[Chem. Pharm. Bull. 26(12)3765—3771(1978)]

UDC 547.944.057 : 547.587.42.04

Stereochemical Studies. LIV.[1] A Biogenetic-type Asymmetric Synthesis of optically Active Galanthamine from L-Tyrosine[2]

Kimihiro Shimizu, Kiyoshi Tomioka, Shun-ichi Yamada, and Kenji Koga

Faculty of Pharmaceutical Sciences, University of Tokyo[3]

(Received June 17, 1978)

A biogenetic-type asymmetric synthesis of optically active galanthamine ((+)-**4** and (−)-**4**) is described. Norbelladine derivative (**10**), having C_2 symmetry in the aromatic moiety of C_6–C_1–N part, was prepared from L-tyrosine, and was converted to narwedine-type enone (**11**) by oxidation and highly specific asymmetric cyclization. Phosphorylation of phenolic hydroxyl group followed by sodium borohydride reduction afforded **14** having galanthamine skeleton. N-Methylation followed by removal of the methoxycarbonyl and phosphate moieties afforded (+)-galanthamine ((+)-**4**).

Formal total synthesis of (−)-galanthamine ((−)-**4**) from L-tyrosine *via* enantiomeric interconversion of narwedine derivative (**12**) is also described.

Keywords——biogenetic-type synthesis; total synthesis; asymmetric cyclization; phenolic oxidative coupling; (+)-galanthamine; (−)-galanthamine; enantiomeric interconversion; *p,o'*-coupling

Phenolic oxidative coupling has long been recognized as a pivotal step in the biosynthesis of many natural products having biaryl and related systems.[4] In the case of Amaryllidaceae

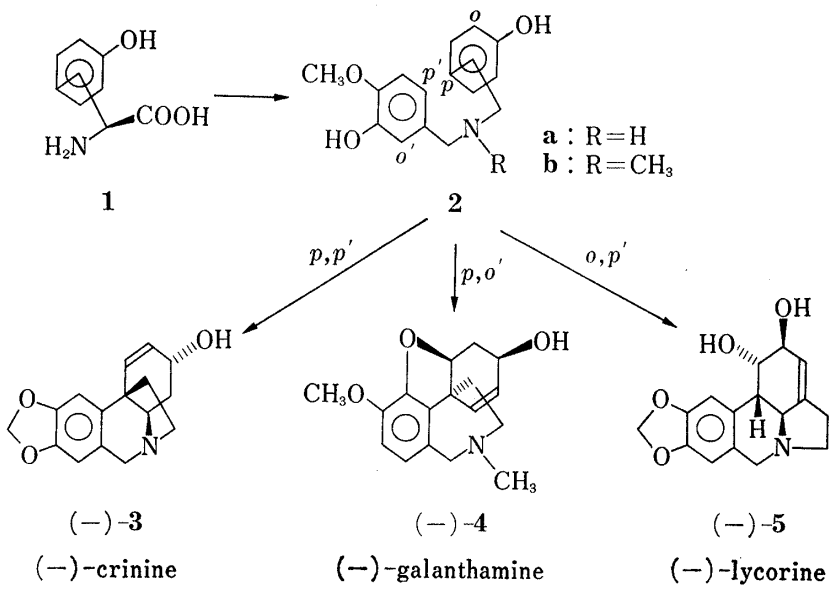
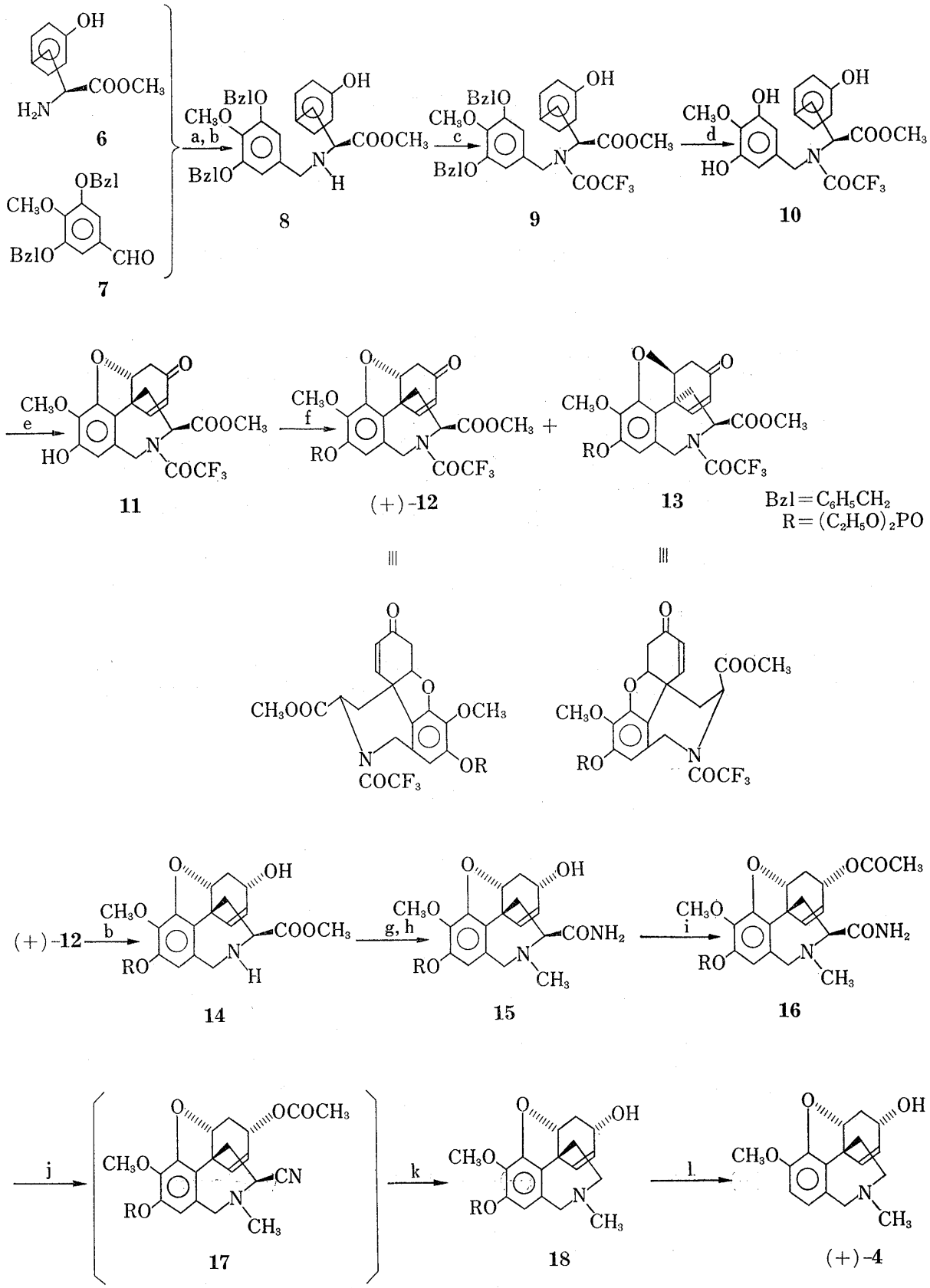


