Tetrahedron: *Asymmetry* xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Convenient synthesis of memantine analogues containing a chiral cyclopropane skeleton as a sigma-1 receptor agonist

Tetsuya Ezawa, Yuya Kawashima, Takuya Noguchi, Seunghee Jung, Nobuyuki Imai *

Faculty of Pharmacy, Chiba Institute of Science, 15-8 Shiomi-cho, Choshi, Chiba 288-0025, Japan

ARTICLE INFO

Article history:
Received 26 September 2016
Revised 9 November 2016
Accepted 13 December 2016
Available online xxxx

ABSTRACT

We have achieved a convenient enantioselective synthesis of memantine analogues containing a chiral cyclopropane skeleton as a sigma-1 receptor agonist in 19–40% overall chemical yields from the corresponding 2-arylbut-2-ene-1,4-diols with moderate to excellent asymmetric yields via regioselective acetylation using porcine pancreas lipase, catalytic enantioselective Simmons-Smith reactions, and amidation in aqueous organic solvent. This synthetic route is more efficient and less expensive than conventional methods.

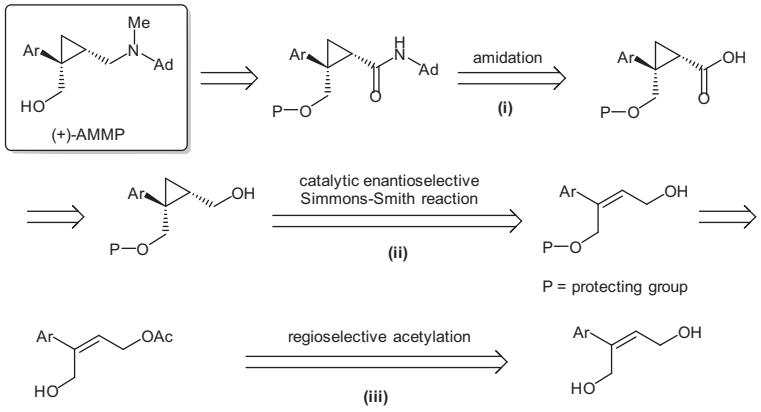
1. Introduction

Sigma receptors have recently attracted attention as a new action site of therapeutic medicine for several diseases such as amnesia, pain, stroke, retinal neuroprotection, HIV infection, cancer, amyotrophic lateral sclerosis (ALS), depression, and Alzheimer's disease.[1] Sigma-1 and sigma-2 receptors, as the two established subtypes, are both highly expressed in the central nervous system (CNS) and can be distinguished by their distinct pharmacological profiles and molecular characteristics.[2] It was reported that the sigma-1 receptor regulates protein folding/degradation, endoplasmic reticulum (ER)/oxidative stress, and cell survival through the molecular chaperone activity.[3] Therefore, the sigma-1 receptor is significantly influential in the homeostasis of tissue, which is incapable of repairing, and it is anticipated that the agonists activated by the sigma-1 receptor become the therapeutic agents of diseases caused by cell damage. For instance, it has been elucidated that patients with ALS carry mutations in the sigma-1 receptor gene and the dysfunction of the sigma-1 receptor protein.[4] It has been suggested that 1-[2-(3,4-dimethoxyphenyl) ethyl]-4-(3-phenylpropyl)piperazine (SA4503)[5] promotes regeneration and maturation of nerves as a selective sigma-1 receptor agonist.[6] Currently, Phase Ⅱ trials for SA4503 have been carried out in Europe as a medicine against CNS disorders, which are caused by major depression and strokes.[7] The sigma agonists protect cultured neurons against amyloid β $(A\beta)_{25-35}$-induced toxicity,[8] and prevent memory deficits when $A\beta_{25-35}$ is injected intracerebroventricularly in mice.[9] Therefore, the induction or activation of sigma-1 receptors could improve the clinical symptoms of Alzheimer's disease and protect against the associated neuropathologic changes. Indeed, tetrahydro-*N*,*N*-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73), which exhibits neuroprotective effects and prevents tau hyperphosphorylation, has been examined in Phase IIa for Alzheimer's disease trials as a sigma-1 receptor agonist since January, 2015.[10] As a part of interim studies for the planned analysis, it was announced that a positive dose–response relationship has been observed in its ongoing Phase IIa clinical trials of ANAVEX 2–73 as a potential treatment for mild-to-moderate Alzheimer's disease by November, 2015. For these reasons, sigma-1 receptor agonists have become key targets for therapeutic approaches to treat these diseases and have elicited significant interest in medicinal chemistry.

Recently, (+)-(2*R*,3*S*)-4-(*N*-adamant-1-yl-*N*-methylamino)-2,3-methano-2-phenylbutan-1-ol [(+)-AMMP] was reported as a high affinity probe for sigma receptors by Marrazzo et al.[11] However, the synthetic route of (+)-AMMP afforded 9% overall yield from 2-oxo-1-phenyl-3-oxabicyclo[3.1.0]hexane as the starting material and the reagents used for the synthesis of (+)-AMMP were relatively expensive. Additionally, it was necessary to prepare various chiral lactones as the starting materials in order to synthesize the substituted aryl analogues of (+)-AMMP. Therefore, it was desirable to develop a more efficient and inexpensive synthetic method for synthesis of (+)-AMMP analogues. We have recently reported a convenient asymmetric synthesis of (+)-AMMP via reactions,[12] such as (i) the regioselective acetylation using porcine pancreas lipase (PPL);[13] (ii) the catalytic enantioselective Simmons-Smith reaction in the presence of our developed chiral ligand which was prepared cheaply and easily from L-phenylalanine in five steps;[14] and (iii) the convenient amidation of mixed carbonic

* Corresponding author. Tel./fax: +81 479 30 4610.
E-mail address: nimai@cis.ac.jp (N. Imai).

http://dx.doi.org/10.1016/j.tetasy.2016.12.010
0957-4166/



Scheme 1. Retrosynthetic analysis of memantine analogues containing a chiral cyclopropane skeleton via the three key reactions.

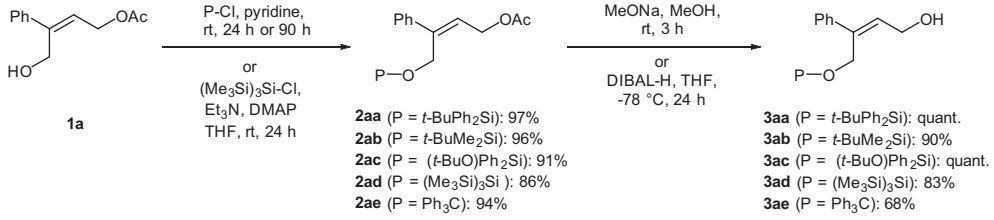
carboxylic anhydrides in aqueous organic solvent.[15] Particularly, the cyclopropane moiety with two stereogenic carbon centers was constructed in quantitative yield and with 71% ee via catalytic enantioselective Simmons-Smith reaction and the sterically hindered 1-adamantanamine moiety was successfully introduced by our developed amidation.

Herein we report a convenient enantioselective synthesis of (+)-AMMP and memantine analogues containing a chiral cyclopropane skeleton, a 4-substituted aryl group, and a 1-adamantanamine or memantine (3,5-dimethyl-1-adamantanamine) moiety via our developed reactions as shown in Scheme 1.

2. Results and discussion

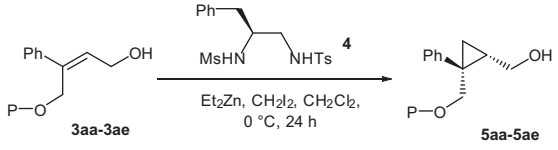
4-*O*-Protected (*Z*)-3-phenylbut-2-en-1-ols **3aa**–**3ae** were initially prepared for substrates in the catalytic enantioselective Simmons-Smith reaction in order to select a suitable protecting group as indicated in Scheme 2. Monoacetate **1a**, a key intermediate, was easily obtained via regioselective monoacetylation of (*Z*)-2-phenylbut-2-ene-1,4-diol using PPL.[13a] The hydroxy group of monoacetate **1a** was protected by various protecting groups to give the corresponding protected monoacetates **2aa**–**2ae** in 86–97% yields, followed by deacetylation to afford the desired **3aa**–**3ae** in 68%-quantitative yields.

In a preliminary investigation, the reaction of (*Z*)-4-*tert*-butyldiphenylsiloxy-3-phenylbut-2-en-1-ol **3aa** with 2.0 equiv of Et_2Zn and 3.0 equiv of CH_2I_2 in the presence of 0.1 equiv of the chiral ligand **4** in anhydrous CH_2Cl_2 at 0 °C for 3 h afforded (+)-*cis*-4-*tert*-butyldiphenylsiloxy-2,3-methano-3-phenylbutan-1-ol **5aa** in quantitative yield and with 71% ee (see entry 1 of Table 1). (*Z*)-4-Tris(trimethylsilyl)siloxy-3-phenylbut-2-en-1-ol **3ad** was converted into the corresponding 2,3-methano-3-phenylbutan-1-ol **5ad** in 90% yield and with 68% ee (see entry 3). Lower enantioselectivities (48% and 21% ee) were obtained in the reactions of 4-siloxy



Scheme 2. Preparation of 4-*O*-protected (*Z*)-3-phenylbut-2-en-1-ols **3aa**–**3ae**.

Table 1
Simmons-Smith reaction of 4-*O*-protected (*Z*)-3-phenylbut-2-en-1-ols **3aa**–**3ae**[a]



Entry	Product	P	Yield (%)	ee (%)[b]
1[c]	**5aa**	*t*-$BuPh_2Si$	Quant.	71
2	**5ab**	*t*-$BuMe_2Si$	93	48
3	**5ac**	*t*-$BuOPh_2Si$	66	21
4	**5ad**	$(Me_3Si)_3Si$	90	68
5[c]	**5ae**	Ph_3C	89	19

[a] All reactions were carried out with 4-*O*-protected (*Z*)-3-phenylbut-2-en-1-ols **3aa**–**3ae**, 2.0 equiv of Et_2Zn, and 3.0 equiv of CH_2I_2 in anhydrous CH_2Cl_2.
[b] Determined by HPLC analysis with a 95:5 mixture of hexane and 2-propanol as an eluent using Chiralcel OD (1.0 mL/min).
[c] Stirred for 3 h.

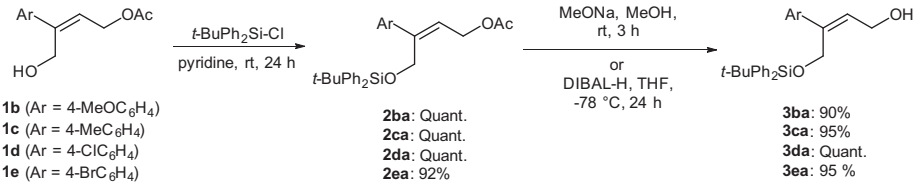
(*Z*)-3-phenylbut-2-en-1-ols **3ab** and **3ac**, respectively (see entries 2 and 3). The reaction of (*Z*)-4-triphenylmethoxy-3-phenylbut-2-en-1-ol **3ae** proceeded to give the corresponding 2,3-methano-3-phenylbutan-1-ol **5ae** in 89% yield, but the enantioselectivity (19% ee) was low (see entry 5). The results of these reactions are summarized in Table 1. It is suggested that larger protecting groups such as *tert*-butyldiphenylsilyl and tris(trimethylsilyl)silyl group, are more efficient in terms of the enantioselectivity and that the silyl groups decrease the Lewis basicity on the oxygen atom of the hydroxy group and are more suitable than trityl group in this reaction.

As optimized above, *tert*-butyldiphenylsilyl group was chosen for preparation of various 4-*O*-protected (*Z*)-3-arylbut-2-en-1-ols **3ba**–**3ea**. The allylalcohols **3ba**–**3ea** were converted from (*Z*)-3-arylbut-2-en-1-yl acetates **1b**–**1e** in 87%-quantitative yields in 2 steps, which were prepared by our developed regioselective acetylation (see Scheme 3).

Next, we attempted the cyclopropanation of (*Z*)-4-*tert*-butyldiphenylsiloxy-3-arylbut-2-en-1-ols **3ba**–**3ea** as shown in Table 2. The reactions of allylalcohols **3ba**–**3ea** with various oriented substituents on the aromatic ring worked smoothly. Methyl- and halo-substituted cinnamyl alcohols **3ca**–**3ea** gave the corresponding cyclopropane products **5ca**–**5ea** in excellent yields and with satisfactory enantioselectivities (see entries 3–5). However, the reaction of methoxy-substituted cinnamyl alcohol **3ba** proceeded in 70% yield and with low enantioselectivity (36% ee). It was suggested that the oxygen atom of the methoxy group acts as a Lewis base to the catalyst (see entry 2 of Table 2).

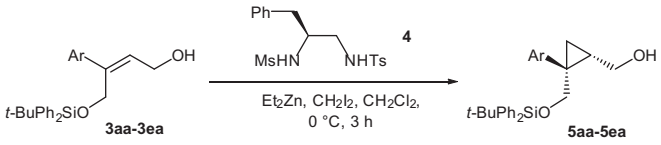
Subsequently, the 2,3-methano-3-arylbutan-1-ols **5aa**–**5ea** were oxidized with 2-iodoxybenzoic acid (IBX) in dimethylsulfoxide (DMSO) at rt for 3 h to afford the corresponding 2,3-methano-3-arylbutan-1-als **6aa**–**6ea** in 94–96% yields, which were converted with $NaClO_2$, H_2O_2, and NaH_2PO_4 in MeCN–H_2O at rt for 3 h to the corresponding 2,3-methano-3-arylbutanoic acids **7aa**–**7ea** in 95–98% yields as indicated in Scheme 4.

Next, we attempted to introduce 1-adamantanamine with steric hindrance into carboxylic acids **7aa**–**7ea**. Recently, we reported that the amidation of α-amino acids with 1.0 M aqueous NH_4Cl solution via the mixed carbonic carboxylic anhydrides provided the corresponding primary amides in excellent yields.[15a,c] Therefore, we supposed it was feasible to efficiently introduce the salt of 1-adamantanamine hydrochloride or sulfate into carboxylic acids



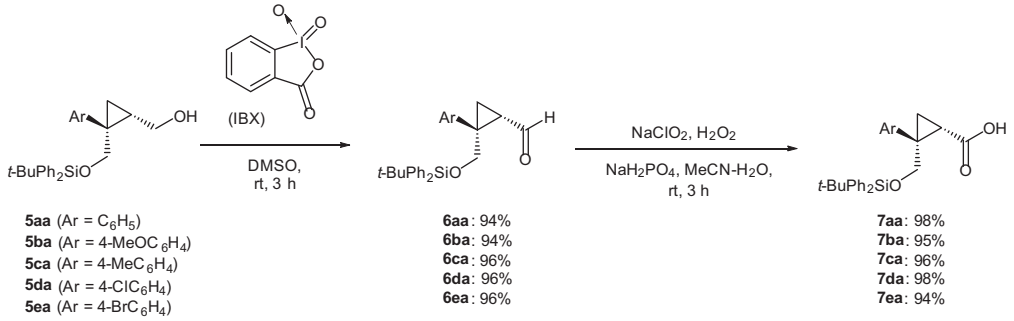
Scheme 3. Preparation of (*Z*)-4-*tert*-butyldiphenylsiloxy-3-arylbut-2-en-1-ols **3ba**–**3ea**.

Table 2
Simmons-Smith reaction of (*Z*)-4-*tert*-butyldiphenylsiloxy-3-arylbut-2-en-1-ols **3aa**–**3ea**[a]



Entry	Product	Ar	Yield (%)	ee (%)[b]
1	**5aa**	C_6H_5	Quant.	71
2	**5ba**	4-$MeOC_6H_4$	70	36
3	**5ca**	4-MeC_6H_4	Quant.	65
4	**5da**	4-ClC_6H_4	97	66[c]
5	**5ea**	4-BrC_6H_4	97	73[d]

[a] All reactions were carried out with (*Z*)-4-*tert*-butyldiphenylsiloxy-3-arylbut-2-en-1-ols **3aa**–**3ea**, 2.0 equiv of Et_2Zn, and 3.0 equiv of CH_2I_2 in anhydrous CH_2Cl_2.
[b] Determined by HPLC analysis with a 95:5 mixture of hexane and 2-propanol as an eluent using Chiralcel OD (1.0 mL/min).
[c] Determined by HPLC analysis with hexane containing 0.1% 2-propanol as an eluent using Chiralcel OD-H after acetylation (1.0 mL/min).
[d] Determined by HPLC analysis with a 99:1 mixture of hexane and 2-propanol as an eluent using Chiralcel OD (1.0 mL/min).



Scheme 4. Preparation of the 2,3-methano-3-arylbutanoic acids **7aa**–**7ea**.

7aa–**7ea**. At first, we examined the amidation of 3-phenylpropionic acid **7′** with sterically hindered 1-adamantanamine in an aqueous organic solvent in order to optimize the reaction conditions. The results are summarized in Table 3. Treatment of **7′** with 1.1 equiv of 1-adamantanamine hydrochloride (amantadine®) in the presence of 1.1 equiv of $ClCO_2Et$ and 1.1 equiv of Et_3N in MeCN–H_2O afforded *N*-adamant-1-yl-3-phenylpropanamide **8′** in 27% yield (see entry 1). The reaction of 1-adamantanamine sulfate, which is less expensive than amantadine®, did not afford the corresponding amide **8′** because 1-adamantanamine sulfate is hardly dissolved in organic solvents or water (see entry 2). The amidation of **7′** with 1-adamantanamine sulfate in the presence of 2.0 equiv of 1.0 M aqueous $NaHCO_3$ and NaOH solution gave the desired amide **8′** in 16% and 42% yield, respectively (see entries 3 and 4). Moreover, the amidation of **7′** with 1-adamantanamine sulfate in the presence of 2.0 equiv of 1.0 M aqueous NaOH solution was carried out for 6 h, 24 h, and 48 h to afford the amide **8′** in 58%, 84%, and 82% yield, respectively (see entries 5, 6, and 7). The reaction with a stoichiometric and an excess amount of 1.0 M aqueous NaOH solution gave 46% and 65% yield, respectively (see entries 8 and 9).

