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Synthesis of (−)-aphanorphine using a sulfur-directed aryl radical cyclization

Osamu Tamura, Takehiko Yanagimachi and Hiroyuki Ishibashi*

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920-0934, Japan

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Abstract—Treatment of radical precursor **15a** having a vinyl sulfide moiety with Bu_3SnH in the presence of AIBN in boiling benzene afforded exclusively the 6-*exo* cyclization product **16a**, whereas similar treatment of the *exo*-methylene compound **15b** gave a mixture of the 6-*exo* cyclization product **16b** and the *endo*-olefin product **17** formed by a 1,5-hydrogen shift. Based on these findings, the synthesis of (−)-aphanorphine was achieved using a sulfur-directed 6-*exo*-selective aryl radical cyclization of **22**.

1. Introduction

(−)-Aphanorphine **1** is an alkaloid isolated from the freshwater blue–green alga *Aphanizomenon flos-aquae*.[1] Since the structural features of **1** are closely related to those of analgesics such as pentazocine and eptazocine, significant attention has been focused on the synthesis of **1** (Fig. 1).[2–5]

All reported syntheses of **1** involve carbon–nitrogen bond formation (path a) to construct an aphanorphine skeleton from either intermediate **2** or **3** which already has the asymmetric quaternary center (Scheme 1). Formation of an aziridine from **2** followed by reductive cleavage of the benzylic position,[2,3a,b] aminomercuration[3c] or halocyclization[4] of **2**, and *N*-alkylation of **3**[3d] have been used for carbon–nitrogen bond formation. An alternative strategy for the synthesis of **1** involves carbon–carbon bond formation (path b), which builds the aphanorphine skeleton with construction of the benzylic quaternary carbon.

We have previously reported[6] that treatment of **4a** with Bu_3SnH in the presence of AIBN generated aryl radical **5** (R = H), which underwent cyclization to give the 6-*endo* product **6**,[7] whereas a similar reaction of **4b** having a phenylthio group at the terminus of the alkenic bond lead to exclusive formation of the 5-*exo* cyclization product **7** (Scheme 2). This sulfur-directed *exo*-selective aryl radical cyclization onto methylenecycloalkanes provided an excellent method for construction of benzylic quaternary centers. Recently, we reported a total synthesis of **1** using this methodology for the formation of a carbon–carbon bond (path b in Scheme 1),[8] and we present a full account of this work herein.

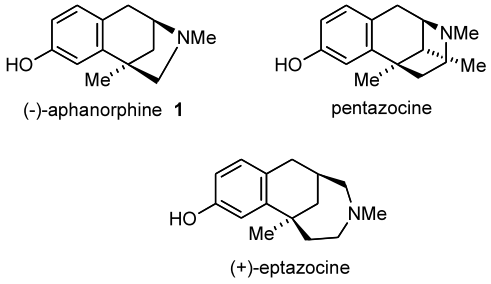
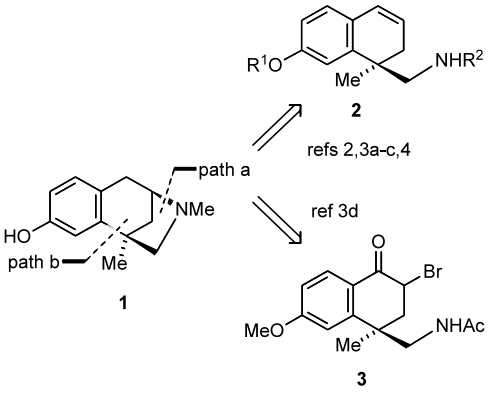


Figure 1.



Scheme 1.

* Corresponding author. E-mail: isibasi@mail.p.kanazawa-u.ac.jp

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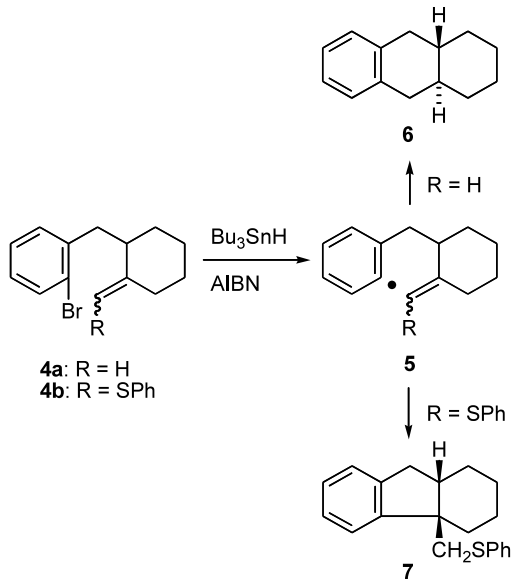
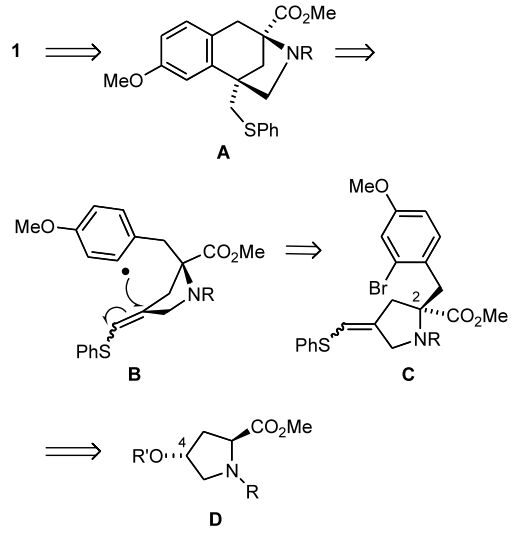


Scheme 2.



Scheme 3.

2. Results and discussion

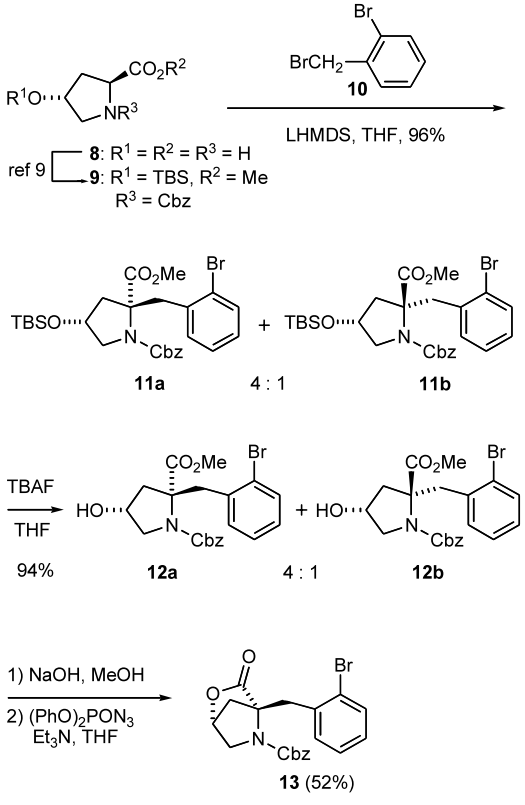
Our plan for the synthesis of **1** involving carbon–carbon bond formation (Scheme 1) by sulfur-directed aryl radical cyclization is as follows. 6-*exo* Cyclization of aryl radical **B** generated from bromide **C** would provide tricyclic compound **A**, which possesses the structural characteristics of **1**. The requisite stereochemistry of the 2-position of **C** could be formed by alkylation of 4-hydroxy-L-proline derivative **D** from a less-hindered side (Scheme 3).