Chart 1

1) Part LIII: K. Okamura and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **26**, 2305 (1978).
2) Preliminary communication: K. Shimizu, K. Tomioka, S. Yamada, and K. Koga, *Heterocycles*, **8**, 277 (1977).
3) Location: *Hongo, Bunkyo-ku, Tokyo 113, Japan.*
4) A.R. Battersby and W.I. Taylor, "Oxidative Coupling of Phenols," Dekker, New York, 1967.



a) molecular sieves 4A. b) $NaBH_4$. c) $(CF_3CO)_2O$, pyridine. d) 10% Pd-C/H_2. e) $Mn(acac)_3$. f) $(C_2H_5O)_2POCl$, Et_3N. g) 35% aq. HCHO, $(HCHO)_n$, 85% aq. HCOOH. h) NH_3. i) $(CH_3CO)_2O$, pyridine. j) $POCl_3$, pyridine. k) $LiAlH_4$. l) Na, liq. NH_3.

Chart 2

alkaloids,[5] it is well known that three skeletally different types of compounds are biosynthesized from their common precursor norbelladine derivative (**2**)[6] as shown in Chart 1. They are crinine-type alkaloids by *p,p'*-coupling, galanthamine-type alkaloids by *p,o'*-coupling, and lycorine-type alkaloids by *o,p'*-coupling. Synthetic approaches to these three types of compounds have been a subject of extensive investigations.[7]

In previous papers,[8] we reported a biogenetic-type asymmetric synthesis of (+)-maritidine, one of the crinine-type alkaloids, from L-tyrosine (**1**) *via* intramolecular *p,p'*-coupling. The present paper is concerned with a biogenetic-type asymmetric synthesis of optically active galanthamine ((+)- and (−)-**4**) *via* formal *p,o'*-coupling from **1** as shown in Chart 2. Although biogenetic-type syntheses of galanthamine have already been reported in optically active form (*via* resolution)[9] and in racemic form,[10] we describe here our approach to the problem of how to carry out *p,o'*-coupling reaction effectively and of how to get optically active compounds. The strategy of the present synthesis involves (a) the use of N-(3,5-dihydroxy-4-methoxy)benzyl derivative (**10**) having C_2 symmetry in the aromatic moiety as the substrate for oxidative coupling[11] for the purpose of obtaining the *p,o'*-coupled product after reductive elimination of the remaining phenolic hydroxyl group[12] of the resulting **11**, (b) the use of asymmetric cyclization of **10** to **11** under the influence of the chiral center of **10**, followed by elimination of the original chirality by reductive decyanization,[8,13–15] and (c) the enantiomeric transformation of (+)-**12** to its antipode ((−)-**12**) by utilizing optical instability of narwedine-type enone skeleton.[9]

The Schiff base, prepared from L-tyrosine methyl ester (**6**) and 3,5-dibenzyloxy-4-methoxybenzaldehyde (**7**), was reduced with sodium borohydride to give the corresponding amine (**8**). Treatment of **8** with trifluoroacetic anhydride in pyridine followed by catalytic hydrogenolysis afforded norbelladine derivative (**10**). The oxidation of **10** with five equivalents of manganic tris (acetylacetonate)[16] in acetonitrile gave the cyclized narwedine-type enone (**11**) in 49% yield after chromatographic purification.

