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FURTHER STUDIES ON A SAMARIUM DIIODIDE-PROMOTED REDUCTIVE CARBON-NITROGEN BOND CLEAVAGE RECTION: SYNTHESIS OF (+)-APHANORPHINE†

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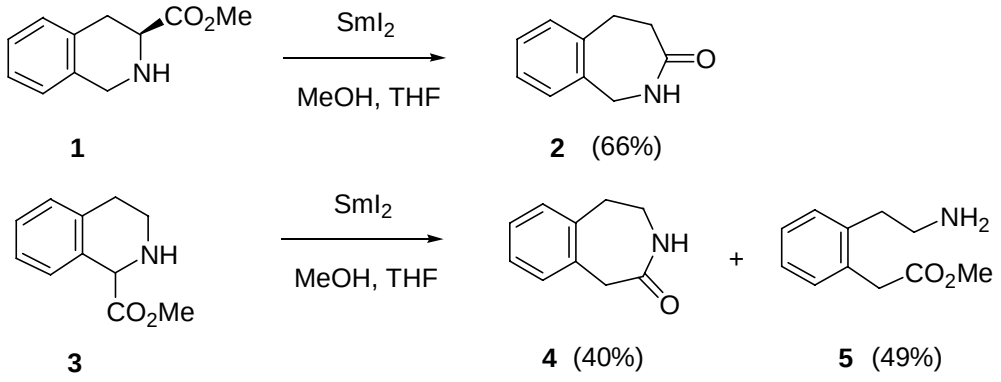
Abstract – Samarium diiodide-promoted carbon-nitrogen bond cleavage reaction was applied to the 1,2,3,4-tetrahydroisoquinoline derivatives bearing an ester group at the 1- or 3-position to give the corresponding benzazepinones. Synthesis of (+)-aphanorphine was established by utilizing this reaction, as a key step.

Recently, we have developed a samarium diiodide-promoted reductive deamination reaction of α-amino esters.[1] By application of this reaction to proline derivatives, the corresponding δ-lactams were obtained in good yields, where a carbon-nitrogen bond cleavage reaction, followed by a recyclization of the resulting amino-esters occurred, simultaneously. This reaction seemed to be a useful synthetic tool for a construction of ring-enlarged lactams, and we successfully applied this strategy to the synthesis of various types of biologically active compounds including natural products.[2] To extend the usefulness of this strategy, we are interested in a conversion of 1,2,3,4-tetrahydroisoquinoline derivatives having an ester group at the 1- or 3-position to the corresponding benzazepinones.

Thus, (3*S*)-3-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (**1**)[3] was treated with samarium diiodide in THF-HPMA in the presence of methanol as the proton source to give the corresponding lactam (**2**) in 66% yield. Similar reaction of 1-methoxycarbonyl-1,2,3,4-tetrahydroisoquinoline (**3**)[3] also provided the desired lactam (**4**) together with the ring-opened primary amine (**5**), in 40 and 49% yields, respectively. The later (**5**) could be converted to the former (**4**) by heating in benzene or by treatment with sodium methoxide.



Scheme 1. Samarium diiodide-promoted reductive deamination of isoquinoline derivatives.

Since transformation of the isoquinoline derivatives having an ester group at the 1- or 3-position to the corresponding lactams was found to be successful by application of a samarium diiodide-promoted reductive carbon-nitrogen bond cleavage reaction, we planned to utilize this strategy to the synthesis of (-)-aphanorphine, isolated from the freshwater blue-green alga, *Aphanizomenon flosaquae*,[4] aiming at searching new analgesic candidates. Our synthetic plan was based on an intramolecular cyclization[5] of a seven-membered lactam, probably derived from a corresponding 1-carboalkoxy-1,2,3,4-tetrahydro-isoquinoline derivative, as depicted in Figure 1.

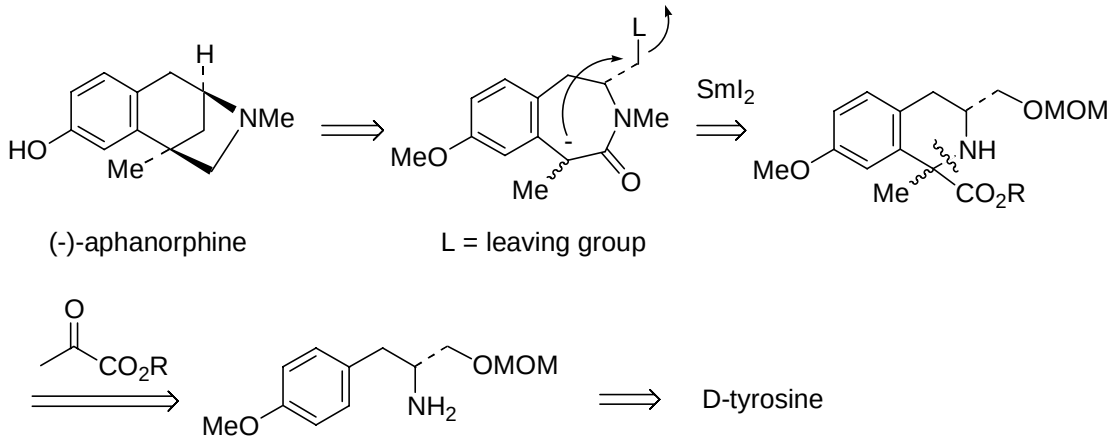
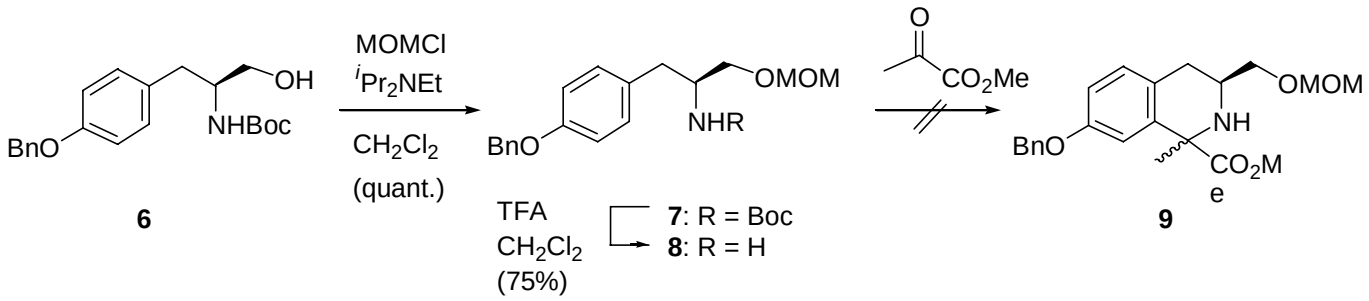