Our investigation began by alkylation of fully protected amino acid **9**[9] obtained from commercially available *trans*-4-hydroxy-L-proline **8** with 2-bromobenzyl bromide **10**. Enolization of **9** with LHMDS followed by treatment with bromide **10** gave alkylation products **11a** and **11b** as a 4:1 inseparable mixture in 96% yield.[10]

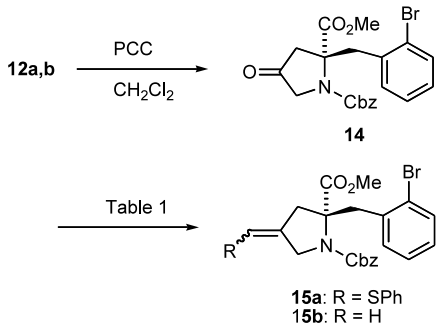
Without separation, the mixture of **11a** and **11b** was treated with TBAF, and a mixture of alcohols **12a** and **12b** was obtained in 94% yield. The *cis*-stereochemistry between the methoxycarbonyl group and the hydroxyl group of the major isomer **12a** was determined on the basis of chemical transformation. Alkaline-hydrolysis of the mixture of **12a** and **12b** followed by treatment with diphenylphosphoryl azide (DPPA) and triethylamine gave lactone **13** in 52% yield (Scheme 4).

The next task was introduction of a phenylthiomethylene group onto the pyrrolidine ring of **12** via ketone **14**. Oxidation of alcohol **12** (4:1 diastereomeric mixture) with PCC gave ketone **14**. Although the oxidation proceeded without any difficulty, Horner reaction of ketone **14**, unexpectedly, was not easy (Scheme 5, Table 1). Treatment of **14** with lithium salt of $Ph_2P(O)CH_2SPh$[11] gave only a small quantity of phenylthiomethylene compound **15a** (entry 1). A similar treatment of **14** with HMPA gave a slightly improved yield (entry 2). The best result was obtained by sequential treatments of **14** with the lithium salt of $Ph_2P(O)CH_2SPh$ in the presence of $CeCl_3$[12] followed by NaH, and this method gave radical precursor **15a** in 73% yield from ketone **14** (entry 3). A similar difficulty was encountered in the preparation of compound **15b** having no substituent at the olefin terminus. Neither Wittig reaction of **14** with $Ph_3P{=}CH_2$ nor Peterson reaction with $TMSCH_2Li$ gave **15b**, and only the Tebbe reagent[13] afforded **15b** although in low yield (entry 4).

With radical precursors **15a** and **15b** in hand, we next examined their radical cyclization. Vinyl sulfide **15a**, on



Scheme 4.

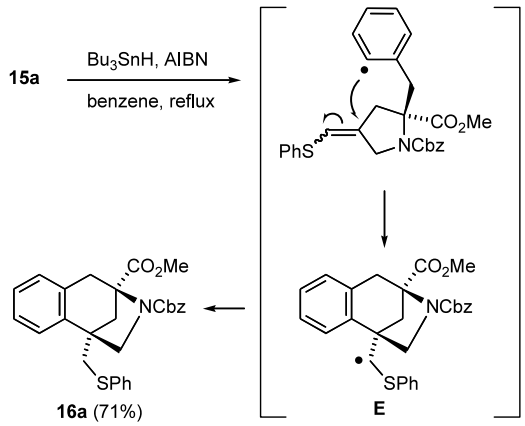


Scheme 5.

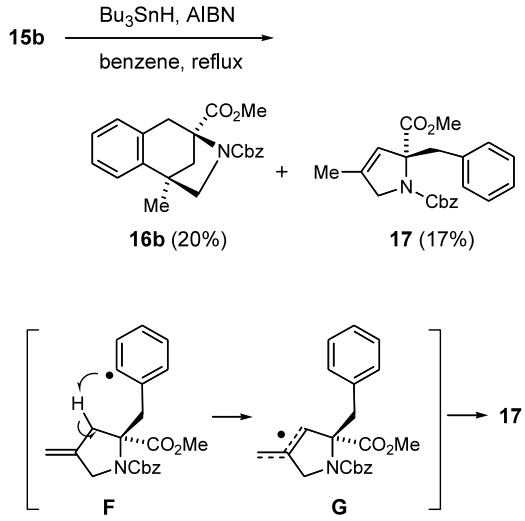
treatment with 1.5 equiv. of Bu_3SnH and a catalytic amount of AIBN in boiling benzene, exclusively afforded 6-*exo* aryl radical cyclization product **16a** in 71% yield. The ^{13}C NMR spectrum of **16a** exhibited two sets of signals at δ 46.1, 46.9 and δ 66.9, 67.3 ppm, which were indicative of the two quaternary carbon atoms of **16a** as rotamers (Scheme 6).

In contrast, a similar treatment of *exo*-methylene compound **15b** with Bu_3SnH and AIBN gave a complex mixture of products, from which the 6-*exo* cyclization product **16b** (20%) and *endo* olefin **17** (17%) were isolated. Olefin **17** might result from a 1,5-hydrogen shift of the initially formed aryl radical **F** followed by a reduction with Bu_3SnH at a less-hindered position of allyl radical **G** (Scheme 7). The radical reactions of **15a** and **15b** clearly showed that the phenylthio group of **15a** was essential for efficient 6-*exo* cyclization, probably as a result of radical-stabilization ability in radical **E** (Scheme 6).

With these results of model experiments in hand, we turned our attention to the total synthesis of (–)-aphanorphine **1**. First, radical precursor **21** was prepared from **9** by a synthetic route similar to that for **15a**. Alkylation of ester **9** with 2-bromo-4-methoxybenzyl bromide **18**[14] in the presence of LHMDS gave a 4:1 mixture of **19a** and **19b** in 91% yield. Without separation, desilylation with TBAF followed by recrystallization of the resulting 4:1 mixture of alcohols from hexane–ethyl acetate furnished diastereomerically pure alcohol **20** in 68% yield from **19**. Oxidation of alcohol **20** followed by phenylthiomethylenation of the resulting ketone **21** by a protocol similar to that used for **15a** afforded vinyl sulfide **22** in 78% yield from **20**. As expected, the key radical cyclization of **22** with Bu_3SnH and AIBN proceeded smoothly to give tricyclic compound **23** in 76% yield (Scheme 8).



