Asymmetric Total Synthesis of Tacamonine (Pseudovincamone I) *via* Radical Cyclization

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The radical cyclizations of (±)-(*E*)-3-((2-(bromomethyl)butoxy)carbonyl)prop-2-enoates **11** and **12** and (±)-ethyl (*E*)-3-{*N*-[2-(bromomethyl)butyl]-*N*-[2-(3-indolyl)ethyl]carbamoyl}prop-2-enoate (**25**) were carried out with $(TMS)_3SiH$ or Bu_3SnH in the presence of AIBN. (−)-(2*S*)-2-((*tert*-Butyldimethylsilyloxy)methyl)butan-1-ol (**6**), which was prepared by two different methods, was converted into (+)-**25**. The radical cyclization of (+)-**25** produced piperidinone **18** as a diastereomeric mixture, which was transformed into tacamonine (**1**).

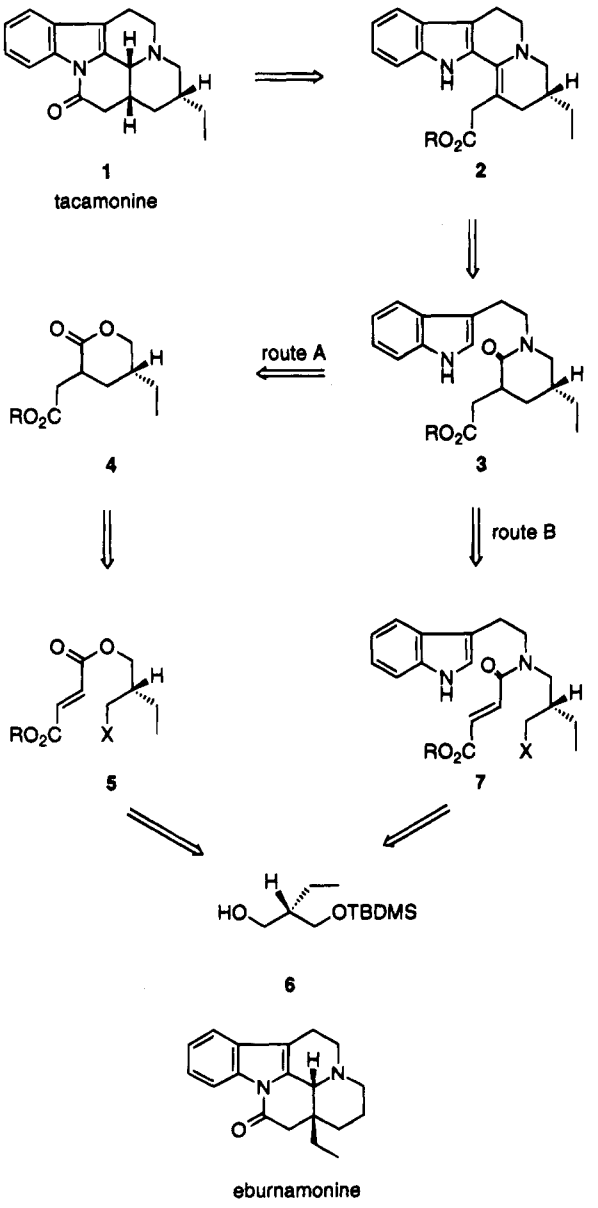
Introduction

Tacamonine (**1**) was isolated in 1984 by van Beek and his co-workers[1] from *Tabernaemontana eglandulosa*, the root of which is used to treat snake bites in Zaire. Massiot *et al.*[2] had synthesized the racemate of **1** (pseudovincamone I) prior to the isolation of tacamonine (**1**). The structural similarity between **1** and *Hunteria* alkaloids, eburnamonines, which possess vasodilator and hypotensive activities, promoted us to explore the asymmetric synthesis of **1**.[3] We considered piperidinone **3** as a key synthetic intermediate that could be transformed into **1** *via* **2** using standard chemistry[2] (Scheme 1). We planned to construct **3** by two approaches, both utilizing the radical cyclization[4] as the key step. Route A involves the cyclization of **5** and the conversion of the resulting lactone **4** into **3**. By route B, **3** could be directly assembled by the ring closure of **7**. It was envisioned that both substrates of the key steps (**5** and **7**) could be derived from chiral propane-1,3-diol **6**.[5,6]

Results and Discussion

Radical Cyclization According to Route A. As a preliminary study, bromides **11** and **12** were prepared from diol **8** as the racemate (Scheme 2). The acetalization of **8** and Hanessian ring opening[7] of the resulting acetal provided benzoate **9** in 83% overall yield. Hydrolysis of **9** with lithium hydroxide afforded, in 95% yield, alcohol **10**, which was allowed to react with fumaric acid monoesters in the presence of 1,3-dicyclohexylcarbodiimide (DCC) and DMAP to give **11** and **12** in 97 and 93% yield, respectively.

Scheme 1



The radical cyclizations of **11** and **12** were carried out with tributyltin hydride (Bu_3SnH) or tris(trimethylsilyl)-silane [$(TMS)_3SiH$][8] in the presence of 2,2-azoisobutyronitrile (AIBN) in refluxing benzene (Table 1). When

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(2) Massiot, G.; Oliveira, F. S.; Lévy, J. *Bull. Soc., Chim. Fr. II* **1982**, 185–190.

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(5) Ihara, M.; Takahashi, M.; Taniguchi, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1987**, 619–620. Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 897–903.

(6) Ihara, M.; Fukumoto, K. Asymmetric Synthesis of Bioactive Natural Products and Related Compounds from Propane-1,3-diols and Analogous. In *Studies Natural Products Chemistry*; Atta-ur-Rahaman, Basha, F. Z., Eds.; Elsevier: Amsterdam, 1993; Vol. 13, pp 53–105.

(7) Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1035–1044.

0022-3263/94/1959-5317$04.50/0

Scheme 2

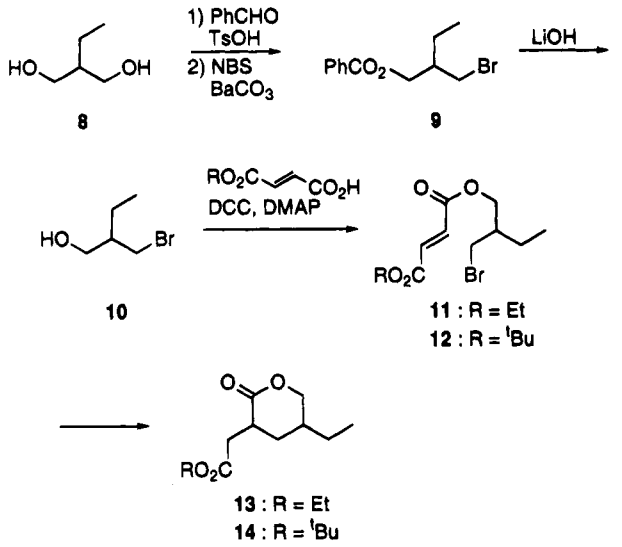


Table 1. Radical Cyclization of 11 or 12 Providing 13 or 14[a]

entry	substrate	(concentration)	reagents	yield, %
1	**11**	(1.0 w/v %)	Bu_3SnH, AIBN	0
2	**11**	(0.1 w/v %)	Bu_3SnH, AIBN	92
3	**11**	(1.0 w/v %)	$(TMS)_3SiH$, AIBN	82
4	**11**	(0.1 w/v %)	$(TMS)_3SiH$, AIBN	91
5	**12**	(0.1 w/v %)	Bu_3SnH, AIBN	87
6	**12**	(0.5 w/v %)	$(TMS)_3SiH$, AIBN	84

