A Catalytic Asymmetric Synthesis of Tubifolidine

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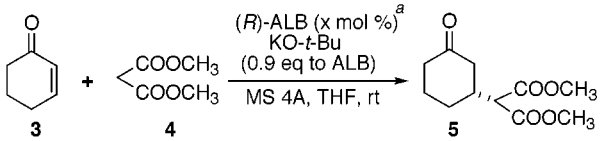
The *strychnos* alkaloids, which include tubifolidine (**1**), tubifoline, and strychnine, constitute an important group of architecturally complex and widely distributed monoterpenoid indole alkaloids.[2] Total syntheses of these natural products in the racemic or naturally occurring form have already been achieved by several groups.[3] To date, however, no catalytic asymmetric syntheses of the *strychnos* alkaloids have been accomplished except for syntheses involving enzymatic methods. We therefore initiated a research program into the catalytic asymmetric synthesis of these indole alkaloids. 20-Deethyltubifolidine (**2**) and tubifolidine (**1**) were selected as the first target compounds. In this note we report the catalytic asymmetric synthesis of **1** and **2** in which a highly practical catalytic asymmetric Michael addition of dimethyl malonate (**4**) to cyclohexenone (**3**), as well as a one-pot construction of the ABDE ring systems using DDQ, were involved as key steps.

The related compounds of the racemic Michael adduct **5** have already been utilized, by Magnus and co-workers,[4] for the synthetic studies of these alkaloids. We thus concentrated first on the efficient synthesis of **5** in a catalytic asymmetric manner. We previously developed a variety of heterobimetallic asymmetric complexes, which we used to realize many efficient catalytic asymmetric reactions, including a Michael addition.[5] In fact, **5** was efficiently synthesized in up to 93% ee using either $LaNa_3$tris(binaphthoxide) complex, AlLibis(binaphthoxide) complex (ALB), or GaNabis(binaphthoxide) complex. Among these catalysts, we concluded that ALB was the most effective for the present Michael addition. Moreover, we have developed a strategy for the activation of ALB: the addition of nearly 1 equiv of bases, such as BuLi and KO-*t*-Bu, to ALB can accelerate a catalytic asymmetric Michael addition without lowering the high enantiomeric excess.[5,6] However, 3−5 mol % of the catalyst is still required to obtain the product in excellent yield and high enantiomeric excess. We intended to improve the catalytic asymmetric Michael addition to a practically useful level. After many attempts, we were pleased to find that addition of MS 4A[7] to the reaction medium greatly improved the catalytic asymmetric Michael addition. Actually, as shown in Table 1, the use of ALB (0.3 mol %), KO-*t*-Bu (0.27 mol %), and MS 4A gave **5**[8] in 99% ee and 94% yield even at room temperature. Furthermore, we successfully carried out this reaction on a 100 g scale. Addition of MS 4A appears to remove a trace amount of H_2O that would otherwise gradually decompose the ALB−KO-*t*-Bu catalyst.

Table 1. A Greatly Impoved Catalytic Asymmetric Michael Addition of 4 to 3



run	ALB (x mol %)	KO-*t*-Bu	MS 4A	time (h)	yield (%)	ee (%)
1[b]	10	-	-	72	90	93
2[c]	5	+	-	48	97	98
3[c]	0.3	+	-	120	74	88
4[c]	0.3	+	+[e]	120	94	99
5[d]	1.0	+	+[f]	72	96	99

a: (*R*)-AlLibis(binaphthoxide). *b*: 200 mg scale reaction. *c*: 400 mg scale reaction. *d*: 100 g scale reaction. *e*: MS 4A (8.3 g) was used for ALB (1 mmol). *f*: MS 4A (2.0 g) was used for ALB (1 mmol).

Having obtained nearly optically pure **5** in large quantities, we next efficiently converted **5** to the indole derivative **6** in 92% overall yield, through a highly regioselective Fischer method[4,9] followed by decarbalkoxylation (Scheme 1). Also at this stage, the enantiomeric excess of **6** was confirmed to be 99%.[10] The indole derivative **6** was further transformed into the amine **7** in a three-step reaction sequence (38% overall yield). It was expected that treatment of **7** with DDQ would produce the tetracyclic compound **8** in a one-pot reaction through the dehydrogenated intermediate.[11] Indeed, we could find that exposure of **7** to DDQ (1.1 molar equiv) and Na_2HPO_4 (10 molar equiv) in degassed THF at 0 °C for 1 h gave **8** in 77% yield. To the best of our knowledge, this is the only example of a one-pot construction of the

(1) Present address: The Institute of Scientific and Industrial Research, Osaka University, 8-1 Mihogaoka, Ibaraki, Osaka 567-0047, Japan.

(2) For a review, see: Bosch, J.; Bonjoch, J.; Amot, M. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1996; vol. 48, pp 75−189.

(3) (a) (±)-**2**: Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299−6312 and references therein. (b) (±)-**1**: Bonjoch, J.; Sóle, D.; Garcia-Rubio, S.; Bosch, J. *J. Am. Chem. Soc.* **1997**, *119*, 7230−7240 and references therein. See also ref 3a. (c) (−)-**1**: Amat, M.; Coll, M.-D.; Bosch, J.; Espinosa, E.; Molins, E. *Tetrahedron Asymmetry* **1997**, *8*, 935−948. See also ref 3b. (d) (±)-strychnine: Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1993**, *58*, 7490−7497. Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685−2686 and references therein. (e) (−)-strychnine: Magnus, P.; Giles, M.; Bonnert, R.; Johnson, G.; McQuire, L.; Deluca, M.; Merritt, A.; Kim, C. S.; Vicker, N. *J. Am. Chem. Soc.* **1993**, *115*, 8116−8129. Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776−5788 and references therein.

(4) Magnus, P.; Sear, N. L.; Kim, C. S.; Vicker, N. *J. Org. Chem.* **1992**, *57*, 70−78. In this paper, the resolution of cyclohexanone-3-acetic acid using quinine was also described.

(5) For a review, see: Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256.

