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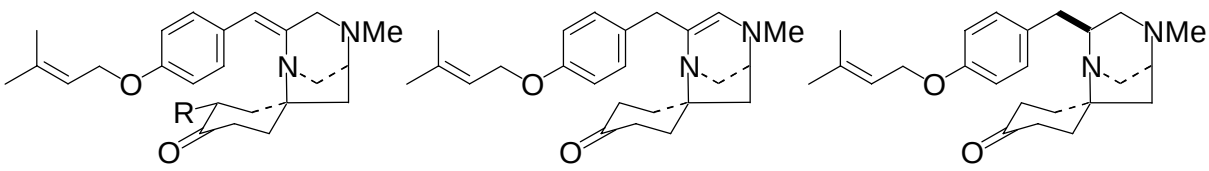
A FORMAL SYNTHESIS OF A MUSCARINIC M_1 RECEPTOR ANTAGONIST, (-)-TAN1251A

Hirotake Mizutani, Jun Takayama, Yukio Soeda, and Toshio Honda*

Faculty of Pharmaceutical Sciences, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan

Abstract – An aromatic oxidation reaction of a secondary amine, prepared from L-tyrosine and glycine, with hypervalent iodine reagent gave a spirocyclic product, which was further converted into the key intermediate for the synthesis of (-)-TAN1251A.

TAN1251A(**1**), B(**2**), C(**3**) and D(**4**), having unique structural features with a 1,4-diazabicyclo-[3.2.1]octane ring system and a spirocyclic cyclohexanone, were isolated from a *Penicillium thomii* RA-89 by Takeda Industries (Figure 1).[1] TAN1251A and B exhibit cholinergic activity and inhibit the acetylcholine-induced contraction of Guinea-pig ileum with ED_{50} values of 8.0 and 10.0 nM, respectively. TAN1251A is also known as a selective muscarinic M_1 subtype receptor antagonist.[2]



1 TAN1251A (R=H)
2 TAN1251B (R=OH)

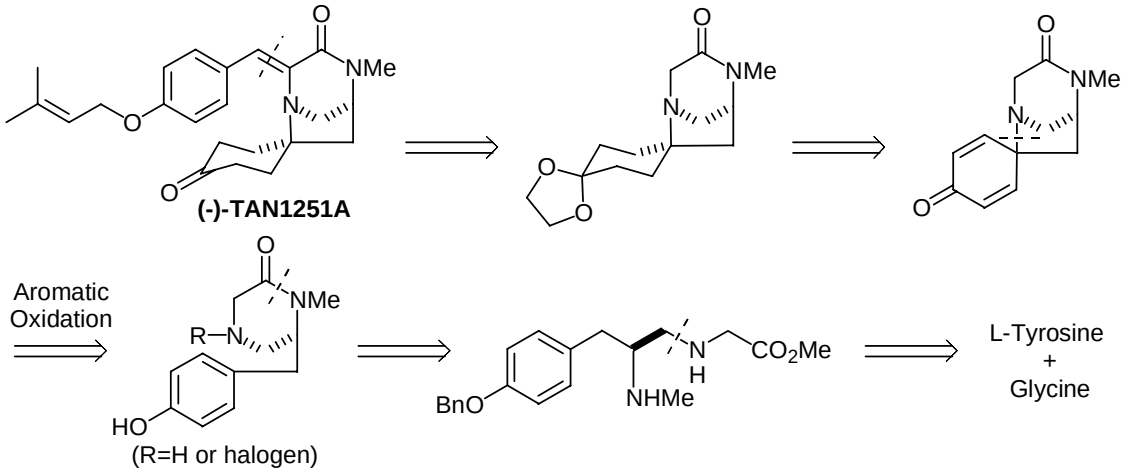
3 TAN1251C

4 TAN1251D

Figure 1

The TAN1251 series of compounds contain intriguing structural features and exhibit the attractive biological activity, which, therefore, led to several total syntheses involving one racemic[3] and three chiral syntheses[4] in the past few years. In the latter chiral syntheses, the problematic spirocyclic carbon-nitrogen bond was constructed by employing a 1,3-dipolar cycloaddition reaction of the chiral nitrone derived from L-tyrosine leading to the determination of their absolute configuration,[4a] and by using an *N*-acylnitrenium ion intermediate as a reactive species.[4b] More recently, a new chiral synthetic route of TAN1251A was achieved starting from *trans*-hydroxy-L-proline as a chiral source by Kawahara and co-workers.[4c] We thought that the carbon-nitrogen bond formation to generate a spirocyclic ring could be achieved by intramolecular aromatic oxidation of secondary amine[5] using hypervalent iodine reagent,[6] or an aminylium ion intermediate generated from the corresponding *N*-halo compound.[7] Herein, we describe full explanation for our synthesis of optically pure (-)-TAN1251A.[8]