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6) *a*) D.H.R. Barton, G.W. Kirby, J.B. Taylor, and G.M. Thomas, *J. Chem. Soc.*, **1963**, 4545; *b*) W.C. Wildman, H.M. Fales, and A.R. Battersby, *J. Am. Chem. Soc.*, **84**, 681 (1962); *c*) W. Doepke, *Heterocycles*, **6**, 551 (1977).

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14) *cf. a*) S. Yamada and H. Akimoto, *Tetrahedron Lett.*, **1969**, 3105; *b*) S. Yamada, M. Konda, and T. Shioiri, *ibid.*, **1972**, 2215; *c*) H. Akimoto, K. Okamura, M. Yui, T. Shioiri, M. Kuramoto, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 2614 (1974); *d*) M. Konda, T. Shioiri, and S. Yamada, *ibid.*, **23**, 1025 (1975); *e*) *Idem*, *ibid.*, **23**, 1063 (1975).

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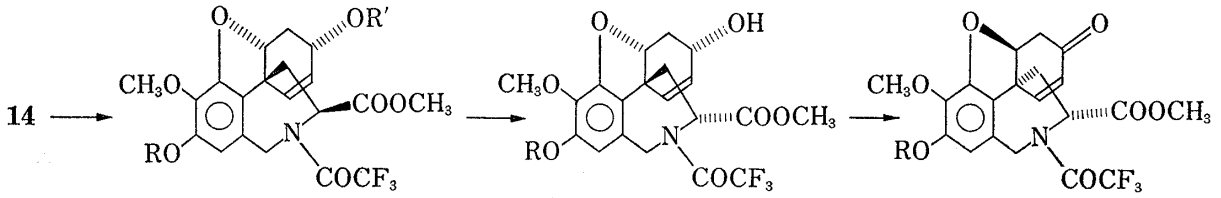
Among the several methods already described for the reductive elimination of phenolic hydroxyl group,[12,17] we selected the method of Birch reduction of diethyl phosphate derivative,[12] since galanthamine skeleton possesses carbon-carbon double bond. The reaction of **11** with diethyl phosphorochloridate in the presence of triethylamine afforded the phosphate ((+)-**12**) in 81% yield, accompanied by a small amount of its diastereomer (**13**). It was found that diastereomeric equilibrium ((+)-**12**: **13**≒13: 1 based on the isolated yield) could be easily attained with a catalytic amount of triethylamine in chloroform. The predominance of (+)-**12** over **13** in the equilibrium may be interpreted by a steric interactions between cyclohexenone moiety and methoxycarbonyl group in **13**, while no such interactions in (+)-**12** in their preferred conformations as shown in Chart 2.

Sodium borohydride reduction of (+)-**12** resulted in the formation of the alcohol (**14**). N-Methylation followed by amidation afforded the amide (**15**), which gave the acetate (**16**). Dehydration of **16** with phosphorus oxychloride in pyridine afforded the unstable amino nitrile (**17**), which was reduced with lithium aluminum hydride in tetrahydrofuran to 10-diethylphosphoroxygalanthamine (**18**).



19 : R′=$COCF_3$
20 : R′=H

21

(−)-**12**

R=$(C_2H_5O)_2PO$

Chart 3

Brief treatment of **18** with excess sodium in liquid ammonia at −78° afforded (+)-galanthamine ((+)-**4**), mp 127—129°, in 72% yield. Physical and spectral data of this sample agreed well with those of the natural (−)-galanthamine except the sign of optical rotation. Although the above result clearly shows that natural (−)-galanthamine can be obtained from unnatural D-tyrosine, we next investigated to find out a method to obtain natural (−)-galanthamine from natural L-tyrosine (**1**). As a result, it was found that treatment of **20**, obtained from **14** in 79% yield, with lithium diisopropylamide in tetrahydrofuran containing tetramethylethylenediamine and hexamethylphosphoramide at −20° under nitrogen afforded the C-6 epimer (**21**) in 11% yield. Oxidation of **21** with pyridinium chlorochromate[18] in methylene chloride afforded (−)-**12** as a glass of $[\alpha]_D^{22}$ −108° ($CHCl_3$) in 72% yield, corresponding to be 78% optically pure. This result means the enantiomeric transformation of (+)-**12** to (−)-**12**, and constitutes the formal total synthesis of natural (−)-galanthamine ((−)-**4**) from L-tyrosine (**1**).

17) *a*) W.H. Pirkle and J.L. Zabriskie, *J. Org. Chem.*, **29**, 3124 (1964); *b*) W.J. Musliner and J.W. Gates, Jr., *J. Am. Chem. Soc.*, **88**, 4271 (1966); *c*) M. Pailer and E. Goessinger, *Monatsh. Chem.*, **100**, 1613 (1969); *d*) F.J. Allan, G.G. Allan, T. Mattila, and P. Mauranen, *Acta. Chem. Scand.*, **23**, 1903 (1969); *e*) A.N. Cherkasov and K.K. Pivnitskii, *Zh. Org. Khim.*, **8**, 211 (1972) [*C.A.*, **77**, 101990*t* (1972)]; *f*) K. Clausz and H. Jensen, *Angew. Chem.*, **85**, 981 (1973); *g*) J.D. Weaver, E.J. Eisenbraun, and L.E. Harris, *Chem. Ind.* (London), **1973**, 187; *h*) J. Furukawa and K. Omura, *Tetrahedron Lett.*, **1973**, 2631; *i*) E. Vowinkel and C. Wolff, *Chem. Ber.*, **107**, 907 (1974); *j*) A. Jung and R. Engel, *J. Org. Chem.*, **40**, 244 (1975); *k*) H.C. Beyerman, E. Buurman, T.S. Lie, and L. Maat, *Rec. Trav. Chim.*, **95**, 43 (1976).

