_2O, TEA, CH_2Cl_2, 0 °C to r.t.; (b) AllylBr, NaH, TBAI, THF, DMF 0 °C to 50 °C; (c) Grubbs' 2nd generation, CH_2Cl_2, reflux

Scheme 1. Formal synthesis of (–)-β-conhydrine **(1)**

Conclusions

This study describes the Lewis-acid-mediated stereoselective nucleophilic allyl addition to α-hydroxy aldimines and its application to the formal synthesis of (–)-β-conhydrine (**1**). The reaction of *O*-benzyl α-hydroxy aldimine mediated by $SnCl_4$ afforded the *syn*-selective product. The reaction mechanism involves α-chelation between the hydroxy group and the imino nitrogen. The resulting *N*-PMP-protected β-amino alcohol was used for the formal synthesis of (–)-β-conhydrine (**1**). Further study and the development of other applications of this methodology are underway, and the results will be reported in due course.

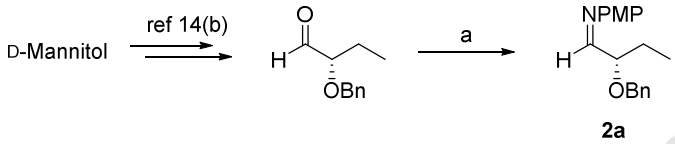
Experimental Section

General Experimental Methods

Optical rotations were measured with a polarimeter in the solvent specified. ^1H and ^{13}C NMR spectroscopic data were recorded with an FT-NMR spectrometer at 101, 175, 400, or 500 MHz. Chemical shift values are reported in ppm relative to TMS or $CDCl_3$ as an internal standard, and coupling constants are reported in Hz. The IR spectra were measured with an FT-IR spectrometer. The mass spectroscopic data were obtained with a high-resolution mass spectrometer using a magnetic sector-electric sector double focusing analyzer. Flash chromatography was performed using mixtures of ethyl acetate and hexane as the eluents. Unless otherwise

stated, all non-aqueous reactions were performed under an argon atmosphere with commercial grade reagents and solvents. THF was distilled from sodium and benzophenone (indicator). CH_2Cl_2 was distilled from calcium hydride.

General procedure for the allylation reactions



2a

Reagents and conditions : (a) Ti(O*i*Pr)$_4$, *p*-anisidine, CH_2Cl_2, r.t..

Scheme 2. Preparation of *O*-benzyl α-hydroxy aldimine

To a solution of *O*-benzyl α-hydroxy aldehyde (143 mg, 0.75 mmol) in anhydrous CH_2Cl_2 (7.5 mL) Ti(O*i*Pr)$_4$ (330 mL, 1.12 mmol) was added at room temperature. This solution was stirred for 5 min, and *p*-anisidine (110 mg, 0.9 mmol) diluted with CH_2Cl_2 was added dropwise. The reaction mixture was stirred at ambient temperature for 2 h. The mixture was filtered through a pad of Celite and concentrated *in vacuo*. The resulting aldimine **2a** was used immediately without further purification (Scheme 2).

A solution of $SnCl_4$ (0.9 mL, 1.0 M in CH_2Cl_2, 0.9 mmol) was added slowly to a solution of **2a** in anhydrous CH_2Cl_2 (0.9 mL) at -78 °C. This solution was stirred for 5 min, then allyltributylstannane (0.7 mL, 2.25 mmol) was added dropwise to this reaction mixture at -78 °C. The mixture was stirred at -78 °C for 30 min. The reaction was quenched with aqueous saturated $NaHCO_3$, diluted with EtOAc, and the organic phase was washed with saturated brine, dried with $MgSO_4$, then concentrated *in vacuo*. Purification by silica gel chromatography (hexane/EtOAc, 70:1) gave products **7a** as a yellow oil in 64 % yield and **7a'** as a yellow oil in 8% yield, respectively.