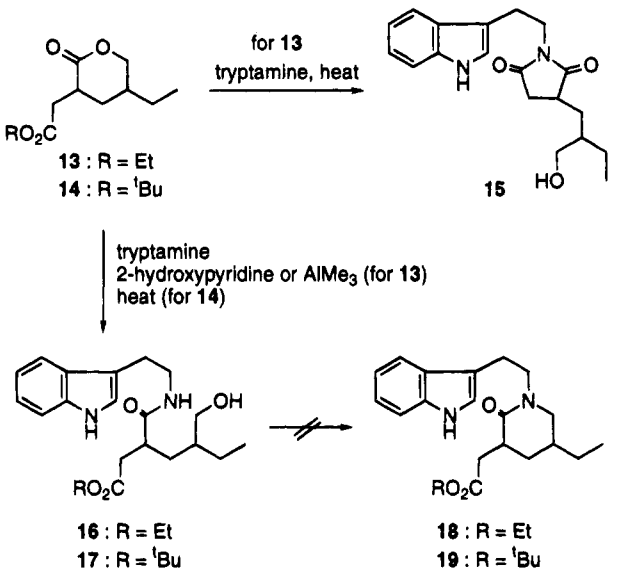
[a] All reactions were carried out for 5 h in refluxing benzene.

Bu_3SnH was used, the yield of lactone **13** was considerably dependent upon the reaction concentration. At a 1.0% w/v concentration of **11** in benzene (entry 1), no formation of **13** was observed, and only the unwanted reduction product was formed. Heating **11** at a 0.1% w/v concentration produced a 1.3:1 diastereoisomeric mixture of **13** in 92% yield (entry 2). When $(TMS)_3SiH$ was used, the yield and the diastereoselectivity were less sensitive to reaction concentration; the mixture of stereoisomers **13** was obtained in the same ratio as with Bu_3SnH (entries 3 and 4). Both reagents gave two isomers of *tert*-butyl esters **14** in a 1.2:1 ratio from **12** (entries 5 and 6). Thus, the 6-*exo*-*trig* ring closure forming **13** and **14** was preferred over the 7-*endo*-*trig* ring closure.[9]

Next, transformation of lactones **13** and **14** into lactams **18** and **19** was investigated (Scheme 3). Heating **13** with tryptamine afforded only imide **15**, but treatment of **13** with tryptamine in the presence of 2-hydroxypyridine[10] in refluxing toluene gave amide **16** in 23% yield. Amide **16** was also prepared in 25% yield with trimethylaluminum for activation.[11] Simply heating *tert*-butyl ester **14** with tryptamine in refluxing toluene furnished amide **17** in 97% yield. However, a number of attempts to convert amides **16** and **17** into lactams **18** and **19** failed.

Radical Cyclization According to Route B. Racemic substrates **25**–**28** for route B were prepared by two different processes as shown in Scheme 4. The Mit-

Scheme 3



sunobu reaction[12] of racemate **6** with phthalimide in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) afforded imide **20** in 99% yield. After treatment of **20** with hydrazine hydrate, the resulting amine was allowed to react with indole-3-acetic acid in the presence of DCC and DMAP to provide amide **21** in 98% overall yield. Reduction of **21** with sodium bis(2-methoxyethoxy)aluminum hydride gave the corresponding amino alcohol, which, after the reprotection of the hydroxyl group, was treated with fumaric acid monoethyl ester in the presence of DCC and DMAP to furnish amide **23** in 51% overall yield.

Amide **23** was also synthesized starting from alcohol **10** as follows. After protection of **10** with the *tert*-butyldimethylsilyl group (96% yield), bromide **22** was converted into **23** in two steps (60% overall yield): treatment with tryptamine and subsequent reaction with fumaric acid monoethyl ester under the conditions described above. The protecting group of **23** was quantitatively removed by the action of dilute acetic acid to afford alcohol **24**, which was transformed in the usual manner into four substrates (**25**–**28**) for investigation of the key radical cyclization reaction.

The results of the radical cyclizations of **25**–**28** (using Bu_3SnH or $(TMS)_3SiH$ in the presence of AIBN in hot benzene) are listed in Table 2. The best result (62% yield) was obtained in the reaction of bromide **25** with $(TMS)_3SiH$ and AIBN (entry 2). The other three substrates, **26**–**28**, gave poor results (entries 3–7). The stereoselectivity was low, but the ratio of two diastereoisomers **18** could not be determined from the ^1H and ^{13}C NMR spectra of the products because of rotational isomerism.

Next, we undertook the asymmetric synthesis of tacamonine (**1**) by means of route B.

Asymmetric Synthesis of Tacamonine (1). We previously reported the asymmetric synthesis of chiral propane-1,3-diol **6** from half menthyl ester **29**. Compound **29** was obtained in a highly diastereoselective manner by a crystallization induced asymmetric transformation (second-order asymmetric transformation).[5] Compound **6** was also prepared in high optical purity by the method of Evans (Scheme 5).[13] Namely, reaction of

(8) Kanabus-Kaminska, J. M.; Hawari, J. A.; Griller, D.; Chatgilialoglu, C. *J. Am. Chem. Soc.* **1987**, *109*, 5267–5268. Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3641–3642. Giese, B.; Kopping, B. *Tetrahedron Lett.* **1989**, *30*, 681–684.
(9) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.
(10) Openshaw, H. T.; Whittaker, N. *J. Chem. Soc. C* **1969**, 89–91.
(11) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171–4174.
(12) Mitsunobu, O. *Synthesis* **1981**, 1–28.