(6) (a) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem. Eur. J.* **1996**, *2*, 1368−1378. (b) Arai, T.; Sasai, H.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 441−442.

(7) Molecular sieves (MS) 4A was dried at 180 °C for 6 h under reduced pressure prior to use.

(8) The absolute configuration of **5** has already been determined. See: Sasai, H.; Arai, T.; Satow, Y.; Houk. K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194−6198. The enantiomeric excess was determined by chiral stationary phase HPLC analysis [DAICEL CHIRALPAK AS, hexane/2-propanol (90:10, v/v), flow rate: 0.5 mL/min, retention time: 50 min (*R*)-isomer and 60 min (*S*)-isomer, detection at 215 nm].

(9) Berger, L.; Corraz, A. J. U.S. Patent 4,009,181, 1977.

(10) The enantiomeric excess was determined by chiral stationary phase HPLC analysis [DAICEL CHIRALPAK AD, hexane/2-propanol (90:10, v/v), flow rate: 1.0 mL/min, retention time: 14 min (*S*)-isomer and 17 min (*R*)-isomer, detection at 254 nm].

(11) Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1977**, *42*, 1213−1216. It is well-known that, for example, treatment of tetrahydrocarbazole with DDQ and H_2O gives tetrahydrocarbazol-4-one. See also ref 4.

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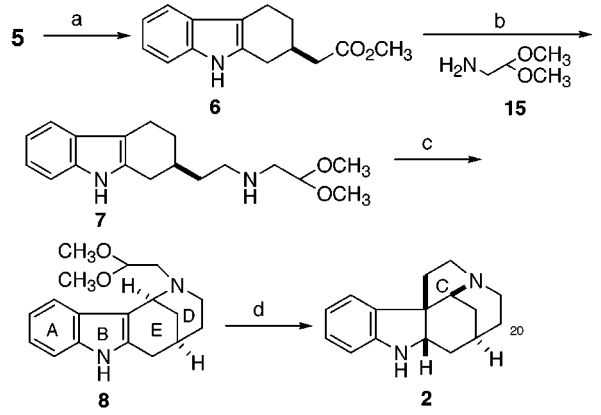
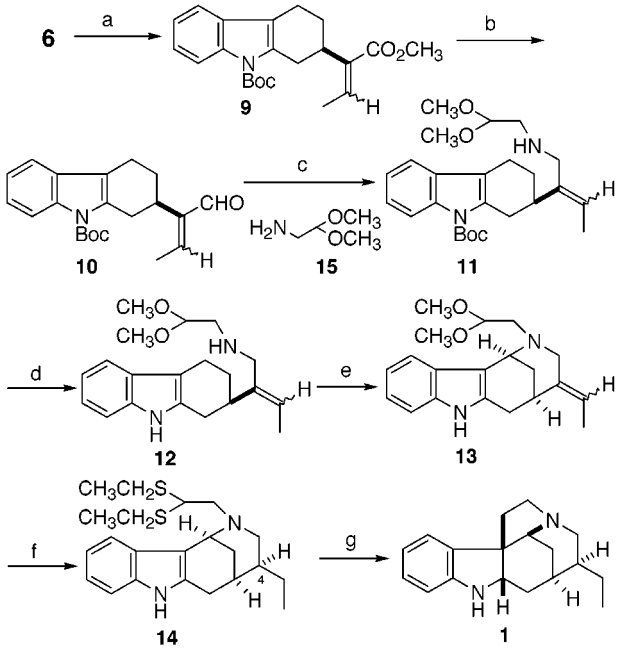
Scheme 1. A Catalytic Asymmetric Synthesis of 20-Deethyltubifolidine (2)[a]



[a]Reagents and conditions: (a) 1. $PhNHNH_2$•HCl (1.05 equiv), AcOH, 80 °C, 2. LiCl (2.0 equiv), H_2O (1.0 equiv), DMSO, 180 °C, 92% (99% ee) (2 steps); (b) 1. LiOH (1.6 equiv), THF- H_2O (3 : 1), rt, 2. **15** (2.4 equiv), HOBt (1.2 equiv), DCC (1.2 equiv), DMAP (cat.), THF, rt, 78% (2 steps), 3. BH_3•THF (2.5 equiv), THF, 60 °C, 49%; (c) DDQ (1.1 equiv), Na_2HPO_4 (10 equiv), degassed THF, 0 °C, 77%; (d) 1. EtSH (excess), BF_3•Et_2O (10 equiv), MS 3A, CH_2Cl_2, 0 °C, 77%, 2. DMTSF (2.1 equiv), CH_2Cl_2, 0 °C, 80%, 3. Raney Ni (W2) (excess), EtOH, reflux, 44%.

Scheme 2. A Catalytic Asymmetric Synthesis of Tubifolidine (1)[a]



[a]Reagents and conditions: (a) 1. $(Boc)_2O$ (1.2 equiv), Et_3N (2.0 equiv), DMAP (cat.), CH_2Cl_2, rt, 97%; 2. LDA (1.3 equiv), THF, -78 °C; acetaldehyde (2.0 equiv) 3. MsCl (1.5 equiv), *i*-Pr_2NEt (3.0 equiv), toluene, rt; DBU (4.3 equiv), 50 °C, 89% (2 steps); (b) 1. DIBAL (3.0 equiv), toluene, -78 °C, conv. 97%; 2. MnO_2 (excess), pentane, rt, 94%; (c) **15** (2.1 equiv), Ti(O-*i*-Pr)$_4$ (2.5 equiv), toluene, rt; $NaBH_4$ (10 equiv), CH_3OH, 0 °C, 96%; (d) TFA (excess), anisole (10 equiv), 0 °C, 98%; (e) DDQ (1.1 equiv), Na_2HPO_4 (10 equiv), degassed THF, -20 °C to 0 °C, conv. 67%; (f) 1. H_2, $(Ph_3P)_3RhCl$ (cat.), benzene - 2-PrOH (5 : 1), rt; 2. EtSH (excess), BF_3•Et_2O (8 equiv), MS 3A, CH_2Cl_2, 0 °C to rt, 66% (2 steps); (g) 1. DMTSF (2.1 equiv), CH_2Cl_2, 0 °C, 68%; 2. $LiAlH_4$ (4.8 equiv), THF, 0 °C; 3. Raney Ni (W2) (excess), EtOH, reflux, 35% (2 steps).

tetracyclic compound starting with **7**. The tetracyclic compound **8** was then transformed into 20-deethyltubifolidine (**2**), in a three-step reaction sequence (27% overall yield), using a procedure reported by Bosch and coworkers.[3a,12] The optical rotation of **2** was $[\alpha]^{21}_D = -10$ (*c* 0.25, $CHCl_3$).