Scheme 6.



Scheme 7.

To synthesize aphanorphine from compound **23**, removal of the methoxycarbonyl group at the bridge head position is required. For this purpose, we first attempted reduction of the ester group to a formyl group, which might be removed by decarbonylation with Wilkinson catalyst.[15] However, reduction of **23** with DIBAL-H did not occur, probably for a steric reason (Scheme 9).

To solve this problem, the Barton decarboxylation protocol[16] was next examined. Alkaline hydrolysis of ester **23** gave carboxylic acid **24**. Condensation of acid **24** with *N*-hydroxy-2-thiopyridone gave thiohyroxamate **25**, which was heated with Bu_3SnH and AIBN to

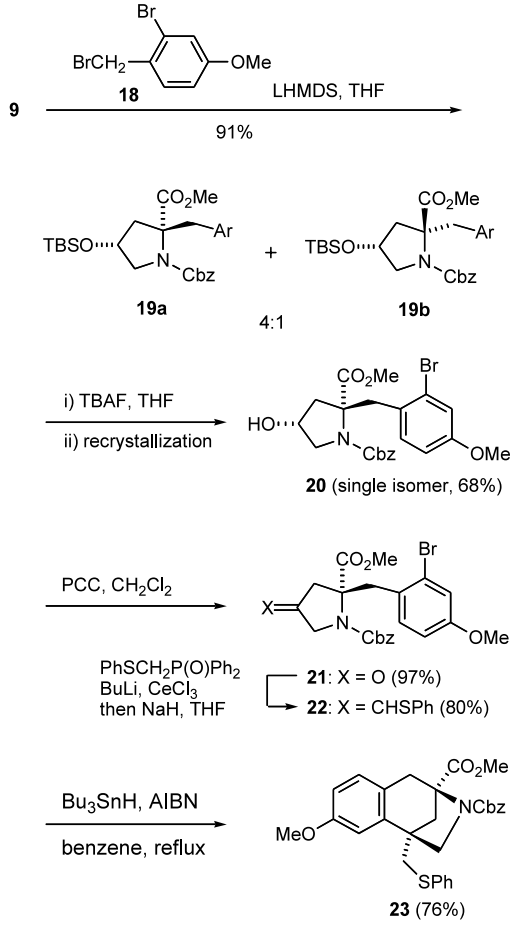
Table 1. Vinyl sulfide formation and methylenation of ketones **14**

Entry	Conditions	Product	Yield (%)
1	$Ph_2P(O)CH_2SPh$ (3 equiv.), BuLi (3 equiv.), THF	**15a**	7
2	$Ph_2P(O)CH_2SPh$ (3 equiv.), BuLi (3 equiv.), THF, HMPA	**15a**	20
3	$Ph_2P(O)CH_2SPh$ (3 equiv.), BuLi (3 equiv.), $CeCl_3$, THF, then NaH, THF	**15a**	73
4	Tebbe reagent	**15b**	28

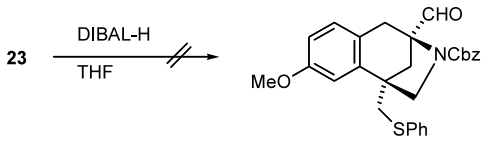
afford decarboxylated compound **26** in 52% yield from **23**. When compound **26** was treated with Raney nickel in boiling methanol, *O*-methylaphanorphine **29** was obtained in 65% yield. Formation of **29** can be explained by a three-step sequence involving deprotection of the benzyloxycarbonyl group, desulfurization, and reductive methylation of the resulting amine **27** via iminium ion **28**, which was generated from amine **27** with formaldehyde derived from methanol.[17] Finally, synthesis of (–)-aphanorphine **1** was accomplished by demethylation of **29** by the previously reported method[3d] (Scheme 10).

3. Conclusions

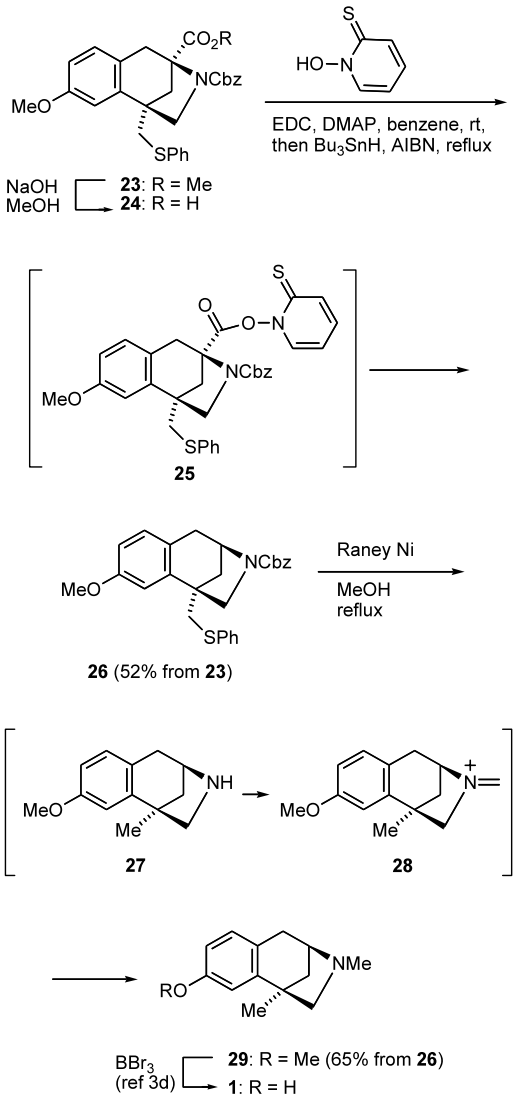
Synthesis of (–)-aphanorphine was accomplished by the use of sulfur-directed aryl radical cyclization. In this synthesis, the phenylthio group plays an important role not only for efficient radical cyclization but also for availability of radical precursors. This synthesis clearly demonstrates the value of sulfur-directed aryl radical cyclization for the construction of a benzylic quaternary center in a considerably complex molecule.



Scheme 8.



Scheme 9.



Scheme 10.

4. Experimental

4.1. General

Melting points are uncorrected. IR spectra were recorded with a Shimazu FTIR-8100 spectrophotometer for solutions in $CHCl_3$. ^1H and ^{13}C NMR spectra were measured on a JEOL JNM-EX 270 or a JEOL JNM-GSX 500 spectrometer. δ Values quoted are relative to tetramethylsilane. High resolution mass spectra (HRMS) were obtained with a JEOL JMS-SX 102 instrument. Column chromatography was performed on silica gel 60 PF_{254} (Nacalai Tesque) under pressure.