Scheme 4

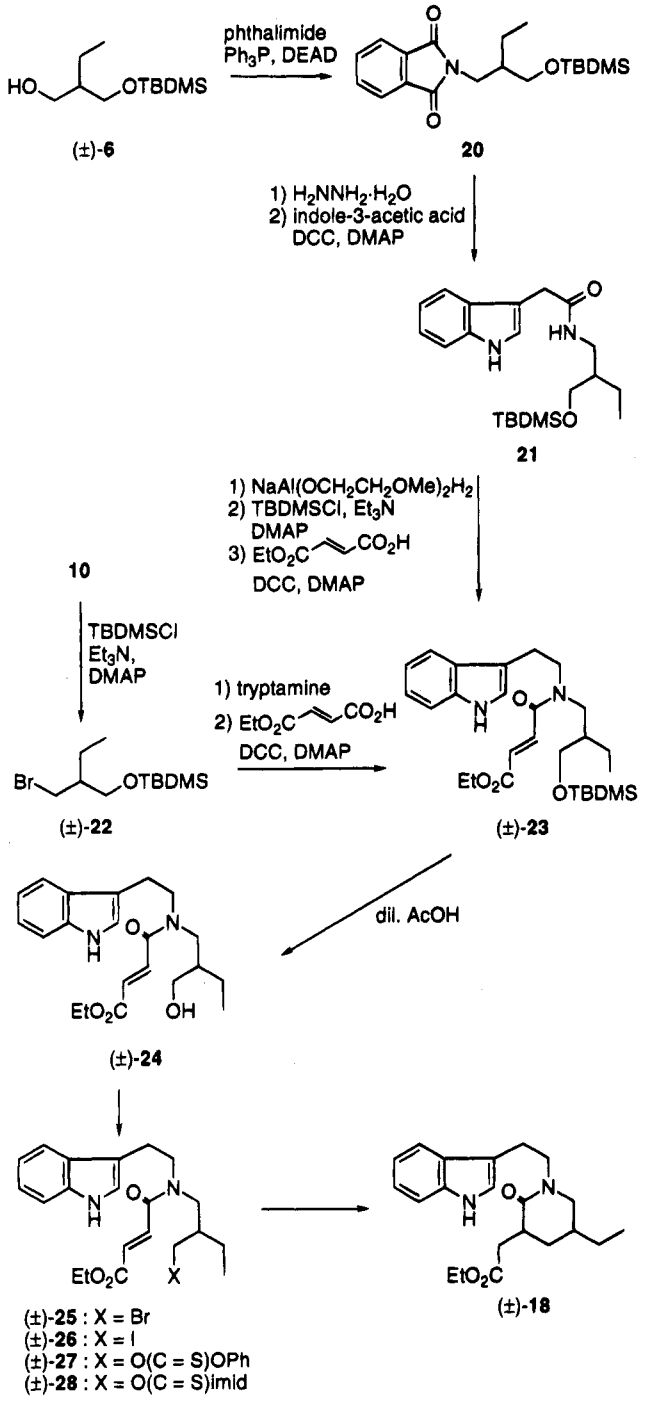


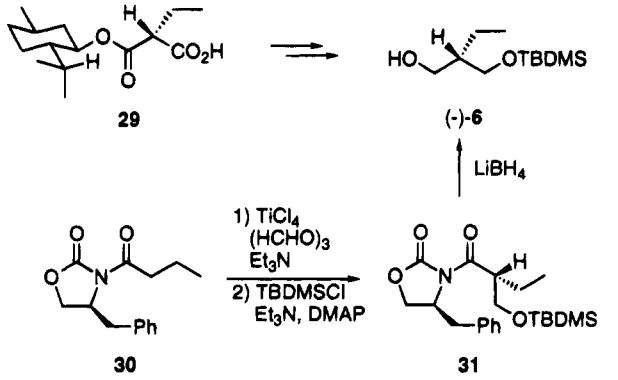
Table 2. Radical Cyclization of (±)-25–28 Providing (±)-18[a]

entry	substrate	reagents	yield, %
1	(±)-**25**	Bu_3SnH, AIBN	44
2	(±)-**25**	$(TMS)_3SiH$, AIBN	62
3	(±)-**26**	Bu_3SnH, AIBN	32
4	(±)-**26**	$(TMS)_3SiH$, AIBN	41
5	(±)-**27**	Bu_3SnH, AIBN	20
6	(±)-**27**	$(TMS)_3SiH$, AIBN	14
7	(±)-**28**	$(TMS)_3SiH$, AIBN	13

[a] All reactions were carried out for 5 h in refluxing benzene.

oxazolidone **30**[13a] with titanium(IV) chloride, triethylamine, and *s*-trioxane and subsquent protection of the hydroxyl group of the product with a *tert*-butyldimethylsilyl group produced **31** diastereoselectively in 48% overall yield. The reduction of **31** with lithium borohydride in the presence of 1 equiv of water[14] provided (−)-**6** in 88% yield. The optical purity (nearly 100% ee) was determined by conversion of **6** into the corresponding (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionate.[5]

Scheme 5



The mesylation of (−)-**6** and the subsequent substitution reaction using lithium bromide formed (−)-**22**, $[\alpha]^{22}_D$ −9.4° (*c* 1.28, $CHCl_3$), in 95% overall yield (Scheme 6). By means of the procedure described above, (−)-**22** was transformed, in 64% overall yield, into (+)-**23**, mp 69–70 °C, $[\alpha]^{21}_D$ +7.1° (*c* 1.01, $CHCl_3$). Removal of the silyl group of (+)-**23** (95% yield), mesylation of (−)-**24**, $[\alpha]^{22}_D$ −12.5° (*c* 0.93, $CHCl_3$), and subsequent bromination gave (+)-**25**, $[\alpha]^{22}_D$ +28.0° (*c* 1.38, $CHCl_3$). The radical cyclization of (+)-**25** with $(TMS)_3SiH$ and AIBN in hot benzene furnished **18** as a diastereoisomeric mixture, $[\alpha]^{22}_D$ +4.5° (*c* 1.32, $CHCl_3$), in 72% yield. Next, **18** was treated with phosphorus oxychloride in refluxing acetonitrile. Reduction of the product with sodium cyanoborohydride followed by treatment of the product with sodium methoxide[2] produced tacamonine (**1**) as a diastereosiomeric mixture, from which **1**, mp 179–181 °C (lit.[1] mp 180–181 °C), was obtained in 9% overall yield. The CD spectrum of **1** was consistent with that reported earlier.[1] Furthermore, the UV, ^1H NMR, and MS spectra were identical with those of (±)-**1**.[2] Thus, the first asymmetric synthesis of tacamonine (**1**) was accomplished.

Experimental Section

General. All reactions were carried out under a positive atmosphere of dry N_2 or Ar. THF and benzene were distilled from Na–benzophenone. MeOH was distilled from Mg–I_2 and stored over 3-Å molecular sieves. Toluene was distilled from Na–benzophenone and stored over Na wire. CH_2Cl_2 and MeCN were distilled from CaH_2 and stored over 4-Å molecular sieves. Et_3N was distilled from KOH and stored over KOH. Silica gel chromatography was carried out with Merck Kieselgel 60 (Art. No. 7734 or 9387). NMR spectra were taken in $CDCl_3$.

(±)-2-(Bromomethyl)-1-butyl Benzoate (9). A mixture of **8** (3.97 g, 38.2 mmol), benzaldehyde (3.51 mL, 34.4 mmol), and TsOH (726 mg, 3.82 mmol) in dry benzene (20 mL) was heated for 3 h under reflux in a Dean–Stark apparatus. After neutralization with saturated $NaHCO_3$, the aqueous layer was extracted with Et_2O. The extract was washed with brine, dried (Na_2SO_4), and evaporated to give a residue, which was used in the next reaction without purification.

(13) (a) Evans, D. A.; Chapman, K. T.; Huang, D. T.; Kawaguchi, A. T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1184–1186. (b) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.