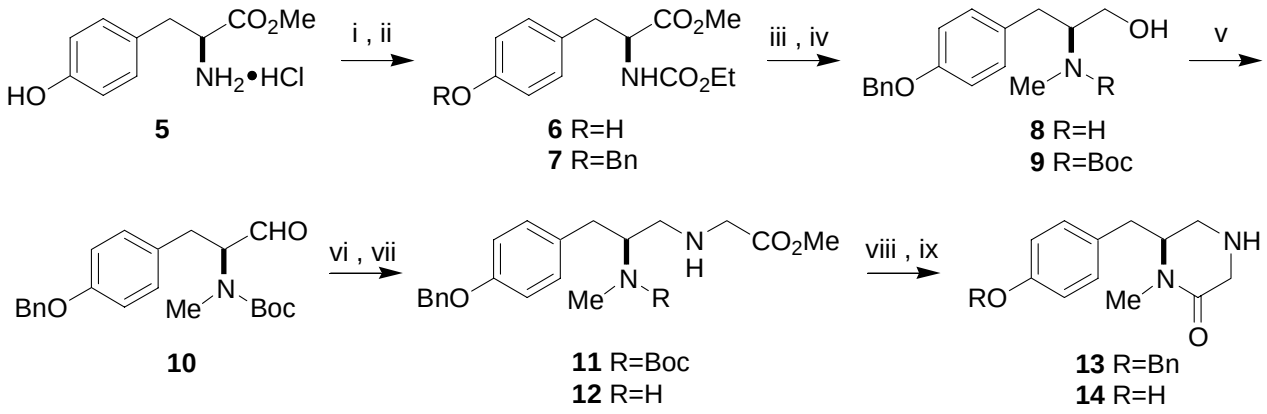
Based on our retrosynthetic strategy, L-tyrosine was chosen as the starting material, since its chirality could be transferred into the chiral center of TAN1251A. Moreover, the requisite secondary amine for aromatic oxidation reaction will readily be obtained by reductive alkylation of a tyrosine derivative with glycine (Scheme 1).



Scheme 1. Retrosynthetic route for TAN1251A.

The secondary amine as a key intermediate was synthesized from tyrosine methyl ester hydrochloride (**5**)

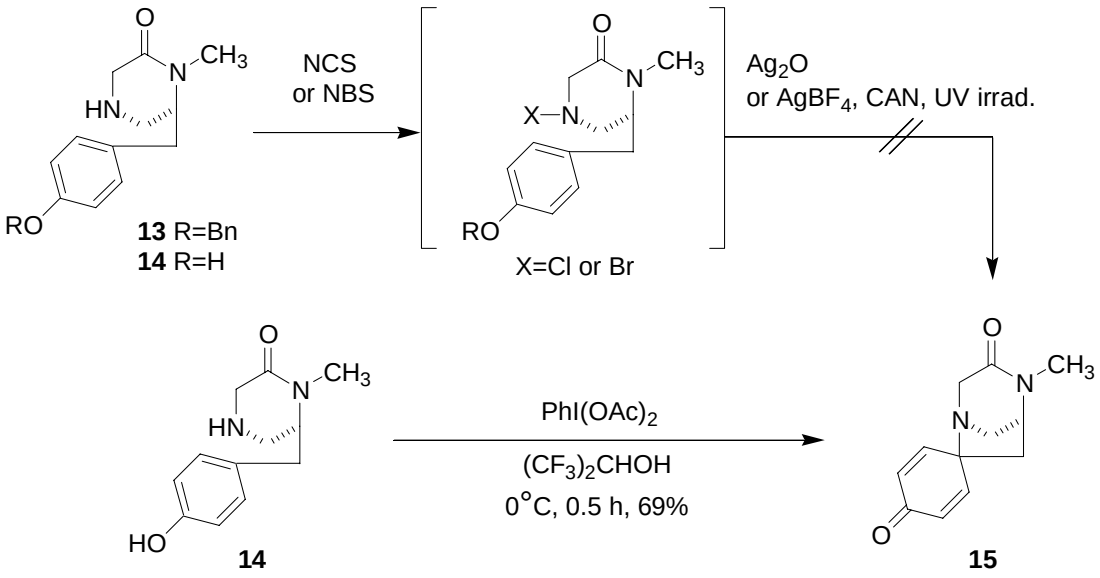
as follows. Compound (**5**) was converted into carbamate (**6**) by treatment with ethyl chlorocarbonate in water in the presence of potassium carbonate, in 84% yield. After protection of the phenolic hydroxyl group of **6** as a benzyl ether in the usual manner, the resulting compound (**7**) was subjected to lithium aluminum hydride reduction providing amino alcohol (**8**) in 81% yield from **6**. The secondary amino group of **8** was then protected as its Boc derivative (**9**) in 92% yield. Dess-Martin oxidation of primary alcohol (**9**) gave aldehyde (**10**), in 86% yield, which on treatment with glycine methyl ester in the presence of sodium cyanoborohydride[9] gave amine (**11**) in 87% yield. The Boc group of **11** was deprotected under acidic condition to afford diamine (**12**), which, on further treatment with 25% ammonium hydroxide in ethanol at room temperature gave piperazinone derivative (**13**) in 88% yield from **11**.