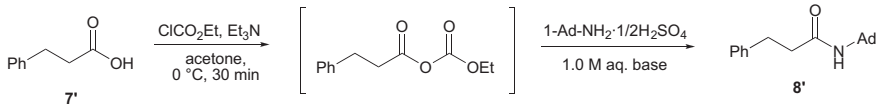
Subsequently, the amidation of the 2,3-methano-3-arylbutanoic acids **7aa**–**7ea** with 1-adamantanamine sulfate was performed under the optimized conditions to afford the corresponding 2,3-methano-3-arylbutanamides **8aa**–**8ea** in 73–97% yields as indicated in Scheme 5.

Furthermore, the conditions for the reduction of *N*-adamant-1-yl-2,3-methano-3-phenylbutanamide **8′** were optimized and the results are shown in Table 4. The reaction of **8′** with 2.0 equiv of $BH_3{\cdot}SMe_2$ in anhydrous THF at 40 °C for 49 h afforded *N*-adamant-1-yl-3-phenylpropylamine **10′** in 6% yield (see entry 1). The use of 5.0 equiv of $BH_3{\cdot}SMe_2$ in anhydrous THF at rt to 40 °C for 71 h gave the desired amine **10′** in 58% yield (see entry 3), and **10′** was obtained in 69% yield when the reaction was carried at rt to 70 °C for 23 h in anhydrous toluene (see entry 4). The yield obtained when Meyer's method was used was 20% (see entry 5).[16] The yield (88%) greatly improved under the conditions using 5.0 equiv of $LiAlH_4$ in toluene at 40 to 70 °C for 19 h (see entry 8). The reduction of the chiral amide **8″** containing a cyclopropane ring with 5.0 equiv of $LiAlH_4$ proceeded smoothly at 70 °C for 13 h to afford the corresponding chiral amine **10″** in 92% yield without cleavage of the cyclopropane skeleton (see entry 9 of Table 4).

Fortunately, the treatment of the chiral 2,3-methano-3-phenylbutanamide **8aa** with 5.0 equiv of $LiAlH_4$ in anhydrous toluene at 70–100 °C for 18 h afforded the corresponding chiral 2,3-methano-2-phenylbutan-1-ol **10a** in 72% yield with 86% ee through simultaneous reduction of the amide and silyl moieties as shown in pathway A of Scheme 6.[12] In pathway B, the silyl group of **8aa** was cleaved by tetrabutylammonium fluoride (TBAF) to give the corresponding chiral 4-hydroxyamide **9a** in 93% yield, followed by reduction with $LiAlH_4$ to afford **10a** in 87% yield and with 86% ee. The overall yield in 2 steps was 81%, which is better than the yield of pathway A.

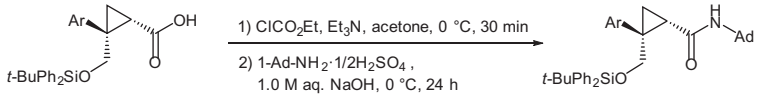
The chiral 2,3-methano-2-arylbutan-1-ols **10b**–**10e** were prepared efficiently from the corresponding chiral amides **8ba**–**8ea** in excellent yields in two steps as described in Scheme 7. We were able to convert (+)-*cis*-4-*tert*-butyldiphenylsiloxy-2,3-methano-3-arylbutan-1-ols **5aa**–**5ea** into the corresponding chiral alcohols **10b**–**10e** in five steps without a significant loss of enantiomeric excess in all cases.

Table 3
Optimization of the reaction conditions for the amidation of 3-phenylpropionic acid **7′**[a]



Entry	Base	Equiv of base	Time (h)	Yield (%)[d]
1[b]	Free	—	6	27
2[c]	Free	—	8	0
3	$NaHCO_3$	2.0	20	16
4	NaOH	2.0	1	42
5	NaOH	2.0	6	58
6	NaOH	2.0	24	84
7	NaOH	2.0	48	82
8	NaOH	1.1	24	46
9	NaOH	3.0	24	65

[a] All reactions were carried out with 0.5 mmol of 3-phenylpropionic acid **7′**, 1.1 equiv of 1-adamantanamine sulfate (Ad-$NH_2{\cdot}1/2H_2SO_4$), 1.1 equiv of $ClCO_2Et$, and 1.1 equiv of Et_3N in 10 mL of acetone.
[b] 1-Adamantanamine hydrochloride (1-Ad-$NH_2{\cdot}HCl$) was used instead of 1-adamantanamine sulfate (1-Ad-$NH_2{\cdot}1/2H_2SO_4$) in a mixture of 10 mL of MeCN and 0.5 mL of water.
[c] A mixture of 10 mL of MeCN and 1.0 mL of water was used instead of acetone.
[d] Isolated yield.

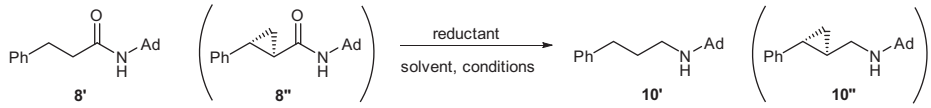


7aa (Ar = C_6H_5)
7ba (Ar = 4-$MeOC_6H_4$)
7ca (Ar = 4-MeC_6H_4)
7da (Ar = 4-ClC_6H_4)
7ea (Ar = 4-BrC_6H_4)

8aa: 88%
8ba: 84%
8ca: 97%
8da: 73%
8ea: 78%

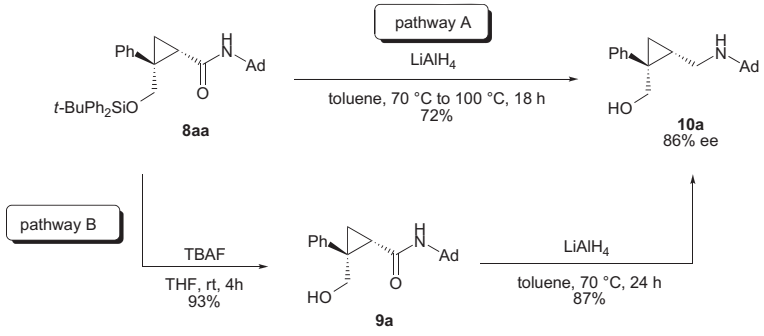
Scheme 5. Preparation of the 2,3-methano-3-arylbutanamides **8aa**–**8ea**.

Table 4
Optimaization of the reaction conditions for reduction of *N*-adamant-1-yl-2,3-methano-3-phenylbutanamide (**8′**)[a]

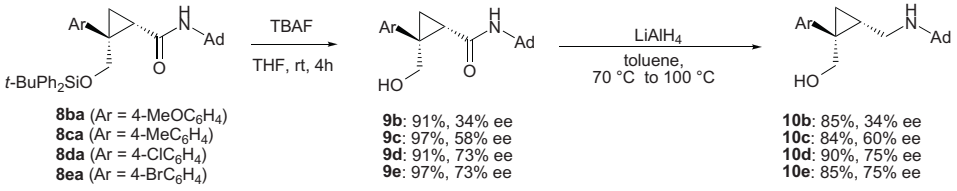


Entry	Reductant	Equiv	Solvent	Conditions	Yield (%)[b]
1	$BH_3{\cdot}SMe_2$	2.0	THF	40 °C, 49 h	6
2	$BH_3{\cdot}SMe_2$	2.0	THF	50 °C to reflux, 70 h	31
3	$BH_3{\cdot}SMe_2$	5.0	THF	rt to 40 °C, 71 h	58
4	$BH_3{\cdot}SMe_2$	5.0	Toluene	rt to 70 °C, 23 h	69
5[c]	$NaBH_4$, I_2	2.5, 1.0	THF	40 °C, 72 h	20
6	$LiAlH_4$	5.0	THF	rt to reflux, 65 h	48
7	$LiAlH_4$	2.5	Toluene	rt to 70 °C, 46 h	54
8	$LiAlH_4$	5.0	Toluene	40 °C to 70 °C, 19 h	88
9[d]	$LiAlH_4$	5.0	Toluene	70 °C, 13 h	92

[a] All reactions were carried out with 50 mg (0.18 mmol) of **8′**.
[b] Isolated yield.
[c] The reaction was carried out with 50 mg (0.18 mmol) of **8′**, 2.5 equiv of $NaBH_4$, and 1.0 equiv of I_2 in anhydrous THF.
[d] **8″** was used as the starting material instead of **8′**.



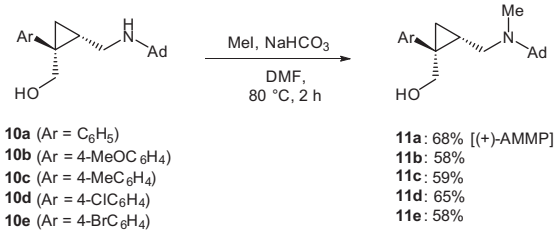
Scheme 6. Preparation of the chiral 2,3-methano-2-pheylbutan-1-ol **10a** via two pathways.



Scheme 7. Preparation of the chiral 2,3-methano-2-arylbutan-1-ols **10b–10e** in two steps from the chiral 2,3-methano-3-arylbutanamides **8ba–8ea**.

Additionally, (+)-AMMP analogues **11a–11e** were acquired in 58–68% yields via methylation of the amino alcohols **10a–10e** with MeI as indicated in Scheme 8.

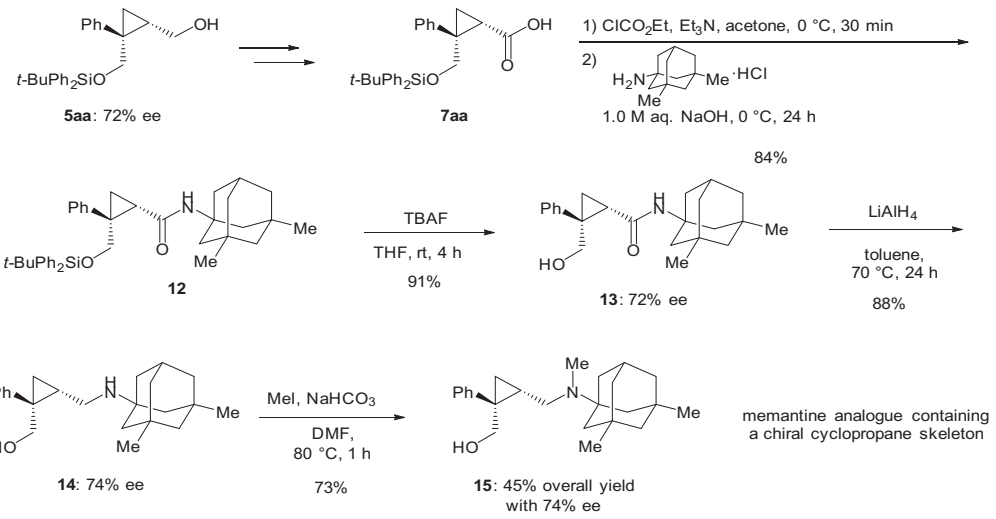
Finally, we succeeded in synthesizing memantine (3,5-dimethyl-1-adamantanamine) analogue **15** containing a chiral cyclopropane skeleton as shown in Scheme 9. The amidation of



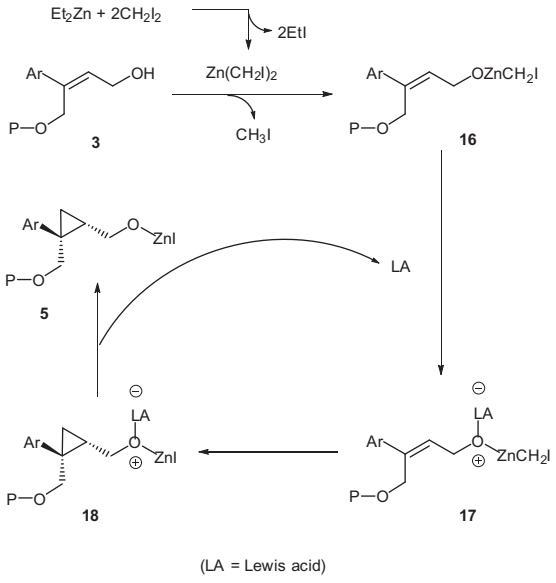
Scheme 8. Synthesis of (+)-AMMP analogues by methylation from the chiral 2,3-methano-2-arylbutan-1-ols **10a–10e**.

the 2,3-methano-3-phenylbutanoic acid **7aa** with memantine hydrochloride worked easily to give the corresponding amide **12** in 84% yield, followed by desilylation, reduction, and methylation to afford the memantine derivative **15** in 45% overall yield and with 74% ee from **5aa**.

We have recently reported the detail of the cyclopropanation of various allylic alcohols using L-tyrosine-derived fluorous disulfonamide as a chiral ligand and described the proposed reaction pathway (see Scheme 10) and a possible transition state (see Fig. 1) of the cyclopropanation.[17,18] The iodomethylzinc alkoxide **16** is produced by the addition of $Zn(CH_2I)_2$ to the allylic alcohol **3**, and complex **17** is formed from the species **16** and Lewis acid. The cyclopropane derivative **5** is generated from the disulfonamide **4**-zinc complex (Lewis acid) via complexes **17** and **18**. We propose a possible transition state for the enantioselective cyclopropanation with L-phenylalanine-derived disulfonamide **4** as shown in Figure 1. We speculated that the zinc derived from the carbenoid to the double bond of allylic alcohol **3** is accelerated by the oxygen atom of the methanesulfonamide group. Allylic alcohol **3** would



Scheme 9. Synthesis of memantine analogue containing a chiral cyclopropane skeleton from **5aa.**



Scheme 10. Proposed reaction pathway of the cyclopropanation.

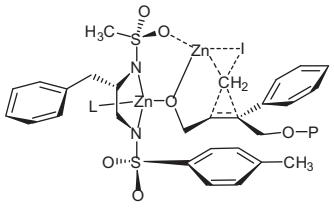


Figure 1. Possible transition state of the cyclopropanation.

take the opposite side of the benzene ring derived from L-phenylalanine in order to avoid the steric hindrance, then the carbenoid approaches the allylic alcohol **3** from the opposite side of the *p*-toluenesulfonamide group.

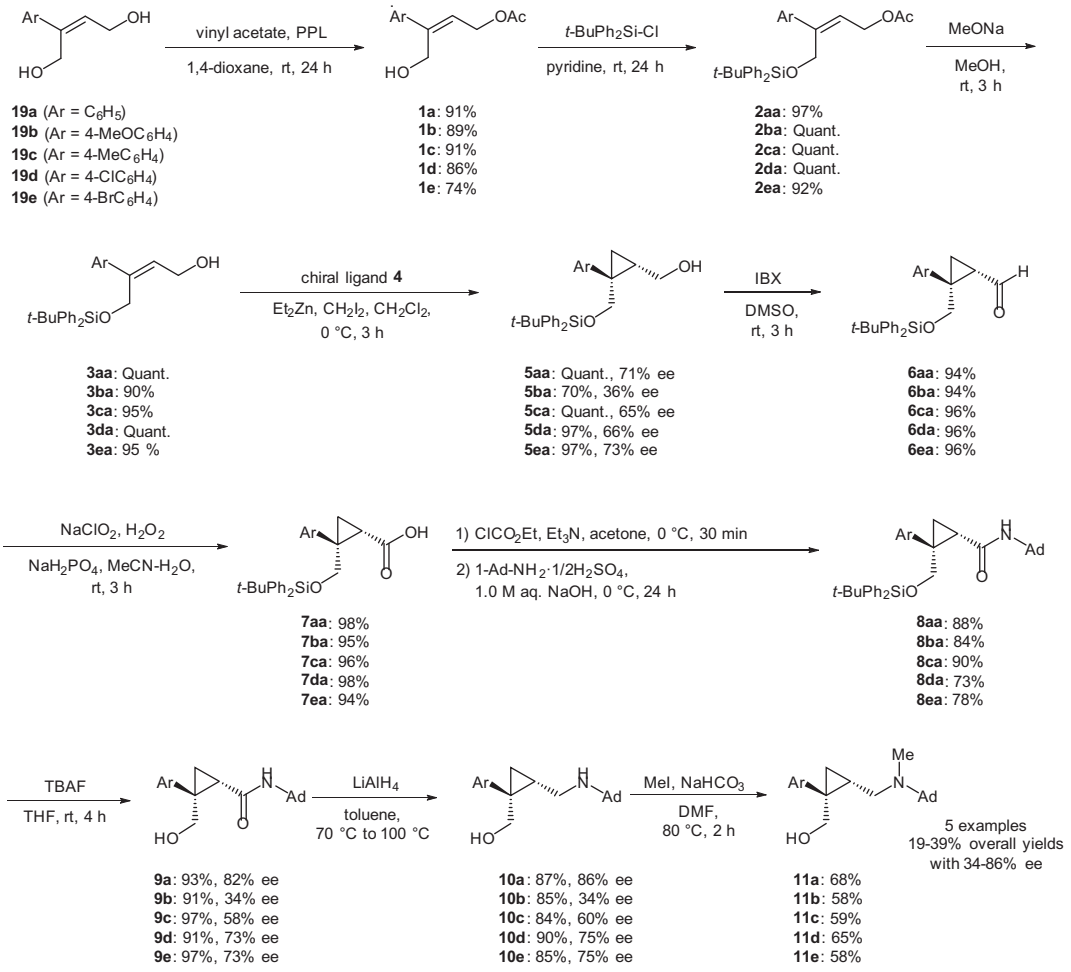
3. Conclusions

We have achieved a convenient enantioselective synthesis of (+)-*cis*-4-(*N*-adamant-1-yl-*N*-methylamino)-2,3-methano-2-phenylbutan-1-ol [(+)-AMMP] analogues **11a**–**11e** containing a chiral cyclopropane skeleton in 19–39% overall yields from the starting 2-arylbut-2-ene-1,4-diols **19a**–**19e** without the significant loss of enantiomeric excess as summarized in Scheme 11. The reagents used in our synthetic route are relatively inexpensive, and the key reactions are as follows; (i) the regioselective acetylation using PPL,[13] (ii) the catalytic enantioselective Simmons-Smith reaction in the presence of L-phenylalanine-derived disulfonamide,[14] and (iii) the convenient amidation of mixed carbonic carboxylic anhydrides in aqueous organic solvent.[15] Additionally, we have also succeeded in synthesizing memantine analogue **15** containing a chiral cyclopropane skeleton with 74% ee in 45% and 40% overall yield from the corresponding amide **5aa** and 1,4-diol **19a**, respectively.