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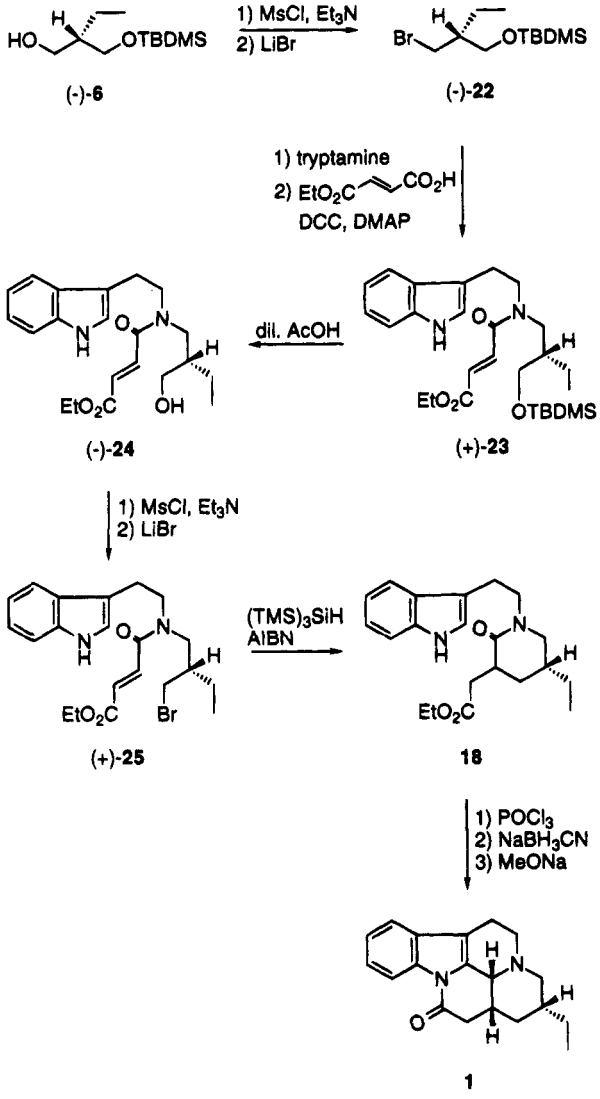
Scheme 6



A mixture of the product, NBS (7.95 g, 44.7 mmol), and $BaCO_3$ (4.75 g, 24.1 mmol) in CCl_4 (50 mL) was heated for 3 h under reflux. After the mixture was filtered through Celite, the filtrate was washed with brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue on silica gel with AcOEt–hexane (1:9 v/v) as eluent gave **9** (7.73 g, 83%) as a yellowish oil: IR (neat) 1715 cm^{-1}; ^1H NMR (300 MHz) δ 1.00 (t, 3H, J = 7.5 Hz), 1.50–1.62 (m, 2H), 2.01–2.14 (m, 1H), 3.56 (dd, 1H, J = 5.4, 11.7 Hz), 3.62 (dd, 1H, J = 5.7, 11.7 Hz), 4.30 (dd, 1H, J = 7.2, 11.4 Hz), 4.43 (dd, 1H, J = 4.5, 11.4 Hz), 7.60–8.00 (m, 5H); MS m/z 270 (M^+); HRMS calcd for $C_{12}H_{15}BrO_2$ (M^+) 270.0255, found 270.0235.

(±)-2-(Bromomethyl)-1-butanol (10). To a stirred solution of **9** (2.83 g, 10.5 mmol) in MeOH (25 mL) was added at 0 °C LiOH (480 mg, 11.4 mmol) in H_2O (5 mL), and the mixture was stirred for 3 h at rt. After evaporation, the residue was taken up into Et_2O. The organic solution was washed with brine, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to chromatography on silica gel. Elution with AcOEt–hexane (1:4 v/v) provided **10** (1.65 g, 95%) as a yellowish oil: IR (neat) 3350 cm^{-1}; ^1H NMR (300 MHz) δ 0.95 (t, 3H, J = 7.3 Hz), 1.38–1.45 (m, 2H), 1.50–1.60 (br s, 1H), 1.70–1.82 (m, 1H), 3.53 (dd, 1H, J = 5.5, 9.9 Hz), 3.63 (dd, 1H, J = 4.0, 9.9 Hz), 3.63–3.74 (m, 2H); MS m/z 167 (M^+); HRMS calcd for $C_5H_{11}BrO$ (M^+) 167.0072, found 167.0050.

(±)-Ethyl (*E*)-3-((2-(Bromomethyl)butoxy)carbonyl)-prop-2-enoate (11). To a stirred mixture of fumaric acid monoethyl ester (656 mg, 4.55 mmol), **10** (633 mg, 3.79 mmol), and DMAP (100 mg, 0.819 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was slowly added a solution of DCC (1.02 g, 4.94 mmol) in dry CH_2Cl_2 (5 mL), and the mixture was stirred for 2 h at rt. After evaporation, the residue was taken up into Et_2O, and the mixture was filtered through Celite. Evaporation of the filtrate gave a residue, which was chromatographed on silica gel. Elution with AcOEt–hexane (1:19 v/v) afforded **11** (1.68 g, 97%) as a colorless oil: IR (neat) 1722, 1645 cm^{-1}; ^1H NMR (500 MHz) δ 0.96 (t, 3H, J = 7.4 Hz), 1.31 (t, 3H, J = 7.0 Hz), 1.43–1.52 (m, 2H), 1.93–2.01 (m, 1H), 3.47 (dd, 1H, J = 5.5, 10.4 Hz), 3.52 (dd, 1H, J = 4.3, 10.0 Hz), 4.18 (dd, 1H, J = 7.4, 11.0 Hz), 4.26 (q, 2H, J = 7.0 Hz), 4.27 (dd, 1H, J = 5.2, 11.0 Hz), 6.84 (s, 2H); MS m/z 293 (M^+ + 1); HRMS calcd for $C_{11}H_{18}BrO_4$ (M^+ + 1) 293.0389, found 293.0402.

(±)-*tert*-Butyl (*E*)-3-((2-(Bromomethyl)butoxy)carbonyl)prop-2-enoate (12). The reaction of **10** (833 mg, 4.99 mmol) with fumaric acid mono-*tert*-butyl ester (1.01 g, 5.87 mmol) in the presence of DCC (1.36 g, 6.59 mmol) and DMAP (201 mg, 1.65 mmol) as described above provided **12** (1.75 g, 93%) as a colorless oil: IR (neat) 1720 cm^{-1}; ^1H NMR (300 MHz) δ 0.97 (t, 3H, J = 7.4 Hz), 1.40–1.50 (m, 2H), 1.50 (s, 9H), 1.92–2.05 (m, 1H), 3.48 (dd, 1H, J = 5.5, 10.6 Hz), 3.54 (dd, 1H, J = 4.7, 10.6 Hz), 4.18 (dd, 1H, J = 7.0, 11.5 Hz), 4.27 (dd, 1H, J = 5.1, 11.5 Hz), 6.75 (s, 2H); MS m/z 321 (M^+ + 1); HRMS calcd for $C_{13}H_{22}BrO_4$ (M^+ + 1) 321.0702, found 321.0719.

(±)-4-Ethyl-2-((ethoxycarbonyl)methyl)-5-pentanolide (13). (A) A mixture of **11** (54.0 mg, 0.184 mmol), Bu_3SnH (0.054 mL, 0.201 mmol), and AIBN (3.0 mg, 0.02 mmol) in dry benzene (50 mL) was heated for 5 h under reflux. Evaporation of the solvent gave a residue, which was subjected to silica gel chromatography. Elution with AcOEt–hexane (1:5 v/v) yielded **13** (36.2 mg, 92%) as a colorless oil.