Scheme 2. i: $ClCO_2Et$, K_2CO_3, H_2O, rt (84%); ii: BnBr, K_2CO_3, DMF, rt (88%); iii: $LiAlH_4$, THF, reflux (92%); iv: $(Boc)_2O$, K_2CO_3, THF:H_2O(1:1), rt (92%); v: Dess-Martin periodinane, CH_2Cl_2, 0°C (86%); vi: glycine methyl ester, $NaBH_3CN$, MeOH, rt (87%); vii: CF_3CO_2H, CH_2Cl_2, rt (96%); viii: 25% NH_4OH, EtOH, rt (92%); ix: 10% Pd-C, H_2, MeOH, rt (96%)

First, we attempted a carbon-nitrogen bond formation at this stage *via* an aminylium ion intermediate by halogenation of **13** with NCS or NBS, followed by treatment with silver(I) oxide[7] or the other conditions [$AgBF_4$,[10] $Ce(NH_4)_2(NO_2)_6$, or UV irradiation]. However, none of the desired product could be isolated. We found that the strategy using the aminylium intermediate was not effective for the formation of the

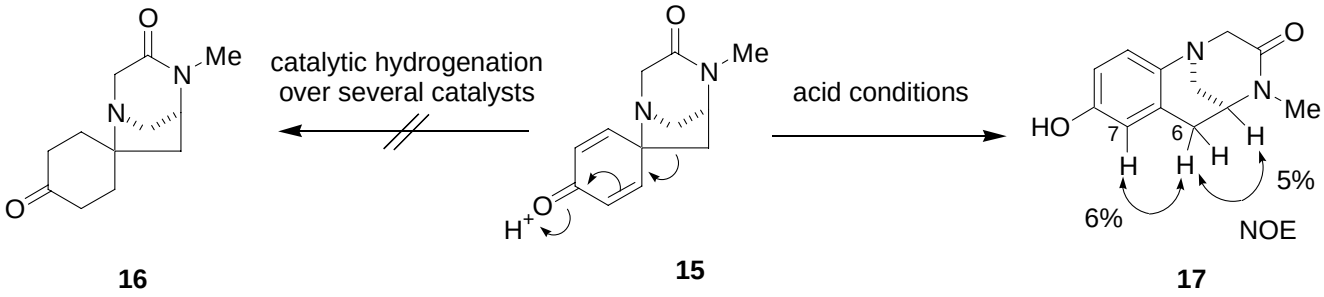
desired product even with the use of a phenolic compound (**14**), derived from **13**. On the other hand, the aromatic oxidation reaction of **14** with iodobenzene diacetate in 2,2,2-trifluoroethanol provided the desired spirocyclic compound (**15**) in 43% yield. At this point, this oxidation reaction was carried out in hexafluoroisopropanol as the solvent, and the yield was increased to 69% (Scheme 3). Unfortunately, the use of iodobenzene ditrifluoroacetate as an oxidizing agent under the same reaction conditions produced a desired product (**15**) in less than 10% yield.



Scheme 3. Construction of the spiro-ring system.

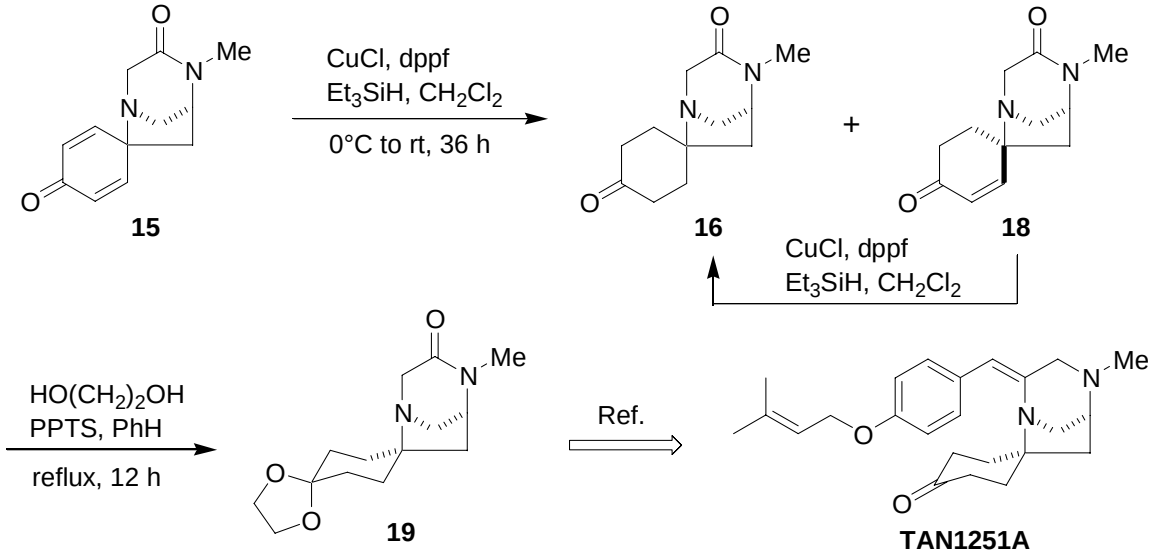
In the reduction of dienone (**15**), difficulties were initially encountered in obtaining the desired products by hydrogenation with various catalysts, or by hydrogenation after reduction of the carbonyl group. Since this compound was found to be labile especially to acid conditions taking place a dienone-phenol rearrangement. In fact, when dienone (**15**) was subjected to a ketalization, the carbon at the spiro center was migrated to the β-position of enone producing rearrangement compound (**17**) as shown in Scheme 4. Consequently, the carbonyl group could not be protected as an acetal form before hydrogenation reduction. The structure of **17** was determined by NMR spectral analysis, in which NOEs were observed between the

6- methylene proton and the 7-aromatic proton.