4. Experimental

4.1. General

All reagents were used without purification except for CH_2Cl_2. CH_2Cl_2 was washed with water twice, dried over molecular sieves 4 Å, heated at reflux for 24 h with CaH_2, and distilled before use. The ^{1}H NMR and ^{13}C NMR spectra were measured with a Bruker Ultrashield™ 400 Plus (400 MHz) spectrometer. The chemical shifts are expressed in parts per million downfield from tetramethylsilane ($\delta = 0.00$) as an internal standard. Chemical shifts (δ) are reported in ppm, and spin–spin coupling constants (J) are given in Hertz. Abbreviations to denote the multiplicity of a particular signal are s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). The high-resolution mass spectra (HRMS) of the compounds with a high molecular weight were recorded using a Waters LCT Premier (ESI-TOF-MS) spectrometer. Reactions were monitored using thin-layer chromatography with silica gel 60 F_{254}. Purification of the reaction products was carried out by column chromatography using silica gel (64–210 mesh). HPLC analysis was carried out with Chiralcel OD, OJ, OB, OK (10 mm, 46 × 250 mm), Chiralpak AD, AS (10 mm, 46 × 250 mm), and Chiralcel OD-H (5 mm, 46 × 250 mm) coupled to a photodiode array detector or a dual λ absorbance detector, and HPLC grade solvents were used for HPLC analysis. Melting points were determined with a hot plate apparatus. Optical rotations were measured on a digital polarimeter with a sodium lamp at room temperature. Infrared (IR) spectra were recorded on HORIBA FT-IR Fourier transform infrared spectrophotometer.



Scheme 11. Convenient enantioselective total synthesis of (+)-AMMP analogues containing a chiral cyclopropane skeleton from **19a**–**19e**.

4.2. Typical procedure for the acetylation of (*Z*)-2-pheylbut-2-ene-1,4-diol 19a using PPL

To a pale yellow suspension of 164 mg (1.00 mmol, 1.0 equiv) of (*Z*)-2-phenylbut-2-ene-1,4-diol **19a**, 0.92 mL (10.0 mmol, 10 equiv) of vinyl acetate, and 82 mg (50 w/w%) of PPL in 3 mL of 1,4-dioxane was stirred at rt for 24 h. The reaction suspension was diluted with 10 mL of AcOEt and dried over anhydrous $MgSO_4$. The residue was chromatographed on silica gel with a 1:2 mixture of AcOEt and hexane to afford 187 mg (91% yield) of **1a**.

4.2.1. (*Z*)-4-Hydroxy-3-phenylbut-2-en-1-yl acetate 1a

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H, CH_3CO), 2.45 (brs, 1H, OH), 4.60 (s, 2H, CH_2OH), 4.88 (d, J = 7.2 Hz, 2H, CH_2OAc), 5.92 (t, J = 7.2 Hz, 1H, =CH), 7.28–7.38, 7.48–7.50 (m, m, 3H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 60.1, 61.2, 124.3, 126.4, 128.0, 128.6, 140.1, 143.9, 171.5; HRMS (ESI-TOF): Calcd for $C_{12}H_{14}O_3Na$ $(M+Na)^+$: 229.0835, found: 229.0815.

4.2.2. (*Z*)-4-Hydroxy-3-(4-methoxyphenyl)but-2-en-1-yl acetate 1b

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H, CH_3CO), 2.43 (t, J = 6.1 Hz, 1H, OH), 3.81 (s, 3H, OCH_3), 4.58 (d, J = 6.1 Hz, 2H, CH_2OH), 4.85 (d, J = 7.4 Hz, 2H, CH_2OAc), 5.86 (t, J = 7.4 Hz, 1H, =CH), 6.91, 7.14 (d, d, J = 8.8 Hz, J = 8.8 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 55.3, 60.0, 61.3, 113.9, 122.5, 127.6, 132.4, 143.4, 159.5, 171.5; HRMS (ESI-TOF): Calcd for $C_{13}H_{16}O_4Na$ $(M+Na)^+$: 259.0941, found: 259.0915.

4.2.3. (*Z*)-4-Hydroxy-3-(4-methylphenyl)but-2-en-1-yl acetate 1c

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H, CH_3CO), 2.35 (s, brs, 3H, 1H, $ArCH_3$, OH), 4.59 (d, J = 5.4 Hz, 2H, CH_2OH), 4.87 (d, J = 7.4 Hz, 2H, CH_2OAc), 5.90 (t, J = 7.4 Hz, 1H, =CH), 7.16, 7.39 (d, d, J = 8.2 Hz, J = 8.2 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 21.1, 60.0, 61.2, 123.4, 126.3, 129.3, 137.1, 137.9, 143.8, 171.4; HRMS (ESI-TOF): Calcd for $C_{13}H_{16}O_3Na$ $(M+Na)^+$: 243.0992, found: 243.1007.

4.2.4. (*Z*)-3-(4-Chlorophenyl)-4-hydroxybut-2-en-1-yl acetate 1d

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H, CH_3CO), 2.49–2.54 (m, 1H, OH), 4.56 (d, J = 6.0 Hz, 2H, CH_2OH), 4.86 (d, J = 7.2 Hz, 2H, CH_2OAc), 5.90 (t, J = 7.2 Hz, 1H, =CH), 7.31, 7.44 (d, d, J = 8.6 Hz, J = 8.6 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 59.9, 61.1, 124.7, 127.8, 128.7, 133.9, 138.6, 142.8, 171.5; HRMS (ESI-TOF): Calcd for $C_{12}H_{13}ClO_3Na$ $(M+Na)^+$: 263.0445, found: 263.0425.

4.2.5. (*Z*)-3-(4-Bromophenyl)-4-hydroxybut-2-en-1-yl acetate 1e

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 3H, CH_3CO), 2.50 (brs, 1H, OH), 4.57 (d, J = 5.5 Hz, 2H, CH_2OH), 4.86 (d, J = 7.4 Hz, 2H, CH_2OAc), 5.91 (t, J = 7.4 Hz, 1H, =CH), 7.38, 7.48 (d, d, J = 8.6 Hz, J = 8.6 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$):

δ 21.1, 59.9, 61.1, 122.0, 124.7, 128.1, 131.6, 139.1, 142.8, 171.5; HRMS (ESI-TOF): Calcd for $C_{12}H_{13}BrO_3Na$ $(M+Na)^+$: 306.9940, found: 306.9964.

4.3. Typical procedure for the preparation of (*Z*)-4-(*tert*-butyldiphenylsiloxy)-3-phenylbut-2-en-1-yl acetate 2aa

To a colorless solution of 206 mg (1.00 mmol, 1.0 equiv) of (*Z*)-4-hydroxy-3-phenylbut-2-en-1-yl acetate **1a** in 5 mL of pyridine were added 330 mg (1.20 mmol 1.2 equiv) of *t*-$BuPh_2SiCl$ under an argon atmosphere. After stirring at rt for 24 h, the reaction mixture was quenched with 10 mL of water and extracted with 10 mL ×3 of AcOEt. The organic layers were combined, washed with 5 mL of brine, and dried over anhydrous $MgSO_4$. The residue was chromatographed on silica gel with a 1:8 mixture of AcOEt and hexane to afford 431 mg (97% yield) of **2aa**.

4.3.1. (Z)-4-(*tert*-Butyldiphenylsiloxy)-3-phenylbut-2-en-1-yl acetate (2aa)

Reaction time: 24 h; Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H, $(CH_3)_3C$), 2.03 (s, 3H, CH_3CO), 4.60 (s, 2H, CH_2OSi), 4.65 (d, *J* = 6.8 Hz, 2H, CH_2OAc), 5.84 (t, *J* = 6.8 Hz, 1H, =CH), 7.25–7.31, 7.34–7.44, 7.62–7.65 (m, m, m, 3H, 8H, 4H, C_6H_5×3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 20.8, 26.6, 61.0, 61.3, 124.2, 126.8, 127.3, 127.6, 128.0, 129.7, 133.1, 135.5, 140.3, 142.8, 170.5; HRMS (ESI-TOF): Calcd for $C_{28}H_{32}O_3SiNa$ $(M+Na)^+$: 467.2013, found: 467.2010.

4.3.2. (*Z*)-4-(*tert*-Butyldimethylsiloxy)-3-phenylbut-2-en-1-yl acetate 2ab

Reaction time: 24 h; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.00 (s, 6H, $(CH_3)_2Si$) 0.80 (s, 9H, $(CH_3)_3C$), 2.04 (s, 3H, CH_3CO), 4.54 (s, 2H, CH_2OSi), 4.83 (d, *J* = 6.8 Hz, 2H, CH_2OAc), 5.83 (t, *J* = 6.8 Hz, 1H, =CH), 7.20–7.29, 7.33–7.36 (m, m, 3H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.4, 18.2, 21.0, 25.8, 61.0, 61.3, 124.3, 126.7, 127.5, 128.1, 140.7, 143.2, 171.0; HRMS (ESI-TOF): Calcd for $C_{18}H_{28}O_3SiNa$ $(M+Na)^+$: 343.1700, found: 343.1694.

4.3.3. (*Z*)-4-(*tert*-Butoxydiphenylsiloxy)-3-phenylbut-2-en-1-yl acetate 2ac

Reaction time: 24 h; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (s, 9H, $(CH_3)_3C$), 2.04 (s, 3H, CH_3CO), 4.67 (d, *J* = 6.9 Hz, 2H, CH_2-OAc), 4.69 (s, 2H, CH_2OSi), 5.85 (t, *J* = 6.9 Hz, 1H, =CH), 7.26–7.32, 7.36–7.40, 7.55–7.58 (m, m, m, 7H, 4H, 4H, C_6H_5 ×3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 31.9, 60.1, 61.1, 74.0, 124.5, 126.8, 127.5, 127.6, 128.2, 129.9, 134.6, 135.0, 140.4, 142.6, 170.8; HRMS (ESI-TOF): Calcd for $C_{28}H_{32}O_4SiNa$ $(M+Na)^+$: 483.1962, found: 483.1963.

4.3.4. (*Z*)-3-Phenyl-4-{tris(trimethylsilyl)siloxy}but-2-en-1-yl acetate 2ad

Reaction time: 24 h; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.19 (s, 27H, $(CH_3)_3Si$ ×3), 2.08 (s, 3H, CH_3CO), 4.42 (s, 2H, CH_2OSi), 4.86 (d, *J* = 6.7 Hz, 2H, CH_2OAc), 5.82 (t, *J* = 6.7 Hz, 1H, =CH), 7.23–7.37 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.3, 21.0, 61.4, 66.2, 124.4, 126.7, 127.4, 128.1, 140.9, 143.2, 170.9; HRMS (ESI-TOF): Calcd for $C_{21}H_{40}O_3Si_4Na$ $(M+Na)^+$: 475.1947, found: 475.1951.

4.3.5. (*Z*)-3-Phenyl-4-(triphenylmethoxy)but-2-en-1-yl acetate 2ae

Reaction time: 90 h; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 3H, CH_3CO), 4.02 (s, 2H, CH_2OCPh_3), 4.67 (d, *J* = 6.9 Hz, 2H, CH_2OAc), 5.96 (t, *J* = 6.9 Hz, 1H, =CH), 7.21–7.33, 7.41–7.44 (m, m, 14H, 6H, C_6H_5 ×4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 61.0, 61.4, 87.1, 125.5, 126.7, 127.1, 127.5, 127.8, 128.1, 128.7, 140.5, 141.2, 143.8, 170.8; HRMS (ESI-TOF): Calcd for $C_{31}H_{28}O_3Na$ $(M+Na)^+$: 471.1931, found: 471.1919.

4.3.6. (*Z*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-methoxyphenyl)but-2-en-1-yl acetate 2ba

Reaction time: 24 h; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 9H, $(CH_3)_3C$), 2.03 (s, 3H, CH_3CO), 3.81 (s, 3H, CH_3O), 4.57 (s, 2H, CH_2OSi), 4.62 (d, *J* = 6.9 Hz, 2H, CH_2OAc), 5.78 (t, *J* = 6.9 Hz, 1H, =CH), 6.83, 7.31 (d, d, *J* = 8.8 Hz, *J* = 8.8 Hz, 2H, 2H, C_6H_4), 7.35–7.45, 7.63–7.65 (m, m, 6H, 4H, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 21.0, 26.7, 55.3, 61.2, 61.4, 113.5, 122.7, 127.7, 128.0, 129.7, 132.8, 133.3, 135.7, 142.4, 159.1, 170.8; HRMS (ESI-TOF): Calcd for $C_{29}H_{34}O_4SiNa$ $(M+Na)^+$: 497.2119, found: 497.2125.

4.3.7. (*Z*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-methylphenyl)but-2-en-1-yl acetate 2ca

Reaction time: 24 h; Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 9H, $(CH_3)_3C$), 2.03 (s, 3H, CH_3CO), 2.34 (s, 3H, CH_3), 4.57 (s, 2H, CH_2OSi), 4.65 (d, *J* = 6.9 Hz, 2H, CH_2OAc), 5.82 (t, *J* = 6.9 Hz, 1H, =CH), 7.10, 7.25–7.27, 7.34–7.45, 7.63–7.65 (d, m, m, m, *J* = 7.8 Hz, 2H, 2H, 6H, 4H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 21.0, 21.1, 26.7, 61.3, 61.5, 123.6, 126.7, 127.7, 128.8, 129.7, 133.3, 135.7, 137.2, 137.5, 142.7, 170.1; HRMS (ESI-TOF): Calcd for $C_{29}H_{34}O_3SiNa$ $(M+Na)^+$: 481.2175, found: 481.2178.

4.3.8. (*Z*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-chlorophenyl)but-2-en-1-yl acetate 2da

Reaction time: 24 h; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 9H, $(CH_3)_3C$), 2.04 (s, 3H, CH_3CO), 4.56 (s, 2H, CH_2OSi), 4.59 (d, *J* = 6.8 Hz, 2H, CH_2OAc), 5.81 (t, *J* = 6.8 Hz, 1H, =CH), 7.24–7.29, 7.35–7.46, 7.60–7.63 (m, m, m, 4H, 6H, 4H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 20.9, 26.7, 61.0, 61.1, 124.6, 127.7, 128.2, 129.8, 133.1, 133.3, 135.6, 138.8, 141.9, 170.7; HRMS (ESI-TOF): Calcd for $C_{28}H_{31}ClO_3SiNa$ $(M+Na)^+$: 501.1623, found: 501.1608.

4.3.9. (*Z*)-3-(4-Bromophenyl)-4-(*tert*-butyldiphenylsiloxy)but-2-en-1-yl acetate 2ea

Reaction time: 24 h; Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H, $(CH_3)_3C$), 2.04 (s, 3H, CH_3CO), 4.59 (s, 2H, CH_2OSi), 4.62 (d, *J* = 6.9 Hz, 2H, CH_2OAc), 5.81 (t, *J* = 6.9 Hz, 1H, =CH), 7.22, 7.35–7.46, 7.60–7.62 (d, m, m, *J* = 8.6 Hz, 2H, 8H, 4H, C_6H_4, C_6H_5 ×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 20.9, 26.7, 61.0, 61.0, 121.5, 124.7, 127.8, 128.6, 129.8, 131.2, 133.1, 135.6, 139.3, 141.9, 170.7; HRMS (ESI-TOF): Calcd for $C_{28}H_{31}BrO_3SiNa$ $(M+Na)^+$: 545.1118, found: 545.1114.

4.4. Typical procedure for the preparation of (*Z*)-4-(*tert*-butyldiphenylsiloxy)-3-phenylbut-2-en-1-ol 3aa

To a colorless solution of 907 mg (2.03 mmol) of (*Z*)-4-(*tert*-butyldiphenylsiloxy)-3-phenylbut-2-en-1-yl acetate **2aa** in 58 ml of 1:1 mixture of Et_2O–MeOH was added a catalytic amount (3 drops) of 28% MeONa solution in MeOH. The mixture was stirred at rt for 5 h and quenched with 5 mL of saturated aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted with 10 mL ×2 of AcOEt. The organic layers were combined, washed with 10 mL of brine, and dried over anhydrous $MgSO_4$. The residue was chromatographed on silica gel with a 5:1 mixture of hexane and AcOEt to afford 821 mg (quantitative yield) of **3aa**.