N-((4*S*,5*S*)-5-(Benzyloxy)hept-1-en-4-yl)-4-methoxyaniline (7a)

$[\alpha]_D^{25}$ +31.5 (*c* 0.5, $CHCl_3$); IR (neat) γ_{max} 3725, 3708, 3624, 2924, 2854, 1716, 1619, 1511, 1456, 1241, 1041, 818, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.2 Hz, 3H), 1.67 (dsxt, *J* = 16.3, 7.2 Hz, 2H), 2.35 (t, *J* = 7.2 Hz, 2H), 3.38–3.49 (m, 2H), 3.73 (s, 3H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.99–5.06 (m, 2H), 5.78 (ddt, *J* = 17.5, 9.8, 7.6 Hz, 1H) 6.48–6.54 (m, 2H), 6.72–6.74 (m, 2H), 7.26–7.39 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.6, 23.3, 36.0, 55.2, 55.9, 72.4, 80.9, 114.1, 115.0, 117.0, 127.7, 127.9, 128.4, 136.0, 138.7, 142.2, 151.6; HRMS (EI+) [(M)$^+$] *m/z* calcd for $C_{21}H_{27}NO_2$ 325.2042; found 325.2044.

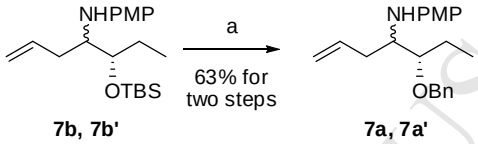
N-((4*R*,5*S*)-5-(Benzyloxy)hept-1-en-4-yl)-4-methoxyaniline (7a')

$[\alpha]_D^{25}$ +64.6 (*c* 1.0, $CHCl_3$); IR (neat) γ_{max} 3725, 3706, 3625, 3597, 3387, 3064, 3029, 2932, 2875, 2831, 1638, 1618, 1509, 1455, 1409, 1356, 1237, 1208, 1179, 1039, 913, 819, 736, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.5 Hz, 3H), 1.61 (dq, *J* = 14.3, 7.1 Hz, 1H), 1.72 (dq, *J* = 14.3, 7.1 Hz, 1H), 2.28–2.46 (m, 2H), 3.42–3.52 (m, 2H), 3.73 (s, 3H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.99–5.12 (m, 2H), 5.87 (ddt, *J* = 17.1, 10.0, 7.2 Hz, 1H) 6.47–6.53 (m, 2H), 6.72–6.77 (m, 2H), 7.25–7.38 (m, 5H); ^{13}C NMR (101

MHz, $CDCl_3$) δ 10.2, 23.8, 34.1, 55.8, 56.0, 72.6, 76.8, 77.1 ,77.4, 81.6, 114.9, 115.1, 117.0, 127.6, 127.7, 128.4, 136.1, 138.9, 142.0, 152.0; HRMS (EI+) [$(M)^+$] *m/z* calcd for $C_{21}H_{27}NO_2$ 325.2042; found 325.2044.

***N*-((4*S*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)hept-1-en-4-yl)-4-methoxyaniline (7b)**

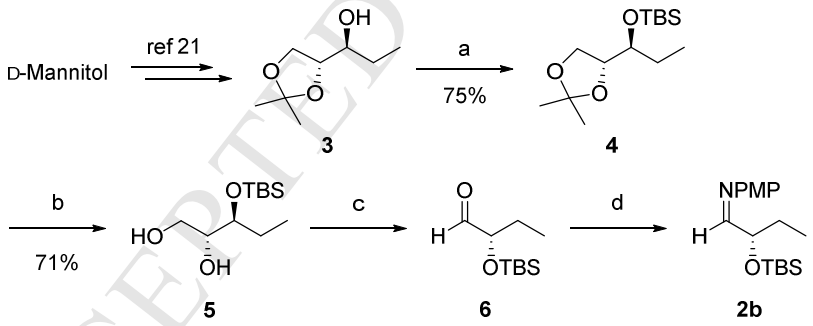
$[\alpha]_D^{25}$ +23.3 (*c* 0.5, $CHCl_3$); IR (neat) γ_{max} 3728, 3693, 3635, 3624, 3595, 3142, 2924, 2853, 1689, 1619, 1511, 1463, 1377, 1242, 1079, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.05–0.15 (m, 6H), 0.82 (t, *J* = 7.5 Hz, 3H), 0.91–0.97 (m, 9H), 1.45 (dq, *J* = 14.0, 7.1 Hz, 1H), 1.63 (dq, *J* = 14.3, 7.1 Hz, 1H), 2.22–2.36 (m, 2H), 3.26–3.39 (m, 1H), 3.69–3.73 (m, 1H), 3.75 (s, 3H), 4.99–5.17 (m, 2H), 5.82 (ddt, *J* = 17.1, 10.0, 7.2 Hz, 1H) 6.48–6.59 (m, 2H), 6.70–6.82 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ –4.2, –3.8, 10.6, 18.4, 26.2, 27.0, 36.1, 56.1, 56.2, 74.6, 114.4, 115.3, 116.8, 136.5; HRMS (EI+) [$(M)^+$] *m/z* calcd for $C_{20}H_{35}NO_2Si$ 349.2437; found 349.2435. The determination of stereochemistry was carried out as follows (Scheme 3).