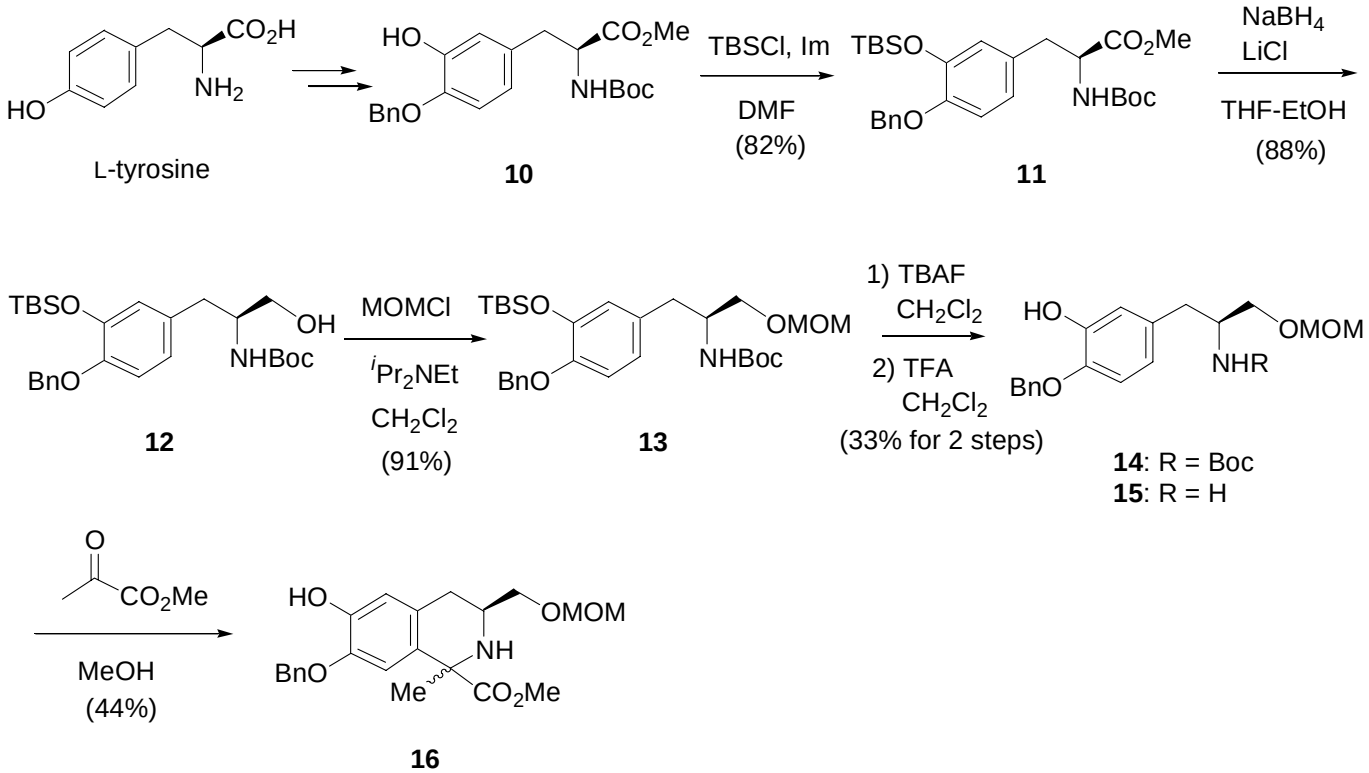
Figure 1. Synthetic plan for (-)-aphanorphine.

In this synthesis, we decided to exploit a readily accessible (*S*)-tyrosine derivative as a starting material to synthesize (+)-aphanorphine, the enantiomer of natural aphanorphine,[6] since the use of the antipodal starting material, (*R*)-tyrosine, should lead to the synthesis of the natural product, if this synthetic strategy can be established.



Scheme 2

First, we attempted to prepare 1-methoxycarbony-1-methyl-1,2,3,4-tetrahydroisoquinoline derivative (**9**) starting from the known L-tyrosinol (**6**)[7] via **7** and **8**, however, a cyclization of **8** with methyl pyruvate could not give **9** under various reaction conditions, unfortunately. We thought that the failed cyclization is probably due to low reactivity of the aromatic ring. (Scheme 2)

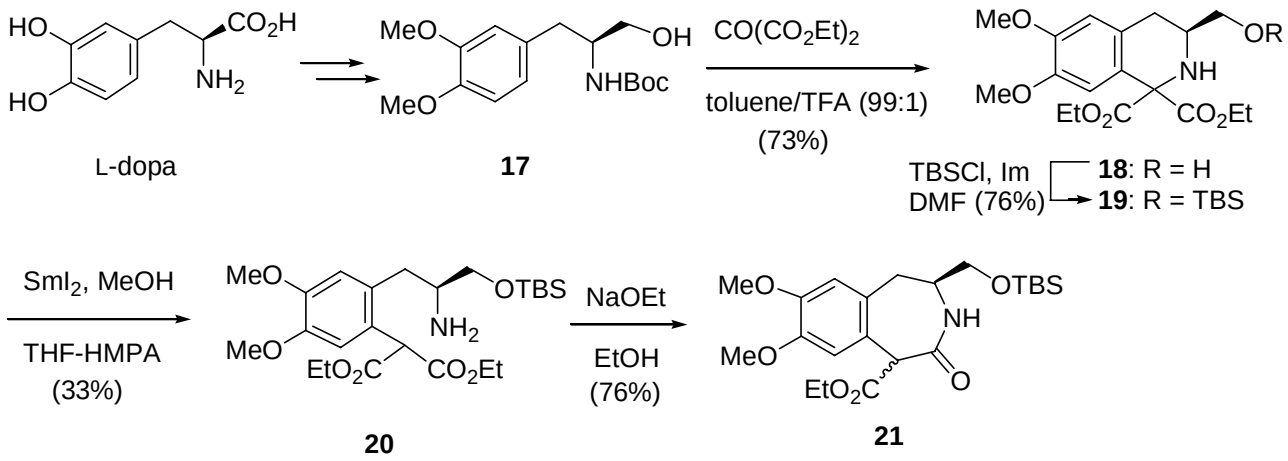


Scheme 3. Preparation of the 1-methy-1,2,3,4-tetrahydroisoquinoline derivative.

Thus, L-dopa analogue was chosen as the starting material, in order to activate reactivity of the aromatic ring and due to its accessibility, although the final product would be an antipodal form of the natural compound. The ester (**10**), prepared from L-tyrosine according to the literature known procedure,[8] was converted to the alcohol (**12**), *via* the silyl ether (**11**). After protection of **12** with methoxymethyl chloride, the resulting methoxymethyl ether (**13**) was treated with tetrabutylammonium fluoride to afford the phenolic compound (**14**), which on further treatment with trifluoroacetic acid, gave the primary amine (**15**). Condensation of **15** with methyl pyruvate in methanol at rt furnished the desired isoquinoline derivative (**16**) in 44% yield. (Scheme 3)

However, the synthetic procedure for **16** requires long reaction sequences, and the overall yield was not high enough for its further conversion to the target compound. Therefore, we turned our attention on the synthesis of the diester as follows.

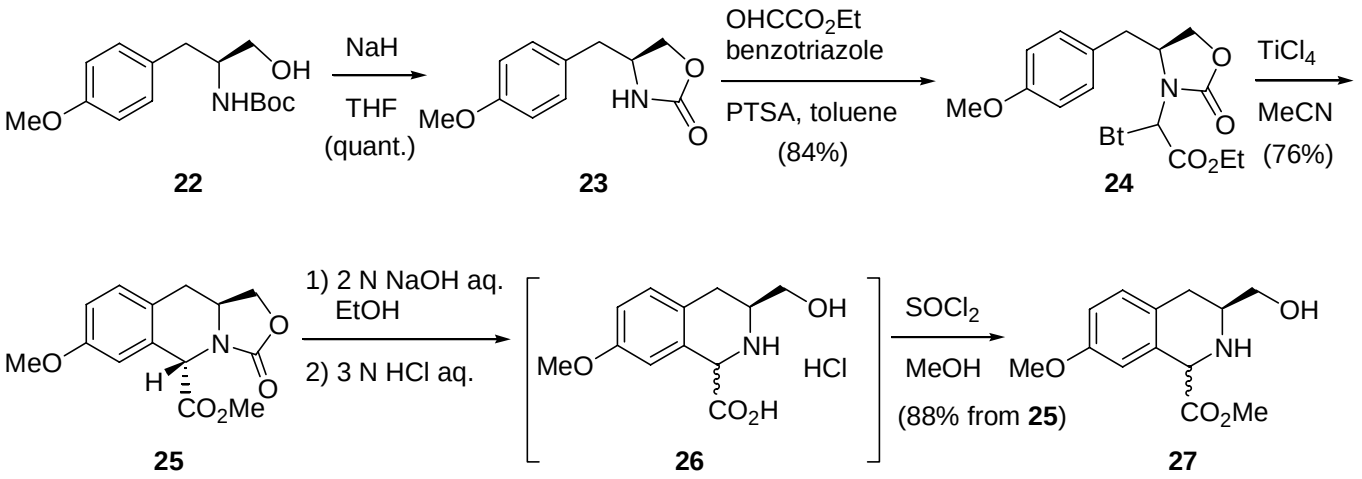
The known primary alcohol (**17**),[9] readily accessible from L-dopa, was treated with diethyl ketomalonate in toluene-trifluoroacetic acid (99:1) at 85°C to give the 1,2,3,4-tetrahydroisoquinoline derivative (**18**),[10] in 73% yield, which was further converted to its *tert*-butyldimethylsilyl ether (**19**), in 76% yield. Reductive deamination of **19** with samarium diiodide in THF-HMPA in the presence of methanol as the proton source provided the ring-opened amine (**20**) and the recovered starting material (**19**), in 33 and 33% yields, respectively. The amine (**20**) was successfully transformed to the desired lactam (**21**) by treatment with sodium ethoxide in ethanol in 76% yield. (Scheme 4)



Scheme 4. Preparation of the benzazepinone compound by a reductive deamination with SmI_2.