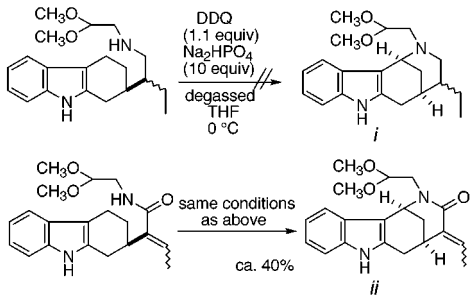
Having achieved a practical catalytic asymmetric synthesis of **2**, we next pursued a catalytic asymmetric synthesis of tubifolidine (**1**). Toward this end, **6** was first protected as a *tert*-butyl carbamate, and the resulting carbamate underwent aldol condensation followed by dehydration through the mesylate to give **9** in 86% overall yield (*E*:*Z* = 8:1) (Scheme 2). The ester **9** thus obtained was reduced with DIBAL and then oxidized with MnO_2 to furnish **10** in 91% overall yield. The next transformation of **10** to **11** constituted a relatively problematic step. After several attempts, it was found that treatment of **10** with **15** (2.1 molar equiv) and Ti(O-*i*-Pr)$_4$ (2.5 molar equiv)[13] followed by reduction with $NaBH_4$ in CH_3OH gave **11** in 96% yield. The resulting **11** was deprotected by treatment with trifluoroacetic acid and anisole to afford **12** in 98% yield. Again, we were faced with the challenge of a crucial one-pot construction step using DDQ.[14] We were pleased to find that treatment of **12** with DDQ (1.1 molar equiv) and Na_2HPO_4 (10 molar equiv) in degassed THF at −20 °C to 0 °C for 2 h gave **13** in 52% yield (67% yield based on consumed **12**). The tetracyclic compound **13** was converted to **14** in 66% overall yield, through a stereoselective reduction followed by acetal exchange.[15] The dithioacetal **14** was finally transformed into tubifolidine (**1**) in a three-step reaction sequence (24% overall yield).[3a,12] The optical rotation of **1** was $[\alpha]^{19}_D = -61$ (*c* 0.36, $CHCl_3$; 99% ee[16]) [lit.[17] $[\alpha]^{29}_D = -67 \pm 3$ (*c* 0.61, $CHCl_3$), lit.[3c] $[\alpha]^{22}_D = -41.6$ (*c* 0.61, $CHCl_3$; 95.3% ee)]. Thus, a catalytic asymmetric synthesis of **1** was achieved in a highly stereocontrolled manner.

In conclusion, we have developed a catalytic asymmetric synthesis of 20-deethyltubifolidine (**2**) and tubifolidine (**1**), in which only 0.3 mol % of the heterobimetallic asymmetric catalyst (ALB−KO-*t*-Bu-MS 4A) at room temperature is required for the efficient catalytic asymmetric Michael addition of **4** to **3**. In addition, the one-pot construction of the tetracyclic synthetic intermediates from the tricyclic intermediates using DDQ was noteworthy. We also believe that the indole derivative **6** readily obtainable in nearly optically pure form would

(12) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529−6530.

(13) (a) Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552−2554. (b) Bhattacharyya, S. *Tetrahedron Lett.* **1994**, *35*, 2401−2404.

(14) We also tried to apply this type of reaction with DDQ to the other substrates. The desired tetracyclic compound ***i***, however, could not be obtained at all, most likely due to the steric hindrance of the ethyl group. On the other hand, ***ii*** could be obtained in moderate yield.



be an interesting building block for the preparation of a variety of optically active ligands. Further studies are currently under investigation.

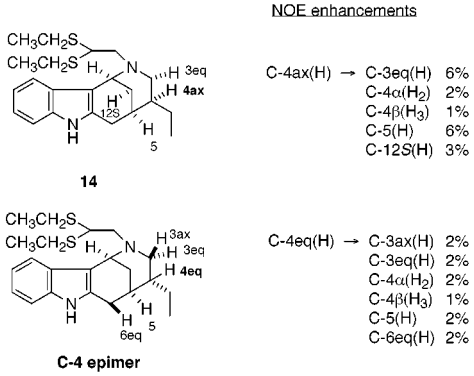
Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR spectra were measured with $CDCl_3$ or C_6D_6 as solvents. Chemical shifts are reported in ppm on the δ scale relative to TMS ($\delta = 0.00$ for ^{1}H NMR) or using residual $CHCl_3$ ($\delta = 7.26$ for ^{1}H NMR and $\delta = 77.0$ for ^{13}C NMR) or benzene ($\delta = 7.15$ for ^{1}H NMR and $\delta = 128.0$ for ^{13}C NMR) as an internal reference, respectively. All solvents used in the reactions were dried prior to use. All reagents were purified by standard methods. Powdered molecular sieve 4A (MS 4A) was dried at 180 °C under reduced pressure for more than 6 h prior to use. All experiments were performed under anhydrous conditions in an atmosphere of Ar, unless otherwise mentioned, and monitored with analytical TLC (Merck Art. No. 5715, silica gel 60 F_{254} plate). Spectral data of compounds **1**, **2**, **6**−**14** were obtained, using chromatographically homogeneous samples. In the case of compounds **9**−**13**, ^{1}H NMR and ^{13}C NMR spectroscopic data have been assigned only for the *E*-isomer. Because **9**−**13** were a mixture of isomers, the optical rotations α_D were not recorded.