4.4.1. (*Z*)-4-(*tert*-Butyldiphenylsiloxy)-3-phenylbut-2-en-1-ol 3aa

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 9H, $(CH_3)_3C$), 1.64 (brs, 1H, OH), 4.16 (dd, *J* = 6.4, 6.4 Hz, 2H, CH_2OH), 4.59 (s, 2H, CH_2OSi), 5.97 (t, *J* = 6.4 Hz, 1H, =CH), 7.23–7.46, 7.64–7.66 (m, m, 11H, 4H, C_6H_5×3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 26.7, 59.3, 61.6, 126.8, 127.3, 127.7, 128.1, 129.7, 129.8, 133.2, 135.7, 140.8,

Please cite this article in press as: Ezawa, T.; et al. *Tetrahedron: Asymmetry* (2017), http://dx.doi.org/10.1016/j.tetasy.2016.12.010

141.3; HRMS (ESI-TOF): Calcd for $C_{26}H_{30}O_2SiNa$ $(M+Na)^+$: 425.1907, found: 425.1915.

4.4.2. (*Z*)-4-(*tert*-Butyldimethylsiloxy)-3-phenylbut-2-en-1-ol 3ab

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.08 (s, 6H, $(CH_3)_2Si$) 0.88 (s, 9H, $(CH_3)_3C$), 2.25 (t, J = 6.2 Hz, 1H, OH), 4.37 (dd, J = 6.2, 6.6 Hz, 2H, CH_2OH), 4.59 (s, 2H, CH_2OSi), 6.07 (t, J = 6.6 Hz, 1H, =CH), 7.25–7.39 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.3, 18.2, 25.8, 59.3, 61.7, 126.5, 127.3, 128.3, 130.2, 141.4, 142.2; HRMS (ESI-TOF): Calcd for $C_{16}H_{26}O_2SiNa$ $(M+Na)^+$: 301.1594, found: 301.1585.

4.4.3. (*Z*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-chlorophenyl)but-2-en-1-ol 3da

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H, $(CH_3)_3C$), 1.53 (t, J = 6.2 Hz, 1H, OH), 4.11 (dd, J = 6.2, 6.5, 2H, CH_2OH), 4.56 (s, 2H, CH_2OSi), 5.93 (t, J = 6.5 Hz, 1H, =CH), 7.24–7.29, 7.36–7.47, 7.62–7.64 (m, m, m, 4H, 6H, 4H, C_6H_4, $C_6H_5\times2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 26.7, 59.2, 61.2, 127.8, 128.1, 128.3, 129.9, 130.0, 133.1, 135.7, 139.1, 140.1; HRMS (ESI-TOF): Calcd for $C_{26}H_{29}ClO_2SiNa$ $(M+Na)^+$: 459.1518, found: 459.1526.

4.4.4. (*Z*)-3-(4-Bromophenyl)-4-(*tert*-butyldiphenylsiloxy)but-2-en-1-ol 3ea

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H, $(CH_3)_3C$), 1.50 (brs, 1H, OH), 4.11 (dd, J = 6.3, 6.6 Hz, 2H, CH_2OH), 4.55 (s, 2H, CH_2OSi), 5.94 (t, J = 6.6 Hz, 1H, =CH), 7.21, 7.36–7.47, 7.62–7.64 (d, m, m, J = 8.6 Hz, 2H, 8H, 4H, C_6H_4, $C_6H_5\times2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 26.7, 59.2, 61.1, 121.3, 127.8, 128.5, 129.9, 130.0, 131.2, 133.1, 135.7, 139.6, 140.1; HRMS (ESI-TOF): Calcd for $C_{26}H_{29}BrO_2SiNa$ $(M+Na)^+$: 503.1012, found: 503.1017.

4.5. Typical procedure for the preparation of (*Z*)-4-(*tert*-butoxydiphenylsiloxy)-3-phenylbut-2-en-1-ol 3ac

To a colorless solution of 187 mg (0.41 mmol) of (*Z*)-4-(*tert*-butoxydiphenylsiloxy)-3-phenylbut-2-en-1-yl acetate **2ac** in 3 mL of anhydrous THF were added dropwise 0.84 mL (0.86 mmol, 2.1 equiv) of a 1.02 M DIBAL-H solution in hexane under an argon atmosphere at −78 °C. The mixture was stirred at −78 °C for 24 h and then quenched at −78 °C with 2 mL of MeOH. To the reaction mixture was added a solution of 7.20 g of potassium sodium tartarate in 20 mL of water. After stirring at rt for 3 h, the reaction mixture was extracted with 20 mL ×3 of AcOEt. The AcOEt layers were combined, washed with brine, and dried over anhydrous $MgSO_4$. The residue was chromatographed on silica gel with a 5:1 mixture of hexane and AcOEt to afford 170 mg (quantitative yield) of **3ac**.

4.5.1. (*Z*)-4-(*tert*-Butoxydiphenylsiloxy)-3-phenylbut-2-en-1-ol 3ac

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 9H, $(CH_3)_3C$), 1.51 (t, J = 6.3 Hz, 1H, OH), 4.16 (dd, J = 6.3, 6.7 Hz, 2H, CH_2OH), 4.69 (s, 2H, CH_2OSi), 5.97 (t, J = 6.7 Hz, 1H, =CH), 7.24–7.42, 7.56–7.59 (m, m, 11H, 4H, $C_6H_5\times3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.9, 59.2, 60.2, 74.1, 126.7, 127.3, 127.7, 128.2, 129.8, 130.0, 134.6, 135.0, 140.7, 140.8; HRMS (ESI-TOF): Calcd for $C_{26}H_{30}O_3SiNa$ $(M+Na)^+$: 441.1856, found: 441.1872.

4.5.2. (*Z*)-3-Phenyl-4-{tris(trimethylsilyl)siloxy}but-2-en-1-ol 3ad

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.21 (s, 27H, $(CH_3)_3Si\times3$), 2.48 (brs, 1H, OH), 4.31 (d, J = 6.8 Hz, 2H, CH_2OH), 4.44 (s, 2H, CH_2OSi), 6.08 (t, J = 6.8 Hz, 1H, =CH), 7.24–7.34 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.4, 59.2, 67.1, 126.5, 127.3, 128.2, 130.4, 141.6, 142.7; HRMS (ESI-TOF): Calcd for $C_{19}H_{38}O_2Si_4Na$ $(M+Na)^+$: 433.1841, found: 433.1854.

4.5.3. (*Z*)-3-Phenyl-4-(triphenylmethoxy)but-2-en-1-ol 3ae

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 1.71 (brs, 1H, OH), 4.03 (s, 2H, CH_2OCPh_3), 4.16 (dd, J = 5.2, 6.0 Hz, 2H, CH_2OH), 6.10 (t, J = 6.8 Hz, 1H, =CH), 7.21–7.34, 7.41–7.44 (m, m, 14H, 6H, $C_6H_5\times4$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 59.4, 61.3, 87.2, 126.7, 127.1, 127.4, 127.7, 127.9, 128.1, 128.2, 128.7, 131.0, 139.7, 141.0, 143.7; HRMS (ESI-TOF): Calcd for $C_{29}H_{26}O_2Na$ $(M+Na)^+$: 429.1825, found: 429.1830.

4.5.4. (*Z*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-methoxyphenyl)but-2-en-1-ol 3ba

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 9H, $(CH_3)_3C$), 1.55–1.58 (m, 1H, OH), 3.82 (s, 3H, CH_3O), 4.13 (dd, J = 6.2, 6.7 Hz, 2H, CH_2OH), 4.57 (s, 2H, CH_2OSi), 5.92 (t, J = 6.7 Hz, 1H, =CH), 6.82, 7.29 (d, d, J = 8.9 Hz, J = 8.9 Hz, 2H, 2H, C_6H_4), 7.36–7.46, 7.64–7.67 (m, m, 6H, 4H, $C_6H_5\times2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 26.7, 55.3, 59.3, 61.6, 113.5, 127.7, 127.9, 128.2, 129.8, 133.2, 135.7, 140.7, 159.0; HRMS (ESI-TOF): Calcd for $C_{27}H_{32}O_3SiNa$ $(M+Na)^+$: 455.2013, found: 455.2038.

4.5.5. (*Z*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-methylphenyl)but-2-en-1-ol 3ca

Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (s, 9H, $(CH_3)_3C$), 1.63 (brs, 1H, OH), 2.34 (s, 3H, CH_3), 4.15 (dd, J = 6.6, 6.6 Hz, 2H, CH_2OH), 4.57 (s, 2H, CH_2OSi), 5.96 (t, J = 6.6 Hz, 1H, =CH), 7.09, 7.24 (d, d, J = 8.2 Hz, J = 8.2 Hz, 2H, 2H, C_6H_4), 7.36–7.46, 7.64–7.67 (m, m, 6H, 4H, $C_6H_5\times2$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 21.1, 26.7, 59.3, 61.7, 126.6, 127.7, 128.8, 129.0, 129.8, 133.2, 135.7, 137.0, 137.9, 141.1; HRMS (ESI-TOF): Calcd for $C_{27}H_{32}O_2SiNa$ $(M+Na)^+$: 439.2064, found: 439.2090.

4.6. Typical procedure for the cyclopropanation of 3aa in the presence of a catalytic amount of 4

To a colorless solution of 201 mg (0.50 mmol, 1.0 equiv) of (*Z*)-4-(*tert*-butyldiphenylsiloxy)-3-phenylbut-2-en-1-ol **3aa** and 19 mg (0.05 mmol, 0.1 equiv) of the disulfonamide **4** in 7.5 mL of anhydrous CH_2Cl_2 were added dropwise at −40 °C under an argon atmosphere 1.0 mL (1.00 mmol, 2.0 equiv) of 1.0 M Et_2Zn solution in hexane and 121 μL (1.50 mmol, 3.0 equiv) of CH_2I_2. After stirring at 0 °C for 3 h, the reaction mixture was quenched with 0.3 mL of Et_3N and extracted with 20 mL ×3 of AcOEt. The organic layers were combined, washed with 5 mL of brine, and dried over $MgSO_4$. The residue was chromatographed on silica gel with a 8:1 mixture of hexane and AcOEt to afford 208 mg (quantitative yield) of **5aa**.

4.6.1. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-phenylbutan-1-ol 5aa

Colorless oil; 71% ee; $[\alpha]_D^{28}$ = +51.2 (*c* 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.69 (dd, J = 5.3, 5.3 Hz, 1H, CH_A of cyclopropane), 0.96 (s, 9H, $(CH_3)_3C$), 0.96–0.99 (m, 1H, CH_B of cyclopropane), 1.81–1.89 (m, 1H, $CHCH_2OH$), 3.45–3.59 (m, 2H, CH_AOH, OH), 3.55 (d, J = 11.2 Hz, 1H, CH_AOSi), 4.06 (d, J = 11.2 Hz, 1H, CH_BOSi), 4.12–4.19 (m, 1H, CH_BOH), 7.05–7.07, 7.11–7.15, 7.28–7.45, 7.56–7.59 (m, m, m, m, 2H, 2H, 9H, 2H, $C_6H_5\times3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0, 19.0, 25.8, 26.7, 32.5, 63.7, 69.2, 126.8, 127.5, 127.9, 128.2, 129.5, 129.8, 130.6, 131.7, 132.7, 135.4, 135.5, 143.9; HRMS (ESI-TOF): Calcd for $C_{27}H_{32}O_2SiNa$ $(M+Na)^+$: 439.2064, found: 439.2069. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 5.1 min, T_r(minor) 4.3 min (er 85.7:14.3).

4.6.2. (2*S*,3*R*)-4-(*tert*-Butyldimethylsiloxy)-2,3-methano-3-phenylbutan-1-ol 5ab

Colorless oil; 48% ee; $[\alpha]_D^{25}$ = +4.0 (*c* 0.15, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.28 (s, 3H, CH_3Si), −0.16 (s, 3H, CH_3Si), 0.74 (dd, *J* = 5.1, 5.3 Hz, 1H, CH_A of cyclopropane), 0.81 (s, 9H, $(CH_3)_3$C), 1.03 (dd, *J* = 5.1, 8.5 Hz, 1H, CH_B of cyclopropane), 1.69–1.75 (m, 1H, C*H*CH_2OH), 3.37–3.43 (m, 1H, OH), 3.58–3.64 (m, 2H, CH_AOSi, C*H*$_A$OH), 4.06–4.14 (m, 2H, CH_BOSi, C*H*$_B$OH), 7.20–7.23, 7.26–7.31, 7.36–7.39 (m, m, m, 1H, 2H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ −6.0, -5.9, 16.1, 18.1, 25.7, 25.8, 32.5, 63.7, 68.8, 126.6, 128.0, 130.1, 144.1; HRMS (ESI-TOF): Calcd for $C_{17}H_{28}O_2SiNa$ (M+Na)$^+$: 315.1751, found: 315.1725. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 4.6 min, T_r(minor) 4.2 min (er 74:26).

4.6.3. (2*S*,3*R*)-4-(*tert*-Butoxydiphenylsiloxy)-2,3-methano-3-phenylbutan-1-ol 5ac

Colorless oil; 21% ee; $[\alpha]_D^{25}$ = +2.30 (*c* 0.19, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71 (dd, *J* = 5.2, 5.4 Hz, 1H, CH_A of cyclopropane), 1.00 (dd, *J* = 5.2, 8.6 Hz, 1H, CH_B of cyclopropane), 1.13 (s, 9H, $(CH_3)_3$C), 1.79–1.86 (m, 1H, C*H*CH_2OH), 3.38–3.44 (m, 2H, C*H*$_A$OH, OH), 3.59 (d, *J* = 11.2 Hz, 1H, CH_AOSi), 4.07–4.14 (m, 1H, C*H*$_B$OH), 4.28 (d, *J* = 11.2 Hz, 1H, CH_BOSi), 7.19–7.43, 7.50–7.53 (m, m, 13H, 2H, C_6H_5 ×3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 25.9, 31.7, 32.3, 63.6, 68.2, 74.0, 126.7, 127.7, 127.8, 128.2, 129.9, 130.0, 130.2, 133.6, 134.2, 134.7, 144.0; HRMS (ESI-TOF): Calcd for $C_{27}H_{32}O_3SiNa$ (M+Na)$^+$: 455.2013, found: 455.2033. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 5.4 min, T_r(minor) 4.4 min (er 60.3:39.7).

4.6.4. (2*S*,3*R*)-2,3-Methano-3-phenyl-4-{tris(trimethylsilyl) siloxy}butan-1-ol 5ad

Colorless oil; 68% ee; $[\alpha]_D^{22}$ = +35.0 (*c* 0.98, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.09 (s, 27H, $(CH_3)_3$Si ×3), 0.72 (dd, *J* = 5.2, 5.3 Hz, 1H, CH_A of cyclopropane), 1.05 (dd, *J* = 5.2, 8.5 Hz, 1H, CH_B of cyclopropane), 1.63–1.70 (m, 1H, C*H*CH_2OH), 3.27–3.33 (m, 1H, OH), 3.52 (d, *J* = 10.5 Hz, 1H, CH_AOSi), 3.65 (dd, *J* = 1.2, 11.9 Hz, 1H, C*H*$_A$OH), 3.87 (d, *J* = 10.5 Hz, 1H, CH_BOSi), 4.08 (dt, *J* = 11.9, 5.2 Hz, 1H, C*H*$_B$OH), 7.18–7.22, 7.25–7.29, 7.34–7.37 (m, m, m, 1H, 2H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 0.1, 16.2, 26.3, 32.9, 63.7, 73.4, 126.6, 128.1, 130.1, 144.3; HRMS (ESI-TOF): Calcd for $C_{20}H_{40}O_2Si_4Na$ (M+Na)$^+$: 447.1998, found: 447.1974. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 3.5 min, T_r(minor) 3.1 min (er 84:16).

4.6.5. (2*S*,3*R*)-2,3-Methano-3-phenyl-4-(triphenylmethoxy)butan-1-ol 5ae

Colorless oil; 19% ee; $[\alpha]_D^{25}$ = +16.0 (*c* 0.17, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.50 (dd, *J* = 5.1, 5.3 Hz, 1H, CH_A of cyclopropane), 0.94 (dd, *J* = 5.1, 8.6 Hz, 1H, CH_B of cyclopropane), 1.81–1.88 (m, 1H, C*H*CH_2OH), 2.49 (d, *J* = 10.0 Hz, 1H, CH_AOC), 2.81–2.88 (m, 1H, OH), 3.45 (dd, *J* = 1.7 11.9 Hz, 1H, C*H*$_A$OH), 3.85 (d, *J* = 10.0 Hz, 1H, C*H*$_B$OC), 3.91 (dt, *J* = 11.9, 5.0 Hz, 1H, C*H*$_B$OH), 7.17–7.22 (m, 15H, C_6H_5 ×3), 7.35–7.39, 7.43–7.47, 7.60–7.62 (m, m, m, 1H, 2H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 25.4, 30.7, 63.1, 69.5, 87.1, 127.0, 128.0, 128.2, 128.4, 130.6, 143.4, 144.3; HRMS (ESI-TOF): Calcd for $C_{30}H_{28}O_2Na$ (M+Na)$^+$: 443.1982, found: 443.1961. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 6.2 min, T_r(minor) 5.6 min (er 59.6:40.4).

4.6.6. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-(4-methoxyphenyl)butan-1-ol 5ba

Colorless oil; 36% ee; $[\alpha]_D^{23}$ = +34.8 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.65 (dd, *J* = 5.2, 5.3 Hz, 1H, CH_A of cyclopropane), 0.91–0.94 (m, 1H, CH_B of cyclopropane), 0.97 (s, 9H, $(CH_3)_3$C), 1.76–1.84 (m, 1H, C*H*CH_2OH), 3.43–3.59 (m, 3H, OH, C*H*$_A$OH, CH_AOSi), 3.85 (s, 3H, CH_3O), 4.03 (d, *J* = 11.0 Hz, 1H, CH_BOSi), 4.11–4.18 (m, 1H, C*H*$_B$OH), 6.85, 7.08–7.16, 7.29–7.45, 7.56–7.59 (d, m, m, m, *J* = 8.8 Hz, 2H, 4H, 6H, 2H, C_6H_4, C_6H_5×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 19.0, 26.0, 26.7, 31.7, 55.4, 63.8, 69.4, 113.5, 127.5, 127.8, 129.5, 129.8, 131.6, 131.8, 132.8, 135.4, 135.6, 136.2, 142.3; HRMS (ESI-TOF): Calcd for $C_{28}H_{34}O_3SiNa$ (M+Na)$^+$: 469.2169, found: 469.2178. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 5.2 min, T_r(minor) 4.7 min (er 68:32).

