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Convenient synthesis of (+)-*cis*-4-(*N*-adamantyl-*N*-methylamino)-2,3-methano-2-phenylbutan-1-ol as a candidate of anti-Alzheimer's medicine via catalytic enantioselective Simmons–Smith reaction using L-phenylalanine-derived disulfonamide

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ABSTRACT

The catalytic enantioselective Simmons–Smith reaction of (*Z*)-4-*tert*-butyldiphenylsiloxy-3-phenylbut-2-en-1-ol using L-phenylalanine-derived disulfonamide afforded (+)-*cis*-4-*tert*-butyldiphenylsiloxy-2,3-methano-3-phenylbutan-1-ol in quantitative yield with 71% ee. The 2,3-methano-3-phenylbutan-1-ol was easily converted to the corresponding 2,3-methano-3-phenylbutanoic acid, followed by amidation of the carboxylic acid with 1-adamantanamine sulfate in aqueous organic solvent to afford the corresponding 2,3-methano-3-phenylbutanamide in excellent yields. Convenient enantioselective synthesis of (+)-*cis*-4-(*N*-adamantyl-*N*-methylamino)-2,3-methano-2-phenylbutan-1-ol ((+)-AMMP) was achieved in 35% overall yield from the starting 1,4-diol via our developed key reactions.

Alzheimer's disease (AD) is the most common type of dementia and a progressive brain disease that destroys cognitive function, then eventually leads to death.[1] The increase in degenerative brain diseases including AD has become a social issues as the global aging proceeds. According to the world health organization (WHO), dementia sufferers including AD were nearly 35.6 million people in 2012. This number is expected to double by 2030 (65.7 million) and more than triple by 2050 (115.4 million). Therefore, pathological elucidation of AD and urgent development of medicine for AD are demanded.

Sigma receptor has recently attracted attention as a new action site of therapeutic medicine for AD. The two established subtypes, sigma-1 and sigma-2, are both highly expressed in the central nervous system (CNS) and can be distinguished by their distinct pharmacological profiles and molecular characteristics. Particularly, it was reported that sigma-1 receptor regulates protein folding/degradation, endoplasmic reticulum (ER)/oxidative stress, and cell survival through the molecular chaperone activity.[2] In addition, a variety of sigma agonists protect against amyloid β $(Aβ)_{25–35}$-induced toxicity in cultured neurons,[3] and prevent memory deficits when $Aβ_{25–35}$ is injected intracerebroventricularly in mice.[4] Therefore, induction or activation of sigma-1 receptors could improve clinical symptoms of AD and protect against associated neuropathologic changes. Indeed, tetrahydro-*N*,*N*-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73) has been examined in Phase I for AD trial as a sigma-1 receptor agonist since March of 2011.[5] On the other hand, (+)-*cis*-4-(*N*-adamantyl-*N*-methylamino)-2,3-methano-2-phenylbutan-1-ol ((+)-AMMP) was reported as a high affinity probe for sigma receptors by Marrazzo et al.[6] However, the overall yield was 9% from (+)-2,3-methano-2-phenyllactone as the starting material and the reagents used in the total synthesis of (+)-AMMP were relatively expensive.

Recently, we have developed useful reactions such as the regioselective acetylation using porcine pancreas lipase (PPL),[7] the catalytic enantioselective Simmons–Smith reaction in the presence of L-phenylalanine-derived disulfonamide as a chiral ligand,[8] and the convenient amidation of mixed carbonic carboxylic anhydrides in aqueous organic solvent.[9] It is simple and inexpensive to carry these reactions out. The high regioselective monoacetylation of 2-substituted (*Z*)-but-2-ene-1,4-diols has been achieved easily in the presence of PPL.[7] Substituted cinnamyl alcohols were converted to the corresponding 2,3-methanopropan-1-ols up to quantitative yield and 86% ee by 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.[8] Then, the amidations of mixed carbonic carboxylic anhydrides afforded dipeptides, primary amides, and