Preparation of (*R*)-AlLibis(binaphthoxide) ((*R*)-ALB) Complex in THF Solution. To a suspension of freshly opened $LiAlH_4$ (powder, 189.8 mg, 5.0 mmol) in THF (20 mL) was slowly added (*R*)-BINOL (2.864 g, 10.0 mmol) in THF (20 mL, plus 5 mL × 2) via cannula at 0 °C. After being stirred at the same temperature for 30 min and then at room temperature for additional 1 h, the resulting mixture was kept standing without stirring overnight. The supernatant was used as 0.1 M ALB THF solution.

Catalytic Asymmetric Michael Addition Using (*R*)-AlLibis(binaphthoxide) Complex ((*R*)-ALB), KO-*t*-Bu, and MS 4A: Synthesis of (*R*)-3-[Bis(methoxycarbonyl)methyl]-cyclohexanone (5). (1) 400 mg scale reaction (using the ALB−KO-*t*-Bu catalyst (0.3 mol %)): To a mixure of (*R*)-ALB (in THF, 0.05 M; 120 μL, 6.0 μmol) and powdered MS 4A (50 mg) in THF (1.2 mL) were successively added at 0 °C KO-*t*-Bu (in THF, 0.099 M; 55 μL, 5.4 μmol), dimethyl malonate (**4**) (229 μL, 2.00 mmol), and cyclohexenone (**3**) (194 μL, 2.00 mmol). After being stirred for 120 h at room temperature, the reaction mixture was diluted with AcOEt and filtered over a Celite pad to remove the MS 4A. The filtrate was washed with 1 N HCl and extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (acetone/hexane, 1:9) to give the Michael adduct **5** (427 mg, 1.87 mmol; 94%) in 99% ee. The spectral and analytical data of **5** were in agreement with those that we reported (ref 8).

(15) The C-4 epimer was also obtained in 9% overall yield. The stereochemistry of the epimers could be confirmed by carrying out NOE measurements.



(16) The enantiomeric excess was confirmed by chiral stationary phase HPLC analysis, ref 3c.

(17) For the isolation and structural elucidation of this alkaloid, see: Kump, W. G.; Patel, M. B.; Rowson, J. M.; Schmid, H. *Helv. Chim. Acta* **1964**, *47*, 1497−1503.

(2) 100 g scale reaction (using the ALB−KO-*t*-Bu catalyst (1.0 mol %)): To a mixure of (*R*)-ALB (in THF, 0.05 M; 100 mL, 5.0 mmol) and powdered MS 4A (10 g) were successively added at 0 °C KO-*t*-Bu (in THF, 0.253 M; 17 mL, 4.3 mmol), dimethyl malonate (**4**) (57.1 mL, 0.50 mol), and cyclohexenone (**3**) (48.4 mL, 0.50 mol). After being stirred for 72 h at room temperature, the reaction mixture was quenched as described above. The crude product (99% ee) was purified by repeated recrystallization (toluene/hexane, 1:1) to afford a combined yield of pure **5** (94.1 g). The remaining mother liquor was concentrated and passed through an alumina flash column (acetone/hexane, 1:9 to 1:6). The fractions (containing **5**) were concentrated, and **5** spontaneously recrystallized (9.5 g). The remaining mother liquor was again concentrated to give a residue which was then purified by silica gel flash chromatography (acetone/hexane, 1:9) to give another 6.0 g of **5**. That is, the combined yield of **5** was 109.6 g (0.48 mol; 96%). Most of the BINOL was recovered during chromatography as a fraction eluted after the main product **5**.

Synthesis of (*R*)-1,2,3,4-Tetrahydro-2-[(methoxycarbonyl)methyl]-9*H*-carbazole (6). To a solution of ketone **5** (2.06 g, 9.03 mmol) in AcOH (15 mL) was added phenylhydrazine hydrochloride (1.37 g, 9.47 mmol). After being stirred for 2 h at 80 °C, the reaction mixture was concentrated to give a residue, which was dissolved in AcOEt. After addition of saturated aqueous $NaHCO_3$, the organic layer was separated. The aqueous layer was further extracted with AcOEt. The combined organic layers were successively washed with saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated to give the tricyclic compound, which was used without further purification. To a solution of the indole compound in DMSO (10 mL) were added lithium chloride (0.763 g, 18.0 mmol) and H_2O (160 μL, 8.9 mmol). After being stirred for 1 h at 180 °C, the reaction mixture was quenched with water and AcOEt, and the organic layer was separated. The aqueous layer was further extracted twice with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by alumina flash chromatography (AcOEt/hexane, 1:5) to give the methyl ester **6** (2.03 g, 8.34 mmol; 92% (two steps)) as a solid. $[\alpha]^{22}_D = +67.1$ (*c* 0.82, $CHCl_3$) (99% ee); mp 87−88 °C (AcOEt); IR (KBr) 3372, 2938, 1720 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.47 (d, $J = 7.6$ Hz, 1H), 7.28 (d, $J = 7.9$ Hz, 1H), 7.15−7.07 (m, 2H), 3.73 (s, 3H), 2.89 (m, 1H), 2.81 (m, 1H), 2.73 (m, 1H), 2.52−2.43 (m, 4H), 2.03 (m, 1H), 1.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 135.9, 132.8, 127.4, 121.1, 119.2, 117.8, 110.4, 109.6, 51.5, 40.2, 31.5, 29.3, 29.1, 19.9; EI-MS *m*/*z* 243 (M^+), 212 ($M^+ - OCH_3$), 143 ($M^+ - CH_2CHCH_2COOCH_3$); Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04, N, 5.76. Found: C, 73.84; H, 6.94, N, 5.69.