4.6.7. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-(4-methylphenyl)butan-1-ol 5ca

Colorless oil; 65% ee; $[\alpha]_D^{20}$ = +56.7 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.66 (dd, *J* = 5.2, 5.3 Hz, 1H, CH_A of cyclopropane), 0.93–0.96 (m, 1H, CH_B of cyclopropane), 0.97 (s, 9H, $(CH_3)_3$C), 1.78–1.86 (m, 1H, C*H*CH_2OH), 2.40 (s, 3H, CH_3), 3.44–3.60 (m, 3H, OH, C*H*$_A$OH, CH_AOSi), 4.05 (d, *J* = 11.1 Hz, 1H, CH_BOSi), 4.11–4.18 (m, 1H, C*H*$_B$OH), 7.05–7.13, 7.27–7.45, 7.56–7.59 (m, m, m, 6H, 6H, 2H, C_6H_4, C_6H_5×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 19.0, 21.1, 25.9, 26.7, 32.0, 63.8, 69.3, 127.5, 127.8, 128.8, 129.5, 129.8, 130.4, 131.8, 132.8, 135.4, 135.6, 136.3, 141.0; HRMS (ESI-TOF): Calcd for $C_{28}H_{34}O_2SiNa$ (M+Na)$^+$: 453.2220, found: 453.2231. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 4.5 min, T_r(minor) 4.1 min (er 82.4:17.6).

4.6.8. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-chlorophenyl)-2,3-methanobutan-1-ol 5da

Colorless oil; 66% ee; $[\alpha]_D^{21}$ = +75.8 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70 (dd, *J* = 5.3, 5.4 Hz, 1H, CH_A of cyclopropane), 0.93 (dd, *J* = 5.3, 8.6 Hz, 1H, CH_B of cyclopropane), 0.97 (s, 9H, $(CH_3)_3$C), 1.76–1.83 (m, 1H, C*H*CH_2OH), 3.45–3.57 (m, 3H, OH, C*H*$_A$OH, CH_AOSi), 4.02 (d, *J* = 10.8 Hz, 1H, CH_BOSi), 4.11–4.18 (m, 1H, C*H*$_B$OH), 7.09–7.12, 7.15–7.19, 7.24–7.46, 7.54–7.56 (m, m, m, m, 2H, 2H, 8H, 2H, C_6H_4, C_6H_5×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 19.0, 26.0, 26.8, 31.9, 63.6, 69.0, 127.6, 127.8, 128.3, 129.7, 129.9, 131.8, 132.6, 135.4, 135.5, 142.3; HRMS (ESI-TOF): Calcd for $C_{27}H_{31}ClO_2SiNa$ (M+Na)$^+$: 473.1674, found: 473.1676. The enantiomeric ratio was determined by HPLC (Chiralcel OD-H: hexane/2-propanol = 99.9/0.01) after acetylation T_r(major) 18.0 min, T_r(minor) 14.5 min (er 83:17).

4.6.9. (2*S*,3*R*)-3-(4-Bromophenyl)-4-(*tert*-butyldiphenylsiloxy)-2,3-methanobutan-1-ol 5ea

Colorless oil; 73% ee; $[\alpha]_D^{22}$ = +82.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.70 (dd, *J* = 5.2, 5.2 Hz, 1H, CH_A of cyclopropane), 0.93 (dd, *J* = 5.2, 8.6 Hz, 1H, CH_B of cyclopropane), 0.97 (s, 9H, $(CH_3)_3$C), 1.77–1.81 (m, 1H, C*H*CH_2OH), 3.45–3.57 (m, 3H, OH, C*H*$_A$OH, CH_AOSi), 4.02 (d, *J* = 11.2 Hz, 1H, CH_BOSi), 4.11–4.18 (m, 1H, C*H*$_B$OH), 7.09–7.11, 7.16–7.24, 7.32–7.45, 7.54–7.56 (m, m, m, m, 2H, 4H, 6H, 2H, C_6H_4, C_6H_5×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 19.0, 25.9, 26.8, 32.0, 63.5, 68.9, 120.7, 127.6, 127.9, 129.7, 129.9, 131.2, 131.6, 132.2, 132.6, 135.4, 135.5, 143.0; HRMS (ESI-TOF): Calcd for $C_{27}H_{31}BrO_2SiNa$ (M+Na)$^+$: 517.1169, found: 517.1159. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 99/1) T_r(major) 9.0 min, T_r(minor) 8.2 min (er 86.6:13.4).

4.7. Typical procedure for the oxidation of alcohol 5aa into aldehyde 6aa

To a solution of 204 mg (0.46 mmol, 1.0 equiv) of (2*S*,3*R*)-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-phenylbutan-1-ol **5aa** in 5 mL of dimethylsulfoxide (DMSO) were added 320 mg (1.14 mmol, 2.5 equiv) of 2-iodoxybenzoic acid (IBX) at rt. After

stirring at rt for 3 h, 10 mL of AcOEt were added to the reaction mixture. The suspension was filtered through Celite. The filtrate was combined with 10 mL of half brine and extracted with 10 mL ×3 of AcOEt. The AcOEt layers were combined, washed with brine, and dried over anhydrous $MgSO_4$. The residue was chromatographed on silica gel with a 8:1 mixture of hexane and AcOEt to afford 191 mg (94% yield) of **6aa**.

4.7.1. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-phenylbutanal 6aa

Colorless oil; 71% ee derived from **5aa**; $[\alpha]_D^{28}$ = +57.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 9H, $(CH_3)_3C$), 1.49 (dd, *J* = 4.9, 8.1 Hz, 1H, CH_A of cyclopropane), 1.79 (dd, *J* = 4.9, 5.3 Hz, 1H, CH_B of cyclopropane), 2.30 (dt, *J* = 8.1, 5.3 Hz 1H, C*H*CHO), 3.76 (d, *J* = 11.0 Hz, 1H, CH_AOSi), 4.04 (d, *J* = 11.0 Hz, 1H, CH_BOSi), 7.19–7.43, 7.49–7.52 (m, m, 13H, 2H, C_6H_5 ×3), 9.63 (d, *J* = 5.3 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 19.1, 26.6, 34.3, 41.1, 66.5, 127.4, 127.5, 127.7, 128.4, 129.5, 129.7, 129.8, 132.8, 132.9, 135.4, 135.5, 142.0, 200.1; HRMS (ESI-TOF): Calcd for $C_{27}H_{30}O_2SiNa$ $(M+Na)^+$: 437.1907, found: 437.1900.

4.7.2. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-(4-methoxyphenyl)butanal 6ba

Colorless oil; 36% ee derived from **5ba**; $[\alpha]_D^{20}$ = +29.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H, $(CH_3)_3C$), 1.46 (dd, *J* = 4.8, 8.1 Hz, 1H, CH_A of cyclopropane), 1.76 (dd, *J* = 4.8, 5.3 Hz, 1H, CH_B of cyclopropane), 2.24 (dt, *J* = 8.1, 5.3 Hz, 1H, C*H*CHO), 3.73 (d, *J* = 11.0 Hz, 1H, CH_AOSi), 3.83 (s, 3H, CH_3O), 4.02 (d, *J* = 11.0 Hz, 1H, CH_BOSi), 6.85, 7.20–7.43, 7.50–7.52 (d, m, m, *J* = 8.8 Hz, 2H, 10H, 2H, C_6H_4, C_6H_5×2), 9.61 (d, *J* = 5.3 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8, 19.1, 26.7, 34.7, 40.4, 55.4, 66.7, 113.7, 127.5, 127.7, 129.5, 129.7, 130.8, 132.9, 133.0, 134.3, 135.5, 135.5, 158.9, 200.2; HRMS (ESI-TOF): Calcd for $C_{28}H_{32}O_3SiNa$ $(M+Na)^+$: 467.2013, found: 467.2010.

4.7.3. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-(4-methylphenyl)butanal 6ca

Colorless oil; 65% ee derived from **5ca**; $[\alpha]_D^{20}$ = +53.2 (*c* 1.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (s, 9H, $(CH_3)_3C$), 1.46 (dd, *J* = 4.8, 8.1 Hz, 1H, CH_A of cyclopropane), 1.78 (dd, *J* = 4.8, 5.3 Hz, 1H, CH_B of cyclopropane), 2.26 (dt, *J* = 8.1, 5.4 Hz, 1H, C*H*CHO), 2.37 (s, 3H, CH_3), 3.75 (d, *J* = 11.0 Hz, 1H, CH_AOSi), 4.04 (d, *J* = 11.0 Hz, 1H, CH_BOSi), 7.12–7.14, 7.19–7.42, 7.50–7.52 (m, m, m, 2H, 10H, 2H, C_6H_4, C_6H_5 ×2), 9.61 (d, *J* = 5.4 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.7, 19.1, 21.1, 26.7, 34.5, 40.8, 66.6, 127.5, 127.7, 129.0, 129.5, 129.6, 129.7, 132.9, 133.0, 135.5, 135.5, 137.1 139.1, 200.2; HRMS (ESI-TOF): Calcd for $C_{28}H_{32}O_2SiNa$ $(M+Na)^+$: 451.2064, found: 451.2087.

4.7.4. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-chlorophenyl)-2,3-methanobutanal 6da

Colorless oil; 66% ee derived from **5da**; $[\alpha]_D^{20}$ = +69.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 9H, $(CH_3)_3C$), 1.44 (dd, *J* = 5.0, 8.2 Hz, 1H, CH_A of cyclopropane), 1.77 (dd, *J* = 5.0, 5.2 Hz, 1H, CH_B of cyclopropane), 2.25 (dt, *J* = 8.2, 5.2 Hz, 1H, C*H*CHO), 3.75 (d, *J* = 11.1 Hz, 1H, CH_AOSi), 4.00 (d, *J* = 11.1 Hz, 1H, CH_BOSi), 7.21–7.43, 7.48–7.50 (m, m, 12H, 2H, C_6H_4, C_6H_5 ×2), 9.61 (d, *J* = 5.2 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 19.1, 26.7, 34.2, 40.4, 66.3, 127.6, 127.7, 128.5, 129.6, 129.8, 131.1, 132.7, 132.8, 133.3, 135.4, 135.5, 140.5, 199.6; HRMS (ESI-TOF): Calcd for $C_{27}H_{29}ClO_2SiNa$ $(M+Na)^+$: 471.1518, found: 471.1496.

4.7.5. (2*S*,3*R*)-3-(4-Bromophenyl)-4-(*tert*-butyldiphenylsiloxy)-2,3-methanobutanal 6ea

Colorless oil; 73% ee derived from **5ea**; $[\alpha]_D^{19}$ = +77.5 (*c* 1.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (s, 9H, $(CH_3)_3C$), 1.44 (dd, *J* = 5.0, 8.2 Hz, 1H, CH_A of cyclopropane), 1.77 (dd, *J* = 5.0, 5.2 Hz, 1H, CH_B of cyclopropane), 2.25 (dt, *J* = 8.1, 5.2 Hz, 1H, C*H*CHO), 3.75 (d, *J* = 11.1 Hz, 1H, CH_AOSi), 4.00 (d, *J* = 11.1 Hz, 1H, CH_BOSi), 7.21–7.50 (m, 14H, C_6H_4, C_6H_5×2), 9.61 (d, *J* = 5.2 Hz, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 19.1, 26.7, 34.1, 40.5, 66.3, 121.4, 127.6, 127.7, 129.6, 129.8, 131.4, 132.7, 132.8, 135.4, 135.5, 141.1, 199.5; HRMS (ESI-TOF): Calcd for $C_{27}H_{29}BrO_2SiNa$ $(M+Na)^+$: 515.1012, found: 515.1010.

4.8. Typical procedure for the oxidation of the aldehyde 6aa into carboxylic acid 7aa

To a colorless solution of 187 mg (0.45 mmol, 1.0 equiv) of (*2S,3R*)-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-phenylbutanal **6aa** and 16 mg (0.14 mmol, 0.3 equiv) of NaH_2PO_4 in 5.5 mL of a 10:1 mixture of MeCN and water were added 61 μL (0.54 mmol, 1.2 equiv) of 35% aq H_2O_2 solution and a solution of 76 mg (0.68 mmol, 1.5 equiv) of $NaClO_2$ in 2 mL of water at 0 °C. After stirring at rt for 3 h, 1 mL of sat. aq. Na_2SO_3 solution was added to the reaction mixture. The resulted mixture was adjusted to pH 3 with 1.0 M aq HCl solution and extracted with 10 mL ×3 of AcOEt. The combined AcOEt layers were washed with brine and dried over anhydrous $MgSO_4$. The residue was chromatographed on silica gel with a 5:1 mixture of hexane and AcOEt to afford 190 mg (98% yield) of **7aa**.

4.8.1. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-phenylbutanoic acid 7aa

Colorless solid; 71% ee derived from **5aa**; $[\alpha]_D^{28}$ = +57.4 (*c* 1.00, $CHCl_3$); mp 143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 9H, $(CH_3)_3C$), 1.38 (dd, *J* = 4.8, 8.0 Hz, 1H, CH_A of cyclopropane), 1.55 (dd, *J* = 4.8, 5.7 Hz, 1H, CH_B of cyclopropane), 2.18 (dd, *J* = 5.7, 8.0 Hz, 1H, C*H*CO_2H), 3.98 (s, 2H, CH_2OSi), 7.15–7.23, 7.28–7.38, 7.43–7.46, 7.50–7.52 (m, m, m, m, 4H, 7H, 2H, 2H, C_6H_5×3), 11.59 (brs, 1H, CO_2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 24.5, 26.5, 39.6, 66.4, 127.2, 127.4, 127.6, 128.2, 129.3, 129.5, 130.1, 133.2, 133.4, 135.4, 135.5, 142.7, 178.2; HRMS (ESI-TOF): Calcd for $C_{27}H_{30}O_3SiNa$ $(M+Na)^+$: 453.1856, found: 453.1852.

4.8.2. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-(4-methoxyphenyl)butanoic acid 7ba

Colorless solid; 36% ee derived from **5ba**; $[\alpha]_D^{20}$ = +38.0 (*c* 1.00, $CHCl_3$); mp 93–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 9H, $(CH_3)_3C$), 1,32–1.36 (m, 1H, CH_A of cyclopropane), 1.52 (dd, *J* = 4.9, 5.6 Hz, 1H, CH_B of cyclopropane), 2.11–2.16 (m, 1H, C*H*CO_2H), 3.84 (s, 3H, CH_3O), 3.95 (s, 2H, CH_2OSi), 6.86, 7.17–7.39, 7.50–7.52 (d, m, m, *J* = 8.7 Hz, 2H, 10H, 2H, C_6H_4, C_6H_5×2), 9.55 (brs, 1H, CO_2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 19.4, 24.6, 26.6, 38.8, 55.4, 66.5, 113.5, 127.4, 127.5, 129.3, 129.5, 131.1, 133.2, 133.4, 134.9, 135.5, 135.5, 158.8, 177.1; HRMS (ESI-TOF): Calcd for $C_{28}H_{32}O_4SiNa$ $(M+Na)^+$: 483.1962, found: 483.1978.

4.8.3. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-2,3-methano-3-(4-methylphenyl)butanoic acid 7ca

Colorless solid; 65% ee derived from **5ca**; $[\alpha]_D^{25}$ = +69.3 (*c* 0.96, $CHCl_3$); mp 124–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 9H, $(CH_3)_3C$), 1,32–1.37 (m, 1H, CH_A of cyclopropane), 1.53 (dd, *J* = 4.8, 5.7, 1H, CH_B of cyclopropane), 2.12–2.18 (m, 1H, C*H*CO_2H), 2.39 (s, 3H, CH_3), 3.97 (s, 2H, CH_2OSi), 7.13–7.38, 7.49–7.53 (m, m, 12H, 2H, C_6H_4, C_6H_5×2), 11.80 (brs, 1H, CO_2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 19.4, 21.1, 24.7, 26.5, 39.2, 66.5, 127.4, 127.5, 128.8, 129.2, 129.4, 129.9, 133.2, 133.4, 135.5, 135.5, 136.8, 139.7, 178.3; HRMS (ESI-TOF): Calcd for $C_{28}H_{32}O_3SiNa$ $(M+Na)^+$: 467.2013, found: 467.2036.

Please cite this article in press as: Ezawa, T.; et al. *Tetrahedron: Asymmetry* (2017), http://dx.doi.org/10.1016/j.tetasy.2016.12.010

4.8.4. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-3-(4-chlorophenyl)-2,3-methanobutanoic acid 7da

Colorless solid; 66% ee derived from **5da**; $[\alpha]_D^{18}$ = +87.8 (*c* 1.00, $CHCl_3$); mp 42–44 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 9H, $(CH_3)_3C$), 1,35 (dd, *J* = 4.8, 8.0 Hz, 1H, CH_A of cyclopropane), 1.54 (dd, *J* = 4.8, 5.9 Hz, 1H, CH_B of cyclopropane), 2.11 (dd, *J* = 5.9, 8.0 Hz, 1H, $CHCO_2H$), 3.93 (d, *J* = 10.7 Hz, 1H, CH_AOSi), 3.97 (d, *J* = 10.7 Hz, 1H, CH_BOSi), 7.18–7.39, 7.47–7.49 (m, m, 12H, 2H, C_6H_4, C_6H_5 ×2), 11.06 (brs, 1H, CO_2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 24.5, 26.6, 38.7, 66.2, 127.5, 127.6, 128.3, 129.4, 129.6, 131.3, 133.0, 133.1, 133.2, 135.4, 135.5, 141.1, 177.0; HRMS (ESI-TOF): Calcd for $C_{27}H_{29}ClO_3SiNa$ $(M+Na)^+$: 487.1467, found: 487.1465.