Scheme 4. Rearrangement of dienone **15**

Fortunately, we found that dienone (**15**) could be converted to ketone (**16**) by treatment with 2 equivalent of triethylsilane[11] in the presence of 20 mol% of copper(I) chloride and 20 mol% of dppf in dichloromethane at 0°C for 36 h in 30% yield, together with enone (**18)** produced by the partial reduction of the less hindered olefin of **16**,[12] in 42% yield. Enone (**18**) could also be converted to ketone (**16**) by further reduction under the same reaction conditions as above in 80% yield. When the reduction of **15** was carried out with 3 equivalent of triethylsilane, the desired ketone (**16**) was isolated in 60% yield together with enone (**18**) in 9% yield (Scheme 5).



Scheme 5. Reduction of dienone compound.

Finally, protection of ketone (**16**) with ethylene glycol and a catalytic amount of pyridinium *p*-toluenesulfonate in refluxing benzene afforded ketal (**19**) that is known key intermediate for the synthesis of (-)-TAN1251A. The spectroscopic data of **19** including its optical rotation {$[\alpha]_D$ +15.6° (c 0.71, $CHCl_3$); lit.,[4b] $[\alpha]_D$ +15.2° ($CHCl_3$)} were identical with those reported. Since compound (**19**) has already been transformed into (-)-TAN1251A by Wardrop and co-workers,[4b] this synthesis constitutes its formal total synthesis.

In conclusion, we have succeeded in a facile synthesis of optically pure (-)-TAN1251A, where aromatic oxidation reaction of the secondary amine with iodobenzene diacetate was involved as the key reaction. This synthetic strategy would be applicable to the synthesis of other TAN series of compound, and study on the synthesis of TAN1251C and D by using tyrosine dimmer as the starting material is in progress.

EXPERIMENTAL

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were obtained using a JASCO FT/IR-200 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on JEOL LAMBDA-270 (^{1}H-NMR: 270 MHz, ^{13}C-NMR: 67.8 MHz) instrument for solutions in $CDCl_3$ unless otherwise noted, and chemical shifts are reported on the δ scale from internal TMS. MS spectra were measured with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed on a Yanaco-MT5.

L-*N*-Ethoxycarbonyltyrosine methyl ester (6): To a mixed solution of potassium carbonate (21.5 g, 0.16 mol) in dioxane:H_2O (1:1, 200 mL) was added L-tyrosine methyl ester hydrochloride (18.0 g, 77.7 mmol) at 0°C. After stirring for 0.5 h, ethyl chloroformate (8.9 mL, 93.1 mmol) was added to the mixture and the whole was allowed to stir for 2 h at 0°C. After quenching by addition of 10% HCl, the resulting mixture was extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Removal of volatiles under reduced pressure gave a residue, which was purified by silica gel column chromatography (CH_2Cl_2:MeOH, 30:1 v/v) to yield 17.4 g of **6** (84%) as a colorless oil. $[\alpha]_D^{23}$ +51.2° (c 0.96, $CHCl_3$); IR (thin film) cm^{-1}: 3350, 1700, 1520; ^{1}H-NMR ($CDCl_3$) δ: 6.96 (d, *J*=8.4 Hz, 2H), 6.73 (d, *J*=8.4 Hz, 2H), 5.23 (d, *J*=8.4 Hz, 1H), 4.60 (dd, *J*=14.2, 6.1 Hz, 1H), 4.10 (q, *J*=7.1 Hz, 2H), 3.72 (s, 3H),

2.93-3.09 (m, 2H), 1.22 (t, *J*=7.1 Hz, 3H); ^{13}C-NMR δ: 14.4, 37.4, 52.4, 54.9, 61.4, 67.0, 77.2, 115.5, 127.1, 130.3, 155.3, 156.2, 172.5; MS *m/z* calcd for $C_{13}H_{17}NO_5$ (M^+): 267.1106. Found: 267.1094.

Methyl (2*S*)-3-(4-benzyloxyphenyl)-2-ethoxycarbonylaminopropionate (7): To a solution of **6** (21.5 g, 80.4 mmol) in acetone (200 mL) were added potassium carbonate (22.2 g, 0.16 mol) and benzyl bromide (10.0 mL, 84.1 mmol) at 0°C, and the resulting mixture was allowed to stir for 12 h at rt. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. After addition of AcOEt, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residual mixture was purified by silica gel column chromatography (*n*-hexane:AcOEt, 4:1 v/v) to yield 25.3 g of **7** (88%) as a white solid (mp 61.0~61.7°C). $[\alpha]_D^{20}$ +46.8° (c 0.71, $CHCl_3$); IR (KBr) cm^{-1}: 1720, 1510, 1240; ^{1}H-NMR ($CDCl_3$) δ: 7.29-7.45 (m, 5H), 7.03 (ddd, *J*=6.6, 8.7, 11.5 Hz, 2H), 6.90 (ddd, *J*=6.6, 8.7, 11.5 Hz, 2H), 5.09 (d, *J*=8.1 Hz, 1H), 5.04 (s, 2H), 4.60 (dd, *J*=5.6, 8.1 Hz), 4.10 (q, *J*=7.1 Hz, 2H), 3.71 (s, 3H), 3.04 (d, *J*=5.6 Hz, 2H), 1.23 (t, *J*=7.1 Hz, 3H); ^{13}C-NMR δ: 14.5, 37.4, 52.3, 54.7, 61.1, 70.0, 114.9, 127.5, 128.0, 128.6, 130.3, 136.9, 157.9, 172.2; MS *m/z* calcd for $C_{20}H_{23}NO_5$ (M^+): 357.1576. Found: 357.1582; Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.30; H, 6.54; N, 3.90.