(B) To mixture of **11** (90.0 mg, 0.31 mmol) and AIBN (5.5 mg, 0.03 mmol) in dry benzene (90 mL) was added $(TMS)_3SiH$ (0.1 mL, 0.32 mmol) at rt. The reaction mixture was heated for 5 h under reflux and worked up as above to provide **13** (60.0 mg, 91%): IR (neat) 1740, 1732 cm^{-1}; ^1H NMR (500 MHz) δ 0.94 (t, 1.29H, J = 7.3 Hz), 0.95 (t, 1.71H, J = 7.3 Hz), 1.26 (t, 1.29H, J = 7.3 Hz), 1.27 (t, 1.71H, J = 7.3 Hz), 1.27–1.48 (m, 2H), 1.60–1.64 (m, 0.43H), 1.69–1.78 (m, 0.57H), 1.83 (ddd, 0.57H, J = 6.8, 8.6, 13.8 Hz), 1.88–2.01 (m, 1H), 2.08–2.16 (m, 0.43H), 2.46 (dd, 0.57H, J = 6.7, 17.1 Hz), 2.68 (dd, 0.43H, J = 4.3, 17.1 Hz), 2.78 (dd, 0.43H, J = 4.3, 17.1 Hz), 2.82 (dd, 0.57H, J = 6.7, 17.1 Hz), 2.82–3.04 (m, 1H), 3.99–4.20 (m, 3H), 4.30 (dd, 0.57H, J = 4.9, 11.0 Hz), 4.37 (ddd, 0.43H, J = 2.1, 4.9, 11.0 Hz); MS m/z 214 (M^+); HRMS calcd for $C_{11}H_{18}O_4$ (M^+) 214.1205, found 214.1196.

(±)-4-Ethyl-2-((*tert*-butoxycarbonyl)methyl)-5-pentanolide (14). (A) By means of the above procedure, the reaction of **12** (415 mg, 1.29 mmol) with Bu_3SnH (0.383 mL, 1.42 mmol) in the presence of AIBN (15.0 mg, 0.091 mmol) in dry benzene (415 mL) provided **14** (271 mg, 87%) as a colorless oil.

(B) Similarly, the cyclization of **12** (1.75 g, 5.45 mmol) with $(TMS)_3SiH$ (1.78 mL, 5.77 mmol) and AIBN (86.0 mg, 0.524 mmol) in dry benzene (285 mL) afforded **14** (1.11 g, 84%): IR (neat) 1720 cm^{-1}; ^1H NMR (300 MHz) δ 0.92 and 0.94 (each t, 3H, each J = 7.0 Hz), 1.25–1.50 (m, 2H), 1.46 (s, 9H), 1.72–2.12 (m, 3H), 2.38 (dd, 0.55H, J = 8.0, 16.4 Hz), 2.61 (dd, 0.45H, J = 5.8, 16.4 Hz), 2.70 (dd, 0.45H, J = 5.8, 16.4 Hz), 2.75 (dd, 0.55H, J = 8.0, 16.4 Hz), 2.78–3.05 (m, 1H), 3.96–4.06 (m, 1H), 4.31 (dd, 0.55H, J = 4.9, 11.0 Hz), 4.38 (ddd, 0.45H, J = 2.0, 4.9, 11.0 Hz); MS m/z 186 (M^+ − t-Bu); HRMS calcd for $C_9H_{12}O_4$ (M^+ − t-Bu) 186.0892, found 186.0884.

(±)-Ethyl 3-{*N*-[2-(3-Indolyl)ethyl]carbamoyl}-5-(hydroxymethyl)heptanoate (16). (A) A mixture of **14** (33.0 mg, 0.154 mmol), tryptamine (49.4 mg, 0.308 mmol), and 2-hydroxypyridine (17.6 mg, 0.185 mmol) in toluene (1 mL) was heated for 1 h under reflux. After dilution with CH_2Cl_2, the mixture was washed with 1% HCl, H_2O, saturated $NaHCO_3$, and H_2O, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to chromatography on silica gel. Elution with AcOEt–hexane (7:3 v/v) afforded **16** (13.0 mg, 23%) as a yellowish oil.

(B) To a stirred mixture of tryptamine (50.0 mg, 0.312 mmol) and 1.03 M $AlMe_3$–hexane (0.274 mL, 0.283 mmol) in dry CH_2Cl_2 (5 mL) at rt was added a solution of **14** (60.6 mg, 0.283 mmol) in dry CH_2Cl_2 (5 mL), and the mixture was stirred for

3 h at 40 °C. The reaction was carefully quenched with 10% HCl at 0 °C and the mixture was extracted with CH_2Cl_2. The organic extract was washed with brine, dried (Na_2SO_4), and evaporated to give a residue, which was chromatographed on silica gel. Elution with AcOEt–hexane (7:3 v/v) afforded **16** (26.6 mg, 25%): IR (neat) 3400, 1720, 1660 cm^{-1}; ^1H NMR (500 MHz) δ 0.83 (t, 3H, J = 7.2 Hz), 1.18–1.40 (m, 7H), 1.70–1.82 (m, 2H), 2.32–2.39 (m, 1H), 2.56–2.78 (m, 2H), 2.94–3.00 (m, 2H), 3.30–3.50 (m, 2H), 3.55–3.70 (m, 2H), 4.00–4.10 (m, 2H), 6.04–6.22 (m, 1H), 7.09–7.63 (m, 5H), 8.08–8.12 (br s, 1H); MS m/z 374 (M^+); HRMS calcd for $C_{21}H_{30}N_2O_4$ (M^+) 374.2188, found 374.2206.

(±)-*tert*-Butyl 3-{*N*-[2-(3-Indolyl)ethyl]carbamoyl}-5-(hydroxymethyl)heptanoate (17). A mixture of **13** (76.0 mg, 0.314 mmol) and tryptamine (101 mg, 0.630 mmol) in dry toluene (1 mL) was heated under reflux. After 5 h of stirring, the mixture was purified by silica gel chromatography. Elution with AcOEt–hexane (7:3 v/v) provided **17** (123 mg, 97%) as a yellowish oil: IR (neat) 3400, 1710, 1650, 1550 cm^{-1}; ^1H NMR (500 MHz) δ 0.81 and 0.82 (each t, 3H, J = 8.0 Hz), 1.15–1.45 (m, 4H), 1.40 (s, 9H), 1.70–1.85 (m, 2H), 2.15–2.25 (m, 1H), 2.52–2.60 (m, 2H), 2.85–3.02 (m, 2H), 3.30–3.50 (m, 2H), 3.55–3.70 (m, 2H), 6.03–6.08 (m, 0.5H), 6.10–6.15 (m, 0.5H), 7.09–7.61 (m, 5H), 8.03–8.05 (br s, 1H); MS m/z 402 (M^+) HRMS calcd for $C_{23}H_{34}N_2O_4$ (M^+) 402.2549, found 402.2519.