Although the synthetic procedure for the desired benzazepinone (**21**) could be established as above, the conversion yield of **19** to **20** was not satisfactory. Moreover, it was found that the reaction conditions for the cyclization of **17** leading to **18** could not be applied to tyrosine derivatives, unfortunately, under the various reaction conditions attempted. Thus, we decided to adopt an alternative synthetic pathway for (+)-aphanorphine.

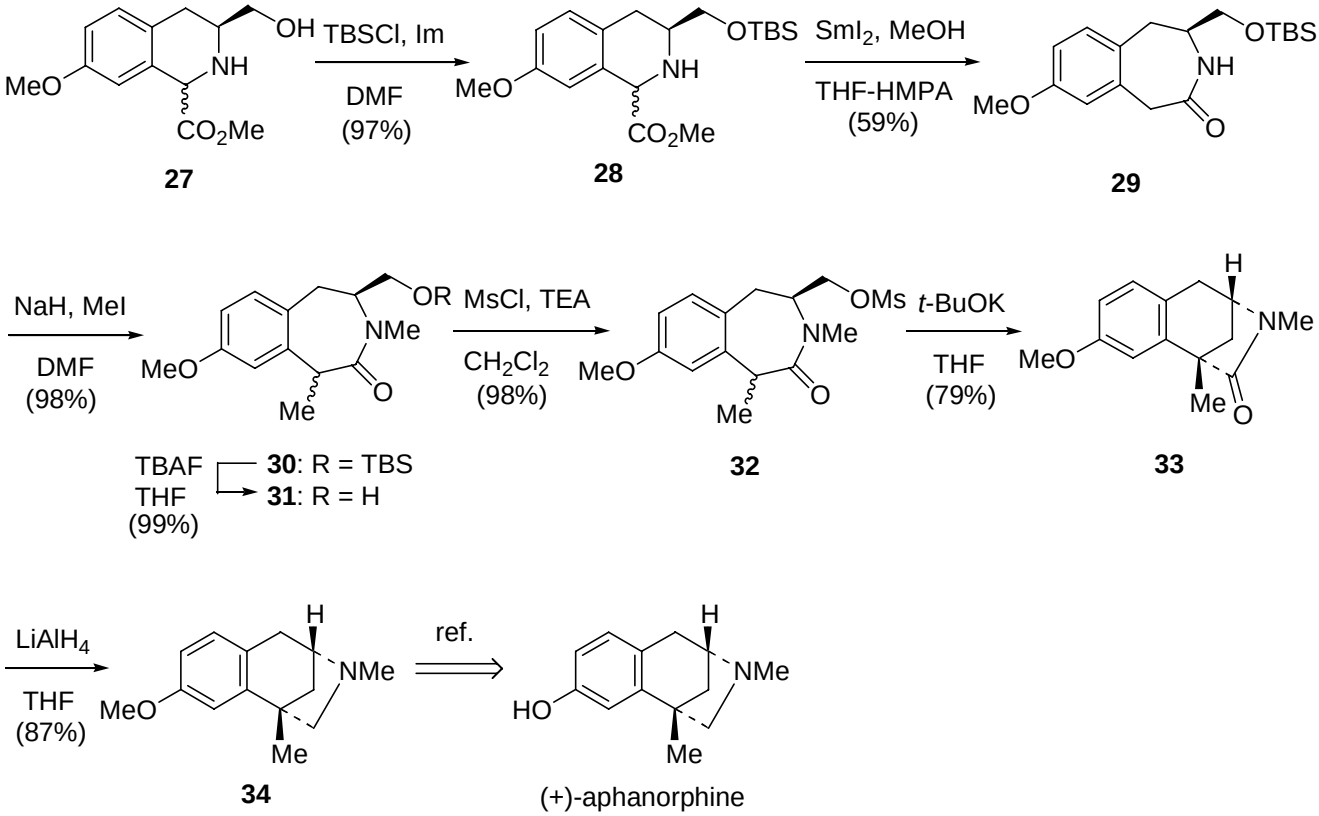
The known compound (**22**)[11] was converted to the oxazolidinone (**23**), which on treatment with ethyl glyoxylate and benzotriazole in the presence of *p*-toluenesulfonic acid in refluxing toluene afforded the ester (**24**). Reaction of **24** with $TiCl_4$ in acetonitrile[12] afforded the corresponding isoquinoline derivative (**25**),[13] as a single stereoisomer, in 76% yield. Hydrolysis of **25** with 2 N NaOH, followed by acidification with 3 N HCl gave the acid (**26**), which, without purification was esterified with thionyl chloride in methanol to provide the ester (**27**) as an inseparable diastereoisomeric mixture, in a ratio of *ca*. 3:1, in 88% yield from **25**. In this conversion, partial epimerization at the 1-position obviously occurred, however, this stereogenic center will be removed at the later stage of this synthesis. Therefore, the ester (**27**) was used without separation in the next step. (Scheme 5)



Scheme 5

After silylation of **27** with *tert*-butyldimethylsilyl chloride and imidazole in the usual manner, the resulting silyl derivative (**28**) was subjected to the samarium diiodide-promoted ring expansion reaction in THF-HMPA in the presence of methanol as the proton source to furnish the desired benzazepinone (**29**), as the sole product, in 59% yield. Methylation of **29** with iodomethane in the presence of sodium hydride in

DMF afforded the *N*- and *C*-methylated lactam (**30**) in 98% yield. Deprotection of the silyl group of **30** with tetrabutylammonium fluoride gave the alcohol (**31**) as a mixture of the diastereomers in a ratio of 3.3:1. The stereochemistry of the *C*-methyl group of the major product would be assumed to *R* configuration by comparison of its ^{1}H NMR data with that of the racemic compound.[6m] The primary alcohol (**31**) was further converted to the mesylate (**32**) by treatment with methanesulfonyl chloride and triethylamine in 98% yield. Finally, treatment of **32** with potassium *tert*-butoxide in refluxing THF gave the amide (**33**), in 79% yield, which on reduction with lithium aluminum hydride provided (-)-8-*O*-methylaphanorphine (**34**). The spectroscopic data for the synthesized compound (**34**) including specific optical rotation {$[\alpha]_D$ –9.72 (c=0.67, $CHCl_3$); lit.,[12] $[\alpha]_D$ –7.40 (c=0.35, $CHCl_3$)} were identical with those reported.[13] Since (-)-**34** was already converted to (+)-aphanorphine (**35**) by a demethylation,[14] this synthesis constitutes its total synthesis. (Scheme 6)



Scheme 6

In summary, a samarium diiodide-promoted reductive deamination reaction was successfully applied to 1,2,3,4-tetrahydroisoquinoline derivatives providing the corresponding ring expanded seven-membered lactams. This strategy was also utilized in the synthesis of aphanorphine. Based on these results, the strategy developed here would provide a useful tool for the construction of nitrogen containing heterocycles including natural products.

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.

1,2,4,5-Tetrahydro-3*H*-2-benzazepin-3-one (2): To a stirred solution of SmI_2 (0.2 M in THF, 11.8 mL, 2.4 mmol) containing HMPA (0.41 ml, 2.35 mmol) was added a solution of the ester (**1**) (0.09 g, 0.47 mmol) in THF (2.0 mL) under argon at 0°C. After addition of MeOH (0.05 mL, 1.18 mmol), the resulting mixture was stirred at rt for 12 h. The mixture was treated with saturated $NaHCO_3$ solution, and filtered through a Celite pad to remove insoluble materials. The filtrate was concentrated to give a residue, which was taken up with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (1:5) afforded the lactam (**2**) as a pale yellowish solid; mp 127-128 °C; IR (thin film) 3520, 3220, 2920, 2370, 1650 cm^{-1}; ^{1}H-NMR δ 2.74-2.84 (m, 2H), 3.05-3.13 (m, 2H), 4.35 (d, *J* = 5.5 Hz, 2H), 7.10-7.30 (m, 4H); EIMS (*m/z*) 161 (M^+); HRMS calcd for $C_{10}H_{11}NO$ (M^+) 161.0841, found 161.0864.