(2*S*)-3-(4-Benzyloxyphenyl)-2-methylaminopropan-1-ol (8): To a suspension of lithium aluminum hydride (6.6 g, 0.17 mol) in THF (300 mL) was added a solution of **7** (25 g, 69.9 mmol) in THF (50 mL) under argon atmosphere, and the mixture was stirred for 1 h at rt and then stirred for 4 h at reflux temperature. The reaction was quenched by addition of 1N NaOH at 0°C, and the resulting mixture was filtered through a pad of Celite. After removal of volatiles of the filtrate under reduced pressure, the residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH, 4:1 v/v) to yield 17.6 g of **8** (92%) as a white solid (mp 106.0~107.5°C). $[\alpha]_D^{21}$ +14.8° (c 0.95, $CHCl_3$); IR (KBr) cm^{-1}: 3300, 2890, 1610, 1520, 1250; ^{1}H-NMR ($CDCl_3$) δ: 7.30-7.46 (m, 5H), 7.10 (d, *J*=8.6 Hz, 2H), 6.92 (d, *J*=8.6 Hz, 2H), 5.05 (s, 2H), 3.63 (dd, *J*=3.5, 10.7 Hz, 1H), 3.33 (dd, *J*=4.6, 10.7 Hz, 1H), 2.61-2.79 (m, 3H), 2.40 (s, 3H), 1.91 (br, 2H); ^{13}C-NMR δ: 33.6, 36.5, 61.8, 62.0, 70.0, 114.9, 127.4, 127.9, 128.5, 130.1, 130.8, 137.0, 157.4; MS *m/z* calcd for $C_{17}H_{21}NO_2$ (M^+): 271.1572. Found: 271.1597; Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 74.99; H, 7.74; N, 5.19.

(1*S*)-3-(4-Benzyloxyphenyl)-2-[(*N*)-*tert*-butoxycarbonyl]methylaminopropan-1-ol (9): To a stirred solution of **8** (17.4 g, 64.1 mmol) in THF:H_2O (1:1, 200 mL) were added potassium carbonate (12.4 g, 89.7 mmol) and $(Boc)_2O$ (16.8 g, 77.0 mmol) at 0°C, and the mixture was allowed to stir for 12 h at rt. Citric acid was added to the reaction mixture until the solution became acidic (pH 3) and the resulting mixture was extracted with AcOEt. The organic layer was washed with saturated solution of aqueous citric acid and brine, dried over Na_2SO_4, and concentrated to afford a residue, which was purified by silica gel column chromatography (*n*-hexane:AcOEt, 1:1 v/v) to yield 21.8 g of **9** (92%) as a colorless oil. $[\alpha]_D^{22}$ -40.5° (c 1.34, $CHCl_3$); IR (thin film) cm^{-1}: 3420, 2980, 1670, 1510; ^{1}H-NMR ($CDCl_3$) δ: 7.31-7.44 (m, 5H), 7.09 (br m, 2H), 6.89 (d, *J*=8.7 Hz, 2H), 5.04 (s, 2H), 3.70 (br m, 2H), 2.67 (br m, 5H), 1.41 (s, 9H); ^{13}C-NMR δ: 28.3, 31.5, 33.8, 34.2, 59.7, 60.1, 62.8, 63.2, 70.0, 80.0, 114.8, 127.4, 127.8, 128.5, 129.8, 130.5, 136.8, 137.0, 156.9, 157.3; MS *m/z* calcd for $C_{22}H_{29}NO_4$ (M^+): 371.2096. Found: 371.2081.

(1*S*)-3-(4-Benzyloxyphenyl)-2-[(*N*)-*tert*-butoxycarbonyl]methylaminopropanal (10): To a solution of **9** (21.0 g, 56.5 mmol) in CH_2Cl_2 (200 mL) was added Dess-Martin periodinane (30.3 g, 71.4 mmol) at 0°C, and the resulting mixture was stirred for 2 h at the same temperature. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated to give a residue, which was purified by silica gel column chromatography (*n*-hexane:AcOEt, 2:1 v/v) to yield 17.9 g of **10** (86%) as a colorless oil. $[\alpha]_D^{23}$ -97.9° (c 0.41, $CHCl_3$); IR (thin film) cm^{-1}: 2980, 1780, 1520; ^{1}H-NMR ($CDCl_3$) δ: 9.65 (s, 1H), 7.29-7.45 (m, 5H), 7.09 (d, *J*=8.6 Hz, 2H), 6.91 (d, *J*=8.6 Hz, 2H), 5.04 (s, 2H), 4.16 (dd, *J*=4.8, 10.2 Hz, 0.45H), 3.94 (dd, *J*=4.0, 10.2 Hz, 0.55H), 3.24 (dd, *J*=4.6, 14.3 Hz, 1H), 2.80-2.99 (m, 1H), 2.63 and 2.68 (each s, 3H), 1.38-1.43 (each s, 9H); ^{13}C-NMR δ: 28.1, 28.2, 31.8, 32.6, 34.6, 35.0, 68.3, 69.5, 69.9, 80.4, 81.1, 114.9, 115.0, 127.3, 127.8, 128.5, 129.7, 130.0, 130.6, 136.9, 157.5, 198.9, 199.4; MS *m/z* calcd for $C_{22}H_{27}NO_4$ (M^+): 369.1940. Found: 369.1961.