***N*-[2-((*tert*-Butyldimethylsiloxy)methyl)butyl]-phthalimide (20).** To a stirred mixture of **6** (1.00 g, 4.59 mmol), PPh_3 (1.81 g, 6.90 mmol), and phthalimide (1.01 g, 6.87 mmol) in dry THF (80 mL) at 0 °C was added diethyl azodicarboxylate (1.01 mL, 6.42 mmol), and the mixture was stirred for 3 h at rt. Evaporation of the solvent gave a residue, which was subjected to chromatography on silica gel. Elution with AcOEt–hexane (1:19 v/v) afforded **20** (1.57 g, 99%), which was recrystallized from MeOH–H_2O to provide colorless plates, mp 54–57 °C: IR ($CHCl_3$) 1772, 1712 cm^{-1}; ^1H NMR (500 MHz) δ −0.04 (s, 3H), −0.02 (s, 3H), 0.84 (s, 9H), 0.94 (t, 3H, J = 7.4 Hz), 1.28–1.46 (m, 2H), 1.91–1.99 (m, 1H), 3.57 (dd, 1H, J = 6.0, 10.0 Hz), 3.60 (dd, 1H, J = 6.0, 10.0 Hz), 3.62 (dd, 1H, J = 7.0, 14.0 Hz), 3.74 (dd, 1H, J = 7.6, 14.0 Hz), 7.70 (dd, 2H, J = 3.0, 6.0 Hz), 7.83 (dd, 2H, J = 3.0, 6.0 Hz); MS m/z 290 (M^+ − t-Bu); HRMS calcd for $C_{15}H_{20}NO_3Si$ (M^+ − t-Bu) 290.1212, found 290.1218. Anal. Calcd for $C_{19}H_{29}NO_3Si$: C, 65.71; H, 8.36; N, 4.03. Found: C, 65.64; H, 8.30, N, 4.09.

***N*-[2-((*tert*-Butyldimethylsiloxy)methyl)butyl]-3-indolylacetamide (21).** A mixture of **20** (209 mg, 0.601 mmol) and $H_2NNH_2{\cdot}H_2O$ (0.032 mL, 0.657 mmol) in EtOH (10 mL) was heated for 2 h under reflux. After addition of 10% aqueous NaOH, the mixture was thoroughly extracted with $CHCl_3$. The extract was dried (K_2CO_3) and evaporated to give the crude amine, which was used in the next reaction without purification.

To a stirred solution of the above amine, indole-3-acetic acid (581 mg, 3.32 mmol), and DMAP (35 mg, 0.287 mmol) in CH_2Cl_2–MeCN (1:1 v/v) at 0 °C was added dropwise a solution of DCC (343 mg, 1.66 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 15 h at rt, and then the solvents were evaporated. The residue was taken up into MeCN and then filtered through Celite. Concentration of the filtrate *in vacuo* gave a residue, which was chromatographed on silica gel with hexane–AcOEt (3:2 v/v) as eluent to afford **21** (221 mg, 98%) as a yellowish oil: IR ($CHCl_3$) 3480, 3420, 1657 cm^{-1}; ^1H NMR (500 MHz) δ −0.13 (s, 3H), −0.11 (s, 3H), 0.78 (s, 9H), 0.84 (t, 3H, J = 7.4 Hz), 1.12–1.22 (m, 2H), 1.44–1.53 (m, 1H), 3.16 (ddd, 1H, J = 6.0, 8.0, 12.0 Hz), 3.27–3.36 (m, 1H), 3.32 (dd, 1H, J = 6.0, 10.0 Hz), 3.42 (dd, 1H, J = 5.0, 10.0 Hz), 3.72 (s, 2H), 6.07 (br s, 1H), 7.11 (s, 1H), 7.13 (t, 1H, J = 8.0 Hz), 7.21 (t, 1H, J = 8.0 Hz), 7.38 (d, 1H, J = 8.0 Hz), 7.55 (d, 1H, J = 8.0 Hz), 8.44 (br s, 1H); MS m/z 374 (M^+); HRMS calcd for $C_{21}H_{34}N_2O_2Si$ (M^+) 374.2390, found 374.2392. Anal. Calcd for $C_{21}H_{34}N_2O_2Si$: C, 67.38; H, 9.09; N, 7.49. Found: C, 67.29; H, 9.16; N, 7.50.

(±)-1-Bromo-2-((*tert*-butyldimethylsiloxy)methyl)butane (22). To a mixture of **10** (1.00 g, 5.99 mmol), TBDMSCl (1.35 g, 8.96 mmol), and DMAP (219 mg, 1.80 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was slowly added Et_3N (1.67 mL, 12.0 mmol). After 1 h of stirring at rt, the resulting mixture was partitioned between H_2O and CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue on silica gel with AcOEt–hexane (1:9 v/v) as eluent produced **22** (1.62 g, 96%) as a colorless oil: ^1H NMR (300 MHz) δ 0.00 (s, 6H), 0.84 (s, 9H), 0.85 (t, 3H, J = 7.5 Hz), 1.28–1.40 (m, 2H), 1.60–1.70 (m, 1H), 3.41–3.59 (4H, m); MS m/z 223 (M^+ − t-Bu): HRMS calcd for $C_7H_{16}BrOSi$ (M^+ − t-Bu) 223.0141, found 223.0154.

(±)-Ethyl (*E*)-3-{*N*-[2-((*tert*-Butyldimethylsiloxy)methyl)butyl]-*N*-[2-(3-indolyl)ethyl]carbamoyl}prop-2-enoate (23). (A) A mixture of **22** (58.0 mg, 0.206 mmol) and tryptamine (66.0 mg, 0.412 mmol) in dry DMF (2 mL) was heated for 12 h at 80 °C. After dilution with benzene–AcOEt (1:1 v/v), the mixture was washed with 10% aqueous NaOH, and the aqueous layer was thoroughly extracted with benzene–AcOEt (1:1 v/v). The combined extract was washed with brine, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to the following reaction without purification.

To a mixture of the product, fumaric acid monoethyl ester (94.0 mg, 0.652 mmol), and DMAP (25.0 mg, 0.206 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C was slowly added a solution of DCC (128 mg, 0.620 mmol) in dry CH_2Cl_2 (2 mL). After 5 h of stirring, followed by evaporation, the residue was dissolved in MeCN, and the mixture was filtered through Celite. Evaporation of the filtrate afforded a residue, which was subjected to chromatography on silica gel. Elution with AcOEt–hexane (1:4 v/v) provided (±)-**23** (60 mg, 60%) as a yellowish solid, mp 102–103 °C: IR ($CHCl_3$) 3500, 1720, 1650 cm^{-1}; ^1H NMR (500 MHz) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.87 (s, 4.5H), 0.87 (t, 1.5H, J = 7.0 Hz), 0.89 (s, 4.5H), 0.91 (t, 1.5H, J = 7.0 Hz), 1.26 (t, 1.5H, J = 7.0 Hz), 1.32 (t, 1.5H, J = 7.0 Hz), 1.23–1.40 (m, 2H), 1.81–1.89 (m, 1H), 2.94–3.08 (m, 2H), 3.20–3.84 (m, 6H), 4.08–4.17 (m, 1H), 4.22–4.28 (m, 1H), 6.50 (d, 0.5H, J = 15.2 Hz), 6.85 (d, 0.5H, J = 15.2 Hz), 7.05 (d, 0.5H, J = 15.2 Hz), 7.41 (d, 0.5H, J = 15.2 Hz), 7.00–7.68 (m, 5H), 8.48–8.52 (br s, 0.5H), 8.53–8.57 (br s, 0.5H); MS m/z 486 (M^+). Anal. Calcd for $C_{27}H_{42}N_2O_4Si$: C, 66.63; H, 8.64; N, 5.76. Found: C, 66.46; H, 8.57; N, 5.67.