Synthesis of (*S*)-2-[2-[*N*-(2,2-Dimethoxyethyl)amino]-ethyl]-1,2,3,4-tetrahydro-9*H*-carbazole (7). To a solution of ester **6** (3.69 g, 15.2 mmol) in THF (45 mL) and H_2O (15 mL) was added $LiOH \cdot H_2O$ (0.91 g, 23.9 mmol). After being stirred for 63 h at room temperature, the reaction mixture was quenched with aqueous citric acid and diluted with AcOEt. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give the carboxylic acid, which was used without further purification. To a solution of the carboxylic acid in THF (150 mL) were added (2,2-dimethoxy)ethylamine **15** (3.9 mL, 35.8 mmol), HOBt (2.76 g, 18.0 mmol), DCC (3.72 g, 18.0 mmol), and DMAP (160 mg, 1.3 mmol). After being stirred for 40 h at room temperature, the reaction mixture was concentrated to give a residue, which was dissolved in CH_3CN and filtered. The filtrate was concentrated to give a residue which was then purified by silica gel flash chromatography (CH_3OH/CH_2Cl_2, 0:1 to 1:40) to give the amide (3.76 g, 11.9 mmol; 78% (two steps)) as a foam.

To a solution of the amide (34.6 mg, 109 μmol) in THF (3 mL) was added $BH_3 \cdot$THF (in THF, 1.0 M; 270 μL, 270 μmol). After being stirred for 5 h at 60 °C, the reaction mixture was diluted with Et_2O and then quenched with 6 N aqueous NaOH. The whole mixture was stirred for 1 h at room temperature, and the organic layer was separated. The aqueous layer was further extracted twice with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated to give a residue which was then purified by silica gel flash chromatography (Et_2NH/Et_2O,

1:150 to 1:50) to give the amine **7** (16.1 mg, 53.2 μmol; 49%) as an oil. $[\alpha]^{22}_D = +57.0$ (*c* 1.00, $CHCl_3$) (99% ee); IR (neat) 3402, 2815, 1453 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.78 (s, 1H), 7.59 (d, J = 7.0 Hz, 1H), 7.28−7.21 (m, 3H), 4.49 (t, J = 5.5 Hz, 1H), 3.17 (s, 3H), 3.16 (s, 3H), 2.81 (d, J = 5.5 Hz, 2H), 2.72 (m, 1H), 2.62−2.53 (m, 3H), 2.49 (dd, J = 15.9, 5.2 Hz, 1H), 2.10 (dd, J = 15.9, 9.5 Hz, 1H), 1.82−1.76 (m, 2H), 1.47−1.28 (m, 3H), 1.11 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 136.7, 133.7, 128.4, 121.0, 119.3, 118.2, 110.8, 109.8, 104.3, 53.4, 51.8, 48.0, 36.8, 32.8, 30.2, 29.8, 20.7; EI-MS *m*/*z* 303 ($M^+ + H$), 302 (M^+), 227 ($M^+ - CH(OCH_3)_2$), 170 ($M^+ - (CH_2)_2NHCH_2CH(OCH_3)_2$), 75 ($CH(OCH_3)_2$); EI−HRMS Calcd for $C_{18}H_{26}N_2O_2$ (M^+): 302.1994, Found: 302.1979.

Synthesis of (1*S*,5*R*)-2-(2,2-Dimethoxyethyl)-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (8). To a mixture of amine **7** (9.2 mg, 30.4 μmol) and Na_2HPO_4 (43.3 mg, 305 μmol) in degassed THF (3 mL) at 0 °C was added DDQ (7.6 mg, 33.4 μmol) in degassed THF (3 mL) during 15 min. After being stirred for additional 45 min at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with AcOEt. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (Et_2NH/Et_2O, 1:150) to give the tetracyclic amine **8** (7.0 mg, 23.3 μmol; 77%) as a solid. $[\alpha]^{22}_D = +78.4$ (*c* 0.52, EtOH) (99% ee); mp 139−140 °C (AcOEt); IR (KBr) 2928, 1467 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.78 (m, 1H), 7.25 (s, 1H), 7.21−7.12 (m, 3H), 4.68 (dd, J = 5.2, 5.2 Hz, 1H), 4.31 (dd, J = 5.8, 2.8 Hz, 1H), 3.27 (s, 3H), 3.15 (dd, J = 13.4, 5.2 Hz, 1H), 3.13 (s, 3H), 2.64−2.59 (m, 2H), 2.36 (dd, J = 13.4, 5.2 Hz, 1H), 2.26−2.14 (m, 3H), 2.04−1.94 (m, 2H), 1.71 (m, 1H), 1.36 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 136.4, 136.2, 128.9, 121.0, 120.0, 119.2, 110.7, 107.4, 104.1, 59.3, 52.9, 52.7, 51.7, 45.8, 33.8, 33.6, 29.4, 25.8; EI-MS *m*/*z* 301 ($M^+ + H$), 300 (M^+), 225 ($M^+ - CH(OCH_3)_2$); EI−HRMS Calcd for $C_{18}H_{24}N_2O_2$ (M^+): 300.1838, Found: 300.1846.