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anilides in the presence of primary amines, ammonium chloride, and anilines in aqueous organic solvent.[9]

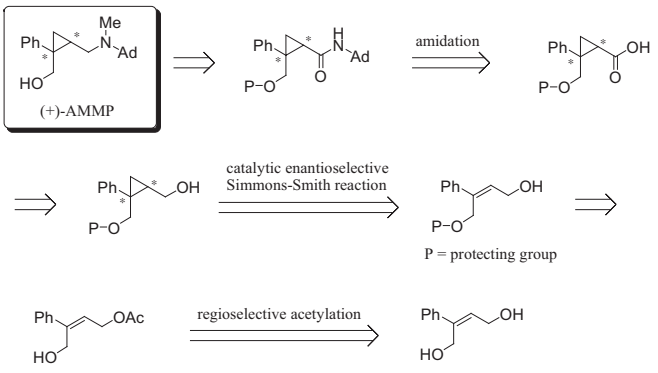
Herein, we describe convenient enantioselective synthesis of (+)-AMMP via our developed reactions as shown in Scheme 1.

4-*O*-Protected (*Z*)-3-phenylbut-2-en-1-ols **3a**–**3e** were initially prepared for substrates in the catalytic enantioselective Simmons–Smith reaction in order to select the suitable protecting group as indicated in Scheme 2. The monoacetate **1** was easily prepared in the regioselective monoacetylation of (*Z*)-2-phenylbut-2-ene-1,4-diol using PPL.[7a] The hydroxy group of the monoacetate **1** was protected by various protecting groups to give the corresponding protected monoacetates **2a**–**2e** in 86–97% yields, followed by deacetylation to afford the desired **3a**–**3e** in 68%-quantitative yields.[10]

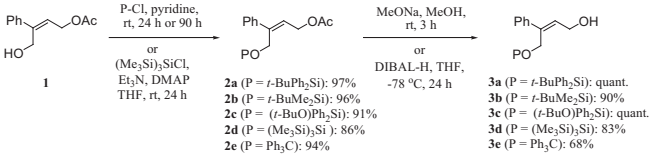
In a preliminary investigation, the reaction of (*Z*)-4-*tert*-butyldiphenylsiloxy-3-phenylbut-2-en-1-ol (**3a**) with 2.0 equiv of Et_2Zn and 3.0 equiv of CH_2I_2 in the presence of 0.1 equiv of chiral ligand **4** in anhydrous CH_2Cl_2 at 0 °C for 3 h afforded (+)-*cis*-4-*tert*-butyldiphenylsiloxy-2,3-methano-3-phenylbutan-1-ol (**5a**) in quantitative yield with 71% ee (see entry 1 of Table 1).[11] (*Z*)-4-*tert*-Butyldimethylsiloxy-3-phenylbut-2-en-1-ol (**3b**) was converted to the corresponding 2,3-methano-3-phenylbutan-1-ol **5b** in 93% yield with 48% ee (see entry 2). Then, lower enantioselectivities (21% and 2% ee) were obtained in the reactions of 4-siloxy (*Z*)-3-phenylbut-2-en-1-ols **3c** and **3d**, respectively (see entries 3 and 4). The reaction of (*Z*)-4-triphenylmethoxy-3-phenylbut-2-en-1-ol (**3e**) proceeded to give the corresponding 2,3-methano-3-phenylbutan-1-ol **5e** in 89% yield, but the enantioselectivity (19% ee) was also low (see entry 5). The results of these reactions are summarized in Table 1.

Subsequently, the 2,3-methano-3-phenylbutan-1-ol **5a** was oxidized with 2-iodoxybenzoic acid (IBX) in dimethylsulfoxide (DMSO) at rt for 3 h to afford the corresponding 2,3-methano-3-phenylbutan-1-al **6a** in 94% yield, which was converted with $NaClO_2$, H_2O_2, and NaH_2PO_4 in acetonitrile (MeCN)–H_2O at rt for 3 h to the corresponding 2,3-methano-3-phenylbutanoic acid **7a** in 98% yield as indicated in Scheme 3.