(B) After addition of a solution of **21** (293 mg, 1.85 mmol) in dry toluene (20 mL) to a solution of $NaAl(OCH_2CH_2OMe)_2H_2$ (1.46 g, 7.23 mmol) in dry toluene (30 mL), the mixture was heated for 10 h under reflux. After being cooled, the resulting mixture was washed with 10% aqueous NaOH. The aqueous layer was thoroughly extracted with $CHCl_3$. The combined organic layer was dried (K_2CO_3) and evaporated to give a residue, which was treated for 9.5 h at rt with TBDMSCl (840 mg, 5.57 mmol), DMAP (25.0 mg, 0.21 mmol), and Et_3N (1.07 mL, 7.72 mmol) in dry CH_2Cl_2 (8 mL). After dilution with CH_2Cl_2, the mixture was washed with saturated $NaHCO_3$, dried (K_2CO_3), and evaporated to give a crude amine, which was used in the next reaction without purification.

To a stirred solution of the above amine, fumaric acid monoethyl ester (807 mg, 5.60 mmol), and DMAP (70.0 mg, 0.573 mmol) in CH_2Cl_2–MeCN (1:1 v/v, 40 mL) at 0 °C was slowly added a solution of DCC (1.15 g, 5.58 mmol) in CH_2Cl_2 (20 mL). After being stirred for 2 h at rt, the mixture was evaporated to give a residue, which was taken up into MeCN. Filtration through Celite, followed by evaporation of the filtrate, afforded a residue, which was purified by chromatography on silica gel. Elution with hexane–AcOEt (4:1 v/v) provided (±)-**23** (460 mg, 51% overall yield), which was identical in all respects with the compound prepared by method A.

(±)-Ethyl (*E*)-3-{*N*-[2-(Hydroxymethyl)butyl]-*N*-[2-(3-indolyl)ethyl]carbamoyl}prop-2-enoate (24). To a solution of (±)-**23** (161 mg, 0.331 mmol) in dry THF (2 mL) was added AcOH–H_2O (1:1 v/v, 2 mL), and the mixture was heated for 16 h at 40 °C. After neutralization with saturated $NaHCO_3$ under ice cooling, the mixture was thoroughly extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue on silica gel using AcOEt–hexane (1:1 v/v) as eluent afforded (±)-**24** (123 mg, 100%) as a yellowish oil: IR ($CHCl_3$) 3480, 3420, 1715, 1642 cm^{-1}; ^1H NMR (500 MHz) δ 0.94 (t, 0.6H, J = 7.4 Hz), 0.96 (t, 2.4H, J = 7.4 Hz), 1.26 (t, 3H, J = 7.3 Hz), 1.30–1.40

(m, 2H), 1.50–1.60 (m, 1H), 1.71 (br s, 1H), 3.01–3.90 (m, 8H), 4.11–4.27 (m, 2H), 6.62 (d, 0.8H, J = 16.5 Hz), 6.87 (d, 0.2H, J = 16.5 Hz), 7.07 (d, 0.8H, J = 16.5 Hz), 7.53 (d, 0.2H, J = 16.5 Hz), 6.95–7.70 (m, 5H), 8.09–8.12 (br s, 0.8H), 8.17–8.20 (br s, 0.2H); MS m/z 372 (M^+). Anal. Calcd for $C_{21}H_{28}N_2O_4$: C, 67,72; H, 7.58; N, 7.52. Found: C, 67.81; H, 7.59; N, 7.37.

(±)-Ethyl (*E*)-3-{*N*-[2-(Bromomethyl)butyl]-*N*-[2-(3-indolyl)ethyl]carbamoyl}prop-2-enoate (25). To a mixture of (±)-**24** (167 mg, 0.449 mmol) and Et_3N (0.130 mL, 0.933 mmol) in dry benzene (2 mL) at 0 °C was slowly added MsCl (0.053 mL, 0.674 mmol). After 3 h of stirring at rt, followed by dilution with AcOEt, the resulting mixture was washed with 10% HCl, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated to give a residue, which was used in the following reaction without purification.

A mixture of the above product and LiBr (234 mg, 2.69 mmol) in dry THF (5 mL) was heated for 1 h under reflux. After dilution with CH_2Cl_2, the mixture was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue with AcOEt–hexane (3:7 v/v) as eluent gave (±)-**25** (171 mg, 88%) as a yellowish oil: IR ($CHCl_3$) 3475, 1715, 1645 cm^{-1}; ^1H NMR (500 MHz) δ 0.82 (t, 2H, J = 8.0 Hz), 0.87 (t, 1H, J = 8.0 Hz), 1.25 (t, 2H, J = 7.5 Hz), 1.32 (t, 1H, J = 7.5 Hz), 1.42 (m, 2H), 2.05–2.15 (m, 1H), 2.95–3.10 (m, 2H), 3.25–3.60 (m, 4H), 3.85–3.91 (m, 2H), 4.05–4.12 (m, 2H), 6.50 (d, 0.67H, J = 15.0 Hz), 6.85 (d, 0.33H, J = 15.0 Hz), 6.98 (d, 0.67H, J = 15.0 Hz), 7.42 (d, 0.33H, J = 15.0 Hz), 6.95–7.68 (m, 5H), 8.00–8.05 (m, 1H); MS m/z 434 (M^+). Anal. Calcd for $C_{21}H_{27}BrN_2O_3$: C, 57.94; H, 6.25; N, 6.43. Found: C, 57.74; H, 6.31; N, 6.45.

(±)-3-((Ethoxycarbonyl)methyl)-5-ethyl-*N*-(2-(3-indolyl)-ethyl)piperidin-2-one (18). A mixture of (±)-**25** (552 mg, 1.27 mmol), $(TMS)_3SiH$ (0.6 mL, 1.94 mmol), and AIBN (210 mg, 1.28 mmol) in dry benzene (280 mL) was heated for 16 h under reflux. After evaporation, the residue was subjected to chromatography on silica gel. Elution with AcOEt–hexane (2:3 v/v) yielded (±)-**18** (280 mg, 62%) as a yellowish oil: IR ($CHCl_3$) 3480, 1730, 1675 cm^{-1}; ^1H NMR (300 MHz) δ 0.60–2.00 (m, 11H), 2.40–4.25 (m, 11H), 7.00–7.95 (m, 5H), 8.28–8.34 (br s, 0.4H), 8.34–8.40 (br s, 0.6H); MS m/z 356 (M^+); HRMS calcd for $C_{21}H_{28}N_2O_3$ (M^+) 356.2100, found 356.2081.

(+)-(4*S*)-3-[(2′*R*)-2′-((*tert*-Butyldimethylsiloxy)methyl)-butanoyl]-4-benzyl-2-oxazolidinone (31). To a stirred solution of **30**[13a] (1.20 g, 4.85 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added $TiCl_4$ (0.586 mL, 5.34 mmol). After 10 min of stirring at 0 °C, Et_3N (0.75 mL, 5.38 mmol) was added, and the mixture was stirred for 30 min at 0 °C. To the resulting mixture were added a solution of *s*-trioxane (484 mg, 5.37 mmol) in CH_2Cl_2 (5 mL) and $TiCl_4$ (0.586 mL, 5.34 mmol) at 0 °C. After 1.5 h of stirring at 0 °C, the mixture was diluted with CH_2Cl_2 and then washed with 10% aqueous NH_4Cl, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to the next reaction without purification.