Methyl *N*-[(2*S*)-3-(4-benzyloxyphenyl)-2-(*tert*-butoxycarbonylmethylamino)propyl]aminoacetate (11): To a solution of $NaBH_3CN$ (2.64 g, 42.0 mmol) and glycine methyl ester hydrochloride (10.5 g, 88.4 mmol) in MeOH (200 mL) was added slowly a solution of **10** (15.5 g, 42.0 mmol) in MeOH (30 mL) at 0°C, and the mixture was stirred for 4 h at the same temperature. The reaction mixture was quenched by

saturated solution of aqueous $NaHCO_3$, and the resulting mixture was extracted with $CHCl_3$:MeOH (9:1). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to afford a residue, which was purified by silica gel column chromatography (CH_2Cl_2:MeOH, 20:1 v/v) to yield 16.2 g of **11** (87%) as a colorless oil. $[\alpha]_D^{24}$ -15.1° (c 0.43, $CHCl_3$); IR (thin film) cm^{-1}: 2980, 1740, 1690, 1510; ^{1}H-NMR ($CDCl_3$) δ: 7.26-7.44 (m, 5H), 7.03-7.12 (m, 2H), 6.88 (d, *J*=8.6 Hz, 2H), 5.03 (s, 2H), 4.31-4.46 (br m, 1H), 3.72 (br s, 3H), 3.42 (q, *J*=17.5 Hz, 2H), 2.71-2.85 (m, 2H), 2.67 and 2.77 (each s, 3H), 2.61 (dd, *J*=4.9, 12.2 Hz, 2H), 1.30 and 1.37 (each s, 9H); ^{13}C-NMR δ: 28.2, 28.9, 35.9, 49.9, 50.2, 50.3, 51.6, 55.8, 57.1, 69.9, 77.2, 79.4, 114.7, 127.3, 127.8, 128.4, 129.8, 130.7, 137.0, 156.0, 157.3, 172.6; MS *m/z* calcd for $C_{25}H_{34}N_2O_5$ (M^+): 442.2467. Found: 442.2463; Anal. Calcd for $C_{25}H_{34}N_2O_5$: C, 67.85; H, 7.74; N, 6.33. Found: C, 67.57; H, 7.79; N, 6.21.

Methyl *N*-[(2*S*)-3-(4-benzyloxyphenyl)-2-methylaminopropyl]aminoacetate (12): To a solution of **11** (15.0 g, 33.9 mmol) in CH_2Cl_2 (150 mL) was added slowly trifluoroacetic acid (13 mL, 0.17 mol) at 0°C, and the resulting mixture was stirred for 2 h at rt. The reaction mixture was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (CH_2Cl_2:MeOH, 15:1 v/v) to yield 11.1 g of **12** (96%) as a colorless oil. $[\alpha]_D^{24}$ -15.1° (c 0.43, $CHCl_3$); IR (thin film) cm^{-1}: 2980, 1740, 1690, 1510; ^{1}H-NMR ($CDCl_3$) δ: 7.29-7.65 (m, 5H), 7.12 (d, *J*=8.6 Hz, 2H), 6.93 (d, *J*=8.6 Hz, 2H), 5.03 (s, 2H), 3.68 (s, 3H), 3.32 (d, *J*=18.0 Hz, 1H), 3.49 (d, *J*=18.0 Hz, 1H), 2.79-3.17 (m, 5H), 2.73 (s, 3H); ^{13}C-NMR δ: 30.6, 33.7, 47.9, 50.0, 51.8, 60.4, 69.8, 115.1, 127.3, 127.7, 127.8, 128.4, 130.0, 136.7, 157.8, 173.1; MS *m/z* calcd for $C_{25}H_{34}N_2O_5$ (M^+): 442.2467. Found: 442.2463; Anal. Calcd for $C_{25}H_{34}N_2O_5$: C, 67.85; H, 7.74; N, 6.33. Found: C, 67.57; H, 7.79; N, 6.21.

(6*S*)-6-(4-Benzyloxybenzyl)-1-methylpiperazin-2-one (13): To a mixed solution of ammonium hydroxide (25%, 50 mL) and EtOH (80 mL) was added slowly a solution of **12** (10.5 g, 30.7 mmol) in EtOH (50 mL) at 0°C, and the whole was stirred for 12 h at rt. The reaction mixture was concentrated under reduced pressure. The residual mixture was extracted with CH_2Cl_2, and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. After removal of volatiles under reduced pressure, the residue was purified by silica gel column chromatography (CH_2Cl_2:MeOH,

40:1 v/v) to yield 8.6 g of **13** (92%) as a white solid (mp 145~146°C). $[\alpha]_D^{24}$ +33.4° (c 0.54, $CHCl_3$); IR (KBr) cm^{-1}: 3300, 1640, 1510, 1250; ^{1}H-NMR ($CDCl_3$) δ: 7.29-7.45 (m, 5H), 7.09 (ddd, *J*=6.6, 8.6, 11.5 Hz, 2H), 6.93 (ddd, *J*=6.6, 8.6, 11.5 Hz, 2H), 5.05 (s, 2H), 3.47 (s, 2H), 3.29-3.41 (m, 1H), 3.04 (s, 3H), 2.84-3.02 (m, 4H), 1.55 (br s, 1H); ^{13}C-NMR δ: 33.3, 36.4, 45.2, 49.9, 60.3, 69.9, 115.1, 127.4, 127.9, 128.5, 129.8, 130.1, 136.8, 157.6, 168.4; Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.14; N, 9.03. Found: C, 73.39; H, 7.27; N 8.93.