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Experimental[19]

L-(+)-N-(3,5-Dibenzyloxy-4-methoxy)benzyltyrosine Methyl Ester (8)——A mixture of 3,5-dibenzyloxy-4-methoxybenzaldehyde[20] (1.83 g, 5.30 mmol), L-tyrosine methyl ester[8b] (1.03 g, 5.30 mmol) and molecular sieves 4A (10 g) in MeOH (50 ml) was stirred at room temperature for 16 hr. After filtration, the filtrate was diluted with MeOH (50 ml). $NaBH_4$ (0.40 g, 10.6 mmol) was added to this mixture at 0° and the whole was stirred at room temperature for 3 hr. The reaction mixture was evaporated to dryness to leave a colorless oil, which was dissolved in a mixture of AcOEt (200 ml) and satd. aq. NaCl (50 ml). The aqueous layer was seperated and extracted with AcOEt (100 ml×2). The combined organic layer was washed with satd. aq. NaCl and dried over $MgSO_4$. Evaporation of the solvent gave **8** (2.34 g, y. 84%) as a colorless oil.

Neutral oxalate: Colorless powder of mp 181—184°, $[\alpha]_D^{20}$ +17° (c=0.99, DMSO). IR ν_{max}^{KBr} cm^{-1}: 3400, 3000—2400, 1737, 1592, NMR (CD_3OD-d_6-DMSO) δ: 3.0 (2H, m, $ArC\underline{H}_2$–CHN), 3.65 (3H, s, $CO_2C\underline{H}_3$), 3.79 (3H, s, $ArOC\underline{H}_3$), 3.86 (2H, s, Ar–$C\underline{H}_2$–N), 4.4 (1H, m, Ar–CH_2–$C\underline{H}$–N), 5.07 (4H, s, two $OC\underline{H}_2C_6H_5$), 6.70, 6.99 (4H, AB-type q, J=10 Hz, aromatic protons), 6.78 (2H, s, aromatic protons), 7.41 (10H, bs, aromatic protons), *Anal.* Calcd. for $C_{66}H_{68}N_2O_{16}$: C, 69.21; H, 5.98; N, 2.45. Found: C, 69.03; H, 5.95; N, 2.24.

L-(−)-N-(3,5-Dibenzyloxy-4-methoxy)benzyl-N-trifluoroacetyltyrosine Methyl Ester (9)——Trifluoroacetic anhydride (1.25 ml, 9 mmol) was added to a solution of **8** (obtained from **8**-neutral oxalate (1.85 g, 3.2 mmol)) in pyridine (10 ml) at −30°. After stirring at room temperature for 2 hr, the reaction mixture was taken up in AcOEt (50 ml). The AcOEt solution was washed successively with 10% aq. HCl, satd. aq. $NaHCO_3$, satd. aq. NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give **9** as a pale yellow oil (1.81 g, y. 90%). An analytical sample was prepared by preparative TLC (silica gel, ether–hexane (9: 1)) as a colorless oil of $[\alpha]_D^{20}$ −48.1° (c=1.19, MeOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745, 1690, NMR ($CDCl_3$) δ: ~3.2 (2H, m, Ar–$C\underline{H}_2$–CH–N), 3.7 (2H, m, Ar–$C\underline{H}_2$–N), 3.66 (3H, s, $COOC\underline{H}_3$), 3.86 (3H, s, Ar–$OC\underline{H}_3$), 5.01 (4H, s, two $OC\underline{H}_2C_6H_5$), 6.27 (2H, s, aromatic protons), 6.66 (4H, s, aromatic protons), 7.34 (10H, s, two $OCH_2C_6\underline{H}_5$), MS m/e: 623 (M^+). *Anal.* Calcd. for $C_{34}H_{32}F_3NO_7$: C, 64.65; H, 5.27; N, 2.22. Found: C, 64.89; H, 5.30; N, 2.03.

L-(−)-N-(3,5-Dihydroxy-4-methoxy)benzyl-N-trifluoroacetyltyrosine Methyl Ester (10)——Hydrogen gas was bubbled through a vigorously stirred mixture of **9** (1.81 g) and 10% Pd–C (0.1 g) in MeOH (50 ml) for 1 hr. Filtration of the reaction mixture followed by evaporation of the solvent *in vacuo* afforded **10** as a colorless liquid in quantitative yield. Purified sample by column chromatography showed $[\alpha]_D^{20}$ −61.7° (c=1.03, MeOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1740, 1688, NMR (CD_3OD) δ: ~3.3 (4H, m, Ar–$C\underline{H}_2$–N–CH–$C\underline{H}_2$–Ar), 3.63 (3H, s, $COOC\underline{H}_3$), 3.75 (3H, s, Ar–$OC\underline{H}_3$), 6.17 (2H, s, aromatic protons), 6.69, 6.88 (total 4H, AB-type q, J=9 Hz, aromatic protons), MS m/e: 443 (M^+). *Anal.* Calcd. for $C_{20}H_{20}F_3N \cdot 3/4H_2O$: C, 52.57; H, 4.77; N, 3.06. Found: C, 52.64; H, 4.80; N, 2.89.