1,3,4,5-Tetrahydro-2*H*-3-bezazepin-2-one (4) and methyl [2-(2-aminoethyl)phenyl]acetate (5): Reductive deamination of the ester (**3**) (0.06 g, 0.31 mmol) was carried out by the same procedure as for the preparation of **2** using SmI_2 (0.2 M in THF, 7.8 mL, 1.6 mmol) and HMPA (0.27 mL, 1.55 mmol) to

give **4** (0.02 g, 40%) as a yellowish solid, and **5** (0.03 g, 49%) as a yellowish oil; **4:** mp 150.5-151.0 °C; IR (thin film) 3175, 2920, 1655, 1480, 1415 cm^{-1}; ^{1}H-NMR δ 3.05-3.16 (m, 2H), 3.50-3.61 (m, 2H), 5.83 (brs, 2H), 6.65 (brs, 1H), 7.08-7.22 (m, 4H); ^{13}C-NMR δ 33.3, 41.3, 42.4, 125.8, 127.2, 129.8, 130.4, 131.7, 136.8, 173.8; EIMS (*m/z*) 161 (M^+); HRMS calcd for $C_{10}H_{11}NO$ (M^+) 161.0841, found 161.0846. **5:** IR (thin film) 3450, 3020, 2915, 1720, 1615 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 3.23 (dd, *J* = 5.6, 8.9 Hz, 2H), 3.37 (dd, *J* = 5.6, 8.9 Hz, 2H), 3.64 (s, 3H), 3.74 (s, 2H), 6.37 (brs, 2H), 7.14-7.23 (m, 3H), 7.29-7.32 (m, 1H); ^{13}C-NMR (68 MHz, $CDCl_3$) δ 30.3, 38.8, 41.0, 52.8, 127.5, 128.2, 130.2, 130.9, 132.6, 135.4, 173.1; EIMS (*m/z*) 193 (M^+); HRMS calcd for $C_{11}H_{15}NO_2$ (M^+) 193.1103, found 193.1082.

(2*S*)-*N*-(*tert*-Butoxycarbonyl)-1-methoxymethoxy-3-(4-benzyloxyphenyl)-2-propylamine (7): A solution of **6** (0.08 g, 0.21 mmol), ^{i}Pr_2NEt (0.11 mL, 0.64 mmol), and MOMCl (0.49 mL, 0.04 mmol) in CH_2Cl_2 (3.0 mL) was stirred at ambient temperature for 12 h. The solution was treated with saturated NH_4Cl solution, and extracted with CH_2Cl_2. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (1:1) afforded the ether (**7**) (0.09 g, 100%) as a colorless solid; mp 77-79 °C; IR (KBr) 3355, 2955, 1688, 1512 cm^{-1}; ^{1}H-NMR δ 1.33 (s, 9H), 2.63-2.79 (m, 2H), 3.28 (s, 3H), 3.37 (d, *J* = 3.9 Hz, 2H), 3.83 (brs, 1H), 4.53 (s, 2H), 4.72 (brs, 1H), 4.94 (s, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.27 (m, 5H); ^{13}C-NMR δ 27.7, 28.3, 37.0, 55.4, 58.3, 70.0, 96.8, 114.8, 127.4, 127.9, 128.5, 130.2, 130.3, 130.4, 137.1, 155.3, 157.4; EIMS (*m/z*) 401 (M^+); HRMS calcd for $C_{23}H_{31}NO_5$ (M^+) 401.2202, found 401.2209.

(2*S*)-1-Methoxymethoxy-3-(4-benzyloxyphenyl)-2-propylamine (8): To a solution of the ether (**7**) (3.89 g, 9.70 mmol) in CH_2Cl_2 (10.0 mL) was added TFA (7.47 mL, 97 mmol) at 0°C, and the resulting mixture was stirred for further 12 h at ambient temperature. After removal of the solvents, the residue was treated with 5% NH_4OH solution, and extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$:MeOH (4:1) afforded the amine (**8**) (2.20 g, 75%) as a pale yellowish oil; IR (thin film) 3375, 2925, 1610, 1510 cm^{-1}; ^{1}H-NMR δ 1.45 (brs, 2H), 2.50 (dd, *J* = 8.6, 13.5 Hz, 1H), 2.76 (dd, *J* = 5.1, 13.5 Hz, 1H), 3.13-3.26 (m, 1H), 3.32-3.45 (m, 1H), 3.40 (s, 3H), 3.55 (dd, *J* = 4.1, 9.4

Hz, 1H), 4.65 (s, 2H), 5.06 (s, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.35 (m, 5H); ^{13}C-NMR δ 39.8, 52.5, 55.3, 70.0, 72.6, 76.6, 114.8, 127.4, 127.9, 128.5, 130.2, 131.0, 137.1, 157.4; EIMS (*m/z*) 301 (M^+); HRMS calcd for $C_{18}H_{23}NO_3$ (M^+) 301.1678, found 301.1674.

Methyl *O*-benzyl-*N*-*tert*-butoxycarbonyl-3-(*tert*-butyldimethylsiloxy)-L-tyrosinate (11): To a stirred solution of the phenolic compound (**10**) (1.77 g, 4.41 mmol) in DMF (48.0 mL) containing imidazole (0.45 g, 6.62 mmol) was added TBSCl (1.00 g, 6.62 mmol) at 0°C, and the resulting mixture was stirred for further 12 h at rt. After treatment with water, the mixture was extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (3:1) afforded the silyl ether (**11**) (1.87 g, 82%) as a colorless oil; IR (thin film) 3440, 2955, 2930, 2857, 1745, 1716, 1500, 1365, 1250, 1217, 1168, 857, 840, 770 cm^{-1}; ^{1}H-NMR δ 0.11 (s, 6H), 0.91 (s, 9H), 1.41 (s, 9H), 2.97-3.10 (m, 2H), 3.70 (s, 3H), 4.49-4.60 (m, 1H), 4.94-5.02 (m, 1H), 5.06 (s, 2H), 6.82 (dd, *J* = 2.5, 8.1 Hz, 1H), 7.13 (brs, 1H), 7.29-7.42 (m, 5H). CIMS (*m/z*) 516 (M^++1); HRMS calcd for $C_{28}H_{42}NO_6Si$ (M^++1) 516.2781, found 516.2772.

***O*-Benzyl-*N*-*tert*-butoxycarbonyl-3-(*tert*-butyldimethylsiloxy)-L-tyrosinol (12):** To a solution of the silyl ether (**11**) (1.87 g, 3.63 mmol) in THF (12.0 mL) were added LiCl (0.31 g, 7.26 mmol), $NaBH_4$ (0.27 g, 7.26 mmol), and EtOH (12.0 mL) at rt, and the resulting mixture was stirred for further 4 h at the same temperature. The solution was acidified to pH 4 by addition of 10% citric acid solution. After removal of the solvents, the residue was treated with water, and extracted with CH_2Cl_2. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (1:1) afforded the alcohol (**12**) (1.56 g, 88%) as a colorless oil; ^{1}H-NMR δ 0.12 (s, 6H), 0.91 (s, 9H), 1.42 (s, 9H), 2.60-2.86 (m, 2H), 3.49-3.67 (m, 2H), 3.71-3.92 (m, 1H), 5.06 (s, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 7.00-7.10 (m, 1H), 7.24 (d, *J* = 1.8 Hz, 1H), 7.30-7.43 (m, 5H). This compound was subjected to the next reaction without further purification.

(2*S*)-*N*-*tert*-Butoxycarbonyl-1-methoxymethoxy-3-(4-benzyloxy-3-*tert*-butyldimethylsiloxypheny)-2-propylamine (13): A solution of **12** (1.56 g, 3.20 mmol), ^{i}Pr$_2$NEt (1.24 mL, 1.67 mmol), and MOMCl (0.59 mL, 0.56 mmol) in CH_2Cl_2 (24.5 mL) was stirred at ambient temperature for 12 h. The solution was

treated with saturated NH_4Cl solution, and extracted with CH_2Cl_2. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (2:1) afforded the ether (**13**) (1.55 g, 91%) as a colorless oil; ^{1}H-NMR δ 0.11 (s, 6H), 0.91 (s, 9H), 1.42 (s, 9H), 2.70-2.90 (m, 2H), 3.36 (s, 3H), 3.42-3.50 (m, 2H), 3.90 (brs, 1H), 4.58-466 (m, 2H), 4.67-4.90 (m, 1H), 5.06 (s, 2H), 6.83 (d, *J* = 8.2 Hz, 1H), 7.01-7.11 (m, 1H), 7.19-7.22 (m, 1H), 7.30-7.44 (m, 5H). This compound was subjected to the next reaction without further purification.