Next, we undertook to examine the amidation of 3-phenylpropionic acid (**7′**) with sterically hindered 1-adamantanamine in aqueous organic solvent in order to optimize the reaction conditions. The results are summarized in Table 2. 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*-adamantyl-3-phenylpropanamide (**8′**) in 27% yield (see entry 1). The reaction of 1-adamantanamine sulfate, which is cheaper than amantadine®, did not afford the corresponding amide **8′** because 1-adamantanamine sulfate is hardly dissolved in organic solvents nor 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

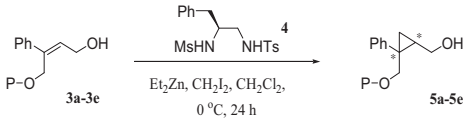


Scheme 1. Retrosynthetic analysis of (+)-AMMP via the three key reactions.



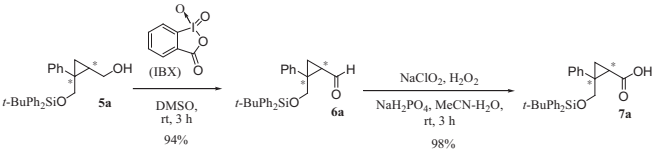
Scheme 2. Preparation of 4-*O*-protected (*Z*)-3-phenylbut-2-en-1-ols **3a**–**3e**.

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



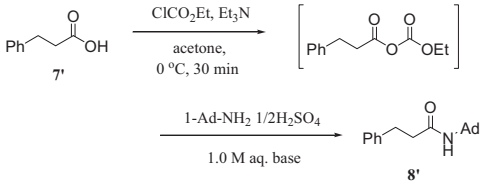
Entry	Product	P	Yield (%)	ee[b] (%)
1	**5a**	*t*-BuPh$_2$Si	Quant.	71
2	**5b**	*t*-BuMe$_2$Si	93	48
3	**5c**	*t*-BuOPh$_2$Si	66	21
4	**5d**	(Me$_3$Si)$_3$Si	38	2
5	**5e**	Ph$_3$C	89	19

[a] All reactions were carried out with 4-*O*-protected (*Z*)-3-phenylbut-2-en-1-ol **3**, 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).



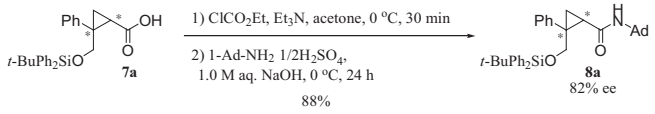
Scheme 3. Preparation of the 2,3-methano-3-phenylbutanoic acid **7a**.

Table 2
The amidation of 3-phenylpropionic acid (**7′**) for optimization of the reaction conditions[a]

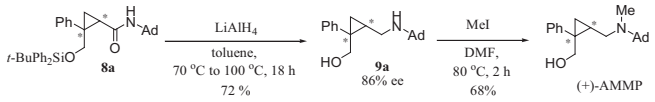


Entry	Base	equiv of base	Time (h)	Yield[d] (%)
1[b]	Free	—	6	27
2[c]	Free	—	8	0
3	$NaHCO_3$	2.0	20	16
4	NaOH	2.0	1	42
5	NaOH	2.0	6	58
6	NaOH	2.0	24	84
7	NaOH	2.0	48	82
8	NaOH	1.1	24	46
9	NaOH	3.0	24	65