(4a*R*,8a*R*,10*S*)-(+)-2-Hydroxy-3-methoxy-6-oxo-11-trifluoroacetyl-4a,5,9,10,11,12-hexahydro-6H-benzofuro[3a,3,2-*ef*][2]benzazepine-10-carboxylic Acid Methyl Ester (11)——A black mixture of **10** (1.33 g, 3.00 mmol) and $Mn(acac)_3$ (4.22 g, 12.0 mmol) in CH_3CN (200 ml) was heated to reflux under stirring for 2.5 hr. The black solid obtained by evaporation of the solvent was suspended in a mixture of ether (300 ml) and $CHCl_3$ (50 ml). This suspension was washed with 10% aq. HCl, H_2O, satd. aq. $NaHCO_3$, H_2O and satd. aq. NaCl successively and dried over $MgSO_4$. Evaporation of the solvent gave a brown oil, which was purified by column chromatography (silica gel) using a mixture of hexane and ether (1: 9) to give **11** (0.65 g, y. 49%) as a pale yellow caramel of $[\alpha]_D^{20}$ +125° (c=1.12, MeOH), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500, 1745, 1693, 1607, NMR ($CDCl_3$) δ: 2.2—3.3 (4H, m, $C\underline{H}_2$–CH–N, CH–$C\underline{H}_2$–CO), 3.77 (3H, s, $COOC\underline{H}_3$), 3.92 (3H, s, Ar–$OC\underline{H}_3$), 4.70 (2H, bs, $ArC\underline{H}_2$–CO), 4.4—5.4 (2H, m, N–$C\underline{H}$–CH_2, $C\underline{H}$–CH_2–CO), 5.8 (1H, bs, Ar–$O\underline{H}$), 6.01 (1H, d, J=10 Hz, CH=C$\underline{H}$–CO), 6.24 (1H, m, $C\underline{H}$=CH–CO), 6.32 (1H, s, Ar–$\underline{H}$). MS m/e: 441 (M^+). *Anal.* Calcd. for $C_{20}H_{18}F_3NO_7$: C, 54.42; H, 4.11; N, 3.17. Found: C, 54.08; H, 4.49; N, 3.15.

(4a*R*,8a*R*,10*S*)-(+)-2-Diethylphosphoroxy-3-methoxy-6-oxo-11-trifluoroacetyl-4a,5,9,10,11,12-hexahydro-6H-benzofuro[3a,3,2-*ef*][2]benzazepine-10-carboxylic Acid Methyl Ester ((+)-12)——A solution of **11** (0.57 g, 1.29 mmol), diethyl phosphorochloridate (0.5 ml) and Et_3N (0.5 ml) in $CHCl_3$ (30 ml) was stirred at room temperature overnight. The reaction mixture was washed successively with 10% aq. HCl, satd. aq. $NaHCO_3$, and satd. aq. NaCl. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give a yellow oil. Purification by silica gel column chromatography using AcOEt gave (+)-**12** (0.60 g, y. 81%) as a pale yellow glass of $[\alpha]_D^{22}$ +138° (c=1.1, $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1747, 1695, NMR ($CDCl_3$) δ: 1.34 (6H,

19) All melting points are not corrected. Optical rotations were taken with a Yanaco Photo Direct Reading Polarimeter, Model OR-50. Infrared (IR) spectra were taken with a Jasco Infrared Spectrometer Model DS-402G. Nuclear magnetic resonance (NMR) spectra were taken with a JNM-PS 100 Spectrometer operating at 100 MHz. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad singlet. Mass spectra (MS) were taken with a JEOL-01 SG-2 Mass Spectrometer.

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t, J=7 Hz, two $OCH_2C\underline{H}_3$), 2.0—3.3 (4H, m, $C\underline{H}_2$–CH–N, CH–$C\underline{H}_2$–CO), 3.77 (3H, s, $COOC\underline{H}_3$), 3.90 (3H, s, Ar–$OC\underline{H}_3$), 4.2 (4H, m, two $CH_3C\underline{H}_2OP$), 4.78 (2H, bs, Ar–$C\underline{H}_2$–N), 4.9—5.4 (2H, m, N–C<u>H</u>–CH_2, O–C<u>H</u>–CH_2–CO), 6.05 (1H, d, J=11 Hz, CH=C<u>H</u>–CO), 6.39 (1H, m, C<u>H</u>=CH–CO), 6.76 (1H, s, Ar–<u>H</u>), MS *m/e*: 577 (M^+). *Anal.* Calcd. for $C_{24}H_{27}O_{10}NF_3P$: C, 49.92; H, 4.71; N, 2.43. Found: C, 49.64; H, 4.78; N, 2.45.