Reagents and conditions : (a) (i) TBAF, THF, 0 °C; (ii) BnBr, NaH, THF, 0 °C to r.t.

Scheme 3. Conversion of protection group to determine *syn*/*anti* ratio

Preparation of *O*-TBS α-hydroxy aldimine (2b)



Reagents and conditions : (a) TBSCl, Imidazole, DMF, r.t.; (b) 50% CF_3CO_2H, CH_2Cl_2, 0 °C; (c) $NaIO_4$, ACN/H_2O, r.t. (d) $Ti(OiPr)_4$, *p*-anisidine, CH_2Cl_2, r.t.;

Scheme 4. Preparation of *O*-TBS α-hydroxy aldimine

***tert*-Butyl((*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)propoxy)dimethylsilane (4)**

To a solution of compound **3** (129 mg, 0.8 mmol) in dimethylformamide (DMF) (1.8 mL), *tert*-butyldimethylchlorosilane (607 mg, 4 mmol) and imidazole (220 mg, 3.2 mmol) were added at room temperature and stirred for 2 h. The reaction was quenched with distilled water, diluted with EtOAc, and the organic phase was washed with saturated brine, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel chromatography (hexane/EtOAc, 20:1) gave product **4** (173 mg, 75%) as a colorless oil. $[\alpha]_D^{25}$ +28.7 (*c* 0.2, $CHCl_3$); IR (neat) γ_{max} 3726, 3705, 3624, 3600, 3324, 3012, 2925, 2854, 1686, 1609, 1591, 1572, 1493,

1473, 1455, 1366, 1293, 1237, 1166, 1089, 886, 761, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.06–0.08 (m, 6H), 0.88–0.91 (m, 12H), 1.33 (s, 3H), 1.39 (s, 3H), 1.53–1.57 (m, 2H), 3.70 (td, *J* = 5.5, 5.0 Hz, 1H), 3.79–3.85 (m, 1H), 3.97–4.01 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ –4.4, –4.2, 8.5, 18.0, 25.5, 25.8, 26.7, 27.0, 66.6, 73.3, 108.8; HRMS (FAB+) [$(M+H)^+$] *m/z* calcd for $C_{14}H_{31}O_3Si$ 275.2042; found 275.2039.

(2*R*,3*S*)-3-(*tert*-Butyldimethylsilyloxy)pentane-1,2-diol (5)

Trifluoroacetic acid (50% in aqueous solution, 12 mL, 0.75 mmol) was added dropwise to a solution of compound **4** (145 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C and stirred for 7 h. The reaction was quenched with aqueous saturated $NaHCO_3$, diluted with EtOAc, and the organic phase was washed with saturated brine, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel chromatography (hexane/EtOAc, 6:1) gave diol **5** (83 mg, 71%) as a colorless oil. $[\alpha]_D^{25}$ +14.4 (*c* 1.0, $CHCl_3$); IR (neat) γ_{max} 3727, 3704, 3680, 3629, 3600, 2955, 2926, 2855 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.08–0.12 (m, 6H), 0.90–0.91 (m, 12H), 1.49 (quind, *J* = 7.2, 1.5 Hz, 1H), 1.61 (quind, *J* = 7.2, 1.5 Hz, 1H), 3.63 (td, *J* = 6.4, 3.5 Hz, 1H), 3.68 (dd, *J* = 11.1, 3.5 Hz, 1H), 3.76 (quin, *J* = 5.9 Hz, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ –4.4, –4.3, 9.7, 18.3, 26.0, 26.7, 63.5, 73.0, 76.3; HRMS (FAB+) [$(M+H)^+$] *m/z* calcd for $C_{11}H_{27}O_3Si$ 235.1729; found 235.1726.

(*S*)-2-(*tert*-Butyldimethylsilyloxy)butanal (6)

To a solution of diol **5** (83 mg, 0.36 mmol) in 60% aq. acetonitrile (1.8 mL) was added $NaIO_4$ (167 mg, 0.72 mmol) in one portion. The mixture was stirred at room temperature for 4 h and then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting aldehyde **6** was used immediately without further purification.