To a mixture of the above product, TBDMSCl (1.1 g, 7.3 mmol), and DMAP (60 mg, 0.49 mmol) in CH_2Cl_2 (10 mL) at 0 °C was slowly added Et_3N (1.36 mL, 9.76 mmol), and the mixture was stirred for 5 h at rt. The resulting mixture was partitioned between H_2O and CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated to give a residue, which was purified by silica gel chromatography. Elution with AcOEt–hexane (1:9 v/v) afforded **31** (914 mg, 48%) as a colorless oil: $[\alpha]^{21}_D$ +23° (*c* 1.18, $CHCl_3$); IR(neat) 1780, 1700 cm^{-1}; ^1H NMR (300 MHz) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 0.95 (t, 3H, J = 7.5 Hz), 1.50–1.80 (m, 2H), 2.61 (dd, 1H, J = 9.6, 13.2 Hz), 3.30 (dd, 1H, J = 3.3, 13.2 Hz), 3.81 (dd, 1H, J = 5.4, 9.0 Hz), 3.92 (t, 1H, J = 9.0 Hz), 3.96–4.23 (m, 3H), 4.66–4.76 (m, 1H), 7.20–7.40 (m, 5H); MS m/z 391 (M^+). Anal. Calcd for $C_{21}H_{33}NO_4Si$; C, 64.41; H, 8.49; N, 3.58. Found; C, 64.64; H, 8.42; N, 3.53.

(−)-(2*S*)-2-((*tert*-Butyldimethylsiloxy)methyl)butan-1-ol (6). To a solution of **31** (45.0 mg, 0.115 mmol) in Et_2O (2 mL) was added H_2O–THF (1:500 v/v, 1 mL, 0.127 mmol) at rt. To the stirred mixture was added in small portions $LiBH_4$ (3.0 mg, 0.14 mmol) in THF (1 mL) at 0 °C. After 5 h of stirring at rt, CH_2Cl_2 was added, and the mixture was washed with 5% aqueous citric acid and brine, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to silica gel column chromatography with AcOEt–hexane (1:9 v/v) as eluent to provide (−)-**6** (22 mg, 88%) as a colorless oil: $[\alpha]^{22}_D$ −10.6° (*c* 0.99, $CHCl_3$), lit.[5] −11.4° (*c* 1.41, $CHCl_3$). The spectral data of the oil were identical with those of authentic **6** prepared from **29**.[5] The optical purity was determined by conversion of **6** into the corresponding (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionate.[5]

(−)-(2*R*)-1-Bromo-2-((*tert*-butyldimethylsiloxy)methyl)-butane (22). To mixture of (−)-**6** (2.18 g, 10.0 mmol) and Et_3N (2.80 mL, 20.1 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was slowly added MsCl (1.16 mL, 15.0 mmol), and the mixture was stirred for 2 h at rt. The resulting mixture was washed with 10% HCl, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated to give a residue, which was used in the next reaction without purification.

A mixture of the product and LiBr (5.00 g, 57.6 mmol) in dry THF (10 mL) was heated for 2 h under reflux. After dilution with CH_2Cl_2, the mixture was washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue on silica gel with AcOEt–hexane (1:19 v/v) as eluent gave (−)-**22** (2.68 g, 95%) as a colorless oil: $[\alpha]^{22}_D$ −9.4° (*c* 1.28, $CHCl_3$), whose spectral data were consistent with those of (±)-**22**.

(+)-Ethyl (*E*)-3-{*N*-[(2*S*)-2-((*tert*-Butyldimethylsiloxy)-methyl)butyl]-*N*-[2-(3-indolyl)ethyl]carbamoyl}prop-2-enoate (23). By means of the procedure used for the preparation of (±)-**23**, (−)-**22** (478 mg, 1.70 mmol) was converted into (+)-**23** (528 mg, 64%). Compound **23** was a yellowish solid, mp 69–70 °C; $[\alpha]^{21}_D$ +7.1° (*c* 1.01, $CHCl_3$), whose IR, ^1H NMR, and MS spectral data were identical with those of (±)-**23**.

(−)-Ethyl (*E*)-3-{*N*-[(2*S*)-2-(Hydroxymethyl)butyl]]-*N*-[2-(3-indolyl)ethyl]carbamoyl}prop-2-enoate (24). According to a procedure similar to that described for the preparation of (±)-**24**, (+)-**23** (528 mg, 1.09 mmol) was converted into (−)-**24** (382 mg, 95%). Compound **24** was a yellowish oil; $[\alpha]^{22}_D$ −12.5° (*c* 0.93, $CHCl_3$), the IR, ^1H NMR, and MS spectral data of which were consistent with those of (±)-**24**.

(+)-Ethyl (*E*)-{*N*-(2*S*)-2-(Bromomethyl)butyl]-*N*-[2-(3-indolyl)ethyl]carbamoyl}prop-2-enoate (25). By means of the procedure described for the preparation of (±)-**25**, (−)-**24** (184 mg, 0.495 mmol) was converted into (+)-**25** (185 mg, 86%) as a yellowish oil; $[\alpha]^{22}_D$ +28.0 ° (*c* 1.38, $CHCl_3$), the IR, ^1H NMR, and MS spectral data of which were consistent with those of (±)-**25**.

(+)-(5*R*)-3-((Ethoxycarbonyl)methyl)-5-ethyl-*N*-[2-(3-indolyl)ethyl]piperidin-2-one (18 and Its Epimer). By means of the procedure for the preparation of (±)-**18**, (+)-**25** (62.0 mg, 0.143 mmol) was converted into mixture **18** (36.7 mg, 72%) as a yellowish oil; $[\alpha]^{22}_D$ + 4.5° (*c* 1.32, $CHCl_3$), whose IR, ^1H NMR, and MS spectral data were identical with those of (±)-**18**.

Tacamonine (1). To hot $POCl_3$ (1.0 mL, 10.7 mmol) was slowly added a solution of (+)-**18** (66.0 mg, 0.185 mmol) in MeCN (1.5 mL), and the mixture was heated for 7 h under reflux. The solvent and $POCl_3$ were removed under reduced pressure, and the residue was used in the following reaction without purification.

To a stirred solution of the product in MeOH (3 mL) at 0 °C was added in small portions $NaBH_3CN$ (60 mg, 0.95 mmol), and the mixture was stirred for 2 h at rt. After evaporation, the residue was dissolved in $CHCl_3$, and the mixture was washed with H_2O and brine, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to the next reaction without purification.

To a stirred solution of the above product in dry MeOH (2 mL) at 0 °C was added a solution of NaOMe (100 mg, 1.85 mmol) in dry MeOH (5 mL), and the mixture was stirred for 3 h at rt. After dilution with $CHCl_3$, the mixture was filtered through silica gel. Evaporation of the filtrate gave a residue, which was subjected to chromatography on silica gel. Elution with MeOH–CH_2Cl_2 (1:19 v/v) afforded **1** (5.0 mg, 9%), which

was recrystallized from acetone to provide colorless needles, mp 179–181 °C (lit.[1] mp 180–181 °C), whose UV, CD, ^{1}H NMR, and MS spectral data were consistent with the reported ones.[1]

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Supplementary Material Available: ^{1}H NMR spectra of **9–14**, **16**, **17**, **18**, and **22** and ^{13}C NMR spectra of **24** and **18** (12 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.