(2*S*)-3-(4-Benzyloxy-3-hydroxyphenyl)-1-methoxymethoxy-2-propylamine (15): To a stirred solution of **13** (1.42 g, 2.67 mmol) in THF (8.0 mL) was added TBAF (1 M in THF) (2.67 mL, 2.67 mmol) at 0°C, and the mixture was stirred for 20 min at ambient temperature. After removal of the solvent, the residue was treatment with water, and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (2:1) afforded the crude alcohol (**14**) (0.93 g, 83%) as a colorless oil, which, without further purification was used in the next reaction. To a solution of the alcohol (**14**) (40 mg, 0.09 mmol), obtained above in CH_2Cl_2 (0.32 mL), was added TFA (80 mL, 0.90 mmol) at 0°C, and the mixture was stirred for further 45 min at rt. After removal of the solvent, the residue was treated with 5% NH_4OH solution and extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$:MeOH (4:1) afforded the amine (**15**) (10 mg, 33%) as a colorless oil; IR (thin film) 3360, 2930, 1585, 1510, 1280, 1215, 1040 cm^{-1}; ^{1}H-NMR δ 2.50 (dd, *J* = 8.2, 13.5 Hz, 1H), 2.72 (dd, *J* = 5.4, 13.5 Hz, 1H), 3.27 (brs, 1H), 3.30-3.43 (m, 1H), 3.38 (s, 3H), 3.55 (dd, *J* = 4.1, 9.5 Hz, 1H), 3.92 (brs, 2H), 4.66 (s, 2H), 5.05 (s, 2H), 6.06 (dd, *J* = 2.1, 8.2 Hz, 1H), 6.81 (d, *J* = 2.1 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 7.33-7.42 (m, 5H). EIMS (*m/z*) 317 (M^+); HRMS calcd for $C_{18}H_{23}NO_4$ (M^+) 317.1627, found 317.1602.

(3*S*)-7-Benzyloxy-6-hydroxy-1-methoxycarbonyl-3-methoxymethoxymethyl-1-methyl-1,2,3,4-tetra-hydroisoquinoline (16): A solution of the amine (**15**) (0.09 g, 0.28 mmol) and methyl pyruvate (0.03 mL, 0.34 mmol) in dry MeOH (0.5 mL) was stirred under argon at rt for 12 h. After evaporation of the solvent,

the residue, was purified by column chromatography on silica gel using hexane:AcOEt (1:1) as an eluent to give the 1,2,3,4-tetrahydroisoquinoline (**16**) (0.05 g, 44%) as a colorless oil; IR (thin film) 2930, 1730, 1510, 1455, 1260, 1120, 1040 cm^{-1}; ^{1}H-NMR δ 1.63 (s, 1.98H), 1.66 (s, 1.02H), 2.49-2.68 (m, 2H), 3.20-3.25 (m, 1H), 3.39 (s, 1.02H), 3.40 (s, 0.98H), 3.42-3.52 (m, 1H), 3.65 (s, 1.98H), 3.66 (s, 1.02H), 3.67-3.74 (m, 1H), 4.60-4.73 (m, 2H), 5.06 (s, 0.68H), 5.10 (s, 1.32H), 6.63 (s, 0.66H), 6.64 (s, 0.34H), 6.85 (s, 0.34H), 7.00 (s, 0.66H), 7.30-7.46 (m, 5H); CIMS (*m/z*) 402 (M^++1); HRMS calcd for $C_{22}H_{28}NO_6$ (M^++1) 402.1916, found 402.1920.

Diethyl (3*S*)-3-(hydroxymethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoqionoline-1,1-dicarboxylate (18)[10]: To a stirred solution of the alcohol (**17**) (0.07 g, 0.23 mmol) in toluene/TFA (99/1) (10.0 mL) was added diethyl ketomalonate (0.04 mL, 0.28 mmol) at rt. The resulting mixture was heated at 85°C for 30 min, and neutralized with 5% NH_4OH solution. The mixture was extracted with AcOEt, and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (4:1) afforded the 1,2,3,4-tetrahydroisoquinoline (**18**) (0.06 g, 73%) as a colorless oil; $[\alpha]_D$ +1.6° (*c* 0.12, $CHCl_3$); IR (thin film) 3340, 2940, 1735, 1615, 1520, 1250 cm^{-1}; ^{1}H-NMR δ 1.22 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 2.45-2.65 (m, 2H), 3.12-3.23 (m, 1H), 3.45 (brs, 1H), 3.54 (dd, *J* = 7.4, 11.0 Hz, 1H), 3.73 (dd, *J* = 3.6, 11.0 Hz, 1H), 3.78 (s, 3H), 3.80 (s, 3H), 4.15-4.27 (m, 4H), 6.51 (s, 1H), 7.05 (s, 1H); ^{13}C-NMR δ 13.8, 30.7, 51.7, 55.5, 55.7, 61.9, 62.1, 65.6, 69.6, 76.5, 111.0, 112.1, 121.5, 127.9, 146.6, 149.7, 169.7, 170.9; CIMS (*m/z*) 368 (M^++1); HRMS calcd for $C_{18}H_{26}NO_7$ (M^++1) 368.1709, found 368.1681.

Diethyl (3*S*)-3-(*tert*-butyldimethylsiloxymethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoqionoline-1,1-dicarboxylate (19): A solution of the alcohol (**18**) (0.06 g, 0.16 mmol), imidazole (0.02 g, 0.32 mmol), and TBSCl (0.05 g, 0.32 mmol) in DMF (2.0 mL) was stirred at rt for 12 h. After addition of water, the mixture was extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with $CHCl_3$:MeOH (4:1) afforded the ether (**19**) (0.05 g, 76%) as a colorless solid; mp 96-98 °C; $[\alpha]_D$ -9.0° (*c* 0.84, $CHCl_3$); IR (thin film) 3350, 2915, 2860, 1740, 1620, 1520 cm^{-1}; ^{1}H-NMR δ 0.08 (s, 6H), 0.92 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 2.47-2.62 (m, 1H), 3.13-3.25 (m, 1H),

3.60 (dd, *J* = 7.6, 9.7 Hz, 1H), 3.74 (dd, *J* = 4.1, 9.7 Hz, 1H), 3.84 (s, 6H), 4.22 (ddd, *J* = 2.0, 7.1, 14.1 Hz, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 6.54 (s, 1H), 7.11 (s, 1H); ^{13}C-NMR δ -5.4, -5.3, 14.0, 14.1, 18.2, 25.9, 31.1, 51.6, 55.7, 55.8, 61.7, 62.1, 66.7, 69.9, 111.1, 112.2, 121.9, 128.0, 146.7, 148.8, 169.9, 171.2; EIMS (*m/z*) 481 (M^+); HRMS calcd for $C_{24}H_{39}NO_7Si$ (M^+) 481.2496, found 481.2516.

Diethyl 2-[(2'*S*)-amino-3'-*tert*-butyldimethylsiloxy]propyl-4,5-dimethoxyphenylmalonate (20): To a stirred solution of SmI_2 (0.2 M in THF, 3.1 mL, 0.6 mmol) containing HMPA (0.11 mL, 0.60 mmol) was added a solution of the diester (**19**) (0.06 g, 0.12 mmol) in THF (2.0 mL) under argon at 0°C. After addition of MeOH (0.01 mL, 0.30 mmol), the resulting mixture was stirred at rt for 12 h. The mixture was treated with saturated $NaHCO_3$ solution, and filtered through a Celite pad to remove insoluble materials. The filtrate was concentrated to give a residue, which was taken up with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (3:1) afforded the amine (**20**) (0.02 g, 33%) as a colorless oil; IR (thin film) 2950, 2930, 1750, 1735, 1610 cm^{-1}; ^{1}H-NMR δ 0.06 (s, 6H), 0.90 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.90 (brs, 2H), 2.49 (dd, *J* = 8.4, 14.0 Hz, 1H), 2.83 (dd, *J* = 5.7, 14.0 Hz, 1H), 2.95-3.07 (m, 1H), 3.43-3.67 (m, 2H), 3.85 (s, 6H), 4.08-4.26 (m, 4H), 4.96 (s, 1H), 6.69 (s, 1H), 7.00 (s, 1H); ^{13}C-NMR δ -5.4, -5.3, 14.0, 18.2, 25.9, 37.1, 52.9, 54.3, 55.8, 55.9, 61.5, 61.6, 67.1, 95.7, 112.3, 113.3, 123.9, 130.1, 147.6, 148.5, 168.6, 168.7; EIMS (*m/z*) 483 (M^+); HRMS calcd for $C_{24}H_{41}NO_7Si$ (M^+) 483.2652, found 483.2630.