Synthesis of (−)-20-Deethyltubifolidine (2). To a mixture of amine **8** (125.5 mg, 0.418 mmol) in CH_2Cl_2 (25 mL) was added MS 3A, EtSH (10 mL), and $BF_3{\cdot}Et_2O$ (500 μL, 4.1 mmol) at 0 °C. After being stirred for 45 h at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (Et_2NH/Et_2O, 1:200) to give the thioacetal (116.0 mg, 0.322 mmol; 77%) as a solid. To a mixture of dimethyl(methylthio)sulfonium fluoroborate (DMTSF) (45 mg, 229 μmol) in CH_2Cl_2 (3 mL) was added thioacetal (39 mg, 108 μmol) in CH_2Cl_2 (10 mL) at 0 °C. After being stirred for 3 h at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (CH_3OH/CH_2Cl_2/aq NH_3, 1:30:0.3) to give the imine (25.8 mg, 86 μmol; 80%) as a foam. To a mixture of imine (9.3 mg, 31.2 μmol) in EtOH (1 mL) was added Raney Ni (W2) (excess). After being stirred for 2 h under reflux, the reaction mixture was diluted with Et_2O, and filtered over a Celite pad. The filtrate was concentrated to give a residue which was then purified by silica gel flash chromatography (Et_2NH/Et_2O, 1:49) to give 20-deethyltubifolidine **2** (3.3 mg, 13.8 μmol; 44%) as a solid. $[\alpha]^{21}_D = -10$ (*c* 0.25, $CHCl_3$) (99% ee); IR (KBr) 3269, 2924, 1606 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.06−7.03 (m, 2H), 6.76 (m, 1H), 6.62 (m, 1H), 3.77 (dd, J = 9.2, 7.6 Hz, 1H), 3.62 (br-s, 1H), 3.37 (br-s, 1H), 3.13 (m, 1H), 3.03 (m, 1H), 2.87 (ddd, J = 12.2, 8.5, 4.0 Hz, 1H), 2.51 (td, J = 11.9, 5.2 Hz, 1H), 2.40 (dt, J = 13.4, 7.9 Hz, 1H), 1.98−1.83 (m, 5H), 1.70−1.51 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 131.5, 127.7, 122.2, 119.1, 109.5, 65.1, 62.3, 54.0, 52.7, 47.7, 42.3, 37.5, 29.1, 26.7, 23.3; EI-MS *m*/*z* 240 (M^+); EI−HRMS Calcd for $C_{16}H_{20}N_2$ (M^+): 240.1622, Found: 240.1626.

Synthesis of (*R*)-9-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydro-2-[1-(methoxycarbonyl)-1-propenyl]-9*H*-carbazole (9). To a mixture of ester **6** (4.91 g, 20.2 mmol; 99% ee) in CH_2Cl_2 (140 mL) were added Et_3N (5.63 mL, 40.4 mmol), di-*tert*-butyl dicarbonate (5.8 mL, 25.2 mmol), and DMAP (250 mg, 2.0 mmol). After being stirred for 12 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1:15) to give the carbamate (6.70 g, 19.5 mmol; 97%) as a solid. To a mixture of LDA (25.5 mmol) in THF (150 mL) was added carbamate (6.70 g, 19.5 mmol) in THF (40 mL) at −78 °C. After being stirred for 1 h at the same temperature, to this mixture was added acetaldehyde (3.58 M in THF; 10.9 mL, 39.0 mmol) slowly via cannula at −78 °C. After being stirred for 1 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1:10 to 1:3) to give the aldol adduct (ca. 7 g) as a foam. To a mixture of the aldol adduct (ca. 7 g) in toluene (130 mL) were added *i*-Pr_2NEt (10.2 mL, 58.6 mmol) and methanesulfonyl chloride (2.3 mL, 29.7 mmol). After being stirred for 1 h at room temperature, DBU (11.6 mL, 77.6 mmol) was added to the mixture, and after being stirred for further 22 h at 50 °C, additional DBU (1 mL, 6.7 mmol) was added. After being stirred for 2 h at 50 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl at 0 °C and diluted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1:15) to give the α,β-unsaturated ester **9** (6.39 g, 17.3 mmol; 89% (two steps)) as a solid. IR (KBr) 2944, 1726 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 7.4 Hz, 1H), 7.26−7.20 (m, 2H), 6.88 (dq, J = 7.4, 1.9 Hz, 1H (olefinic CH) (δ 6.03 corresponds to the *Z*-isomer)), 3.74 (s, 3H), 3.31 (m, 1H), 3.08−3.02 (m, 2H), 2.85 (m, 1H), 2.64 (m, 1H), 2.31 (m, 1H), 1.87 (d, J = 7.4 Hz, 3H), 1.83 (m, 1H), 1.65 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 150.6, 137.7, 136.3, 135.8, 135.5, 129.6, 123.3, 122.4, 117.5, 116.2, 115.4, 83.3, 51.4, 35.0, 30.0, 28.3, 26.5, 21,5, 14.1; EI-MS *m*/*z* 369 (M^+), 57 ($(CH_3)_3C$); EI−HRMS Calcd for $C_{22}H_{27}NO_4$ (M^+): 369.1940, Found: 369.1955.

Synthesis of (*R*)-9-(*tert*-Butoxycarbonyl)-2-(1-formyl-1-propenyl)-1,2,3,4-tetrahydro-9*H*-carbazole (10). To a mixture of ester **9** (756.9 mg, 2.05 mmol) in toluene (20 mL) was added DIBAL (0.95 M in toluene; 6.5 mL, 6.2 mmol). After being stirred for 3 h at −78 °C, the reaction mixture was poured into a vigorously stirred mixture of saturated aqueous potassium sodium tartrate and Et_2O via cannula at 0 °C. The whole mixture was stirred vigorously for 30 min at room temperature. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (AcOEt/hexane, 1:12 to 1:6) yielding **9** (200.6 mg, 0.54 mmol) and the alcohol (497.3 mg, 1.46 mmol; 71% (conv. 97%)) as a foam. To a mixture of the alcohol (490 mg, 1.44 mmol) in pentane (30 mL) was added MnO_2 (ca. 2.5 g). After being stirred for 3 h at room temperature, the reaction mixture was filtered over a Celite pad. The filtrate was concentrated to give the aldehyde **10** (458.5 mg, 1.35 mol; 94%) as a solid. IR (KBr) 2970, 1725, 1678 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.21 (s, 1H), 8.48 (d, J = 8.3 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.32 (m, 1H), 7.23 (m, 1H), 5.82 (q, J = 5.4 Hz, 1H), 3.46 (m, 1H), 3.03 (dd, J = 17.7, 5.2 Hz, 1H), 2.86 (m, 1H), 2.58 (m, 1H), 2.45−2.35 (m, 2H), 1.56 (m, 1H), 1.39 (d, J = 5.4 Hz, 3H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 194.5, 151.0, 150.2, 137.0, 135.8, 130.7, 128.6, 124.2, 123.1, 118.3, 116.9, 116.4, 83.0, 34.2, 30.1, 28.4, 26.7, 22.0, 14.8; EI-MS *m*/*z* 339 (M^+), 57 ($C(CH_3)_3$); EI−HRMS Calcd for $C_{21}H_{25}NO_3$ (M^+): 339.1834, Found: 339.1835.