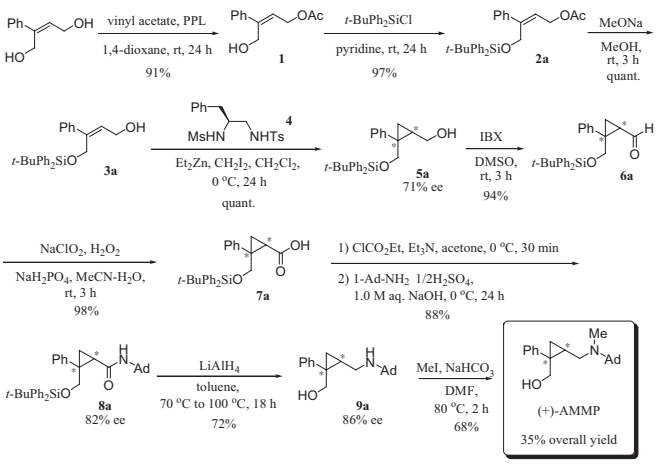
[a] All reactions were carried out with 0.5 mmol of 3-phenylpropionic acid (**7′**), 1.1 equiv of 1-adamantanamine sulfate (1-Ad-NH_2·1/2H_2SO_4), 1.1 equiv of $ClCO_2Et$, and 1.1 equiv of Et_3N in 10 mL of acetone.
[b] 1-adamantanamine hydrochloride (Ad-NH_2·HCl) was used instead of 1-adamantanamine sulfate (1-Ad-NH_2·1/2H_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.



Scheme 4. Preparation of the 2,3-methano-3-phenylbutanamide **8a**.



Scheme 5. Synthesis of (+)-AMMP via reduction and methylation from the 2,3-methano-3-phenylbutanamide **8a**.



Scheme 6. Convenient enantioselective total synthesis of (+)-AMMP.

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, 24, and 48 h to afford the amide **8′** in 58%, 84%, and 82% yield, respectively (see entries 5–7). Then, 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).

Furthermore, the amidation of the 2,3-methano-3-phenylbutanoic acid **7a** with 1-adamantanamine sulfate was performed on the optimized conditions to afford the 2,3-methano-3-phenylbutanamide **8a** in 88% yield as indicated in Scheme 4.[12] It was achieved to convert from (+)-*cis*-4-*tert*-butyldiphenylsiloxy-2,3-methano-3-phenylbutan-1-ol (**5a**) to the corresponding 2,3-methano-3-phenylbutanamide **8a** in three steps without the loss of enantiomeric excess.[13] Fortunately, treatment of the 2,3-methano-3-phenylbutanamide **8a** with 5.0 equiv of lithium aluminium hydride in anhydrous toluene afforded the corresponding 2,3-methano-2-phenylbutan-1-ol **9a** in 72% yield with 86% ee[14] through two reductions in the amide part and the silyl group simultaneously.

Finally, (+)-AMMP[15] was acquired in 68% yield by methylation of the amino alcohol **9a** with methyl iodide as shown in Scheme 5.

In conclusion, we have succeeded in a convenient enantioselective synthesis of (+)-*cis*-4-(*N*-adamantyl-*N*-methylamino)-2,3-methano-2-phenylbutan-1-ol ((+)-AMMP) in 35% overall yield without the loss of enantiomeric excess as summarized in Scheme 6. The reagents used in our synthetic route are relatively cheap. Then, the following three reactions are utilized as a key reaction; the regioselective acetylation using PPL,[7] the catalytic enantioselective Simmons–Smith reaction in the presence of L-phenylalanine-derived disulfonamide,[8] and the convenient amidation of mixed carbonic carboxylic anhydrides in aqueous organic solvent.[9] Currently, we are still working on enantioselective synthesis of (+)-AMMP analogs.