(4a*S*,8a*S*,10*S*)-2-Diethylphosphoroxy-3-methoxy-6-oxo-11-trifluoroacetyl-4a,5,9,10,11,12-hexahydro-6H-benzofuro[3a,3,2-*ef*][2]benzazepine-10-carboxylic Acid Methyl Ester (13)——A solution of (+)-**12** (2.15 g) in $CHCl_3$ (50 ml) containing a drop of Et_3N was stirred at room temperature overnight. The reaction mixture was evaporated to dryness, and the residue was chromatographed on silica gel (300 g). Elution with AcOEt–ether (1: 1) afforded **13** (0.14 g) as a caramel of IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1742, 1695, NMR ($CDCl_3$) δ: 1.37 (6H, t, J 7 Hz, two $OCH_2C\underline{H}_3$), 1.8—3.5 (4H, m, $C\underline{H}_2$–CH–N, CH–$C\underline{H}_2$–CO), 3.78 (3H, s, $COOC\underline{H}_3$), 3.88 (3H, s, Ar–$OC\underline{H}_3$), 4.2 (4H, m, two $CH_3C\underline{H}_2OP$), 4.75 (2H, m, Ar–$C\underline{H}_2$–N), 5.94 (1H, d, J=10 Hz, CH=C<u>H</u>–CO), 6.38 (1H, m, C<u>H</u>=CH–CO), 6.69 (1H, s, Ar–<u>H</u>), MS *m/e*: 577 (M^+). The starting material ((+)-**12**) (1.80 g) was recovered unchanged.

(4a*R*,6*S*,8a*R*,10*S*)-(+)-2-Diethylphosphoroxy-3-methoxy-6-hydroxy-4a,5,9,10,11,12-hexahydro-6H-benzofuro[3a,3,2-*ef*][2]benzazepine-10-carboxylic Acid Methyl Ester (14)——To a stirred solution of (+)-**12** (0.58 g, 1.0 mmol) in MeOH (30 ml) was added $NaBH_4$ (0.08 g, 2.1 mmol) at −20°. After allowing to stand at room temperature for 3 hr, the reaction mixture was evaporated to dryness *in vacuo*. The residue was taken up in a mixture of $CHCl_3$ and water, and the organic layer was extracted with 10% aq. HCl. The acidic aqueous extracts were combined, made slightly alkaline with satd. aq. $NaHCO_3$, and the whole was extracted with $CHCl_3$. The $CHCl_3$ extracts were combined, washed with satd. aq. NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was purified by preparative TLC (silica gel, $CHCl_3$–MeOH (15: 1)) followed by recrystallization from cyclohexane to give **14** (99 mg, y. 21%) as colorless small cubes of mp 122—124°, $[\alpha]_D^{20}$ +45.1° (c=0.82, $CHCl_3$), IR ν_{max}^{KBr} cm^{-1}: 3400, 3270, 1746, NMR ($CDCl_3$) δ: 1.36 (6H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.67 (3H, s, $COOC\underline{H}_3$), 3.86 (3H, s, Ar–$OC\underline{H}_3$), 3.93 (2H, s, Ar–$C\underline{H}_2$–N), 4.2 (4H, m, two $CH_3C\underline{H}_2OP$), —6.0 (2H, m, C<u>H</u>=C<u>H</u>–CHOH), 6.60 (1H, s, Ar–<u>H</u>), MS *m/e*: 483 (M^+). *Anal.* Calcd. for $C_{22}H_{30}NO_9P$: C, 54.65; H, 6.26; N, 2.90. Found: C, 54.61; H, 6.55; N, 3.11.

(4a*R*,6*S*,8a*R*,10*S*)-(+)-2-Diethylphosphoroxy-3-methoxy-6-hydroxy-11-methyl-4a,5,9,10,11,12-hexahydro-6H-benzofuro[3a,3,2-*ef*][2]benzazepine-10-carboxamide (15)——A mixture of **14** (327 mg), 35% aq. formaline (2 ml), paraform (0.1 g) and 85% aq. formic acid (2 ml) in MeOH (50 ml) was heated under reflux for 24 hr and then condensed *in vacuo* to a small volume. The residue was basified with 10% aq. Na_2CO_3, and the whole was extracted with $CHCl_3$. The extracts were combined, washed with satd. aq. NaCl, dried over $MgSO_4$, and then evaporated *in vacuo* to dryness. The residue was dissolved in MeOH (30 ml) and the whole was saturated with NH_3 at 0°. The resulting solution was allowed to stand in a tightly stoppered flask at room temperature for 2 days, and then evaporated to dryness. The residual yellow oil was purified by preparative TLC (silica gel, $CHCl_3$–MeOH (15: 1)) to give **15** (121 mg, y. 37%) as a pale yellow oil of $[\alpha]_D^{20}$ +40.2° (c=1.0, $CHCl_3$), IR ν_{max}^{film} cm^{-1}: 1690, 1620, MS *m/e*: 482 (M^+).

Picrate: mp 126—129°. *Anal.* Calcd. for $C_{28}H_{34}N_5O_{15}P \cdot H_2O$: C, 46.12; H, 4.85; N, 9.37. Found: C, 45.72; H, 4.53; N, 9.43.