Synthesis of (*R*)-9-(*tert*-Butoxycarbonyl)-2-[1-[*N*-(2,2-dimethoxyethyl)aminomethyl]-1-propenyl]-1,2,3,4-tetrahydro-9*H*-carbazole (11). To a mixture of aldehyde **10** (227.3 mg, 0.671 mmol) in toluene (7 mL) was added (2,2-dimethoxy)-ethylamine **15** (150 μL, 1.38 mmol) and Ti(O-*i*-Pr)$_4$ (500 μL, 1.69 mmol). After being stirred for 1 h at room temperature, the mixture was diluted with CH_3OH (11 mL). Then $NaBH_4$ (250 mg, 6.60 mmol) was added at 0 °C. After being stirred for 1 h

at the same temperature, the reaction mixture was poured into the mixture of saturated aqueous NH_4Cl and AcOEt. The whole mixture was stirred vigorously and filtered over a Celite pad. The organic layer of the filtrate was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (Et_2NH/Et_2O/hexane, 1:50:50) to give the amine **11** (275.1 mg, 0.643 mmol; 96%) as an oil. IR (neat) 2931, 1727, 1458 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 8.54 (m, 1H), 7.40 (m, 1H), 7.32 (m, 1H), 7.25 (m, 1H), 5.52 (q, J = 5.9 Hz, 1H), 4.51 (t, J = 4.3 Hz, 1H), 3.20−3.13 (m, 4H), 3.18 (s, 3H), 3.17 (s, 3H), 2.86 (m, 1H), 2.80 (d, J = 4.3 Hz, 2H), 2.61 (m, 1H), 2.46 (m, 1H), 1.85 (m, 1H), 1.76 (m, 1H), 1.57 (d, J = 5.9 Hz, 3H), 1.41 (s, 9H), 1.43−1.37 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 150.7, 141.8, 136.8, 136.0, 130.4, 123.7, 122.8, 121.5, 117.9, 116.5, 116.0, 104.3, 82.5, 53.8, 53.3, 53.2, 51.1, 36.6, 30.7, 28.1, 27.4, 21.7, 13.0; EI-MS m/z 428 (M^+), 353 ($M^+ - CH(OCH_3)_2$); EI−HRMS Calcd for $C_{25}H_{36}N_2O_2$ (M^+): 428.2675, Found: 428.2684.

Synthesis of (*R*)-2-[1-[*N*-(2,2-Dimethoxyethyl)aminomethyl]-1-propenyl]-1,2,3,4-tetrahydro-9*H*-carbazole (12). To a mixture of carbamate **11** (1.17 g, 2.73 mmol) in anisole (3 mL, 27.1 mmol) was added trifluoroacetic acid (30 mL) at 0 °C. After being stirred for 30 min at the same temperature, the reaction mixture was poured into a vigorously stirred mixture of 6 N aqueous NaOH and CH_2Cl_2 via cannula at 0 °C. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (Et_2NH/Et_2O, 1:150) to give the indole compound **12** (0.878 g, 2.67 mmol; 98%) as a solid. IR (KBr) 2926, 1468 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.59 (m, 1H), 7.28−7.13 (m, 3H), 6.86 (br-s, 1H), 5.51 (q, J = 6.8 Hz, 1H), 4.52 (t, J = 5.5 Hz, 1H), 3.34−3.10 (m, 2H), 3.19 (s, 3H), 3.17 (s, 3H), 2.96 (m, 1H), 2.84−2.77 (m, 4H), 2.64 (m, 1H), 2.36 (dd, J = 15.9, 4.9 Hz, 1H), 1.94−1.78 (m, 2H), 1.58 (d, J = 6.8 Hz, 3H), 1.03 (br-s, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.0, 136.8, 134.2, 128.5, 121.6, 121.4, 119.6, 118.4, 110.9, 109.9, 104.5, 53.8, 53.5, 53.4, 51.3, 36.4, 28.8, 28.1, 21.9, 13.2; EI-MS m/z 328 (M^+), 253 ($M^+ - CH(OCH_3)_2$); EI−HRMS Calcd for $C_{20}H_{28}N_2O_2$ (M^+): 328.2151, Found: 328.2153.

Synthesis of (1*S*,5*R*)-2-(2,2-Dimethoxyethyl)-4-ethylidene-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (13). To a mixture of amine **12** (16.6 mg, 50.5 μmol) and Na_2HPO_4 (72 mg, 0.51 mmol) in degassed THF (2 mL) was added DDQ (12.6 mg, 55.5 μmol) in degassed THF (2 mL) during 20 min at −20 °C. The mixture was allowed to warm to 0 °C in 30 min. After being stirred for additional 1 h at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with AcOEt. The organic layer was separated, and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (Et_2NH/Et_2O, 1:300) to give the tetracyclic amine **13** (8.6 mg, 26.3 μmol; 52% (conv. 67%)) as a solid and **12** (3.6 mg, 11.0 μmol). IR (KBr) 3405 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.81 (m, 1H), 7.24−7.18 (m, 3H), 7.14 (m, 1H), 5.22 (qd, J = 6.8, 1.5 Hz, 1H), 4.69 (dd, J = 3.4, 2.8 Hz, 1H), 4.35 (dd, J = 5.1, 5.1 Hz, 1H), 3.27 (s, 3H), 3.21 (dd, J = 13.4, 5.1 Hz, 1H), 3.15 (s, 3H), 3.12 (d, J = 13.8 Hz, 1H), 3.07 (m, 1H), 2.91 (m, 1H), 2.70 (dd, J = 16.8, 6.4 Hz, 1H), 2.43 (dd, J = 13.4, 5.1 Hz, 1H), 2.28 (d, J = 16.8 Hz, 1H), 2.24 (ddd, J = 11.9, 3.4, 3.4 Hz, 1H), 1.71 (ddd, J = 11.9, 2.8, 2.8 Hz, 1H), 1.54 (dd, J = 6.8, 2.1 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 140.7, 136.7, 135.7, 129.1, 121.3, 120.2, 119.4, 117.1, 111.0, 107.6, 104.3, 59.0, 55.4, 53.3, 53.0, 52.1, 33.4, 29.7, 28.5, 12.6; EI-MS m/z 326 (M^+), 251 ($M^+ - CH(OCH_3)_2$), 75 ($CH(OCH_3)_2$); EI−HRMS Calcd for $C_{20}H_{26}N_2O_2$ (M^+): 326.1994, Found: 326.1981.