(*S*)-*N*-(2-(*tert*-Butyldimethylsilyloxy)butylidene)-4-methoxyaniline (2b)

To a solution of the crude aldehyde **6** in anhydrous CH_2Cl_2 (3.6 mL) $Ti(OiPr)_4$ (0.16 ml, 0.54 mmol) was added at room temperature. This solution was stirred for 5 min at the same temperature and *p*-anisidine (53 mg, 0.43 mmol) diluted with CH_2Cl_2 was added dropwise at the same temperature. The reaction mixture was stirred at ambient temperature for 2 h. The mixture was filtered through a pad of Celite and concentrated *in vacuo*. The resulting aldimine **2b** was used immediately without further purification.

Formal synthesis of (–)-β-conhydrine (1)

***tert*-Butyl (4*S*,5*S*)-5-(benzyloxy)hept-1-en-4-ylcarbamate (8)**

Ammonium cerium(IV) nitrate (171 mg, 0.31 mmol) was diluted with distilled water and added dropwise to a solution of compound **7a** (18 mg, 0.078 mmol) in acetonitrile (0.8 mL) at 0 °C. This solution was stirred at room temperature overnight. The reaction was quenched with aqueous saturated $NaHCO_3$, filtered through a pad of Celite, and concentrated *in vacuo*. The resulting free amine was immediately used without further purification. To a solution of the crude amine in anhydrous CH_2Cl_2 (0.8 mL), triethylamine (0.03 mL, 0.19 mmol) was added at 0 °C and di-*tert*-butyl dicarbonate (0.026 ml, 0.12 mmol) was added dropwise at the same temperature. This solution was stirred at room temperature overnight. The reaction was then quenched with aqueous saturated NH_4Cl, diluted with EtOAc, and the organic phase was washed with saturated brine, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel chromatography (hexane/EtOAc, 70:1) gave compound **8** (13 mg, 51%) as a red oil. $[\alpha]_D^{25}$ +42.5 (*c* 0.2, $CHCl_3$); IR (neat) γ_{max} 3725, 3706, 3624, 3601, 2922, 2852, 1720,

1461, 1377 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.5 Hz, 3H), 1.56 (s, 9H), 1.65–1.74 (m, 2H), 2.31 (tt, *J* = 20.2, 7.0 Hz, 2H), 3.34 (tt, *J* = 20.2, 6.2 Hz, 1H), 3.71–3.82 (m, 1H), 4.36–4.73 (m, 2H), 4.99–5.11 (m, 2H), 5.76 (ddt, *J* = 17.5, 10.0, 7.5 Hz, 1H) 7.19–7.42 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 10.3, 23.6, 27.7, 28.4, 29.7, 37.5, 51.7, 72.3, 81.0, 83.7, 117.2, 122.1, 127.7, 127.9, 128.4, 135.3, 138.5, 148.4; HRMS (EI+) $[(M)^+]$ *m/z* calcd for $C_{19}H_{29}NO_3$ 319.2147; found 319.2148.

***tert*-Butyl allyl((4*S*,5*S*)-5-(benzyloxy)hept-1-en-4-yl)carbamate (9)**

To a solution of compound **8** (25 mg, 0.07 mmol) in DMF (0.35 mL) and THF (0.35 mL), NaH (15 mg, 0.35 mmol) and *n*-Bu_4NI (31 mg, 0.08 mmol) was added at 0 °C. Allyl bromide (0.035 mL, 0.42 mmol) was added dropwise at the same temperature and stirred at 50 °C overnight. The reaction was quenched with aqueous saturated NH_4Cl, diluted with EtOAc, and the organic phase was washed with saturated brine, dried with $MgSO_4$, and concentrated *in vacuo*. Purification by silica gel chromatography (hexane/EtOAc, 30:1) gave diene **9** (16 mg, 62%) as a yellow oil. $[\alpha]_D^{25}$ +25.1 (*c* 0.1, $CHCl_3$); IR (neat) γ_{max} 3051, 2990, 2838, 1625, 1435, 1243, 1053, 925, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.44 (s, 9H), 1.52–1.70 (m, 2H), 2.20–2.40 (m, 1H), 2.44–2.56 (m, 1H), 3.41–3.56 (m, 1H), 3.74–4.02 (m, 2H), 4.09–4.26 (m, 1H), 4.44–4.63 (m, 2H), 4.99–5.11 (m, 4H), 5.64–5.97 (m, 2H), 7.19–7.42 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 9.8, 23.9, 28.4, 28.5, 29.7, 34.3, 48.5, 57.8, 72.4, 79.3, 82.3, 115.4, 116.8, 127.3, 127.4, 128.3, 135.8, 136.7, 153.0; HRMS (EI+) $[(M)^+]$ *m/z* calcd for $C_{22}H_{33}NO_3$ 359.2460; found 359.2462.