4.2. (4*R*)-1-Benzyloxycarbonyl-2-[(2-bromophenyl)-methyl]-2-methoxycarbonyl-4-(*tert*-butyldimethylsilyloxy)pyrrolidine, 11

To a stirred solution of **9**[9] (1.71 g, 4.34 mmol) in THF (7 mL) was added dropwise a 1.0 M solution of $LiN(SiMe_3)_2$ in THF (5.21 mL, 5.21 mmol) at −20°C. After 2 h, a solution of 2-bromobenzyl bromide (1.30 g, 5.21 mmol) in THF (4 mL) was added to the mixture at −20°C, and then the mixture was stirred at rt for 3 h. The mixture was diluted with a saturated solution of NH_4Cl, and extracted with AcOEt. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel with hexane–AcOEt (10:1) to give an inseparable 4:1 mixture of **11a** and **11b** (2.34 g, 96%). IR ($CHCl_3$) 1740, 1700 cm^{-1}. Rotamers of both **11a** and **11b** were observed by the ^1H NMR due to their benzyloxycarbonyl group; ^1H NMR (270 MHz, $CDCl_3$) δ (−0.17) to (−0.02) (6H, m), 0.87 (s), 0.88 (s), 0.92 (s), 0.93 (s, total 9H), 1.97–2.25 (1H, m), 2.25–2.85 (1H, m), 3.22–3.42 (1H×4/5, m), 3.35–3.72 (4H, m), 3.63 (s), 3.79 (s), 3.88 (s), 3.90 (s, total 3H), 4.43–4.65 (1H×1/5, m), 5.05–5.45 (2H, m), 6.57–7.44 (9H, m). Anal. calcd for $C_{27}H_{36}BrNO_5Si$: C, 57.65; H, 6.45; N, 2.49. Found: C, 57.57; H, 6.47; N, 2.35.

4.3. (4*R*)-1-Benzyloxycarbonyl-2-[(2-bromophenyl)-methyl]-4-hydroxy-2-(methoxycarbonyl)pyrrolidine, 12

To a stirred solution of **11** (1.91 g, 3.39 mmol) in THF (12 mL) was added dropwise a 1.0 M solution of tetrabutylammonium fluoride in THF (3.73 mL, 3.73 mmol) at rt. After 2 h, the mixture was diluted with water and extracted with AcOEt. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel with hexane–AcOEt (4:1) to give an inseparable 4:1 mixture of **12a** and **12b** (1.43 g, 94%). IR ($CHCl_3$) 3021, 1740, 1698 cm^{-1}. Rotamers of both **12a** and **12b** were observed by the ^1H NMR due to their benzyloxycarbonyl group; ^1H NMR (270 MHz, $CDCl_3$) δ 1.57 (1H, br s), 2.05–2.30 (2H, m), 2.77–2.93 (1H, m), 3.48–3.82 (4H+1H×4/5, m), 3.53 (s), 3.69 (s), 3.75 (s), 3.87 (s, total 3H), 4.30 (1H×1/5, quin, $J=6.4$ Hz), 5.07 (d, $J=11.3$ Hz), 5.12 (d, $J=12.5$ Hz), 5.14 (d, $J=12.5$ Hz), 5.16 (d, $J=11.9$ Hz), 5.23 (d, $J=11.3$ Hz), 5.25 (d, $J=11.9$ Hz), 5.28 (d, $J=12.5$ Hz), 5.34 (d, $J=12.5$ Hz, total 2H), 6.83–6.89 (1H, m), 6.95–7.22 (2H, m), 7.34–7.44 (5H, m), 7.51–7.56 (1H, m). Anal. calcd for $C_{21}H_{22}BrNO_5$: C, 56.26; H, 4.95; N, 3.12. Found: C, 56.09; H, 5.02; N, 3.20.

4.4. Benzyl (1*R*,4*R*)-2-Aza-1-[(2-bromophenyl)methyl]-5-oxa-6-oxobicyclo[2.2.1]heptane-2-carboxylate, 13

A mixture of **12** (114 mg, 0.254 mmol), 5N NaOH (3 mL), and methanol (3 mL) was heated at reflux for 2 h. After cooling, water (20 mL) was added to the mixture, which was washed with Et_2O. The aqueous phase was acidified to pH 1–2 with 5N HCl, and the whole was extracted with $CHCl_3$. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give crude carboxylic acid (117 mg) as an oil. This material was used for the next step without purification. To a solution of the carboxylic acid (83 mg) in THF (8 mL) were added diphenylphosphoryl azide (526 mg, 1.91 mmol) and Et_3N (351 mg, 3.44 mmol) at rt, and the mixture was stirred for 2 h at the same temperature. A saturated solution of $NaHCO_3$ (30 mL) was added to the mixture, and the whole was extracted with AcOEt. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane–AcOEt (4:1) to give **13** (41.2 mg, 52%) as an oil. $[\alpha]_D^{24}$ −51.5 (*c* 0.43, $CHCl_3$); IR ($CHCl_3$) 1792, 1701 cm^{-1}. Rotamers of **13** were observed by the ^1H NMR due to the benzyloxycarbonyl group ^1H NMR (270 MHz, $CDCl_3$) δ 1.91 (1H×1/2, br d, $J=10.9$ Hz), 2.13 (1H×1/2, br d, $J=10.9$ Hz), 2.37–2.61 (1H, m), 3.34–3.98 (4H, m), 4.20–4.35 (1H, m), 5.14 (1H×1/2, d, $J=12.5$ Hz), 5.33 (1H×1/2, d, $J=12.5$ Hz), 5.13–5.20 (1H, m), 6.84–7.55 (9H, m); HRMS calcd for $C_{20}H_{18}{}^{79}BrO_4N$ 415.0419, found 415.0414.

4.5. 1-Benzyloxycarbonyl-2-[(2-bromophenyl)methyl)]-2-methoxycarbonyl-4-oxopyrrolidine, 14

To a stirred solution of **12a** (1.58 g, 3.52 mmol) in CH_2Cl_2 (10 mL) were added PCC (1.52 g, 7.03 mmol) and Florisil® (3 g) at rt. After 10 h, the mixture was diluted with Et_2O and filtered through a pad of silica gel, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane–AcOEt (4:1) to give **14** (1.49 g, 97%) as a colorless oil. IR ($CHCl_3$): 1767, 1748, 1707 cm^{-1}. Rotamers of **14** were observed by the ^1H NMR due to the benzyloxycarbonyl group ^1H NMR (270 MHz, $CDCl_3$) δ 2.75 (1H, d, $J=9.1$ Hz), 2.95 (1H, d, $J=9.1$ Hz), 3.29–3.94 (4H, m), 3.67 (3H×1/2, s), 3.81 (3H×1/2, s), 5.17 (1H, d, $J=12.2$ Hz), 5.32 (1H, d, $J=12.2$ Hz), 6.96 (1H, br s), 7.09 (2H, br s), 7.36–7.40 (5H, m), 7.52–7.54 (1H, m). Anal. calcd for $C_{21}H_{20}BrNO_5$: C, 56.52; H, 4.52; N, 3.14. Found: C, 56.62; H, 4.64; N, 3.10.