Synthesis of (1*S*,4*S*,5*R*)-2-[2,2-Bis(ethylthio)ethyl]-4-ethyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole (14). A suspension of **13** (88.4 mg, 0.271 mmol) and tris(triphenylphosphine)rhodium(I) chloride (25 mg, 40 μmol) in benzene (2.0 mL) and 2-propanol (0.4 mL) was stirred vigorously under 1 atm pressure of hydrogen at room temperature for 27 h. The reaction mixture was filtered over a Celite pad, and the filtrate was concentrated to give a residue which was purified by silica gel flash chromatography (Et_2NH/Et_2O/hexane, 1:100:200) to yield a mixture of the desired compound and the C-4 epimer. To a mixture of acetal and a small amount of MS 3A in CH_2Cl_2 (10 mL) were added EtSH (4 mL) and $BF_3{\cdot}Et_2O$ (0.27 mL, 2.13 mmol) at 0 °C. After being stirred for 17 h at the same temperature, and for additional 12 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (Et_2NH/Et_2O/hexane, 1:50:200) to give the thioacetal **14** (69.4 mg, 0.179 mmol; 66%) as a foam and the C-4 epimer (9.9 mg, 0.026 mmol; 9%) as a solid. $[\alpha]^{21}_D$ = +111 (c 2.62, $CHCl_3$) (99% ee); IR ($CHCl_3$) 3469, 2927 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.91 (br-s, 1H), 7.53 (m, 1H), 7.27 (m, 1H), 7.14−7.03 (m, 2H), 4.19 (t, J = 2.9 Hz, 1H), 4.06 (dd, J = 7.6, 6.4 Hz, 1H), 3.10 (dd, J = 13.5, 7.6 Hz, 1H), 2.81−2.60 (m, 6H), 2.56 (dd, J = 11.3, 4.3 Hz, 1H), 2.47 (dd, J = 13.5, 6.4 Hz, 1H), 2.25 (m, 1H), 2.17 (m, 1H) 1.89 (dt, J = 12.2, 2.9 Hz, 1H), 1.80 (m, 1H), 1.74 (t, J = 11.3 Hz, 1H), 1.29 (t, J = 7.3 Hz, 3H), 1.25 (t, J = 7.3 Hz, 3H), 1.27−1.23 (m, 2H), 0.93 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.3, 135.7, 128.0, 120.8, 119.6, 118.3, 110.3, 107.4, 62.6, 51.0, 49.9, 41.4, 34.2, 28.8, 24.6, 24.5, 24.3, 22.6, 18.4, 14.6, 14.2, 11.5; EI-MS m/z 388 (M^+), 251 ($M^+ - CH(SCH_2CH_3)_2$); EI−HRMS Calcd for $C_{22}H_{32}N_2S_2$ (M^+): 388.2031, Found: 388.2007.

Synthesis of (−)-Tubifolidine (1). To a mixture of dimethyl(methylthio)sulfonium fluoroborate (DMTSF) (84.0 mg, 0.428 mmol) in CH_2Cl_2 (15 mL) was added thioacetal **14** (79.2 mg, 0.204 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After being stirred for 2 h at the same temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give a residue which was then purified by silica gel flash chromatography (Et_2NH/Et_2O/hexane, 1:100:100) to give the imine (45.5 mg, 0.140 mmol; 68%) as a foam. To a mixture of imine (17.5 mg, 53.7 μmol) in THF (2 mL) was added $LiAlH_4$ (10 mg, 0.26 mmol) at 0 °C. After being stirred for 2 h at the same temperature, the reaction mixture was quenched with saturated aqueous Na_2SO_4 (3 drops). The mixture was stirred vigorously for 1 h at room temperature and then dried ($MgSO_4$). The whole mixture was filtered over a Celite pad and concentrated to give the amine, which was used without further purification. To a mixture of amine in EtOH (1 mL) was added Raney Ni (W2) (excess). After being stirred for 1 h under reflux, additional Raney Ni (W2) (excess) was added. After being stirred for 1 h under reflux, the reaction mixture was filtered over a Celite pad. The filtrate was concentrated to give a residue which was then purified by silica gel flash chromatography (Et_2NH/Et_2O/hexane, 1:50:50) to give (−)-tubifolidine (**1**) (5.0 mg, 18.7 μmol; 35% (two steps)) as a solid. $[\alpha]^{19}_D$ = −61 (c 0.36, $CHCl_3$) (99% ee); IR (KBr) 3171, 2923, 1605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.06−7.03 (m, 2H), 6.76 (m, 1H), 6.63 (m, 1H), 3.63 (dd, J = 9.2, 7.6 Hz, 1H), 3.31 (t, J = 3.1 Hz, 1H), 3.13 (m, 1H), 3.03 (dd, J = 12.1, 5.2 Hz, 1H), 2.83 (ddd, J = 11.9, 8.9, 2.8 Hz, 1H), 2.41 (dt, J = 13.8, 8.6 Hz, 1H), 2.05 (t, J = 12.2 Hz, 1H), 2.03−1.65 (m, 7H), 1.29 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 134.2, 127.6, 122.2, 119.1, 109.5, 66.2, 62.8, 55.2, 54.4, 52.8, 42.9, 40.7, 32.8, 28.5, 27.3, 25.5, 11.5; EI-MS m/z 268 (M^+); EI−HRMS Calcd for $C_{18}H_{24}N_2$ (M^+): 268.1939, Found: 268.1946.

Supporting Information Available: ^1H and ^{13}C NMR spectra of **1**, **2**, and **6**−**14** (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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