(*S*)-*tert*-Butyl 6-((*S*)-1-(benzyloxy)propyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (10)

To a solution of diene **9** (16 mg, 0.045 mmol) in anhydrous CH_2Cl_2 (0.45 mL) Grubbs' 2nd generation catalyst (41 mg, 0.05 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then concentrated *in vacuo* and the residue was purified by silica gel chromatography (hexane/EtOAc, 10:1) to give compound **10** (11 mg, 75%) as a colorless oil. $[\alpha]_D^{25}$ −33.7 (*c* 0.2, $CHCl_3$); IR (neat) γ_{max} 2966, 2927, 2855, 1694, 1456, 1411, 1365, 1219, 1173, 1105, 770 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.4 Hz, 3H), 1.42 (s, 9H), 1.43–1.50 (m, 1H), 1.61–1.75 (m, 1H), 2.00–2.13 (m, 1H), 2.34–2.46 (m, 1H), 3.38–3.53 (m, 2H), 4.06–4.29 (m, 1H), 4.31–4.65 (m, 3H), 5.52–5.77 (m, 2H), 7.22–7.27 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.3, 28.4, 28.5, 29.7, 30.1, 34.3, 42.3, 59.3, 72.3, 78.3, 82.3, 124.3, 126.3, 127.3, 127.4, 128.3, 135.8, 136.7, 153.1; HRMS (EI+) $[(M)^+]$ *m/z* calcd for $C_{20}H_{29}NO_3$ 331.2147; found 331.2149.

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References and Notes

1. For reviews: (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149–164; (b) Reetz, M. R. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531–1546; (c) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31–47; (d) Reetz, M. R. *Chem. Rev.*

1999, *99*, 1121–1162; (e) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 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**, 5201–5213; (h) Karjalainen, O. K.; Koskinen, A. M. P. *Org. Biomol. Chem.* **2012**, 10, 4311–4326; (i) Passiniemi, M.; Koskinen, A. M. P. *Beilstein J. Org. Chem.* **2013**, *9*, 2641–2659.

2. Spa¨th, E.; Adler, E. Zur Konstitution des Konhydrins. *Monatsh. Chem.* **1933**, *63*, 127–140.

3. (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem.* **1987**, *99*, 1186-1188; (b) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354; (c) Schirilin, D.; Baltzer, S.; Altenburger, J. M. *Tetrahedron Lett.* **1988**, *29*, 3687-3690; (d) Reetz, M. T. *Pure Appl. Chem*. **1988**, *60*, 1607-1614; (e) Reetz, M. T.; Rölfing, K.; Griebenow, N. *Tetrahedron Lett.* **1994**, *35*, 1969-1972.

4. (a) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 814-816; (b) Claremon, D. A.; Lumma, P. K.; Phillips, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 8265-8266; (c) Franz, T.; Hein, M.; Veith, U.; Jager, V.; Peters, E. M.; Peters, K. Schnering, H. G. *Angew. Chem.* **1994**, *106*, 1308-1311; (d) Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T. *Synthesis* **1994**, 1450-1456; (e) Tronchet, J. M. J.; Balkadjian, M.; Zosimo-Landolfo, G.; Barbalat-Rey, F.; Lichtle, P.; Ricca, Al.; Komaromi, I.; Bernardinelli, G.; Geoffroy, M. J. *Carbohyd. Chem*. **1995**, *14*, 17-34; (f) Merino, P.; Anoro, S.; Castillo, E.; Merchan, F.; Tejero, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1887-1890; (g) Veith, U.; Schwardt, O.; Jager, V. *Synlett* **1996**, 1181-1183.