4.8.5. (2*S*,3*R*)-3-(4-Bromophenyl)-4-(*tert*-butyldiphenylsiloxy)-2,3-methanobutanoic acid 7ea

Colorless sticky oil; 73% ee derived from **5ea**; $[\alpha]_D^{22}$ = +77.9 (*c* 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 9H, $(CH_3)_3C$), 1,34 (dd, *J* = 4.9, 8.0 Hz, 1H, CH_A of cyclopropane), 1.55 (dd, *J* = 4.9, 5.9 Hz, 1H, CH_B of cyclopropane), 2.11 (dd, *J* = 5.9, 8.0 Hz, 1H, $CHCO_2H$), 3.94 (d, *J* = 10.7 Hz, 1H, CH_AOSi), 3.98 (d, *J* = 10.7 Hz, 1H, CH_BOSi), 7.19–7.50 (m, 14H, C_6H_4, C_6H_5×2), 11.71 (brs, 1H, CO_2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 24.5, 26.6, 38.9, 66.2, 121.2, 127.5, 127.6, 129.4, 129.6, 131.3, 131.7, 133.0, 133.2, 135.4, 135.5, 141.6, 177.8; HRMS (ESI-TOF): Calcd for $C_{27}H_{30}BrO_3Si$ $(M+H)^+$: 509.1142, found: 509.1157.

4.9. Typical procedure for the amidation of 7aa with 1-adamantanamine sulfate

To a solution of 124 mg (0.29 mmol, 1.0 equiv) of (2*S*,3*R*)-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-phenylbutanoic acid **7aa** in 6 mL of acetone were added dropwise 30 μL (0.32 mmol, 1.1 equiv) of $ClCO_2Et$ and 44 μL (0.32 mmol, 1.1 equiv) of Et_3N at 0 °C. After stirring at 0 °C for 30 min, 63 mg (0.32 mmol, 1.1 equiv) of 1-adamantanamine sulfate and 0.58 mL (0.58 mmol, 2.0 equiv) of 1.0 M aq. NaOH solution were added at 0 °C to the colorless suspension. The mixture was stirred at 0 °C for 24 h, diluted with 30 mL of AcOEt, washed with 5 mL of brine, and dried over anhydrous $MgSO_4$. The residue was chromatographed on silica gel with a 6:1 mixture of hexane and AcOEt to afford 143 mg (88% yield) of **8aa**.

4.9.1. (2*S*,3*R*)-*N*-Adamant-1-yl-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-phenylbutanamide 8aa

Colorless oil; 82% ee; $[\alpha]_D^{28}$ = +43.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (s, 9H, $(CH_3)_3C$), 1.14 (dd, *J* = 4.7, 8.1 Hz, 1H, CH_A of cyclopropane), 1.43 (dd, *J* = 4.7, 5.7 Hz, 1H, CH_B of cyclopropane), 1.65–1.68 (m, 6H, CH_2×3 of adamantane), 1.82 (dd, *J* = 5.7, 8.1 Hz, 1H, CHCO), 1.98–2.08 (m, 9H, CH_2×3, CH ×3 of adamantane), 3.89 (d, *J* = 10.5 Hz, 1H, CH_AO), 4.05 (d, *J* = 10.5 Hz, 1H, CH_BO), 5.51 (brs, 1H, NH), 7.16–7.50 (m, 15H, C_6H_5 ×3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 19.2, 26.8, 28.3, 29.5, 36.4, 36.8, 41.8, 52.1, 65.9, 126.8, 127.3, 127.5, 127.7, 128.0, 129.2, 129.3, 130.1, 133.4, 133.7, 135.6, 143.6, 169.2; HRMS (ESI-TOF): Calcd for $C_{37}H_{45}NO_2SiNa$ $(M+Na)^+$: 586.3112, found: 586.3122. The enantiomeric ratio was determined by HPLC (Chiralcel OD-H: hexane/^{i}PrOH = 90/10) T_r(major) 8.0 min, T_r(minor) 4.2 min (er 91:9).

4.9.2. (2*S*,3*R*)-*N*-Adamant-1-yl-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-(4-methoxyphenyl)butanamide 8ba

Colorless solid; 36% ee derived from **5ba**; $[\alpha]_D^{19}$ = +24.2 (*c* 1.01, $CHCl_3$); mp 147–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 9H, $(CH_3)_3C$), 1.09 (dd, *J* = 4.6, 8.1 Hz, 1H, CH_A of cyclopropane), 1.39 (dd, *J* = 4.6, 5.7 Hz, 1H, CH_B of cyclopropane), 1.64–1.68 (m, 6H, CH_2×3 of adamantane), 1.77 (dd, *J* = 5.7, 8.1 Hz, 1H, CHCO), 2.01–2.07 (m, 9H, CH_2×3 of adamantane, CH ×3 of adamantane), 3.83 (s, 3H, CH_3O), 3.85 (d, *J* = 10.5 Hz, 1H, CH_AOSi), 4.02 (d, *J* = 10.5 Hz, 1H, CH_BOSi), 5.49 (brs, 1H, NH), 6.83, 7.18–7.21, 7.25–7.38, 7.48–7.50 (d, m, m, m, *J* = 8.7 Hz, 2H, 2H, 8H, 2H, C_6H_4, C_6H_5×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 19.2, 26.9, 28.6, 29.5, 36.1, 36.4, 41.8, 52.1, 55.4, 66.1, 113.4, 127.3, 127.4, 129.2, 129.3, 131.1, 133.5, 133.8, 135.6, 135.6, 135.9, 158.5, 169.2; HRMS (ESI-TOF): Calcd for $C_{38}H_{47}NO_3SiNa$ $(M+Na)^+$: 616.3217, found: 616.3202.

4.9.3. (2*S*,3*R*)-*N*-Adamant-1-yl-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-(4-methylphenyl)butanamide 8ca

Colorless sticky oil; 65% ee derived from **5ca**; $[\alpha]_D^{22}$ = +37.9 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (s, 9H, $(CH_3)_3C$), 1.10 (dd, *J* = 4.7, 8.1 Hz, 1H, CH_A of cyclopropane), 1.41 (dd, *J* = 4.7, 5.7 Hz, 1H, CH_B of cyclopropane), 1.64–1.68 (m, 6H, CH_2×3 of adamantane), 1.79 (dd, *J* = 5.7, 8.1 Hz, 1H, CHCO), 2.01–2.08 (m, 9H, CH_2×3 of adamantane, CH ×3 of adamantane), 2.38 (s, 3H, CH_3), 3.87 (d, *J* = 10.5 Hz, 1H, CH_AOSi), 4.04 (d, *J* = 10.5 Hz, 1H, CH_BOSi), 5.50 (brs, 1H, NH), 7.10–7.12, 7.16–7.20, 7.23–7.38, 7.46–7.49 (m, m, m, m, 2H, 2H, 8H, 2H, C_6H_4, C_6H_5×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 19.2, 21.1, 26.9, 28.4, 29.5, 36.3, 36.4, 41.8, 52.1, 66.1, 127.3, 127.4, 128.7, 129.2, 129.3, 130.0, 133.5, 133.8, 135.6, 135.6, 136.3, 140.6, 169.2; HRMS (ESI-TOF): Calcd for $C_{38}H_{48}NO_2Si$ $(M+H)^+$: 578.3449, found: 578.3462.

4.9.4. (2*S*,3*R*)-*N*-Adamant-1-yl-4-(*tert*-butyldiphenylsiloxy)-3-(4-chlorophenyl)-2,3-methanobutanamide 8da

Colorless solid; 66% ee from **5da**; $[\alpha]_D^{17}$ = +57.6 (*c* 1.00, $CHCl_3$); mp 88–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 9H, $(CH_3)_3C$), 1.09 (dd, *J* = 4.7, 8.1 Hz, 1H, CH_A of cyclopropane), 1.43 (dd, *J* = 4.7, 5.7 Hz, 1H, CH_B of cyclopropane), 1.64–1.68 (m, 6H, CH_2×3 of adamantane), 1.76 (dd, *J* = 5.7, 8.1 Hz, 1H, CHCO), 2.01–2.08 (m, 9H, CH_2×3 of adamantane, CH ×3 of adamantane), 3.86 (d, *J* = 10.6 Hz, 1H, CH_AOSi), 4.05 (d, *J* = 10.6 Hz, 1H, CH_BOSi), 5.49 (brs, 1H, NH), 7.19–7.39, 7.45–7.48 (m, m, 12H, 2H, C_6H_4, C_6H_5×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.2, 19.2, 26.9, 28.3, 29.5, 36.2, 36.4, 41.8, 52.2, 65.7, 127.4, 127.5, 128.1, 129.4, 129.4, 131.4, 132.5, 133.3, 133.5, 135.5, 135.5, 142.1, 168.8; HRMS (ESI-TOF): Calcd for $C_{37}H_{44}ClNO_2SiNa$ $(M+Na)^+$: 620.2722, found: 620.2724.

4.9.5. (2*S*,3*R*)-*N*-Adamant-1-yl-3-(4-bromophenyl)-4-(*tert*-butyldiphenylsiloxy)-2,3-methanobutanamide 8ea

Colorless solid; 73% ee derived from **5ea**; $[\alpha]_D^{19}$ = +66.7 (*c* 1.20, $CHCl_3$); mp 79–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (s, 9H, $(CH_3)_3C$), 1.08 (dd, *J* = 4.7, 8.1 Hz, 1H, CH_A of cyclopropane), 1.43 (dd, *J* = 4.7, 5.7 Hz, 1H, CH_B of cyclopropane), 1.64–1.70 (m, 6H, CH_2×3 of adamantane), 1.75 (dd, *J* = 5.7, 8.1 Hz, 1H, CHCO), 2.02–2.08 (m, 9H, CH_2×3 of adamantane, CH ×3 of adamantane), 3.85 (d, *J* = 10.6 Hz, 1H, CH_AOSi), 4.06 (d, *J* = 10.6 Hz, 1H, CH_BOSi), 5.49 (brs, 1H, NH), 7.18–7.48 (m, 14H, C_6H_4, C_6H_5×2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.1, 19.2, 26.9, 28.2, 29.5, 36.3, 36.4, 41.8, 52.2, 65.7, 120.6, 127.4, 127.5, 129.4, 129.4, 131.1, 131.8, 133.3, 133.5, 135.5, 135.5, 142.6, 168.8; HRMS (ESI-TOF): Calcd for $C_{37}H_{45}BrNO_2Si$ $(M+H)^+$: 642.2397, found: 642.2396.

4.9.6. (2*S*,3*R*)-4-(*tert*-Butyldiphenylsiloxy)-*N*-(3,5-dimethyladamant-1-yl)-2,3-methano-3-phenylbutanamide 12

Colorless solid; 72% ee from **5aa**; $[\alpha]_D^{21}$ = +39.5 (*c* 1.00, $CHCl_3$); mp 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (s, 6H, CH_3×2), 0.91 (s, 9H, $(CH_3)_3C$), 1.10–1.18 (m, 3H, CH_2 of adamantane, CH_A of cyclopropane), 1.26–1.38 (m, 4H, CH_2×2 of adamantane), 1.41–1.43 (m, 1H, CH_B of cyclopropane), 1.63–1.76 (m, 4H,

CH_2×2 of adamantane), 1.80–1.91 (m, 3H, CH_2 of adamantane, CH of adamantane), 2.11–2.14 (m, 1H, CHCO), 3.89 (d, *J* = 10.5 Hz, 1H, CH_AOSi), 4.04 (d, *J* = 10.5 Hz, 1H, CH_BOSi), 5.56 (brs, 1H, NH), 7.15–7.23, 7.27–7.38, 7.48–7.50 (m, m, m, 4H, 9H, 2H, C_6H_5 ×3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.0, 19.2, 26.9, 28.2, 30.1, 30.2, 32.4, 36.9, 40.4, 42.7, 42.7, 47.6, 47.8, 50.6, 53.7, 66.0, 126.8, 127.3, 127.5, 128.1, 129.2, 129.3, 130.2, 133.4, 133.7, 135.6, 143.6, 169.2; HRMS (ESI-TOF): Calcd for $C_{39}H_{49}NO_2SiNa$ $(M+Na)^+$: 614.3425, found: 614.3445.

4.10. Typical procedure for the desilylation of 8aa with TBAF

To a solution of 275 mg (0.49 mmol, 1.0 equiv) of (2*S*,3*R*)-*N*-adamant-1-yl-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-phenylbutanamide **8aa** in 5 mL of THF were added 980 μL (0.98 mmol, 2.0 equiv) of a 1.0 M TBAF solution in THF at rt. After stirring at rt for 3 h, the colorless solution was diluted with 30 mL of AcOEt, washed with 5 mL of half brine, 5 mL of brine, and dried over anhydrous $MgSO_4$. The residue was chromatographed on silica gel with a 2:1 mixture of hexane and AcOEt to afford 147 mg (93% yield) of **9a**.

4.10.1. (2*S*,3*R*)-*N*-Adamant-1-yl-4-hydroxy-2,3-methano-3-phenylbutanamide 9a

Colorless solid; 82% ee; $[\alpha]_D^{25}$ = +73.7 (*c* 1.00, $CHCl_3$); mp 74–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31–1.36 (m, 1H, CH_A of cyclopropane), 1.67–1.72 (m, 8H, CH_B of cyclopropane, CH_2×3 of adamantine, CHCO), 2.02–2.05 (m, 6H, CH_2×3 of adamantane), 2.07–2.12 (m, 3H, CH ×3 of adamantane), 3.76–3.85 (m, 2H, CH_AOH, OH), 4.16 (dd, *J* = 6.4, 11.5 Hz, 1H, CH_BOH), 5.55 (brs, 1H, NH), 7.21–7.35 (m, 5H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7, 29.4, 29.5, 36.3, 36.8, 41.6, 52.5, 65.5, 126.9, 128.3, 128.5, 143.3, 171.5; HRMS (ESI-TOF): Calcd for $C_{21}H_{27}NO_2Na$ $(M+Na)^+$: 348.1934, found: 348.1950. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 12.8 min, T_r(minor) 21.2 min (er 91:9).

4.10.2. (2*S*,3*R*)-*N*-Adamant-1-yl-4-hydroxy-2,3-methano-3-(4-methoxyphenyl)butanamide 9b

Colorless solid; 34% ee; $[\alpha]_D^{19}$ = +42.5 (*c* 1.00, $CHCl_3$); mp 150–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26–1.31 (m, 1H, CH_A of cyclopropane), 1.63–1.66 (m, 2H, CH_B of cyclopropane, CHCO), 1.67–1.72 (m, 6H, CH_2×3 of adamantane), 2.02–2.06 (m, 6H, CH_2×3 of adamantane), 2.06–2.13 (m, 3H, CH ×3 of adamantane), 3.74–3.81 (m, 2H, CH_AOH, OH), 3.79 (s, 3H, CH_3O), 4.07–4.13 (m, 1H, CH_BOH), 5.55 (brs, 1H, NH), 6.84, 7.26 (d, d, *J* = 8.8 Hz, *J* = 8.8 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7, 29.4, 29.5, 36.2, 36.3, 41.6, 52.5, 55.3, 65.7, 113.9, 129.5, 135.4, 158.5, 171.6; HRMS (ESI-TOF): Calcd for $C_{22}H_{29}NO_3Na$ $(M+Na)^+$: 378.2040, found: 378.2039. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 17.0 min, T_r(minor) 15.4 min (er 67:33).

4.10.3. (2*S*,3*R*)-*N*-Adamant-1-yl-4-hydroxy-2,3-methano-3-(4-methylphenyl)butanamide 9c

Colorless solid; 58% ee; $[\alpha]_D^{25}$ = +70.0 (*c* 1.00, $CHCl_3$); mp 161–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29–1.32 (m, 1H, CH_A of cyclopropane), 1.67–1.72 (m, 8H, CH_B of cyclopropane, CHCO, CH_2×3 of adamantane), 2.02–2.06 (m, 6H, CH_2×3 of adamantane), 2.06–2.12 (m, 3H, CH ×3 of adamantane), 2.32 (s, 3H, CH_3), 3.75–3.83 (m, 2H, CH_AOH, OH), 4.13 (dd, *J* = 6.5, 10.7 Hz, 1H, CH_BOH), 5.55 (brs, 1H, NH), 7.12, 7.22 (d, d, *J* = 7.8 Hz, *J* = 7.8 Hz, *J* = 8.1 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7, 21.0, 29.4, 29.5, 36.3, 36.5, 41.6, 52.5, 65.5, 128.2, 129.2, 136.6, 140.3, 171.5; HRMS (ESI-TOF): Calcd for $C_{22}H_{29}NO_2Na$ $(M+Na)^+$: 362.2091, found: 362.2091. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 10.7 min, T_r(minor) 9.3 min (er 79:21).