4.6. 1-Benzyloxycarbonyl-2-[(2-bromophenyl)methyl]-2-methoxycarbonyl-4-(phenythiomethylene)pyrrolidine, 15a (Table 1, entry 3)

A suspension of anhydrous $CeCl_3$ (966 mg, 3.92 mmol) in THF (18 mL) was stirred vigorously for 2 h at rt, and then cooled to −78°C. To the suspension was added a solution of $PhSCHLiP(O)Ph_2$ [prepared by treatment of a solution of $PhSCH_2P(O)Ph_2$ (1.09 g, 3.36 mmol) in THF (11 mL) with a 1.6 M solution of BuLi in hexane (2.1 mL, 3.36 mmol) at −78°C] at −78°C for 20 min. After 30 min, a solution of **14** (500 mg, 1.12 mmol) in THF (10 mL) was added to the mixture at −78°C, and then the mixture was allowed to warm to rt. After stirring at rt for 3 h, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (455 mg, 3.92 mmol) was added

to the mixture, and the mixture was stirred for 30 min. The mixture was diluted with a saturated solution of $NaHCO_3$ (50 mL), and the whole was extracted with $CHCl_3$. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to give a crude adduct of **14** with $PhSCH_2P(O)Ph_2$ as a pale yellow oil. The oil was dissolved in THF (10 mL). To the stirred solution was added NaH (60% dispersion, 161 mg, 6.72 mmol) at rt. After 3 h, the mixture was diluted with a saturated solution of NH_4Cl, and the whole was extracted with AcOEt. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane–AcOEt (4:1) to afford **15a** (449 mg, 73%) as a mixture of geometrical isomers. IR ($CHCl_3$) 1742, 1701, 1584 cm^{-1}. Rotamers of **15a** were observed by the ^1H NMR due to the benzyloxycarbonyl group. ^1H NMR (270 MHz, $CDCl_3$) δ 2.82 (1H, br d, $J=18.6$ Hz), 3.16 (1H×3/5, br d, $J=18.6$ Hz), 3.18 (1H×2/5, br d, $J=18.6$ Hz), 3.48 (3H×2/5, s), 3.79 (3H×3/5, s), 3.51–4.29 (4H, m), 5.14 (1H×3/5, d, $J=12.5$ Hz), 5.19 (1H×2/5, d, $J=12.2$ Hz), 5.28 (1H×2/5, d, $J=12.2$ Hz), 5.30 (1H×3/5, d, $J=12.5$ Hz), 5.74 (1H×3/5, br s), 5.78 (1H×2/5, br s), 6.90–7.50 (14H, m). Anal. calcd for $C_{28}H_{26}BrNO_4S$: C, 60.87; H, 4.74; N, 2.54. Found: C, 60.74; H, 4.80; N, 2.66.

4.7. 1-Benzyloxycarbonyl-2-[(2-bromophenyl)methyl]-2-methoxycarbonyl-4-(methylene)pyrrolidine, 15b (Table 1, entry 4)

To a stirred solution of **14** (120 mg, 0.269 mmol) in THF (1 mL) was added a 0.5 M solution of μ-chloro-μ-methylene[bis(cyclopentadienyl)titanium]dimethylalminum (Tebbe reagent) in toluene (0.54 mL, 0.27 mmol) at −20°C. The mixture was stirred at −20°C for 20 min, then at rt for 3 h. An aqueous 10% solution of NaOH (0.5 mL) and Et_2O (30 mL) were added to the mixture. The mixture was filtered through a pad of Celite®, and the filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane–AcOEt (4:1) to give **15b** (32.9 mg, 28%) as a colorless oil. IR ($CHCl_3$) 1740, 1700 cm^{-1}. Rotamers of **15b** were observed by the ^1H NMR due to the benzyloxycarbonyl group. ^1H NMR (270 MHz, $CDCl_3$) δ 2.75 (1H, br d, $J=15.5$ Hz), 2.94 (1H, d, $J=15.5$ Hz), 3.53–3.70 (3H, m), 3.48 (3H×1/3, s), 3.78 (3H×2/3, s), 4.08–4.18 (1H, m), 4.55 (2H×1/3, br s), 4.65 (2H×2/3, br s), 5.07 (1H×1/3, d, $J=12.0$ Hz), 5.14 (1H×2/3, d, $J=12.5$ Hz), 5.27 (1H×1/3, d, $J=12.0$ Hz), 5.30 (1H×2/3, d, $J=12.5$ Hz), 6.90–6.94 (1H, m), 6.99–7.14 (2H, m), 7.32–7.49 (6H, m); HRMS calcd for $C_{22}H_{22}{}^{79}BrO_4N$ 443.0732, found 443.0750.

4.8. (1*S**,4*R**)-3-Benzyloxycarbonyl-4-methoxycarbonyl-1-(phenylthio)methyl-2,3,4,5-tetrahydro-1,4-methano-3-benzazepine, 16a

To a solution of **15a** (384 mg, 0.695 mmol) in refluxing benzene (70 mL) was added dropwise a solution of Bu_3SnH (303 mg, 1.04 mmol) and AIBN (80 mg, 0.45 mmol) in benzene (30 mL) over 40 min, and the mixture was further heated at reflux for 3 h. After cooling, the mixture was concentrated under reduced pressure. The residue was dissolved in Et_2O (40 mL), and the solution was vigorously stirred with an 8% solution of KF overnight. The organic phase was separated, and the aqueous phase was further extracted with Et_2O. The organic phases were combined, washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane–AcOEt (4:1) to give **16a** (235 mg, 71%) as a colorless oil. IR ($CHCl_3$) 1744, 1700 cm^{-1}. Rotamers of **16a** were observed by the ^1H NMR and ^{13}C NMR due to the benzyloxycarbonyl group. ^1H NMR (270 MHz, $CDCl_3$) δ 2.28 (1H, br d, $J=10.9$ Hz), 2.43 (1H×1/2, br d, $J=10.9$ Hz), 2.44 (1H×1/2, dd, $J=10.9$, 2.1 Hz), 3.34–3.79 (6H, m), 3.44 (3H×1/2, s), 3.81 (3H×1/2, s), 4.94 (1H×1/2, d, $J=12.5$ Hz), 4.95 (1H×1/2, d, $J=12.2$ Hz), 5.10 (1H×1/2, d, $J=12.5$ Hz), 5.21 (1H×1/2, d, $J=12.2$ Hz), 7.12–7.39 (14H, m); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 36.7, 37.8, 38.6, 38.7, 44.1, 45.2, 46.1, 46.9, 52.3, 52.6, 60.4, 61.1, 65.6, 65.9, 66.9, 67.3, 123.8, 124.0, 126.2, 126.4, 127.5, 127.6, 127.8, 128.1, 128.2, 125.4, 128.5, 128.6, 128.7, 129.1, 129.5, 129.6, 129.8, 130.1, 130.7, 133.8, 134.2, 136.1, 136.4, 136.9, 139.8, 140.1, 153.5, 172.3, 172.5. Anal. calcd for $C_{28}H_{28}NO_4S$: C, 71.01; H, 5.75; N, 2.96. Found C, 70.73; H, 5.92; N, 2.96.