(4a*R*,6*S*,8a*R*,10*S*)-(+)-2-Diethylphosphoroxy-3-methoxy-6-acetoxy-11-methyl-4a,5,9,10,11,12-hexahydro-6H-benzofuro[3a,3,2-*ef*][2]benzazepine-10-carboxamide (16)——A solution of **15** (114 mg, 0.237 mmol), and Ac_2O (1 ml) in pyridine (5 ml) was allowed to stand at room temperature overnight. The reaction mixture was dissolved in $CHCl_3$ and the whole was shaken with excess satd. aq. $NaHCO_3$. The organic layer was separated, washed with satd. aq. $CuSO_4$, satd. aq. NaCl, dried over $MgSO_4$, and evaporated *in vacuo* to dryness. The residue was purified by preparative TLC (silica gel, $CHCl_3$–MeOH (20: 1)) to give **16** (111 mg, y. 89%) as an oil of $[\alpha]_D^{20}$ +16.1° (c=1.0, $CHCl_3$), NMR ($CDCl_3$) δ: 1.36 (6H, t, J=7 Hz, two OCH_2-$C\underline{H}_3$), 1.97 (3H, s, $OCOC\underline{H}_3$), 2.13 (3H, s, N–$C\underline{H}_3$), 3.93 (3H, s, Ar–$OC\underline{H}_3$), 4.2 (4H, m, two $CH_3C\underline{H}_2OP$), 5.26 (1H, m, C<u>H</u>–OAc), 5.7—6.2 (2H, m, C<u>H</u>=C<u>H</u>), 6.53 (1H, s, Ar–<u>H</u>), MS *m/e*: 524 (M^+).

Picrate: mp 123—125°. *Anal.* Calcd. for $C_{30}H_{36}N_5O_{16}P$: C, 47.81; H, 4.82; N, 9.42. Found: C, 47.75; H, 4.97; N, 9.43.

(4a*R*,6*S*,8a*R*)-(+)-2-Diethylphosphoroxy-3-methoxy-6-hydroxy-11-methyl-4a,5,9,10,11,12-hexahydro-6H-benzofuro[3a,3,2-*ef*][2]benzazepine (18)——A solution of **16** (380 mg, 0.725 mmol), pyridine (2 ml), $POCl_3$ (0.75 ml, 8 mmol) in $CHCl_3$ (30 ml) was heated under reflux for 15 min. The yellow solution was diluted with $CHCl_3$ (50 ml) and the whole was washed with satd. aq. $NaHCO_3$, satd. aq. $CuSO_4$, and satd. aq. NaCl. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to dryness. The residue was dissolved in THF (30 ml). $LiAlH_4$ (0.3 g, 8 mmol) was added to this solution at −20°, and the whole was stirred at 0° for 30 min. After the addition of MeOH (5 ml), the reaction mixture was evaporated *in vacuo* to a small volume, and the residue was partitioned between $CHCl_3$ and satd. aq. $NaHCO_3$. The organic layer was washed with satd. aq. NaCl, dried over $MgSO_4$, and evaporated *in vacuo* to dryness. The residue was purified by preparative TLC (silica gel, $CHCl_3$–MeOH (15: 1)) to give **18** (134 mg, y. 42%) as an oil of $[\alpha]_D^{20}$ +61.4° (c=1.0, $CHCl_3$), NMR ($CDCl_3$) δ: 1.36 (6H, t, J=7 Hz, two $OCH_2C\underline{H}_3$), 2.37 (3H, s, N–$C\underline{H}_3$), 3.89 (3H, s, Ar–$OC\underline{H}_3$), 4.2 (4H, m, two $CH_3C\underline{H}_2OP$), 5.98 (2H, s, C<u>H</u>=C<u>H</u>), 6.57 (1H, s, Ar–<u>H</u>), MS *m/e*: 439 (M^+).

Picrate: mp 135—138°. *Anal.* Calcd. for $C_{27}H_{33}N_4O_{14}P \cdot 3/2H_2O$: C, 46.62; H, 5.31; N, 8.06. Found: C, 46.71; H, 5.29; N, 7.99.

(+)-Galanthamine ((+)-4)——Sodium metal (46 mg, 2 mmol) was added to liquid NH_3 (*ca.* 30 ml) at −78°, and the whole was stirred for 20 min. A solution of **18** (57 mg, 0.13 mmol) in THF (10 ml) was added dropwise, and the reaction mixture was stirred at −78° for 10 min. Excess NH_4Cl was added to discolor the solution, and the whole was stirred at room temperature to evaporate NH_3. The residue was partitioned between $CHCl_3$ and H_2O. The organic layer was washed with satd. aq. NaCl, dried over $MgSO_4$, and evaporated *in vacuo* to dryness. The residue was purified by preparative TLC (silica gel, $CHCl_3$–MeOH (10: 1)) followed by recrystallization from ether to give (+)-**4** (24 mg, y. 72%) as colorless needles of mp 127—129°, $[\alpha]_D^{26}$ +116° (c=1.0, EtOH) (reported mp 126—127°,[21a] 127—129°[21b] $[\alpha]_D$ −118.8°,[21a] −122°[21b] for natural (−)-galanthamine). This sample showed IR and NMR spectra identical to those of natural (−)-galanthamine. MS *m/e*: 287 (M^+). *Anal.* Calcd. for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.08; H, 7.42; N, 4.97.