4.10.4. (2*S*,3*R*)-*N*-Adamant-1-yl-3-(4-chlorophenyl)-4-hydroxy-2,3-methanobutanamide 9d

Colorless solid; 73% ee; $[\alpha]_D^{17}$ = +92.9 (*c* 1.00, $CHCl_3$); mp 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28–1.32 (m, 1H, CH_A of cyclopropane), 1.67–1.72 (m, 8H, CH_A of cyclopropane, CHCO, CH_2×3 of adamantane), 2.01–2.05 (m, 6H, CH_2×3 of adamantane), 2.07–2.13 (m, 3H, CH ×3 of adamantane), 3.72–3.82 (m, 2H, CH_AOH, OH), 4.11 (dd, *J* = 6.0, 11.7 Hz, 1H, CH_BOH), 5.55 (brs, 1H, NH), 7.28 (s, 4H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9, 29.4, 29.5, 36.1, 36.3, 41.6, 52.6, 65.5, 128.6, 129.8, 132.7, 141.8, 171.1; HRMS (ESI-TOF): Calcd for $C_{21}H_{26}ClNO_2Na$ $(M+Na)^+$: 382.1544, found: 382.1533. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 11.5 min, T_r(minor) 9.2 min (er 86.6:13.4).

4.10.5. (2*S*,3*R*)-*N*-Adamant-1-yl-3-(4-bromophenyl)-4-hydroxy-2,3-methanobutanamide 9e

Colorless solid; 73% ee; $[\alpha]_D^{23}$ = +98.5 (*c* 1.00, $CHCl_3$); mp 159–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27–1.32 (m, 1H, CH_A of cyclopropane), 1.64–1.69 (m, 2H, CH_A of cyclopropane, CHCO), 1.67–1.72 (m, 6H, CH_2×3 of adamantane), 2.01–2.07 (m, 6H, CH_2×3 of adamantane), 2.05–2.13 (m, 3H, CH ×3 of adamantane), 3.71–3.82 (m, 2H, CH_AOH, OH), 4.11 (dd, *J* = 5.9, 11.7 Hz, 1H, CH_BOH), 5.55 (brs, 1H, NH), 7.22, 7.43 (d, d, *J* = 8.5 Hz, *J* = 8.5 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9, 29.4, 36.1, 36.3, 41.6, 52.6, 65.5, 120.8, 130.1, 131.6, 142.3, 171.1; HRMS (ESI-TOF): Calcd for $C_{21}H_{26}BrNO_2Na$ $(M+Na)^+$: 426.1039, found: 426.1034. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 13.7 min, T_r(minor) 10.2 min (er 86.6:13.4).

4.10.6. (2*S*,3*R*)-*N*-(3,5-Dimethyladamant-1-yl)-4-hydroxy-2,3-methano-3-phenylbutanamide 13

Colorless oil; 72% ee; $[\alpha]^{25}{}_D$ + 85.3 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (s, 6H, CH_3×2), 1.13–1.22 (m, 2H, CH of adamantane, CH_A of cyclopropane), 1.29–1.41 (m, 5H, CH_2×2 of adamantane, CH_B of cyclopropane), 1,66–1.71 (m, 6H, CH_2×3 of adamantane), 1.83–1.90 (m, 2H, CH_2 of adamantane), 2.15–2.18 (m, 1H, CHCO), 3.76–3.85 (m, 2H, CH_AOH, OH), 4.15 (dd, *J* = 6.4, 11.1 Hz, 1H, CH_BOH), 5.60 (brs, 1H, NH), 7.21–7.26, 7.29–7.35 (m, m, 1H, 4H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.7, 29.4, 30.1, 30.1, 32.4, 36.9, 40.2, 42.6, 47.5, 47.6, 50.5, 54.2, 65.5, 126.9, 128.4, 128.5, 143.2, 171.6; HRMS (ESI-TOF): $C_{23}H_{31}NO_2Na$ $(M+Na)^+$: 376.2247, found: 376.2247. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol = 95/5) T_r(major) 10.1 min, T_r(minor) 12.7 min (er 86:14).

4.11. Typical procedure for the reduction of 8aa

A solution of 96 mg (0.17 mmol, 1.0 equiv) of (2*S*,3*R*)-*N*-adamant-1-yl-4-(*tert*-butyldiphenylsiloxy)-2,3-methano-3-phenylbutanamide **8aa** in 1 mL of anhydrous CH_2Cl_2 was added at 0 °C under an argon atmosphere to a suspension of 32 mg (0.85 mmol, 5.0 equiv) of $LiAlH_4$ in 5 mL of anhydrous toluene. After stirring at 70 °C for 5 h and 100 °C for 13 h, the colorless suspension was treated with 109 mg (2.55 mmol, 15 equiv) of NaF, diluted with 15 mL of AcOEt, quenched with 61 μL (3.40 mmol, 20 equiv) of water, and filtered through Celite. The filtrate was evaporated and the residue was chromatographed on silica gel with a 9:1:0.2 mixture of hexane, AcOEt, and Et_3N to afford 38 mg (72% yield) of **10a**.

4.12. Typical procedure for the reduction of 9a

A solution of 128 mg (0.39 mmol, 1.0 equiv) of (*2S,3R*)-*N*-adamant-1-yl-4-hydroxy-2,3-methano-3-phenylbutanamide **9a** in 2 mL of anhydrous CH_2Cl_2 was added at 0 °C under an argon atmosphere to a suspension of 74 mg (1.95 mmol, 5.0 equiv) of $LiAlH_4$ in 5 mL of anhydrous toluene. After stirring at 70 °C for 24 h and at 100 °C for 3 h, the colorless suspension was treated with 246 mg (5.85 mmol, 15 equiv) of NaF, diluted at 0 °C with 15 mL of AcOEt, quenched at 0 °C with 140 μL (7.80 mmol, 20 equiv) of water, and filtered through Celite. The filtrate was evaporated and the residue was chromatographed on silica gel with a 9:1:0.2 mixture of hexane, AcOEt, and Et_3N to afford 105 mg (87% yield) of **10a**.

4.12.1. (2*R*,3*S*)-4-(Adamant-1-ylamino)-2,3-methano-2-phenylbutan-1-ol 10a

Colorless solid; 86% ee; $[\alpha]_D^{25}$ = +16.6 (*c* 1.00, $CHCl_3$); mp 89–90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 (dd, *J* = 5.1, 5.1 Hz, 1H, CH_A of cyclopropane), 1.14 (dd, *J* = 5.1, 8.5 Hz, 1H, CH_B of cyclopropane), 1.27–1.34 (m, 2H, *CH*CH_2N*H*), 1.60–1.74 (m, 13H, CH_2×6 of adamantane, OH), 2.05–2.10 (m, 3H, CH ×3 of adamantane), 2.28 (dd, *J* = 11.7, 11.7 Hz, 1H, CH_AN), 3.39 (dd, *J* = 5.0, 11.7 Hz, 1H, CH_BN), 3.51 (d, *J* = 12.2 Hz, 1H, CH_AO), 4.15 (d, *J* = 12.2 Hz, 1H, CH_BO), 7.17–7.21, 7.27–7.33, 7.37–7.39 (m, m, m, 1H, 2H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.5, 25.3, 29.5, 31.9, 36.6, 40.8, 42.4, 50.7, 67.6, 126.0, 128.1, 128.2, 145.2; IR (NaCl, cm^{-1}): 3269, 2906, 2846; HRMS (ESI-TOF): Calcd for $C_{21}H_{30}NO$ $(M+H)^+$: 312.2327, found: 312.2304. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol/Et_2NH = 95/5/0.05) T_r(major) 12.0 min, T_r(minor) 7.5 min (er 93:7).

4.12.2. (2*R*,3*S*)-4-(Adamant-1-ylamino)-2,3-methano-2-(4-methoxyphenyl)butan-1-ol 10b

Reaction conditions: at 70 °C for 19 h; Colorless solid; 34% ee; $[\alpha]_D^{17}$ = +5.8 (*c* 0.99, $CHCl_3$); mp 88–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (dd, *J* = 5.0, 5.0 Hz, 1H, CH_A of cyclopropane), 1.08 (dd, *J* = 5.0, 8.5 Hz, 1H, CH_B of cyclopropane), 1.22–1.28 (m, 1H, *CH*CH_2N), 1.60–1.74 (m, 14H, CH_2×6 of adamantane, OH, NH), 2.03–2.06 (m, 3H, CH ×3 of adamantane), 2.25 (dd, *J* = 11.8, 11.8 Hz, 1H, CH_AN), 3.37 (dd, *J* = 6.8, 11.8 Hz, 1H, CH_BN), 3.48 (d, *J* = 11.9, 1H, CH_AO), 3.79 (s, 3H, CH_3O), 4.06 (d, *J* = 11.9 Hz, 1H, CH_BO), 6.84, 7.31 (d, d, *J* = 8.8 Hz, *J* = 8.8 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 25.0, 29.5, 31.4, 36.6, 40.8, 42.5, 50.7, 55.3, 67.9, 113.6, 129.4, 137.5, 157.9; IR (KBr, cm^{-1}): 3266, 2904, 2846; HRMS (ESI-TOF): Calcd for $C_{22}H_{32}NO_2$ $(M+H)^+$: 342.2428, found: 342.2437. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol/Et_2NH = 95/5/0.1) T_r(major) 14.8 min, T_r(minor) 11.0 min (er 67:33).

4.12.3. (2*R*,3*S*)-4-(Adamant-1-ylamino)-2,3-methano-2-(4-methylphenyl)butan-1-ol 10c

Reaction conditions: at 70 °C for 14 h and 100 °C for 3 h; Colorless solid; 60% ee; $[\alpha]_D^{21}$ = +13.2 (*c* 1.00, $CHCl_3$); mp 128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (dd, *J* = 4.4, 4.4 Hz, 1H, CH_A of cyclopropane), 1.11 (dd, *J* = 4.4, 8.5 Hz, 1H, CH_B of cyclopropane), 1.24–1.31 (m, 1H, *CH*CH_2N), 1.59–1.73 (m, 14H, CH_2×6 of adamantane, OH, NH), 2.04–2.10 (m, 3H, CH ×3 of adamantane), 2.26 (dd, *J* = 11.7, 11.7 Hz, 1H, CH_AN), 2.31 (s, 1H, CH_3), 3.38 (dd, *J* = 5.0, 11.7 Hz, 1H, CH_BN), 3.49 (d, *J* = 12.2, 1H, CH_AO), 4.11 (d, *J* = 12.2 Hz, 1H, CH_BO), 7.11, 7.28 (d, d, *J* = 7.8 Hz, *J* = 7.8 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 21.0, 25.3, 29.5, 31.5, 36.6, 40.8, 42.5, 50.6, 67.7, 128.0, 128.9, 135.5, 142.3; IR (KBr, cm^{-1}): 3267, 2902, 2846, 2360; HRMS (ESI-TOF): Calcd for $C_{22}H_{32}NO$ $(M+H)^+$: 326.2478, found: 326.2460. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol/Et_2NH = 95/5/0.1) T_r(major) 11.5 min, T_r(minor) 6.8 min (er 80:20).

4.12.4. (2*R*,3*S*)-4-(Adamant-1-ylamino)-2-(4-chlorophenyl)-2,3-methanobutan-1-ol 10d

Reaction conditions: at 70 °C for 12 h and 100 °C for 3 h; Colorless solid; 75% ee; $[\alpha]_D^{17}$ = +18.4 (*c* 1.00, $CHCl_3$); mp 98–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (dd, *J* = 4.4, 4.4 Hz, 1H, CH_A of cyclopropane), 1.12 (dd, *J* = 4.4, 8.5 Hz, 1H, CH_B of cyclopropane), 1.23–1.29 (m, 1H, *CH*CH_2N), 1.56–1.73 (m, 14H, CH_2×6 of adamantane, OH, NH), 2.04–2.10 (m, 3H, CH ×3 of adamantane), 2.26 (dd, *J* = 11.8, 11.8 Hz, 1H, CH_AN), 3.39 (dd, *J* = 7.0, 11.8 Hz, 1H, CH_BN), 3.49 (d, *J* = 12.5, 1H, CH_AO), 4.08 (d, *J* = 12.5 Hz, 1H, CH_BO), 7.25, 7.31 (d, d, *J* = 8.7 Hz, *J* = 8.7 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 25.5, 29.5, 31.4, 36.6, 40.7, 42.4, 50.7, 67.4, 128.2, 129.5, 131.7, 143.8; IR (KBr, cm^{-1}): 3267, 2906, 2848, 2360; HRMS (ESI-TOF): Calcd for $C_{21}H_{29}ClNO$ $(M+H)^+$: 346.1932, found: 346.1926. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol/Et_2-NH = 95/5/0.1) T_r(major) 7.9 min, T_r(minor) 6.3 min (er 87.6:12.4).

4.12.5. (2*R*,3*S*)-4-(Adamant-1-ylamino)-2-(4-bromophenyl)-2,3-methanobutan-1-ol 10e

Reaction conditions: at 70 °C for 12 h and 100 °C for 3 h; Colorless solid; 76% ee; $[\alpha]_D^{22}$ = +19.4 (*c* 1.00, $CHCl_3$); mp 114–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (dd, *J* = 4.4, 4.4 Hz, 1H, CH_A of cyclopropane), 1.12 (dd, *J* = 4.4, 8.5 Hz, 1H, CH_B of cyclopropane), 1.22–1.29 (m, 1H, *CH*CH_2N), 1.59–1.73 (m, 14H, CH_2×6 of adamantane, OH, NH), 2.05–2.11 (m, 3H, CH ×3 of adamantane), 2.26 (dd, *J* = 11.7, 11.7 Hz, 1H, CH_AN), 3.38 (dd, *J* = 6.9, 11.7 Hz, 1H, CH_BN), 3.48 (d, *J* = 12.4, 1H, CH_AO), 4.08 (d, *J* = 12.4 Hz, 1H, CH_BO), 7.26, 7.41 (d, d, *J* = 8.6 Hz, *J* = 8.6 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 25.6, 29.5, 31.4, 36.6, 40.7, 42.4, 50.7, 67.3, 119.8, 129.9, 131.2, 144.3; IR (KBr, cm^{-1}): 3269, 2902, 2846; HRMS (ESI-TOF): Calcd for $C_{21}H_{29}BrNO$ $(M+H)^+$: 390.1427, found: 390.1417. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol/Et_2NH = 95/5/0.1) T_r(major) 8.0 min, T_r(minor) 6.8 min (er 88:12).

4.12.6. (2*R*,3*S*)-4-[(3,5-Dimethyladamant-1-yl)amino]-2,3-methano-2-phenylbutan-1-ol 14

Colorless oil; 74% ee; $[\alpha]_D^{19}$ = +13.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 (dd, *J* = 5.2, 5.2 Hz, 1H, CH_A of cyclopropane), 0.85 (s, 6H, CH_3×2 of adamantane), 1.12–1.16 (m, 3H, CH_2 of adamantane, CH_B of cyclopropane), 1.23–1.38 (m, 10H, CH_2×5 of adamantane), 1.45–1.48 (m, 1H, CH of adamantane), 1.56–1.59 (m, 2H, OH, NH), 2.13–2.16 (m, 1H, *CH*CH_2N), 2.27 (t, *J* = 11.6, 11.6 Hz, 1H, CH_AN), 3.39 (dd, *J* = 6.8, 11.6 Hz, 1H, CH_BN), 3.50 (d, *J* = 12.3 Hz, 1H, CH_AO), 4.14 (d, *J* = 12.3 Hz, 1H, CH_BO), 7.17–7.21, 7.27–7.32, 7.36–7.39 (m, m, m, 1H, 2H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 25.4, 30.2, 31.8, 32.4, 41.0, 41.1, 42.9, 48.5, 48.7, 50.9, 52.5, 67.6, 125.9, 128.1, 128.2, 145.2; IR (NaCl, cm^{-1}): 3263, 2900, 2843, 1600; HRMS (ESI-TOF): Calcd for $C_{23}H_{34}NO$ $(M+H)^+$: 340.2635, found: 340.2650. The enantiomeric ratio was determined by HPLC (Chiralcel OD: hexane/2-propanol/Et_2NH = 95/5/0.1) T_r(major) 10.0 min, T_r(minor) 7.7 min (er 87:13).

4.13. Typical procedure for the methylation of 10a

To a colorless solution of 30 mg (0.10 mmol, 1.0 equiv) of (2*R*,3*S*)-4-(adamant-1-ylamino)-2,3-methano-2-phenylbutan-1-ol **10a** and 13 mg (0.15 mmol, 1.5 equiv) of $NaHCO_3$ in 3 mL of anhydrous DMF were added 12 μL (0.19 mmol, 2.0 equiv) of MeI at rt. After stirring at 80 °C for 2 h, the reaction mixture was diluted with 20 mL of a 3:1 mixture of AcOEt and hexane, washed with 10 mL of water and 5 mL of half brine, and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel with a 9:1:0.1 mixture of hexane, AcOEt, and Et_3N to afford 22 mg (68% yield) of **11a** [(+)-AMMP].

4.13.1. (+)-(2*R*,3*S*)-4-(*N*-Adamant-1-yl-*N*-methylamino)-2,3-methano-2-phenylbutan-1-ol 11a [(+)-AMMP]

Colorless oil; 86% ee derived from **10a**; $[\alpha]_D^{28}$ = +42.8 (*c* 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (dd, *J* = 5.1, 5.1 Hz, 1H, CH_A of cyclopropane), 1.21–1.25 (m, 1H, CH_B of cyclopropane), 1.39–1.47 (m, 1H, C*H*CH_2N), 1.60–1.68 (m, 6H, CH_2×3 of adamantane), 1.73–1.77 (m, *J* = 2.8 Hz, 6H, CH_2×3 of adamantane), 2.07–2.12 (m, 3H, CH ×3 of adamantane), 2.36 (s, 3H, CH_3N), 2.66 (dd, *J* = 10.4, 12.7 Hz, 1H, CH_AN), 2.81 (dd, *J* = 5.6, 12.7 Hz, 1H, CH_BN), 3.41 (d, *J* = 12.3 Hz, 1H, CH_AO), 4.12 (d, *J* = 12.3 Hz, 1H, CH_BO), 6.73 (brs, 1H, OH), 7.17–7.21, 7.27–7.31, 7.40–7.43 (m, m, m, 1H, 2H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 24.1, 29.6, 32.2, 32.3, 36.7, 37.9, 48.8, 54.7, 67.4, 125.9, 127.8, 128.2, 145.4; IR (NaCl, cm^{-1}): 2904, 2850, 2366, 2322; HRMS (ESI-TOF): Calcd for $C_{22}H_{32}NO$ $(M+H)^+$: 326.2484, found: 326.2498.