Further elution with the same solvent system afforded the starting material (**19**) (0.02 g, 33%).

(4*S*)-4-(*tert*-Butyldimethylsiloxymethyl)-1-ethoxycarbonyl-3,5-dihydro-2*H*-3-bezazepin-2-one (21): A solution of the amine (**20**) (10 mg, 0.02 mmol) in dry EtOH (1.0 mL) containing NaOEt (1.3 mg, 0.02 mmol) was heated at reflux for 12 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel using AcOEt as an eluent to afford the lactam (**21**) (6.5 mg, 76%) as a colorless oil; ^{1}H-NMR δ 0.05 (s, 6H), 0.89 (s, 5.4H), 0.90 (s, 3.6H), 1.24 (t, *J* = 7.2 Hz, 1.8H), 1.27 (t, *J* = 7.2 Hz, 1.2H), 1.64 (brs, 1H), 2.85-3.10 (m, 2H), 3.40-3.53 (m, 1H), 3.57-3.67 (m, 1H), 3.68-3.78 (m, 1H), 3.85 (s, 3.6H), 3.87 (s, 2.4H), 4.10-4.35 (m, 2H), 4.57 (s, 0.6H), 4.60 (s, 0.4H), 6.59 (s, 0.6H), 6.65 (s, 0.4H), 6.68 (s, 0.6H), 6.76 (s, 0.4H); EIMS (*m/z*) 437 (M^+); HRMS calcd for $C_{22}H_{35}NO_7Si$ (M^+)

483.2652, found 483.2630.

(4*S*)-4-(4-Methoxybenzyl)-1,3-oxazolidin-2-one (23): To a stirred solution of **22** (13.1 g, 46.6 mmol) in THF (393 mL) was added NaH (65-75% in oil, 3.73 g, 93.2 mmol) at 0°C, and the resulting suspension was heated at reflux for 1 h. After cooling to rt, the mixture was treated with saturated NH_4Cl solution, and concentrated to leave an aqueous layer. The aqueous layer was extracted with AcOEt, and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography using hexane:AcOEt (1:1) as an eluent to furnish the oxazolidinone (**23**) (9.7 g, 100%) as a colorless viscous oil; $[\alpha]_D^{32}$ -51.9° (*c* 0.99, $CHCl_3$); ^{1}H-NMR δ 2.77 (dd, *J* = 6.3, 13.7 Hz, 1H), 2.84 (dd, *J* = 6.8, 13.7 Hz, 1H), 3.78 (s, 3H), 3.98-4.20 (m, 2H), 4.40 (t, *J* = 8.1 Hz, 1H), 6.15 (brs, 1H), 6.86 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H); ^{13}C-NMR δ 40.3, 53.7, 55.1, 69.4, 114.2, 127.7, 129.9, 158.6, 159.6; IR (thin film) 3280, 2940, 2920, 1750, 1515, 1250, 1030, 765 cm^{-1}; EIMS (*m/z*): 207 (M^+); HRMS *m/z* calcd for $C_{11}H_{13}NO_3$ (M^+): 207.0895, found 207.0865.

Ethyl (5*S*,10a*S*)-7-methoxy-3-oxo-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-*b*]isoquinoline-5-carboxylate (25): To a suspension of **23** (18.0 g, 87.0 mmol), 1*H*-benzotriazole (11.4 g, 95.7 mmol) and PTSA (1.65 g, 8.70 mmol) in toluene (400 mL), was added a solution of ethyl glyoxylate (9.8 g, 95.7 mmol) in toluene (35 mL). The mixture was heated at reflux with Dean-Stark trap for overnight. The reaction mixture was washed with 2 N NaOH solution and saturated NH_4Cl solution. The organic layer was dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography using AcOEt:hexane (1:2) as an eluent to furnish the ester (**24**) (29.9 g, 84%) as a pale yellow solid. To a solution of **24** (21.0 g, 51.2 mmol) in MeCN (256 mL), $TiCl_4$ (84.3 mL, 76.8 mmol) was added dropwise, and the mixture was stirred at 60°C for 2 days. After cooling to rt, the reaction was quenched with H_2O (150 mL), and the mixture was extracted with Et_2O. The combined organic layer was washed with 2 N NaOH solution and saturated NH_4Cl solution, and then dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (2:3) afforded the isoquinoline derivative (**25**) (11.3 g, 76%) as a colorless viscous oil; $[\alpha]_D^{28}$ -99.0° (*c* 0.96, $CHCl_3$); ^{1}H-NMR δ 1.32 (t, *J* = 7.1 Hz, 1H), 2.80 (dd, *J* = 10.9, 15.3 Hz, 1H), 2.96 (dd, *J* = 4.5, 15.3 Hz, 1H), 3.80 (s, 3H), 4.14 (dd, *J* = 6.3, 8.2 Hz, 1H), 4.24 (m, 2H),

4.38-4.52 (m, 1H), 4.68 (t, *J* = 8.2 Hz, 1H), 5.42 (brs, 1H), 6.84 (dd, *J* = 2.6, 8.6 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 7.12 (dd, *J* = 2.6 Hz, 1H); ^{13}C-NMR δ 14.0, 32.7, 49.1, 54.9, 55.2, 61.8, 69.1, 111.8, 114.6, 123.7, 129.5, 130.4, 156.9, 158.3, 169.7; IR (thin film) 2980, 2935, 2905, 1760, 1740, 1504, 1424, 1278, 1226, 1025, 770 cm^{-1}; EIMS (*m/z*): 291 (M^+); HRMS *m/z* calcd for $C_{15}H_{17}NO_5$ (M^+): 291.1106, found 291.1105.

Methyl (3*S*)-3-(hydroxymethyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (27): A mixture of **25** (7.02 g, 24.1 mmol), 2 N NaOH (48 mL), and EtOH (200 mL) was heated at reflux for 2 days. The mixture was diluted with water and washed with Et_2O. The aqueous layer was acidified to pH 1-2 with 3 N HCl solution, and the whole was evaporated under reduced pressure, and the organic material was extracted with MeOH (150 mL). The methanol solution was filtered through Celite pad and concentrated to afford the hydrochloric salt (**26**) as pale yellow powders. This compound was used for the next step without purification. To a solution of **26** in MeOH (200 mL), at 0°C was added $SOCl_2$ (10.5 mL, 0.14 mmol) dropwise. The reaction mixture was stirred at rt for 1 h and then heated at reflux for overnight. After cooling, the resulting solution was concentrated, and the residue was dissolved in $CHCl_3$. The chloroform solution was washed with saturated $NaHCO_3$ solution, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography using AcOEt as an eluent to furnish the ester (**27**) (5.33 g, 88%) as a colorless solid; ^{1}H-NMR δ 2.42 (brs, 1H), 2.47 (brs, 1H), 2.45-2.68 (m, 2H), 2.98-3.08 (m, 0.4H), 3.34-3.47 (m, 0.6H), 3.47-3.60 (m, 1H), 3.73 (s, 1.8H), 3.74-3.83 (m, 1H), 3.76 (s, 1.2H), 3.77 (s, 1.8H), 3.81 (s, 1.2H), 4.72 (s, 0.6H), 4.83 (s, 0.4H), 6.74-6.80 (m, 1H), 6.87 (d, *J* = 2.6 Hz, 0.4H), 6.91 (d, *J* = 2.6 Hz, 0.6H), 7.01 (d, *J* = 8.4 Hz, 0.6H), 7.02 (d, *J* = 8.4 Hz, 0.4H); IR (KBr) 3300, 2950, 1735, 1611, 1506, 1228, 1040, 805 cm^{-1}; EIMS (*m/z*): 251 (M^+); HRMS *m/z* calcd for $C_{13}H_{17}NO_4$ (M^+): 251.1157, found 251.1170.