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10. The protected allylic alcohols **3a**–**3c** were prepared from the corresponding **2a**–**2c** by the reaction with a catalytic amount (3 drops) of 28% MeONa solution in MeOH in 20 mL of an additional MeOH. The protected allylic alcohols **3d**, **3e** were prepared from the corresponding **2d**, **2e** by the reaction with 2.0 equiv of diisobutylalminium hydride (DIBAL-H) in 5 mL of tetrahydrofuran (THF).
11. *A typical procedure of cyclopropanation of **3a** in the presence of a catalytic amount of **4** as follows:* To a colorless solution of 201 mg (0.50 mmol) of **3a** 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 argon atmosphere 1.0 mL (1.0 mmol, 2.0 equiv) of 1.0 M Et_2Zn solution in hexane and 121 μL (1.5 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 EtOAc. The organic layers were combined, washed with 5 mL of brine, dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography on silica gel with a 8:1 mixture of hexane and EtOAc to afford 208 mg (quantitative yield) of the corresponding 2,3-methano-3-phenylbutan-1-ol **5a**. **5a**: colorless oil; 71% ee; $[\alpha]_D^{28}$ +51.2 (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.69 (t, *J* = 5.3 Hz, 1H, CH_A of cyclopropane), 0.96 (s, 9H, $C(CH_3)_3$), 0.96–0.99 (m, 1H, CH_B of cyclopropane), 1.81–1.89 (m, 1H, *CH*CH$_2$OH), 3.45–3.59 (m, 2H, *CH*$_A$OH, OH), 3.55 (d, *J* = 11.2 Hz, 1H, *CH*$_A$O SiPh$_2$Bu-*tert*), 4.06 (d, *J* = 11.2 Hz, 1H, *CH*$_B$OSiPh$_2$Bu-*tert*), 4.12–4.19 (m, 1H, *CH*$_B$OH), 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 × 3); ^{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.
12. *A typical procedure of the amidation of **7a** with 1-adamantanamine sulfate as follows:* To a solution of 124 mg (0.29 mmol) of the acid **7a** in 6 mL of acetone were added dropwise at 0 °C 30 μL (0.32 mmol, 1.1 equiv) of $ClCO_2Et$ and 44 μL (0.32 mmol, 1.1 equiv) of Et_3N. After stirring for 30 min at 0 °C, 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 aqueous NaOH solution were added at 0 °C to the colorless suspension. The mixture was stirred for 24 h at 0 °C, diluted with 30 mL of EtOAc, washed with 5 mL of brine, and dried over anhydrous $MgSO_4$. The crude product was chromatographed on silica gel with a 6:1 mixture of hexane and EtOAc to afford 143 mg (88% yield) of the corresponding

2,3-methano-3-phenylbutanamide **8a**. **8a**: colorless oil; 82% ee; $[\alpha]_D^{28}$ +43.4 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.92 (s, 9H, $C(CH_3)_3$), 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), 1.67 (br s, 6H, $CH_2 \times 3$ of adamantane), 1.82 (dd, *J* = 5.7, 8.1 Hz, 1H, CHCON), 2.04 (br s, 9H, $CH_2 \times 3$, $CH \times 3$ of adamantane), 3.89 (d, *J* = 10.5 Hz, 1H, CH_AO), 4.05 (d, *J* = 10.5 Hz, 1H, CH_BO), 5.51 (br s, 1H, NH), 7.16–7.50 (m, 15H, $C_6H_5 \times 3$); ^{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 $C_{37}H_{45}O_2SiNa$ $(M+Na)^+$: 586.3112, Found: 586.3122.

13. Determined by HPLC analysis with a 95:5 mixture of hexane and 2-propanol as an eluent using Chiralcel OD-H (1.0 mL/min).
14. Determined by HPLC analysis with a 95:5:0.05 mixture of hexane, EtOH, and Et_2NH as an eluent using Chiralcel OD (1.0 mL/min).
15. *(+)-AMMP:* colorless oil; 86% ee; $[\alpha]_D^{28}$ +42.8 (*c* 0.90, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.76, 1.21–1.25 (t, m, *J* = 5.1 Hz, 1H, 1H, CH_2 of cyclopropane), 1.39–1.47 (m, 1H, $CHCH_2N$), 1.60–1.68 (m, 6H, $CH_2 \times 3$ of adamantane), 1.76 (d, *J* = 2.8 Hz, 6H, $CH_2 \times 3$ of adamantane), 2.10 (br s, 3H, $CH \times 3$ of adamantane), 2.36 (s, 3H, CH_3), 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 (br s, 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.

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