4.13.2. (+)-(2*R*,3*S*)-4-(*N*-Adamant-1-yl-*N*-methylamino)-2,3-methano-2-(4-methoxyphenyl)butan-1-ol 11b

Colorless oil; 34% ee derived from **10b**; $[\alpha]_D^{22}$ = +13.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (dd, *J* = 4.9, 4.9 Hz, 1H, CH_A of cyclopropane), 1.17 (dd, *J* = 3.8, 4.9 Hz, 1H, CH_B of cyclopropane), 1.35–1.41 (m, 1H, C*H*CH_2N), 1.60–1.68 (m, 6H, CH_2×3 of adamantane), 1.72–1.75 (m, *J* = 2.8 Hz, 6H, CH_2×3 of adamantane), 2.07–2.13 (m, 3H, CH ×3 of adamantane), 2.37 (s, 3H, CH_3N), 2.63 (dd, *J* = 10.5, 12.6 Hz, 1H, CH_AN), 2.79 (dd, *J* = 7.1, 12.6 Hz, 1H, CH_BN), 3.39 (d, *J* = 12.2 Hz, 1H, CH_AO), 3.79 (s, 3H, CH_3O), 4.04 (d, *J* = 12.2 Hz, 1H, CH_BO), 6.65 (brs, 1H, OH), 6.84, 7.35 (d, d, *J* = 8.8 Hz, *J* = 8.8 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 23.7, 29.6, 31.8, 32.2, 36.7, 37.9, 48.8, 54.8, 55.3, 67.7, 113.6, 129.1, 137.7, 157.9; IR (NaCl, cm^{-1}): 2906, 2848, 2360, 2332; HRMS (ESI-TOF): Calcd for $C_{23}H_{34}NO_2$ $(M+H)^+$: 356.2584, found: 356.2571.

4.13.3. (+)-(2*R*,3*S*)-4-(*N*-Adamant-1-yl-*N*-methylamino)-2,3-methano-2-(4-methylphenyl)butan-1-ol 11c

Colorless solid; 60% ee derived from **10c**; $[\alpha]_D^{22}$ = +30.7 (*c* 1.00, $CHCl_3$); mp 81–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.73 (dd, *J* = 4.4, 4.4 Hz, 1H, CH_A of cyclopropane), 1.20 (dd, *J* = 4.4, 8.4 Hz, 1H, CH_B of cyclopropane), 1.37–1.42 (m, 1H, C*H*CH_2N), 1.59–1.68 (m, 6H, CH_2×3 of adamantane), 1.73–1.77 (m, 6H, CH_2×3 of adamantane), 2.07–2.12 (m, 3H, CH ×3 of adamantane), 2.31 (s, 3H, CH_3N), 2.36 (s, 3H, C*H*$_3$C$_6$H$_4$), 2.65 (dd, *J* = 12.7, 12.7 Hz, 1H, CH_AN), 2.80 (dd, *J* = 7.1, 12.7 Hz, 1H, CH_BN), 3.40 (d, *J* = 12.1 Hz, 1H, CH_AO), 4.08 (d, *J* = 12.1 Hz, 1H, CH_BO), 6.68 (brs, 1H, OH), 7.11, 7.32 (d, d, *J* = 8.0 Hz, *J* = 8.0 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.6, 21.0, 23.9, 29.6, 32.0, 32.2, 36.7, 37.9, 48.8, 54.7, 67.5, 127.8, 128.9, 135.4, 142.4; IR (KBr, cm^{-1}): 2902, 2846; HRMS (ESI-TOF): Calcd for $C_{23}H_{34}NO$ $(M+H)^+$: 340.2635, found:340.2614.

4.13.4. (+)-(2*R*,3*S*)-4-(*N*-Adamant-1-yl-*N*-methylamino)-2-(4-chlorophenyl)-2,3-methanobutan-1-ol 11d

Colorless solid; 75% ee derived from **10d**; $[\alpha]_D^{17}$ = +30.9 (*c* 1.00, $CHCl_3$); mp 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (dd, *J* = 5.0, 5.0 Hz, 1H, CH_A of cyclopropane), 1.21 (dd, *J* = 5.0, 8.5 Hz, 1H, CH_B of cyclopropane), 1.35–1.41 (m, 1H, C*H*CH_2N), 1.59–1.65 (m, 6H, CH_2×3 of adamantane), 1.70–1.78 (m, 6H, CH_2×3 of adamantane), 2.07–2.12 (m, 3H, CH ×3 of adamantane), 2.34 (s, 3H, CH_3N), 2.65 (dd, *J* = 12.6, 12.6 Hz, 1H, CH_BN), 3.40 (d, *J* = 12.2, 1H, CH_AO), 4.07 (d, *J* = 12.2 Hz, 1H, CH_AN), 2.80 (dd, *J* = 6.4, 12.6 Hz, 1H, CH_BN), 3.40 (d, *J* = 12.2, 1H, CH_AO), 4.07 (d, *J* = 12.2 Hz, 1H, CH_BO), 6.75 (brs, 1H, OH), 7.25, 7.35 (d, d, *J* = 8.7 Hz, *J* = 8.7 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 24.4, 29.5, 31.8, 32.2, 36.7, 37.9, 48.7, 54.8, 67.1, 128.2, 129.2, 131.6, 143.9; IR (KBr, cm^{-1}): 2910, 2848; HRMS (ESI-TOF): Calcd for $C_{22}H_{31}ClNO$ $(M+H)^+$: 360.2089, found: 360.2099.

4.13.5. (+)-(2*R*,3*S*)-4-(*N*-Adamant-1-yl-*N*-methylamino)-2-(4-bromophenyl)-2,3-methanobutan-1-ol 11e

Colorless solid; 76% ee derived from **10e**; $[\alpha]_D^{22}$ = +34.4 (*c* 1.00, $CHCl_3$); mp 108–111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (dd, *J* = 4.4, 4.4 Hz, 1H, CH_A of cyclopropane), 1.21 (dd, *J* = 4.4, 8.5 Hz, 1H, CH_B of cyclopropane), 1.33–1.41 (m, 1H, C*H*CH_2N), 1.59–1.68 (m, 6H, CH_2×3 of adamantane), 1.70–1.77 (m, *J* = 2.7 Hz, 6H, CH_2×3 of adamantane), 2.07–2.13 (m, 3H, CH ×3 of adamantane), 2.33 (s, 3H, CH_3N), 2.65 (dd, *J* = 10.4, 12.7 Hz, 1H, CH_AN), 2.80 (dd, *J* = 7.1, 12.7 Hz, 1H, CH_BN), 3.39 (d, *J* = 12.4, 1H, CH_AO), 4.07 (d, *J* = 12.4 Hz, 1H, CH_BO), 6.76 (brs, 1H, OH), 7.29, 7.40 (d, d, *J* = 8.6 Hz, *J* = 8.6 Hz, 2H, 2H, C_6H_4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 24.4, 29.5, 31.8, 32.2, 36.7, 37.9, 48.7, 54.8, 67.1, 119.7, 129.5, 131.2, 144.4; IR (KBr, cm^{-1}): 2904, 2846; HRMS (ESI-TOF): Calcd for $C_{22}H_{31}BrNO$ $(M+H)^+$: 404.1584, found: 404.1582.

4.13.6. (+)-(2*R*,3*S*)-4-[*N*-(3,5-Dimethyladamant-1-yl)-*N*-methylamino]-2,3-methano-2-phenylbutan-1-ol 15

Colorless oil; 74% ee derived from **14**; $[\alpha]_D^{17}$ = +25.7 (*c* 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.77 (dd, *J* = 5.1, 5.1 Hz, 1H, CH_A of cyclopropane), 0.83–0.87 (m, 6H, CH_3×2 of adamantane), 1.08–1.16 (m, 2H, CH_2 of adamantane), 1.22–1.45 (m, 11H, CH_2×5 of adamantane, CH_B of cyclopropane), 1.57–1.62 (m, 1H, CH of adamantane), 2.15–2.19 (m, 1H, C*H*CH_2N), 2.36 (s, 3H, CH_3N), 2.66 (dd, *J* = 10.6, 12.5 Hz, 1H, CH_AN), 2.81 (dd, *J* = 7.0, 12.5 Hz, 1H, CH_BN), 3.41 (d, *J* = 12.2 Hz, 1H, CH_AO), 4.13 (d, *J* = 12.2 Hz, 1H, CH_BO), 6.80 (brs, 1H, OH), 7.17–7.21, 7.27–7.31, 7.40–7.43 (m, m, m, 1H, 2H, 2H, C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 24.2, 30.2, 30.5, 32.2, 32.4, 32.4, 32.5, 36.3, 43.0, 44.1, 44.2, 49.1, 50.8, 56.7, 67.4, 125.9, 127.7, 128.2, 145.3; IR (NaCl, cm^{-1}): 3201, 2950, 2360, 2341, 1604; HRMS (ESI-TOF): Calcd for $C_{24}H_{36}NO$ $(M+H)^+$: 354.2791, found: 354.2786.

Acknowledgment

This work was supported in part by the Scientific Research Project by CIS (Chiba Institute of Science), Japan.

References

1. Several diseases except ALS see: (a) Maurice, T.; Su, T. P. *Phamacol. Ther.* **2009**, *124*, 195–206. and references cited therein; ALS see: (b) Mavlyutov, T. A.; Guo, L. W.; Epstein, M. L.; Ruoho, A. E. *J. Phamacol. Sci.* **2015**, *127*, 10–16.
2. (a) Maurice, T.; Su, T. P. *Pharmacol. Ther.* **2009**, *124*, 195–206; (b) Quirion, R.; Bowen, W. D.; Itzhak, Y.; Junien, J. L.; Musacchio, M. J.; Rothman, R. B.; Su, T. P.; Tam, S. W.; Taylor, D. P. *Trends Pharmacol. Sci.* **1992**, *13*, 85–86.
3. (a) Hayashi, T. *J. Pharmacol. Sci.* **2015**, *127*, 2–5; (b) Omi, T.; Tanimukai, H.; Kanayama, D.; Sakagami, Y.; Tagami, S.; Okochi, M.; Moriha, T.; Sato, M.; Yanagida, K.; Kitasyoji, A.; Hara, H.; Imaizumi, K.; Maurice, T.; Chevallier, N.; Marchal, S.; Takeda, M.; Kudo, T. *Cell Death Dis.* **2014**, *5*, e1332; (c) Hayashi, T.; Su, T. *Cell* **2007**, *131*, 596–610.
4. (a) Prause, J.; Goswami, A.; Katona, I.; Roos, A.; Schnizler, M.; Bushuven, E.; Dreier, A.; Buchkremer, S.; Johann, S.; Beyer, C.; Deschauer, M.; Troost, D.; Weis, J. *Hum. Mol. Genet.* **2013**, *22*, 1581–1600; (b) Al-Saif, A.; Al-Mohanna, F.; Bohlega, S. *Ann. Neurol.* **2011**, *70*, 913–919.
5. Matsuno, K.; Nakazawa, M.; Okamoto, K.; Kawashima, Y.; Mita, S. *Eur. J. Pharmacol.* **1996**, *306*, 271–279.
6. (a) Banister, S. D.; Kassiou, M. *Curr. Pharm. Des.* **2012**, *18*, 884–901; (b) Niitsu, T.; Iyo, M.; Hashimoto, K. *Curr. Pharm. Des.* **2012**, *18*, 875–883; (c) Hayashi, T.; Tsai, S. Y.; Mori, T.; Fujimoto, M.; Su, T. P. *Expert Opin. Ther. Targets* **2011**, *15*, 557–577; (d) Ishikawa, M.; Hashimoto, K. *J. Receptor Ligand Channel Res.* **2010**, *3*, 25–36.
7. (a) Urfer, R.; Moebius, H. J.; Skoloudik, D.; Santamarina, E.; Sato, W.; Mita, S.; Muir, K. W. *Stroke* **2014**, *45*, 3304–3310; (b) Simona, C.; Raffaella, G.; Annamaria, M.; Andrea, B.; Sara, N.; Francesca, N.; Daniela, R. *Expert Opin. Ther. Pat.* **2013**, *23*, 597–613.
8. (a) Behensky, A.; Yasny, I.; Shuster, A.; Seredenin, S.; Petrov, A.; Cuevas, J. *J. Pharmacol. Exp. Ther.* **2013**, *347*, 468–477; (b) Marrazzo, A.; Caraci, F.; Salinaro, E.; Su, T.; Copani, A.; Ronsisvalle, G. *NeuroReport* **2005**, *16*, 1223–1226.
9. (a) Villard, V.; Espallergues, J.; Keller, E.; Alkam, T.; Nitta, A.; Yamada, K.; Nabeshima, T.; Vamvakides, A.; Maurice, T. *Neuropsychopharmacology* **2009**, *34*, 1552–1566; (b) Meunier, J.; Ieni, J.; Maurice, T. *Br. J. Pharmacol.* **2006**, *149*, 998–1012; (c) Maurice, T.; Su, T.; Privat, A. *Neuroscience* **1998**, *83*, 413–428.

10. (a) Froestl, W.; Muhs, A.; Preifer, A. *J. Alzheimer's Dis.* **2014**, *41*, 961–1019; (b) Villard, V.; Espallergues, J.; Keller, E.; Vamvakides, A.; Maurice, T. *J. Psychopharmacol.* **2011**, *25*, 1101–1117.
11. Marrazzo, A.; Prezzavento, O.; Pappalardo, M. S.; Bousquet, E.; Indanza, M.; Pike, V. W.; Ronsisvalle, G. *IL Farmaco* **2002**, *57*, 45–53.
12. Kawashima, Y.; Ezawa, T.; Yamamura, M.; Harada, T.; Noguchi, T.; Miura, T.; Imai, N. *Tetrahedron Lett.* **2016**, *57*, 668–671.
13. (a) Koyata, N.; Nagai, T.; Kawasaki, M.; Noguchi, T.; Kirihara, M.; Imai, N. *Chem. Lett.* **2009**, *38*, 892–893; (b) Miura, T.; Umetsu, S.; Kanamori, D.; Tsuyama, N.; Jyo, Y.; Kawashima, Y.; Koyata, N.; Murakami, Y.; Imai, N. *Tetrahedron* **2008**, *64*, 9305–9308; (c) Miura, T.; Okazaki, K.; Ogawa, K.; Otomo, E.; Umetsu, S.; Takahashi, M.; Kawashima, Y.; Jyo, Y.; Koyata, N.; Murakami, Y.; Imai, N. *Synthesis* **2008**, *17*, 2695–2700; (d) Miura, T.; Kawashima, Y.; Takahashi, M.; Murakami, Y.; Imai, N. *Synth. Commun.* **2007**, *37*, 3105–3109; (e) Miura, T.; Kawashima, Y.; Umetsu, S.; Kanamori, D.; Tsuyama, N.; Jyo, Y.; Murakami, Y.; Imai, N. *Chem. Lett.* **2007**, *36*, 814–815.
14. (a) Kawashima, Y.; Ezawa, T.; Harada, T.; Noguchi, T.; Kawasaki, M.; Kirihara, M.; Imai, N. *Bull. Chem. Soc. Jpn.* **2016**, *89*, 257–267; (b) Koyata, N.; Miura, T.; Akaiwa, Y.; Sasaki, H.; Sato, R.; Nagai, T.; Fujimori, H.; Noguchi, T.; Kirihara, M. *Tetrahedron: Asymmetry* **2009**, *20*, 2065–2071; (c) Miura, T.; Murakami, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 3067–3069; (d) Imai, N.; Nomura, T.; Yamamoto, S.; Ninomiya, Y. *Tetrahedron: Asymmetry* **2002**, *13*, 2433–2438; (e) Imai, N.; Sakamoto, K.; Maeda, M.; Kouge, K.; Yoshizane, K.; Nokami, J. *Tetrahedron Lett.* **1997**, *38*, 1423–1426.
15. (a) Noguchi, T.; Jung, S.; Imai, N. *Tetrahedron Lett.* **2014**, *55*, 394–396; (b) Jung, S.; Tsukuda, Y.; Kawashima, R.; Ishiki, T.; Matsumoto, A.; Nakaniwa, A.; Takagi, M.; Noguchi, T.; Imai, N. *Tetrahedron Lett.* **2013**, *54*, 5718–5720; (c) Noguchi, T.; Sekine, M.; Yokoo, Y.; Jung, S.; Imai, N. *Chem. Lett.* **2013**, *42*, 580–582; (d) Noguchi, T.; Jung, S.; Imai, N. *Chem. Lett.* **2012**, *41*, 577–579; (e) Noguchi, T.; Tehara, N.; Uesugi, Y.; Jung, S.; Imai, N. *Chem. Lett.* **2012**, *41*, 42–43.
16. McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568–3571.
17. Kawashima, Y.; Ezawa, T.; Yamamura, M.; Harada, T.; Noguchi, T.; Miura, T.; Imai, N. *Tetrahedron* **2015**, *71*, 8585–8592.
18. Charette, A. B.; Brochu, C. *J. Am. Chem. Soc.* **1995**, *117*, 11367–11368.

Please cite this article in press as: Ezawa, T.; et al. *Tetrahedron: Asymmetry* (2017), http://dx.doi.org/10.1016/j.tetasy.2016.12.010