Methyl (3*S*)-3-(*tert*-butyldimethylsiloxymethyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (28): To a solution of **27** (5.00 g, 19.9 mmol) in DMF (200 mL) were added imidazole (1.63 mg, 23.9 mmol) and TBSCl (3.60 g, 23.9 mmol) at rt, and the mixture was stirred for further 1 h. After treatment with saturated NH_4Cl solution, the mixture was extracted with AcOEt, and the extract was washed with H_2O and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was

subjected to column chromatography on silica gel. Elution with hexane:AcOEt (1:4) gave the silyl derivative (**28**) (7.06 g, 97%) as a colorless oil; ^{1}H-NMR δ 0.09 (s, 4.44H), 0.10 (s, 1.56H), 0.92 (s, 2.34H), 0.93 (s, 6.66H), 2.41-2.76 (m, 2H), 2.90-3.00 (m, 0.26H), 3.33 (ddt, *J* = 4.1, 7.6, 14.8 Hz, 0.74H), 3.54 (dd, *J* = 7.6, 9.7 Hz, 0.74H), 3.72-3.79 (m, 1.26H), 3.73 (s, 2.22H), 3.77 (s, 0.78H), 3.79 (s, 2.22 H), 3.81 (s, 0.78H), 4.73 (s, 0.74H), 4.88 (s, 0.26H), 6.74-6.82 (m, 1H), 6.88 (d, *J* = 2.6 Hz, 0.26H), 6.90 (d, *J* = 2.6 Hz, 0.74H), 7.02 (d, *J* = 8.4 Hz, 0.74H); IR (thin film) 3340, 2955, 2925, 1740, 1505, 1255, 840, 775 cm^{-1}; EIMS (*m/z*): 365 (M^+); HRMS *m/z* calcd for $C_{19}H_{31}NO_4Si$ (M^+): 365.2022, found 365.2041.

(4*S*)-4-(*tert*-Butyldimethylsiloxymethyl)-8-methoxy-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one (29): To a stirred solution of **28** (1.00 g, 2.74 mmol) in THF (15 mL) was added a solution of SmI_2 (0.2 M in THF, 68.5 mL, 13.7 mmol) containing HMPA (2.38 mL, 13.7 mmol) and MeOH (0.28 mL, 6.85 mmol) at 0°C. The solution was gradually warmed up to rt, and stirred for overnight. To this solution were added excess of saturated $NaHCO_3$ solution, Et_2O and Celite. After removal of insoluble materials by filtration through Celite pad, and the filtrate was extracted with AcOEt, and the extract was washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with AcOEt:hexane (1:2) gave the benzazepinone (**29**) (541 mg, 59%) as a colorless solid; mp 97-99°C; $[\alpha]_D^{28}$ -11.7° (*c* 0.45, $CHCl_3$); ^{1}H-NMR δ 0.07 (s, 6H), 0.90 (s, 9H), 2.90 (dd, *J* = 4.5, 15.1 Hz, 1H), 2.99 (dd, *J* = 8.9, 15.1 Hz, 1H), 3.41-3.55 (m, 1H), 3.55-3.67 (m, 2H), 3.72 (d, *J* = 15.3 Hz, 1H), 3.78 (s, 3H), 3.83 (d, *J* = 15.3 Hz, 1H), 5.90 (brs, 1H), 6.72-6.78 (m, 2H), 7.05 (d, *J* = 8.9 Hz, 1H); ^{13}C-NMR δ -5.4, 18.1, 25.7, 33.1, 42.7, 55.2, 55.3, 66.3, 112.7, 114.7, 128.1, 129.9, 134.5, 158.6, 170.8; IR (KBr) 3220, 2950, 2930, 2855, 1666, 1565, 1260, 1110, 840, 780 cm^{-1}; EIMS (*m/z*): 335 (M^+); *Anal*.Calcad for $C_{18}H_{29}NO_3Si$: C, 64.44; H, 8.71; N, 4.17. Found: C, 64.53; H, 8.78; N, 4.16.

(4*S*)-4-(*tert*-Butyldimethylsiloxymethyl)-8-methoxy-1,3-dimetyl-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one (30): To a solution of **29** (856 mg, 2.56 mmol) in DMF (18 mL) were added NaH (65-75% in oil, 307 mg, 7.67 mmol) and MeI (477 μL, 7.67 mmol) at 0°C, and the mixture was stirred for further 1.5 h. After treatment with saturated NH_4Cl solution, the mixture was extracted with AcOEt, and the extract was washed with H_2O and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was

subjected to column chromatography on silica gel. Elution with AcOEt:hexane (1:2) gave the lactam (**30**) (0.91 g, 98%) as a colorless oil; ^{1}H-NMR δ 0.05 (s, 0.69H), 0.06 (s, 0.69H), 0.08 (s, 2.31H), 0.09 (s, 2.31H), 0.92 (brs, 9H), 1.50 (d, *J* = 6.9 Hz, 2.31H), 1.55 (d, *J* = 6.9 Hz, 0.69H), 2.82 (s, 2.31H), 2.84-3.13 (m, 1H), 2.93 (s, 0.69H), 3.04-4.04 (m, 0.23H), 3.25-3.55 (m, 2H), 3.61-3.71 (m, 1H), 3.78 (s, 3H), 3.86 (dd, *J* = 3.9, 10.4 Hz, 0.77H), 4.15 (q, *J* = 6.9 Hz, 0.77H), 4.30 (q, *J* = 6.9 Hz, 0.23H), 6.70 (dd, *J* = 2.6, 8.2 Hz, 1H), 6.78-6.94 (m, 1H), 7.04 (d, *J* = 8.2 Hz, 0.23H), 7.10 (d, *J* = 8.2 Hz, 0.77H); IR (thin film) 2955, 2930, 2860, 1645, 1540, 1462, 1255, 1107, 840, 775 cm^{-1}; EIMS (*m/z*): 363 (M^+); HRMS *m/z* calcd for $C_{20}H_{33}NO_3Si$ (M^+): 363.2230, found 363.2225.

(4*S*)-4-Hydroxymethyl-8-methoxy-1,3-dimetyl-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one (31): To a stirred solution of **30** (290 mg, 0.80 mmol) in THF (6 mL) was added dropwise TBAF (1M in THF, 0.96 ml, 0.96 mmol) at 0°C. After 0.5 h, the mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography using AcOEt as an eluent to furnish the alcohol (**31**) (196 mg, 99%) as a colorless solid; ^{1}H-NMR δ 1.41 (dd, *J* = 4.3, 6.9 Hz, 0.23H), 1.52 (d, *J* = 6.9 Hz, 2.31H), 1.56 (d, *J* = 6.9 Hz, 0.69H), 1.89 (dd, *J* = 4.3, 6.9 Hz, 0.77H), 2.87 (s, 2.31H), 2.92-3.12 (m, 1H), 2.95 (s, 0.69H), 3.35-3.57 (m, 2H), 3.66-3.79 (m, 1H), 3.79 (s, 3H), 3.96 (dt, *J* = 4.3, 11.4 Hz, 0.77H), 4.03-4.15 (m, 1H), 4.32 (q, *J* = 6.9 Hz, 0.23H), 6.69-6.75 (m, 1H), 6.81 (d, *J* = 2.5 Hz, 0.77H), 6.85 (d, *J* = 2.5 Hz, 0.23H), 7.07 (d, *J* = 8.2 Hz, 0.23H), 7.13 (d, *J* = 8.2 Hz, 0.77H); EIMS (*m/z*): 249 (M^+); HRMS *m/z* calcd for $C_{14}H_{19}NO_3$ (M^+): 249.1365, found 249.1340.