(6*S*)-6-(4-Hydroxybenzyl)-1-methylpiperazin-2-one (14): To a stirred solution of **13** (4.0 g, 12.9 mmol) in MeOH (70 mL) was added 10% Pd on carbon (400 mg, 10% based on **13**), and the mixture was allowed to stir for 2 h at rt under H_2 atmosphere. The reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and residual mixture was purified by silica gel column chromatography (CH_2Cl_2:MeOH, 6:1 v/v) to yield 2.7 g of **14** (96%) as a white solid (mp 206.5~207.8°C). $[\alpha]_D^{24}$ +45.7° (c 0.95, EtOH); IR (KBr) cm^{-1}: 3120, 2950, 2320, 1620, 1510; ^{1}H-NMR (CD_3OD) δ: 7.06 (ddd, *J*=6.4, 8.4, 11.4 Hz, 2H), 6.74 (ddd, *J*=6.4, 8.4, 11.4 Hz, 2H), 3.46 (ddd, *J*=5.8, 9.4, 13.5 Hz, 1H), 3.35 (s, 2H), 3.31 (quint, *J*=1.6 Hz, 1H), 3.04 (dd, *J*=4.3, 13.5 Hz, 1H), 3.00 (s, 3H), 2.76-2.91 (m, 3H); ^{13}C-NMR δ: 33.9, 37.1, 45.3, 49.7, 61.4, 116.5, 129.5, 131.4, 157.4, 170.8; MS *m/z* calcd for $C_{12}H_{17}N_2O_2$ (M^+): 221.1302. Found: 221.1290; Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.20; H, 7.43; N, 12.49.

(5*S*)-Spiro{4-methyl-1,4-diazabicyclo[3.2.1]octan-3-one-7,1'-cyclohexa-2',5'-dien-4'-one} (15): To a solution of iodobenzene diacetate (1.10 g, 3.42 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (40 mL) was added dropwise a solution of **14** (0.70 g, 3.18 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (5 mL) at 0°C and the resulting mixture was allowed to stir for 1 h at the same temperature. After removal of volatiles, the residual mixture was purified by silica gel column chromatography (CH_2Cl_2:MeOH, 25:1 v/v) to yield 0.48 g of **15** (69%) as a white solid (mp 124.5~126.2°C). $[\alpha]_D^{20}$ -23.52° (c 0.53, $CHCl_3$); IR (KBr) cm^{-1}: 2970, 1670, 1630; ^{1}H-NMR ($CDCl_3$) δ: 6.82-6.76 (m, 2H), 6.29 and 6.14 (each distorted d, *J*=9.7 Hz, each 1H), 3.93 (dd, *J*=4.1, 2.8 Hz, 1H), 3.75 (d, *J*=18.5 Hz, 1H), 3.58 (dd, *J*=18.5, 1.5 Hz, 1H), 3.46 (dd, *J*=12.7, 3.0 Hz, 1H), 3.20 (br d, *J*=12.7 Hz, 1H), 3.00 (s, 3H), 2.30 (dd, *J*=13.8, 2.8 Hz, 1H), 2.11 (dd,

J=13.8, 4.1 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 33.6, 45.1, 57.2, 58.1, 60.7, 63.4, 124.9, 129.3, 146.6, 149.9, 166.8, 184.8; MS *m/z* calcd for $C_{12}H_{14}N_2O_2$ (M^+): 218.1069. Found: 218.1055.