4.9. (1*S**,4*S**)-3-Benzyloxycarbonyl-4-methoxycarbonyl-1-methyl-2,3,4,5-tetrahydro-1,4-methano-3-benzazepine, 16b and 1-benzyloxycarbonyl-2-benzyl-2-methoxycarbonyl-4-methyl-3-pyrroline, 17

Using a procedure similar to that described above for **16a**, compound **15b** (42 mg, 0.095 mmol) was treated with Bu_3SnH (33 mg, 0.113 mmol) and AIBN (2.0 mg, 11 μmol) in boiling benzene (14 mL). After work-up, the crude material was chromatographed on silica gel with hexane–AcOEt (4:1). The first fraction gave **17** (5.9 mg, 17%), and the second fraction gave **16b** (6.9 mg, 20%). **16b**: IR ($CHCl_3$) 1740, 1700 cm^{-1}. Rotamers of **16b** were observed by the ^1H NMR due to the benzyloxycarbonyl group. ^1H NMR (270 MHz, $CDCl_3$) δ 1.55 (3H×1/2, s), 1.56 (3H×1/2, s), 2.13 (1H, dd, $J=10.9$, 9.6 Hz), 2.27 (1H, br d, $J=10.9$ Hz), 3.41–3.56 (4H, m), 3.45 (3H×1/2, s), 3.82 (3H×1/2, s), 4.93 (1H×1/2, d, $J=12.5$ Hz), 4.96 (1H×1/2, d, $J=12.2$ Hz), 5.10 (1H×1/2, d, $J=12.5$ Hz), 5.21 (1H×1/2, d, $J=12.2$ Hz), 7.13–7.40 (9H, m); HRMS calcd for $C_{22}H_{23}NO_4$ 365.1627, found 365.1324. **17**: IR ($CHCl_3$) 1738, 1705 cm^{-1}. Rotamers of **17** were observed by the ^1H NMR due to the benzyloxycarbonyl group. ^1H NMR (270 MHz, $CDCl_3$) δ 2.17 (3H, s), 3.14–3.20 (2H, m), 3.48–4.20 (2H, m), 3.51 (3H×1/3, s), 3.76 (3H×2/3, s), 5.10–5.25 (3H, m), 6.94–6.98 (2H, br d, $J=9.6$ Hz), 7.10–7.40 (8H, m); HRMS calcd for $C_{22}H_{23}NO_4$ 365.1628, found 365.1638.

4.10. (4*R*)-1-Benzyloxycarbonyl-2-[(2-bromo-4-methoxyphenyl)methyl]-4-(*tert*-butyldimethylsilyloxy)-2-(methoxycarbonyl)pyrrolidine, 19

Using a procedure similar to that described above for

11, a solution of **9** (5.75 g, 14.6 mmol) in THF (60 mL) was treated with a 1.0 M solution of $LiN(SiMe_3)_2$ in THF (17.5 mL, 17.5 mmol) followed by a solution of 2-bromo-4-methoxybenzyl bromide (**18**, 4.91 g, 17.5 mmol) in THF (15 mL). After work-up, the crude material was subjected to column chromatography on silica gel with hexane–AcOEt (4:1) to give an inseparable 4:1 mixture of **19a** and **19b** (7.86 g, 91%). IR ($CHCl_3$): 1740, 1698 cm^{-1}. Rotamers of both **19a** and **19b** were observed by the ^1H NMR due to their benzyloxycarbonyl group; ^1H NMR (270 MHz, $CDCl_3$) δ –0.13 to 0.12 (6H, m), 0.75 (s), 0.76 (s), 0.79 (s, total 9H), 1.96–2.23 (1H, m), 2.42–2.67 (1H, m), 3.16–3.26 (1H×4/5, m), 3.36–3.63 (4H, m), 3.50 (s), 3.74 (s), 3.76 (s), 3.77 (s, total 6H), 4.41–4.51 (1H×1/5, m), 4.94–5.33 (2H, m), 6.57–7.44 (8H, m). Anal. calcd for $C_{28}H_{38}BrNO_6Si$: C, 56.75; H, 6.46; N, 2.36. Found: C, 56.95; H, 6.59; N, 2.33.

4.11. (2*R*,4*R*)-1-Benzyloxycarbonyl-2-(2-bromo-4-methoxyphenyl)methyl-4-hydroxy-2-(methoxycarbonyl)-pyrrolidine, 20

Using a procedure similar to that described above for **12**, a solution of **19** (579 mg, 0.98 mmol) in THF (5 mL) was treated with a 1.0 M solution of tetrabutylammonium fluoride in THF (1.1 mL, 1.1 mmol). After work-up, the crude material was chromatographed on silica gel with hexane–AcOEt (4:1) to give a 4:1 mixture of **20** and its diastereomer (451 mg, 97%). The mixture was further purified by recrystallization from hexane–Et_2O to afford **20** (318 mg, 68% from **19**) in diastereomerically pure form. Mp 53–55°C; $[\alpha]_D^{23}$ –154.6 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$) 3021, 1744, 1698 cm^{-1}. Two rotamers (3:2) of **20** were observed by the ^1H NMR due to the benzyloxycarbonyl group; ^1H NMR (270 MHz, $CDCl_3$) δ 2.10 (1H, br d, $J=14.5$ Hz), 2.22 (1H×3/5, dd, $J=14.5$, 4.6 Hz), 2.27 (1H×2/5, dd, $J=14.5$, 5.3 Hz), 2.83 (1H×3/5, dd, $J=11.9$, 4.3 Hz), 2.92 (1×2/5, dd, $J=11.9$, 4.3 Hz), 3.44–3.81 (6H, m), 3.54 (3H×2/5, s), 3.76 (3H×3/5, s), 3.77 (3H×2/5, s), 3.87 (3H×3/5, s), 5.11 (1H×3/5, d, $J=12.5$ Hz), 5.17 (1H×2/5, d, $J=11.9$ Hz), 5.26 (1H×2/5, d, $J=11.9$ Hz), 5.34 (1H×3/5, d, $J=12.2$ Hz), 6.58 (1H×3/5, dd, $J=8.6$, 2.6 Hz), 6.72–6.87 (1H+1H×2/5, m), 7.07 (1H×3/5, d, $J=2.6$ Hz), 7.09 (1H×2/5, d, $J=2.3$ Hz), 7.20–7.50 (4H, m). Anal. calcd for $C_{22}H_{24}BrNO_6$: C, 55.24; H, 5.06; N, 2.93. Found: C, 55.09; H, 5.17; N, 2.93.