5. (a) Alcaide, B.; Dominguez, G.; Lopez-Mardoningo, C.; Perez-Ossorio, R.; Plumet, J. *J. Chem. Soc., Perkin Trans. II* **1986**, 99-103; (b) Dufour, M. N.; Jouin, P.; Poncet, J.; Pantaloni, A.; Castro, B. *J. Chem. Soc. Perkin Trans. I* **1986**, 1895-1899; (c) Maibaum, J.; Rich, D. H. *J. Org. Chem.* **1988**, *53*, 869-873; (d) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866-1875; (e) Dondoni, A.; Perrone, D. *Synthesis* **1993**, 1162-1176; (f) Chung, S. K.; Kang, D. H. *Tetrahedron: Asymmetry* **1997**, *8*, 3027-3030; (g) Hoffman, R. V.; Tao, J. *J. Org. Chem.* **1997**, *62*, 2292-2297; (h) Ballini, R.; Bosica, G.; Marcantoni, E.; Vita, P. *J. Org. Chem.* **2000**, *65*, 5854-5857; (i) Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045-1056.

6. (a) Jager, V.; Muller, I. *Tetrahedron* **1985**, *41*, 3519-3528; (b) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Chem. Soc., Chem. Commun*. **1987**, 746-748; (c) Miller, V. P.; Yang, D.; Weigel, T. M.; Han, O.; Liu, H. *J. Org. Chem.* **1989**, *54*, 4175-4188; (d) Williams, D. R.; Osterhout, M. H.; Reddy, J. *Tetrahdron Lett*. **1993**, *34*, 3271-3274; (e) Banaszek, A.; Karpiesiuk, W. *Carbohydr. Res.* **1994**, *251*, 233-242; (f) Shimizu, M.; Tsukamoto, K.; Fujisawa, T. *Tetrahedron Lett.* **1997**, *38*, 5193-5196; (g) Alonso, E.; Ramon, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 12007-12028.

7. 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.

8. Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438.

9. (a) Lindsay, V.N.G.; Charette, A.B. in *Comprehensive Organic Synthesis II*, 2nd ed. (Eds.: Knochel, P; Molander, G.A.), Elsevier, Oxford, **2014**, pp. 365-394; (b) Marcantoni, E.; Petrini, M. in *Comprehensive Organic Synthesis II*, 2nd ed. (Eds.: Knochel, P; Molander, G.A.), Elsevier, Amsterdam, **2014**, pp. 344-364

10. Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hübel, M.; *Angew. chem. int. ed. engl.* **1991**, *30*, 103-106

11. For selected reviews: (a) Reets, M. T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556–569; (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462–468; (c) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293; (d) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223; (e) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2013**,

113, 5595–5698.

12. Gung. B. W. In *Additions of Allyl, Allenyl, and Propargylstannanes to Aldehydes and Imines*: Overman L. E., Ed.; Organic Reactions, Vol. 64, Chap. 1; John Wiley & Sons, Inc.; New Jersey, 2004, p 1.

13. (a) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681-6684; (b) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1603-1606.

14. (a) Venkataiah, M.; Rao, B. V.; Fadnavis, N. W. *Tetrahedron: Asymmetry* **2009**, *20*, 198–201; (b) Venkataiah, M.; Fadnavis, N. W. *Tetrahedron* **2009**, *65*, 6950–6952.

15. Kumar, J. N.; Reddy, P. R.; Das, B.; Kumar, C. G.; Sujitha, P. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5192–5194.

16. Ishimaru, K.; Tsuru, K.; Yabuta, K.; Wada, M.; Yamamoto, Y.; Akiba, K. *Tetrahedron* **1996**, *52*, 13137–13144.

17. Saksena, A. K.; Girijavallabhan, V. M.; Wang, H.; Lovey, R. G.; Guenter, F.; Mergelsberg, I.; Puar, M. S. *Tetrahedron Lett.* **2004**, *45*, 8249–8251.

18. (a) Cainelli, G.; Giacomini, D.; Treré, A.; Galletti, P. *Tetrahedron: Asymmetry* **1995**, *6*, 1593–1600; (b) Cainelli, G.; Giacomini, D.; Panunzio, M.; Zarantonello, P. *Tetrahedron Lett.* **1992**, *33*, 7783–7786.

19. Evans, J. W.; Ellman, J. A. *J. Org. Chem.* **2003**, *68*, 9948–9957.

20. Menche, D.; Arikan, F.; Li, J.; Rudolph, S. *Org. Lett.* **2007**, *9*, 267-270

21. Johann, M.; Angermann, A.; Muench, W. *Liebigs Ann. Chem.* **1986**, 825-838.

22. Bjørgo, J.; Boyd, D. R.; Watson, C. G. *J. C. S. Perkin II*, **1974**, *9*, 1081-1084