(5*S*)-Spiro{4-methyl-1,4-diazabicyclo[3.2.1]octan-3-one-7,1'-cyclohexan-4'-one} (16) and (5*S*,7*S*)-Spiro{4-methyl-1,4-diazabicyclo[3.2.1]octan-3-one-7,1'-cyclohex-2'-en-4'-one} (18): To a solution of **15** (200 mg, 0.92 mmol) in CH_2Cl_2 (10 mL) were added CuCl (18.1 mg, 0.18 mmol), sodium *tert*-butoxide (24.6 mg, 0.26 mmol) and dppf (101.6 mg, 0.18 mmol) under argon atmosphere. After stirring for 15 min at 0°C, triethylsilane (0.44 mL, 2.75 mmol) was added dropwise to the mixture at 0°C, and the whole was allowed to stir for 36 h at rt. The reaction mixture was quenched by addition of brine, and then extracted with CH_2Cl_2. The extract was washed with brine and dried over Na_2SO_4. After removal of volatiles under reduced pressure, the residual mixture was purified by silica gel column chromatography to yield 121 mg of **16** (60%) as a white solid (mp 98.5~99.5°C) as the first eluent, and 19 mg of **18** (9%) as colorless needles (mp 92.0~93.0°C) as the second eluent. **16**: $[\alpha]_D^{22}$ +8.73° (c 0.90, $CHCl_3$); IR (KBr) cm^{-1}: 2955, 1715, 1646; ^{1}H-NMR ($CDCl_3$) δ: 3.70 (d, *J*=18.5 Hz, 1H), 3.69 (dd, *J*=4.4, 2.5 Hz, 1H), 3.33 (dd, *J*=12.5, 2.5 Hz, 1H), 3.14 (br d, *J*=12.5 Hz, 1H), 2.76 (ddd, *J*=14.5, 11.0, 5.4 Hz, 1H), 2.52-2.18 (m, 3H), 2.17-1.93 (m, 4H), 1.88-1.55 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ: 33.2, 34.5, 38.1, 38.5, 38.6, 45.3, 55.1, 56.4, 59.7, 63.6, 167.5, 210.1; Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.92; H, 8.20; N, 12.51. **18**: $[\alpha]_D^{20}$ +96.0° (c 0.38, $CHCl_3$); IR (KBr) cm^{-1}: 2960, 1678, 1646; ^{1}H-NMR ($CDCl_3$) δ: 6.64 (dd, *J*=10.1, 2.0 Hz, 1H), 6.05 (dd, *J*=10.1, 1.0 Hz, 1H), 3.79 (dd, *J*=4.3, 2.6 Hz, 1H), 3.62 (d, *J*=18.5 Hz, 1H), 3.47 (dd, *J*=18.5, 1.6 Hz, 1H), 3.33 (dd, *J*=12.4, 2.6 Hz, 1H), 3.05 (m, 1H), 2.97 (s, 3H), 2.90 (ddd, *J*=16.8, 13.0, 4.9 Hz, 1H), 2.41-2.32 (m, 1H), 2.27 (dd, *J*=13.7, 2.6 Hz, 1H), 2.10-2.01 (m, 1H), 1.95 (dd, *J*=13.0, 3.8 Hz, 1H), 1.85 (dd, *J*=13.7, 4.3 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 33.4, 35.4, 36.1, 48.3, 56.6, 57.1, 61.0, 63.4, 130.9, 150.9, 167.2, 198.9; MS *m/z* calcd for $C_{12}H_{16}N_2O_2$ (M^+): 220.1212. Found: 220.1204.

(5*S*)-8-Hydroxy-4-methyl-5,6-dihydro-4*H*-1,5-methanobenzo[e][1,4]diazocin-3-one (17): To a stirred solution of **15** (40 mg, 0.18 mmol) in benzene (2 mL) were added a catalytic amount of pyridinium *p*-toluenesulfonate, $MgSO_4$ (40 mg) and ethylene glycol (0.5 mL), and the mixture was stirred for 6 h at reflux temperature. The reaction mixture was concentrated under reduced pressure to afford a residue,

which was purified by silica gel column chromatography (CH_2Cl_2:MeOH, 12:1 v/v) to yield 30.8 mg of **17** (77%) as a colorless needles (mp 264~267°C). $[\alpha]_D^{28}$ -50.9° (c 0.18, MeOH); IR (KBr) cm^{-1}: 3430, 3150, 1618, 1605, 1520, 1440, 1250, 1045, 862; ^{1}H-NMR ($CDCl_3$) δ: 6.88 (d, *J*=8.6 Hz, 1H), 6.62 (dd, *J*=8.6, 2.8 Hz, 1H), 6.54 (d, *J*=2.8 Hz, 1H), 3.86 (d, *J*=17.5 Hz, 1H), 3.79 (m, 1H), 3.52-3.61 (m, 1H), 3.45 (dd, *J*=17.5, 1.8 Hz, 1H), 3.31 (m, 1H), 3.19 (d, *J*=13.4 Hz, 1H), 2.91-3.06 (m, 5H); ^{13}C-NMR ($CDCl_3$: 125.7 Hz) δ: 32.8, 33.8, 50.5, 52.7, 61.8, 116.0, 117.0, 127.1, 128.8, 140.7, 155.8, 170.6; MS *m/z* calcd for $C_{12}H_{14}N_2O_2$ (M^+): 218.1068. Found: 218.1055.

(5”*S*)-Dispiro{4-methyl-1,4-diazabicyclo[3.2.1]octan-3-one-7,1’-cyclohexane-4’,2”-1”,3”-dioxolane} (19): To a stirred solution of **16** (44 mg, 2.00 μmol) in benzene (4 mL) were added a catalytic amount of pyridinium *p*-toluenesulfonate and ethylene glycol (0.5 mL), and the mixture was stirred for 12 h at reflux temperature equipped with Dean-Stark condenser. After quenching by addition of saturated aqueous $NaHCO_3$, the resulting mixture was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and concentrated to afford a residue, which was purified by silica gel column chromatography (CH_2Cl_2:MeOH, 30:1 v/v) to yield 34.7 mg of **19** (66%) as a colorless oil. $[\alpha]_D^{20}$ +15.6° (c 0.71, $CHCl_3$); IR (thin film) cm^{-1}: 2950, 2930, 2890, 1644, 1154; ^{1}H-NMR ($CDCl_3$) δ: 3.88 (br s, 4H), 3.55-3.49 (m, 2H), 3.41 (d, *J*=18.6 Hz, 1H), 3.18 (dd, *J*=12.2, 2.6 Hz, 1H), 2.98 (d, *J*=12.2 Hz, 1H), 2.83 (s, 3H), 1.86-1.62 (m, 7H), 1.60-1.42 (m, 3H); ^{13}C-NMR ($CDCl_3$) δ: 31.8, 32.5, 32.7, 33.3, 36.4, 45.0, 55.0, 56.3, 59.9, 64.1, 64.2, 64.2, 107.9, 168.2; MS *m/z* calcd for $C_{14}H_{22}N_2O_3$ (M^+): 266.1630. Found: 266.1623.

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