4.12. (*R*)-1-Benzyloxycarbonyl-2-(2-bromo-4-methoxyphenyl)methyl-2-methoxycarbonyl-4-oxopyrrolidine, 21

Using a procedure similar to that described above for **14**, a solution of **20** (82.0 mg, 0.172 mmol) in CH_2Cl_2 (0.8 mL) was treated with PCC (100 mg, 0.344 mmol) and Florisil® (200 mg). After work-up, the crude material was purified by column chromatography on silica gel with hexane–AcOEt (4:1) to give **21** (97.4 mg, 97%) as a colorless oil. $[\alpha]_D^{23}$ –85.2 (*c* 1.12, $CHCl_3$); IR ($CHCl_3$) 1767, 1748, 1707 cm^{-1}. Two rotamers of **21** were observed by the ^1H NMR due to the benzyloxycarbonyl group; ^1H NMR (270 MHz, $CDCl_3$) δ 2.74 (1H, d, $J=18.5$ Hz), 2.95 (1H, d, $J=18.5$ Hz), 3.29–3.94 (4H, m), 3.57 (3H×1/2, s), 3.80 (3H×1/2, s), 3.76 (3H, s), 5.16 (1H, d, $J=12.2$ Hz), 5.31 (1H, d, $J=12.2$ Hz), 6.63 (1H, br d, $J=9.6$ Hz), 6.82 (1H, br d, $J=6.8$ Hz), 7.05 (1H, br s), 7.37–7.40 (5H, m). Anal. calcd for $C_{22}H_{22}BrNO_6$: C, 55.48; H, 4.66; N, 2.94. Found: C, 55.23; H, 4.67; N, 2.89.

4.13. (*S*)-1-Benzyloxycarbonyl-2-(2-bromo-4-methoxyphenyl)methyl-2-methoxycarbonyl-4-(phenythiomethylene)pyrrolidine, 22

Using a procedure similar to that described above for **15a**, compound **21** (1.30 g, 2.73 mmol) was treated with $CeCl_3$ (2.35 g, 9.55 mmol) and $PhSCHLiP(O)Ph_2$ [prepared from $PhSCH_2P(O)Ph_2$ (2.66 mg, 8.19 mmol) and a 1.6 M solution of BuLi in hexane (5.15 mL, 8.19 mmol)] in THF (57 mL). After work-up, the crude material was exposed to NaH (60% dispersion, 800 mg, 20 mmol) at rt in THF (50 mL). After work-up, the crude product was purified by column chromatography on silica gel with hexane–AcOEt (4:1) to afford **22** (1.27 g, 80%) as an inseparable mixture of geometrical isomers. IR ($CHCl_3$) 1738, 1701, 1605 cm^{-1}; Two rotamers of **22** were observed by the ^1H NMR due to the benzyloxycarbonyl group; ^1H NMR (270 MHz, $CDCl_3$) δ 2.79 (1H, d, $J=16.8$ Hz), 3.16 (1H, dd, $J=16.8$, 5.6 Hz), 3.44–4.29 (4H, m), 3.47 (3H×1/2, s), 3.65 (3×1/2, s), 3.68 (3H×1/2, s), 3.78 (3H×1/2, s), 5.11 (1H×1/2, d, $J=12.2$ Hz), 5.14 (1H×1/2, d, $J=12.5$ Hz), 5.28 (1H×1/2, d, $J=12.2$ Hz), 5.11 (1H×1/2, d, $J=12.5$ Hz), 5.77 (1H, br d, $J=7.6$ Hz), 6.60 (1H×1/2, dd, $J=8.6$, 2.6 Hz), 6.70 (1H×1/2, dd, $J=8.6$, 2.6 Hz), 6.76 (1H×1/2, d, $J=8.6$ Hz), 6.94 (1H×1/2, d, $J=8.6$ Hz), 7.07 (1H, d, $J=8.6$ Hz), 6.97–7.42 (10H, m). Anal. calcd for $C_{29}H_{28}BrNO_5S$: C, 59.80; H, 4.84; N, 2.40. Found: C, 60.10; H, 4.83; N, 2.20.

4.14. (1*S*,4*R*)-3-Benzyloxycarbonyl-8-methoxy-4-methoxycarbonyl-1-phenylthiomethyl-2,3,4,5-tetrahydro-1,4-methano-3-benzazepine, 23

Using a procedure similar to that described above for **16a**, compound **22** (1.30 g, 2.23 mmol) was treated with Bu_3SnH (974 mg, 3.35 mmol) and AIBN (80 mg, 0.45 mmol) in benzene (250 mL). After work-up, the crude product was purified by column chromatography on silica gel with hexane-AcOEt (4:1) to give **23** (855 mg, 76%) as a colorless oil. $[\alpha]_D^{25}$ –77.6 (*c* 0.60, $CHCl_3$); IR ($CHCl_3$) 1741, 1698 cm^{-1}; Two rotamers (1:1) of **23** were observed by the ^1H NMR due to the benzyloxycarbonyl group; ^1H NMR (270 MHz, $CDCl_3$) δ 2.26 (1H, br d, $J=10.9$ Hz), 2.41 (1H, m), 3.36–3.79 (6H, m), 3.44 (3H×1/2, s), 3.77 (3H, s), 3.80 (3H×1/2, s), 4.94 (1H×1/2, d, $J=12.5$ Hz), 4.96 (1H×1/2, d, $J=12.5$ Hz), 5.10 (1H×1/2, d, $J=12.5$ Hz), 5.20 (1H×1/2, d, $J=12.5$ Hz), 6.77 (1H×1/2, dd, $J=8.2$, 2.6 Hz), 6.79 (1H×1/2, dd, $J=8.3$, 2.6 Hz), 6.86 (1H, d, $J=2.3$ Hz), 7.05 (1H×1/2, d, $J=8.3$ Hz), 7.11 (1H×1/2, d, $J=8.6$ Hz), 7.18–7.38 (10H, m). Anal. calcd for $C_{29}H_{29}NO_5S$: C, 69.16; H, 5.80; N, 2.78. Found: C, 68.89; H, 5.93; N, 2.60.