The mixture was further purified by recrystallization from hexane-acetone to afford **(1*R*)-31** in diastereomerically pure form; mp 131-132 °C; $[\alpha]_D^{25}$ -117.2° (*c* 0.61, $CHCl_3$); ^{1}H-NMR δ 1.52 (d, *J* = 6.9 Hz, 3H), 2.49 (dd, *J* = 4.3, 7.2 Hz, 1H), 2.87 (s, 3H), 2.91-3.02 (m, 1H), 3.43-3.57 (m, 2H), 3.71 (ddd, *J* = 2.5, 7.2, 11.4 Hz, 1H), 3.79 (s, 3H), 3.96 (dt, *J* = 4.3, 11.4 Hz, 1H), 4.12 (q, *J* = 6.9 Hz, 1H), 6.72 (dd, *J* = 2.5, 8.2 Hz, 1H), 6.81 (d, *J* = 2.5 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H); ^{13}C-NMR δ 13.1, 34.0, 36.9, 40.5, 55.3, 63.2, 63.7, 110.5, 111.4, 127.8, 129.2, 142.1, 159.0, 173.7; IR (KBr) 3390, 2940, 1622, 1504, 1463, 1283, 1077, 1037, 735 cm^{-1}; EIMS (*m/z*): 249 (M^+); *Anal*.Calcad for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.17; H, 7.66; N, 5.62.

[(2*S*)-7-Methoxy-3,5-dimethyl-4-oxo-2,3,4,5-tetrahydro-1*H*-3-benzazepin-2-yl]methyl methanesulfonate (32): To a stirred solution of **31** (190 mg, 0.76 mmol) and triethylamine (0.32 mL, 2.28 mmol) in CH_2Cl_2 (14 mL) was added methanesulfonyl chloride (89 μL, 1.14 mmol) at -78°C and the resulting mixture was stirred at the same temperature for 0.5 h. After treatment with saturated NH_4Cl solution, the mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4 and evaporated to give a residue, which was purified by column chromatography on silica gel. Elution with hexane:AcOEt (2:1) afforded the mesylate (**32**) (245 mg, 98%) as a colorless solid; ^{1}H-NMR δ 1.53 (d, *J* = 6.9 Hz, 2.22 H), 1.56 (d, *J* = 6.9 Hz, 0.78H), 2.89 (s, 2.22H), 2.96 (s, 0.78H), 3.01 (s, 0.78H), 3.03-3.14 (m, 1H), 3.07 (s, 2.22H), 3.32 (dd, *J* = 10.4, 14.7 Hz, 0.74H), 3.53-3.61 (m, 0.26H), 3.70-3.83 (m, 1.26H), 3.79 (s, 3H), 3.98 (q, *J* = 6.9 Hz, 0.74H), 4.05-4.27 (m, 0.52H), 4.30 (dd, *J* = 3.6, 10.5 Hz, 0.74H), 4.39 (dd, *J* = 5.4, 10.5 Hz, 0.74H), 6.73 (dd, *J* = 2.5, 8.1 Hz, 1H), 6.80 (d, *J* = 2.5 Hz, 0.74H), 6.85 (d, *J* = 2.5 Hz, 0.26H), 7.08-7.14 (m, 1H); EIMS (*m/z*): 327 (M^+); HRMS *m/z* calcd for $C_{15}H_{21}NO_5Si$ (M^+): 327.1140, found 327.1114.

[(2*S*, 5*R*)-7-Methoxy-3,5-dimehtyl-4-oxo-2,3,4,5-tetrahydro-1*H*-3-benzazepin-2-yl]methyl methanesulfonate (5*R*-32): The mesylate **(5*R*)-31** (89.0 mg, 97%) was synthesized from **(1*R*)-32** (70.0 mg, 0.28 mmol) by the same procedure as described for the preparation of **32**; mp 129-131 °C; $[\alpha]_D^{26}$ -63.0° (*c* 0.62, $CHCl_3$); ^{1}H-NMR δ 1.54 (d, *J* = 6.9 Hz, 3H), 2.89 (s, 3H), 3.07 (s, 3H), 3.10 (dd, *J* = 7.4, 14.7 Hz, 1H), 3.33 (dd, *J* = 10.9, 14.7 Hz, 1H), 3.71-3.82 (m, 1H), 3.79 (s, 3H), 3.98 (q, *J* = 6.9 Hz, 1H), 4.31 (dd, *J* = 3.6, 10.5 Hz, 1H), 4.40 (dd, *J* = 5.4, 10.5 Hz, 1H), 6.73 (dd, *J* = 2.5, 8.1 Hz, 1H), 6.81 (d, *J* = 2.5 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H); ^{13}C-NMR δ 13.5, 34.1, 37.1, 37.7, 41.2, 55.2, 60.2, 69.2, 110.8, 111.6, 126.2, 129.5, 141.7, 159.3, 172.8; IR (KBr) 2940, 1640, 1355, 1175, 967, 830 cm^{-1}; EIMS (*m/z*): 327 (M^+); HRMS *m/z* calcd for $C_{15}H_{21}NO_5Si$ (M^+): 327.1140, found 327.1117.

(1*S*, 4*S*)-8-Methoxy-1,3-dimethyl-1,3,4,5-tetrahydro-2*H*-1,4-methano-3-benzazepin-2-one (33): To a solution of **32** (149 mg, 0.46 mmol) in THF (13 mL) was added *t*BuOK (102 mg, 0.91 mmol) at rt. The reaction mixture was heated at reflux for 1 h. After cooling to rt, the reaction was quenched with H_2O and extracted AcOEt. The extract was washed with brine and dried over Na_2SO_4 and concentrate to give a residue, which was purified by column chromatography on silica gel. Elution with hexane:AcOEt(2:1)

afforded the amide (**33**) (134 mg, 79%) as a colorless solid; mp 144-145 °C; $[\alpha]_D^{25}$ +21.9° (*c* 0.71, $CHCl_3$); ^{1}H-NMR δ 1.55 (s, 3H), 2.02 (d, *J* = 10.7 Hz, 1H), 2.18 (ddd, *J* = 0.9, 5.3, 10.7 Hz, 1H), 2.83 (s, 3H), 2.91-2.97 (m, 2H), 3.78 (s, 3H), 3.84 (dt, *J* = 2.5, 5.3 Hz, 1H), 6.73 (dd, *J* = 2.6, 8.4 Hz, 1H), 6.84 (d, *J* = 2.6 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 1H); ^{13}C-NMR δ 17.4, 27.5, 29.9, 40.7, 45.1, 54.9, 55.2, 110.0, 112.7, 124.4, 130.6, 141.4, 158.1, 177.0; IR (KBr) 2960, 1686, 1490, 1431, 1286, 1042 cm^{-1}; EIMS (*m/z*): 231 (M^+); *Anal*.Calcad for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.79; H, 7.53; N, 6.08.

(-)-8-*O*-Methylaphanorphine (34): To a stirred suspension of $LiAlH_4$ (79.0 mg, 2.08 mmol) in THF (5 mL) was added a solution of **33** (120 mg, 0.52 mmol) in THF (3 mL) at rt, and the resulting mixture was heated at reflux for 3 h. 3 N NaOH solution was carefully added to this mixture, and the insoluble material was filtered off by filtration through Celite pad. The filtrate was concentrated to leave a residue, which was purified by column chromatography on silica gel with ammonia saturated $CHCl_3$: MeOH (40:1) as an eluent to afford aphanorphine methyl ether (**34**) (98 mg, 87%) as a colorless oil; $[\alpha]_D^{30}$ -9.72° (*c* 0.67, $CHCl_3$); ^{1}H-NMR δ 1.47 (s, 3H), 1.85 (d, *J* = 11.0 Hz, 1H), 2.02 (ddd, *J* = 1.3, 5.6, 11.0 Hz, 1H), 2.47 (s, 3H), 2.71-2.88 (m, 3H), 3.02 (brd, *J* = 16.5 Hz, 1H), 3.41 (dt, *J* = 2.8, 5.6 Hz, 1H), 3.78 (s, 3H), 6.68 (dd, *J* = 2.6, 8.4 Hz, 1H), 6.78 (d, *J* = 2.6 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H); ^{13}C-NMR δ 21.4, 35.7, 41.5, 41.7, 43.1, 55.1, 61.1, 71.3, 109.3, 110.8, 126.1, 130.1, 148.0, 157.6; IR (thin film) 2932, 1492, 1292, 1236, 1026, 800 cm^{-1}; EIMS (*m/z*): 217 (M^+); HRMS *m/z* calcd for $C_{14}H_{19}NO$ (M^+): 217.1467, found 217.1464.

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