(4a*R*,6*S*,8a*R*,10*S*)-(+)-2-Diethylphosphoroxy-3-methoxy-6-trifluoroacetoxy-11-trifluoroacetyl-4a,5,9,10,-11,12-hexahydro-6H-benzofuro[3a,3,2-*ef*][2]benzazepine-10-carboxylic Acid Methyl Ester (19)——To a stirred solution of **14** (112 mg, 0.232 mmol) in pyridine (20 ml) was added trifluoroacetic anhydride (0.1 ml, 2.8 mmol) at −40°. The whole was allowed to stand at room temperature for 30 min, and then partitioned between AcOEt and 10% aq. HCl. The organic layer was separated, washed with 10% aq. HCl, satd. aq. $NaHCO_3$, satd. aq. NaCl, dried over $MgSO_4$, and evaporated *in vacuo* to dryness. The oily residue was purified by preparative TLC (silica gel, $CHCl_3$–MeOH (20: 1)) to give **19** (114 mg, y. 92%) as a colorless oil of $[\alpha]_D^{20}$ +46.6° (c=1.0, $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1780, 1751, 1697, 1605, MS *m/e*: 675 (M^+). This sample was used for the next step without further purification.

(4a*R*,6*S*,8a*R*,10*S*)-(+)-2-Diethylphosphoroxy-3-methoxy-6-hydroxy-11-trifluoroacetyl-4a,5,9,10,11,12-hexahydro-6H-benzofuro[3a,3,2-*ef*][2]benzazepine-10-carboxylic Acid Methyl Ester (20)——A solution of **19** (74.7 mg) in a mixture of 5% aq. $KHCO_3$ (3 ml) and MeOH (20 ml) was stirred at room temperature for 20 min. The solution was neutralized with 5% aq. citric acid, and then evaporated *in vacuo* to a small volume. The residue was partitioned between $CHCl_3$ and satd. aq. NaCl. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to dryness. The residue was purified by preparative TLC (silica gel, $CHCl_3$–MeOH (15: 1)) to give **20** (55.3 mg, y. 86%) as a colorless oil of $[\alpha]_D^{20}$ +39.2° (c=1.0, $CHCl_3$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1750, 1699, 1603, NMR ($CDCl_3$) δ: 1.37 (6H, t, J=7 Hz, two $C\underline{H}_3CH_2O$), 3.74 (3H, s, $COOC\underline{H}_3$), 3.91 (3H, s, Ar–$OC\underline{H}_3$), 4.2 (4H, m, two $CH_3C\underline{H}_2OP$), 5.30 (1H, d, J=10 Hz, $C\underline{H}$=CH–CHOH), 6.04 (1H, double d, J=10 and 5 Hz, CH=C$\underline{H}$–CHOH), 6.63 (1H, s, Ar–$\underline{H}$), MS *m/e*: 579 (M^+). *Anal.* Calcd. for $C_{24}H_{29}F_3NO_{10}P$: C, 49.74; H, 5.04; N, 2.42. Found: C, 49.48; H, 5.16; N, 2.50

(4a*R*,6*S*,8a*R*,10*R*)-2-Diethylphosphoroxy-3-methoxy-6-hydroxy-11-trifluoroacetyl-4a,5,9,10,11,12-hexahydro-6H-benzofuro[3a,3,2-*ef*][2]benzazepine-10-carboxylic Acid Methyl Ester (21)——To a stirred solution of **20** (302 mg) in THF (10 ml) containing tetramethylethylenediamine (1 ml), hexamethylphosphoramide (1 ml) and a small amount of *o*-phenanthroline was added a solution of lithium diisopropylamide in THF at −20° under N_2 until the solution became colored. After 5 min, 5% aq. citric acid (6 ml) was added, and the resulting mixture was allowed to warm to room temperature. AcOEt (50 ml) was added to this mixture, and the whole was shaken with 5% aq. citric acid (50 ml). The organic layer was separated, washed with satd. aq. $NaHCO_3$, satd. aq. NaCl, dried over $MgSO_4$, and evaporated *in vacuo* to dryness. The residue was purified by preparative TLC (silica gel, $CHCl_3$–MeOH (20: 1)) followed by column chromatography (silica gel, $CHCl_3$–MeOH (100: 1)) to give **21** (32 mg, y. 11%) as a colorless oil of IR ν_{max}^{film} cm^{-1}: 1750, 1700. This sample was used for the next step without further purification.

(4a*S*,8a*S*,10*R*)-(−)-2-Diethylphosphoroxy-3-methoxy-6-oxo-11-trifluoroacetyl-4a,5,9,10,11,12-hexahydro-6H-benzofuro[3a,3,2-*ef*][2]benzazepine-10-carboxylic Acid Methyl Ester ((−)-12)——To a stirred solution of **21** (32 mg, 0.055 mmol) in CH_2Cl_2 (10 ml) was added pyridinium chlorochromate (*ca.* 0.1 g, *ca.* 0.47 mmol) at room temperature. After 3 hr, the reaction mixture was directly subjected to preparative TLC (silica gel, AcOEt) to give (−)-**12** (23 mg, 72%) of $[\alpha]_D^{22}$ −108° (c=1.1, $CHCl_3$). Spectral data and *Rf* values on TLC were identical with those of (+)-**12** described above.

Acknowledgement The authors are grateful to Dr. H. Irie, Kyoto University, for a gift of natural (−)-galanthamine. They are also indebted to Takeda Science Foundation for partial support of this research.

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