4.15. (1*S*,4*R*)-3-Benzyloxycarbonyl-8-methoxy-1-phenylthiomethyl-2,3,4,5-tetrahydro-1,4-methano-3-benzazepine, 26

A solution of **23** (1.23 g, 2.44 mmol) in 5N aqueous NaOH–MeOH (2:1, 15 mL) was heated at reflux for 2 h. The mixture was diluted with water (40 mL) and washed with Et_2O. The aqueous phase was acidified to pH 1–2 and extracted with $CHCl_3$. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give crude carboxylic acid **24** (1.20 g, quant.) as a pale yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.34 (1H, d, J=11.2 Hz), 2.52 (1H, d, J=11.2 Hz), 3.34–3.80 (6H, m), 3.77 (3H, s), 4.99 (1H, br d, J=12.5 Hz), 5.12 (1H, dd, J=12.2, 8.9 Hz), 6.76–6.88 (2H, m), 7.03 (1H×1/2, d, J=8.3 Hz), 7.11 (1H×1/2, d, J=8.6 Hz), 7.20–7.39 (10H, m). One proton of carboxylic acid was not observed in this spectrum. This compound was used immediately for the next step without further purification. To a stirred solution of the crude acid **24** (1.13 g, 2.30 mmol) in benzene (30 mL) was added a solution of 2-mercaptopyridine *N*-oxide (350 mg, 2.76 mmol), DMAP (421 mg, 3.45 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, 660 mg, 3.45 mmol) in benzene (10 mL) at rt. After 30 min, to the mixture was added a solution of Bu_3SnH (2.00 g, 6.87 mmol) and AIBN (110 mg, 0.67 mmol) in benzene (150 mL), and then the mixture was heated at reflux for 3 h. After cooling, the mixture was concentrated under reduced pressure. The residue was dissolved in Et_2O (40 mL), and then the solution was vigorously stirred with an 8% solution of KF (30 mL) overnight. The organic phase was separated, and the aqueous phase was further extracted with Et_2O. The organic phases were combined, washed with brine, dried ($MgSO_4$) and concentrated under reduce pressure. The residue was purified by column chromatography on silica gel with hexane-AcOEt (4:1) to afford **26** (530 mg, 52%) as a colorless oil. $[\alpha]_D^{25}$ −95.6 (*c* 0.76, $CHCl_3$); IR ($CHCl_3$) 1693 cm^{-1}. Two rotamers (1:1) of **26** were observed by the ^{1}H NMR due to the benzyloxycarbonyl group; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.00–2.06 (2H, m), 2.89–2.96 (1H, m), 3.06 (1H×1/2, d, J=7.2 Hz), 3.20 (1H×1/2, d, J=6.8 Hz), 3.38–3.79 (4H, m), 3.76 (3H, s), 4.44 (1H×1/2, dt, J=5.9, 2.9 Hz), 4.51(1H×1/2, dt, J=5.9, 2.9 Hz), 4.95 (1H×1/2, d, J=12.2 Hz), 5.10 (1H×1/2, d, J=12.5 Hz), 5.12 (1H×1/2, d, J=12.2 Hz), 5.16 (1H×1/2, d, J=12.5 Hz), 6.73–6.78 (1H, m), 6.87 (1H, br s), 7.00 (1H×1/2, d, J=8.6 Hz), 7.06 (1H×1/2, d, J=8.3 Hz), 7.17–7.39 (10H, m). Anal. calcd for $C_{27}H_{27}NO_3S$: C, 72.78; H, 6.11; N, 3.14. Found: C, 72.53; H, 6.28; N, 3.49.

4.16. *O*-Methylaphanorphine, 29

To a solution of **26** (32.0 mg, 0.072 mg) in MeOH (3 mL) was added W-2 Raney nickel (ca. 50 mg), and then the mixture was heated at reflux for 6 h. After cooling, the mixture was filtered through a pad of Celite®, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on alumina with $CHCl_3$–MeOH (50:1) to give **29** (10.0 mg, 65%) as a colorless oil. $[\alpha]_D^{23}$ +9.39 (*c* 0.30, $CHCl_3$), {lit.[3a] $[\alpha]_D^{29}$ +8.5 (*c* 0.35, $CHCl_3$), lit.[3d] $[\alpha]_D^{21}$ +10.4 (*c* 1.24, $CHCl_3$)}; ^{1}H NMR (270 MHz, $CHCl_3$) δ 1.47 (3H, s), 1.84 (1H, d, J=10.9 Hz), 2.00 (1H, dd, J=9.6, 5.9 Hz), 2.46 (3H, s), 2.71 (1H, d, J=8.8 Hz), 2.78–2.91 (3H, m), 3.38 (1H, m), 3.78 (3H, s), 6.68 (1H, dd, J=8.3, 2.6 Hz), 6.78 (1H, d, J=2.6 Hz), 7.02 (1H, d, J=8.3 Hz); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.3, 34.9, 41.2, 41.6, 43.1, 55.3, 61.3, 70.8, 109.1, 111.2, 125.5, 130.2, 147.8, 157.9. These ^{1}H and ^{13}C NMR spectral data are identical with those reported.[3d]

4.17. (−)-Aphanorphine, 1

According to the reported method,[3a,d] compound **29** was converted to **1**, mp 200–210°C (lit.[3a] mp 215–222°C). $[\alpha]_D^{21}$ −23.6 (*c* 0.20, MeOH) {lit.[3d] $[\alpha]_D^{23}$ −24.0 (*c* 0.33, MeOH)}; ^{1}H NMR (270 MHz, CD_3OD) δ 1.44 (3H, s), 1.86 (1H, d, J=10.9 Hz), 2.02 (1H, dd, J=10.9, 5.6 Hz), 2.48 (3H, s), 2.73 (1H, d, J=9.2 Hz), 2.83 (1H, br d, J=16.5 Hz), 2.87 (1H, d, J=9.2 Hz), 3.03 (1H, d, J=16.5 Hz), 3.42 (1H, quin, J=2.6 Hz), 6.91 (1H, dd, J=8.3, 2.3 Hz), 6.65 (1H, d, J=2.3 Hz), 6.52 (1H, d, J=8.3 Hz); ^{13}C NMR (67.8 MHz, CD_3OD) δ 21.6, 36.5, 42.1, 42.7, 44.2, 63.5, 72.6, 110.9, 114.5, 125.2, 131.2, 148.5, 156.5. These ^{1}H and ^{13}C NMR spectral data are identical with those provided by Professor Ogasawara.

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